SYNTHESIS OF PROTOBERBERINE ALKALOIDS

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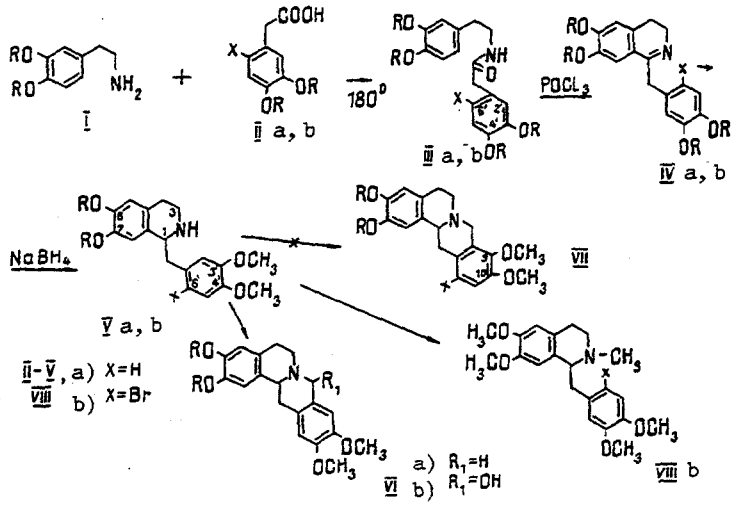
In this review an analysis is made of literature information on the synthesis of protoberberine alkaloids during 1980-1990.

Protoberberine alkaloids, which are based on the diisoquinoline skeleton, contain a large group of natural [1] and synthetic [2] substances. For decades, these substances have attracted the attention of chemists and pharmacologists by their high physiological activity and the possibility of their investigation by various methods of synthesis and chemical transformations connected, in particular, with the inversion of ring D, leading to the transformation of the protoberberine bases into alkaloids of the rheadine, retroprotoberberine, spirobenzylisoquinoline, and benzazepine series [3-9].

Interest in tetrahydroberberine and berberine derivatives has risen in connection with the finding amongst them of antitumoral [10], spasmolytic [11], analgesic [12], sedative [13], hypotensive [12, 14], vasodilating [15], tranquilizing [16], and other types of activity [16a]. A number of substances are used for the treatment of cardiorespiratory diseases [17]. The protoberberine alkaloids berberine, palmatine, and jatrorrizine exhibit, in vitro, an antimalarial activity similar to the of quinine [18].

The synthesis of the protoberberine alkaloids is a promising direction of modern organic chemistry which is developing in interesting fashion and is connected with continuous progress in the methods for their isolation. Information published up to 1980 has been analyzed in a monograph by Shamma [1] and in the reviews [19, 20]. We have attempted to consider and systematize in the present review the most interesting approaches, from our point of view, to the synthesis of this group of substances that have been realized in the last decade.



Scheme 1

The most widely used method for the synthesis of protoberberines is the classical Mannich condensation of 1-benzyltetrahydroisoquinolines with formaldehyde in an acid medium (scheme 1). This route is generally adopted and is the most effective.

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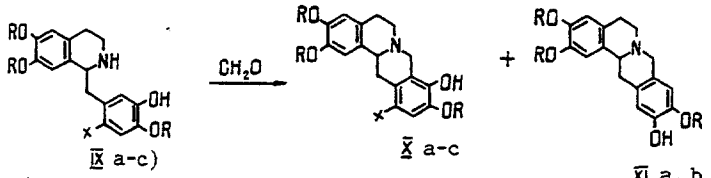
One of the methods of synthesizing the intermediate 1-benzyltetrahydroisoquinolines (V), consists in the condensation of β-phenylethylamines (I) [21], with substituted phenylacetic acids (II) followed by the Bischler–Napieralski cyclization of (III) with phosphorus oxychloride and the reduction of (IV) with sodium tetrahydroborate. The cyclization of (III) and (V) depends on the nature of the substituents and their positions. The effect of a substituent has been studied in detail [22-27] and it has been established that the presence in the benzyl part of the molecule of (V) of two methoxy groups in positions 3 and 4 (Va, X = H) leads to the exclusive formation of the para-products of cyclization (10,11-dimethoxy substituted products, the so-called pseudotetrahydroberberines (VI, R_1 = H) [22, 23].

The introduction of bromine or the blocking of the para- position (Vb, X = Br) does not give the expected (VII), but leads either to cyclization at C-6', bearing the bromine atom, with the formation of (VIb) [22, 28] or to the formation of the N-methyl derivative (VIIIb) [21, 24], which is possibly connected with the deactivating influence of the bromine on the nucleus.

When a hydroxy group is present in position 3 of the benzyl part of the molecule, the cyclization reaction becomes selective, depending on the pH of the medium. At pH 2, the reaction takes place exclusively or predominantly in the para-position. Thus, (IXb) forms a mixture of (XI) and (X) in a ratio of 9:1 [24], while from (IXa) the ratio of the products is 93:7 [26]. With a decrease in the acidity of the medium, the proportion of the ortho-isomer (X) rises, and at pH 7.4-8 the (Xa):(XIa) ratio is 2:1 and the (Xb):(XIb) ratio 1:1, while at pH 10 equal amounts of (Xa) and (XIa) are formed. A difference is also observed in the rates of Pictet–Spengler cyclization: for example, at a pH of about 7 the rate of the reaction is considerably faster than at pH 2. The introduction of bromine into (IXc) gives (Xc) with a good yield even at acid pH values [25].



Mannich cyclization is a convenient method for synthesizing 10,11-dimethoxy-substituted tetrahydroprotoberberines [29] and 8-methyltetrahydroprotoberberines if acetaldehyde is used in place of formaldehyde.

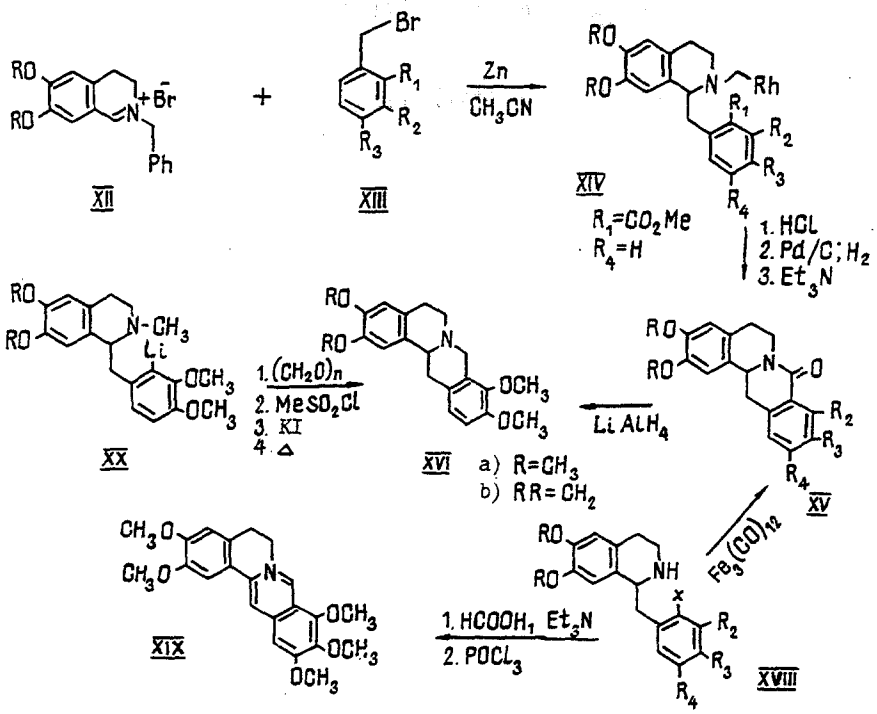
As already mentioned, the key compounds in the synthesis of the tetrahydroprotoberberines by the Mannich reaction are the 1-benzyltetrahydroisoquinolines (V), the synthesis of which is effective and simple with the use of the Bischler–Napieralski [22a] (scheme 1), Pictet–Spengler [22b], Pomeranz–Fritsch [22c], and Schotten–Baumann [22d] methods and their modifications. However, work on the improvement of the methods of synthesizing 1-benzyltetrahydroisoquinolines is continuing. Thus, Shono et al. [30] have proposed to use zinc, promoting the alkylation of the iminium salts (XII) by the alkyl halides (XIII), which enables the 1-benzyltetrahydroisoquinolines (XIV) to be obtained with high yields (86-99%) by scheme 2. 8-Oxoprotoberberines (XV) have been synthesized by this method, opening up a route to tetrahydropalmatine (XIVa) and canadine (XVIb) (see scheme on following page).

Two mechanisms have been proposed for this reaction:

$$RX \xrightarrow{Zn} RZnX \xrightarrow{>C=\overset{+}{N}<} >C(R)-N< \quad (I)$$

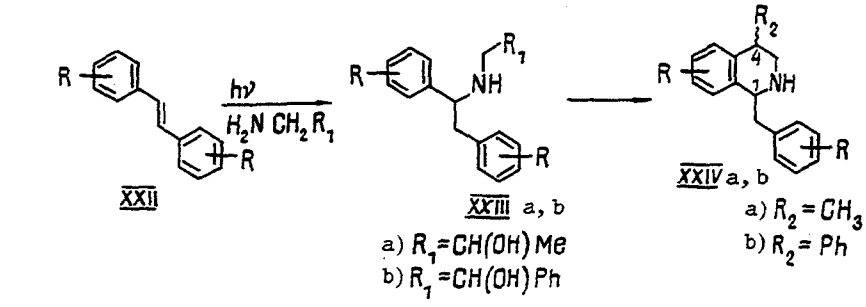
$$>C=\overset{+}{N}< \xrightarrow[+2e]{Zn} >\bar{C}-N< \xrightarrow{RX} >C(R)-N< \quad (II)$$

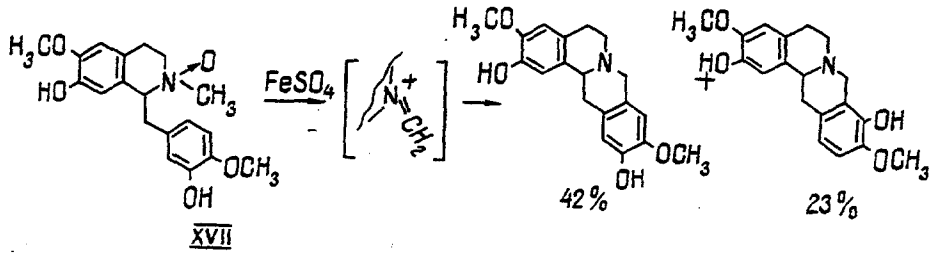
The first takes place as a Zaitsev reaction, and the second with the transfer of an electron to the iminium salt in a similar manner to electroreduction [31]. At the present time, there are no clear proofs of one mechanism or the other.



Scheme 2

One of the possible routes for the synthesis of 1-benzyltetrahydroisoquinolines (XXIV) having a methyl or phenyl substituent in position 4 is the photoreduction of a stilbene (XXII) and an amine in the presence of para-dicyanobenzene to give an N-substituted 1,2-diarylethylamine (XXIII) with a yield, of more than 90%. The latter, on treatment with CF_3SO_3H gives (XXIV) with a yield of 72-88% [38b].

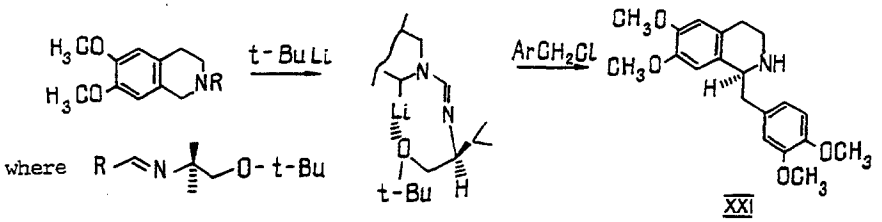




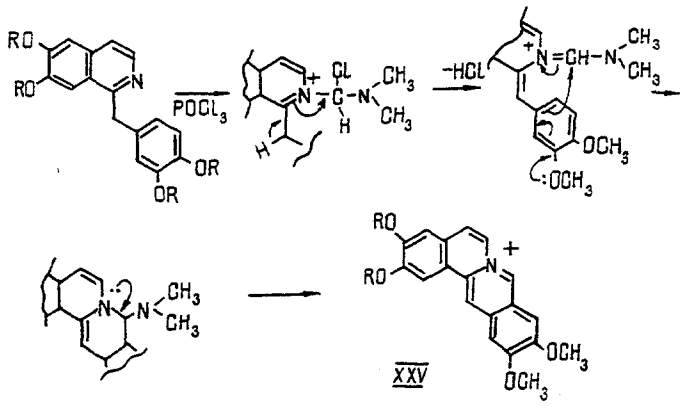
The accessibility of 1-benzyltetrahydroisoquinolines is leading to a search for conditions other than those of the Mannich reaction for their cyclization to protoberberines. Thus, it has been found that cyclization can be achieved by the reduction of (XVII) with ferrous sulfate [32, 33] or by the carbonylation of (XVIII) (X = Br, Scheme 2) both by carbon monoxide (in the presence of palladium diacetate, triphenylphosphine, and tri-n-butylamine) [34], and also through the treatment of (XVIII; X = Br, R_2 = H) with metal carbonyls, $Me_x(CO)_y$. The best results were given by the use of $Co_2(CO)_8$ (73%) and $Fe_3(CO)_{12}$ (60%) [35].

Such a route via N-formylation effected with formic acid in the presence of triethylamine followed by the action of $POCl_3$ on (XVIII) (X = H, $R_2 = R_3 = R_4 = OCH_3$) in acetonitrile leads to the dimethyl ether of glabrine (XIX) in 50% yield [36] (Scheme 2).

The presence of lithium in compound (XX) (Scheme 2) permits 9,10-dimethoxytetrahydroberberines to be obtained [37], and lithium also promotes the formation of chiral 1-benzyltetrahydroisoquinolines [38a], such as (XXI) by the scheme given below:



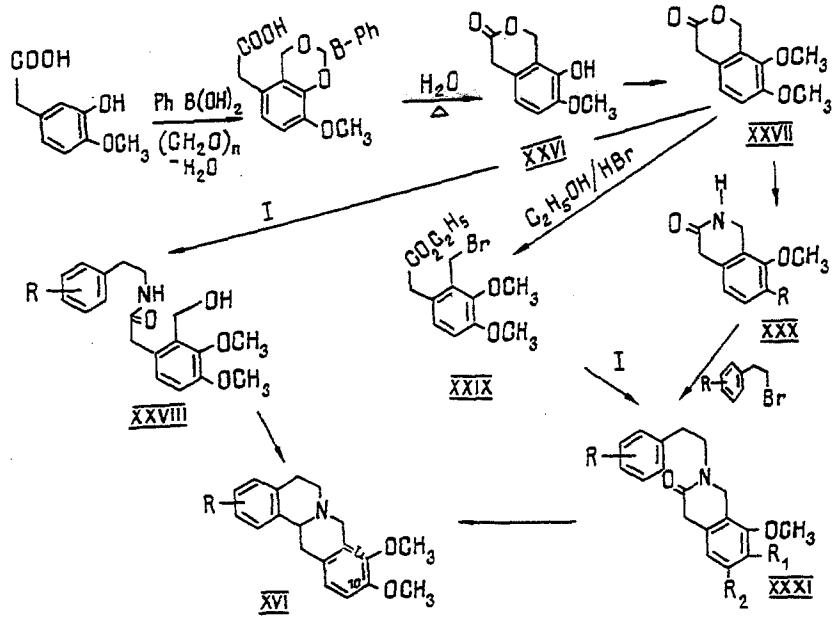
The Vilsmeier—Haack ring-closure of the 1-benzylisoquinoline gives mainly the 10,11-disubstituted protoberberines (XXV) [39].



The schemes considered above are ineffective in the case of the synthesis of 9,10-substituted derivatives, which exhibit a higher physiological activity than the 10,11-isomers [23]. Thus, a different approach was required to the synthesis of the 9,10-dimethoxyprotoberberines, and it was found by Japanese chemists [40]. They, using a route proposed by Battersby et al. [41], were able to solve the problem of the ortho-hydroxymethylation of 3-hydroxy-4-methoxyphenylacetic acid with the aid of phenylboronic acid with 83% yield. The development of an accessible method of obtaining (XXVI) led to the synthesis of a large number of 9,10-unsubstituted protoberberines (XVI) (Table 1) by the Bischler—Napieralski reaction using Scheme 3 (23, 42-57]. It has been shown in a number of publications that in place of the 3-isochromanone (XXVII) it is possible to use the bromo ester (XXIX) [49, 57] or the 3(2H)-isoquinolone (XXX [46] (see scheme on following page).

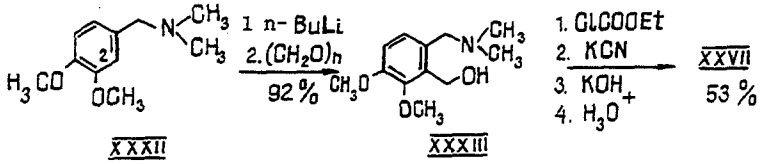
Later, a number of authors [49-55] proposed other methods of obtaining the substituted 3-isochromanone (XXVII). The most promising of them is synthesis through a lithiation stage. An advantage of this method consists in the fact that lithiation takes place readily in positions of difficult access by the usual methods, and the aromatic lithium derivatives formed rea[illegible]apidly with various electron-donating reagents. The position of entry of the lithium into the aromatic ring is determined by complex-formation of the reagent RLi with the electron-donating groups of (XXXII) such as, for example, $-OCH_3$ and $-CH_2-N(CH_3)_2$, which directs the lithium to the ortho position [in (XXXII) such positions may be 2, 5, and 6]. However, in compound (XXXII) the more acidic proton present in position 2 will be replaced by lithium. The replacement of this proton is, of course, impossible in the case of an electrophilic process catalyzed by acids.

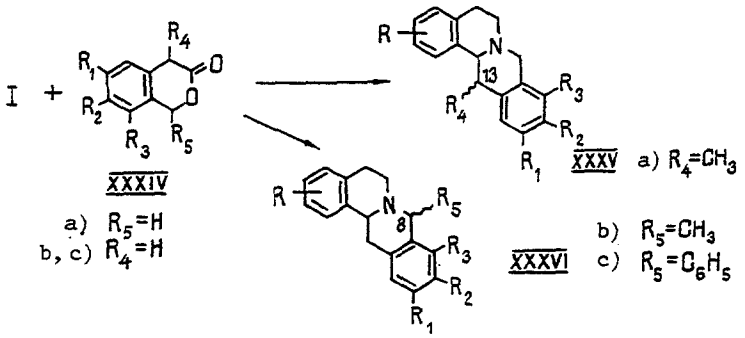
The reactivity of a reagent can be improved by complex-formation with chelating agents, and the activity of the initial aromatic compound by complex-formation with $Cr(CO)_6$ through an increase in the acidity of the aromatic proton. The possibility has been shown of using



Scheme 3

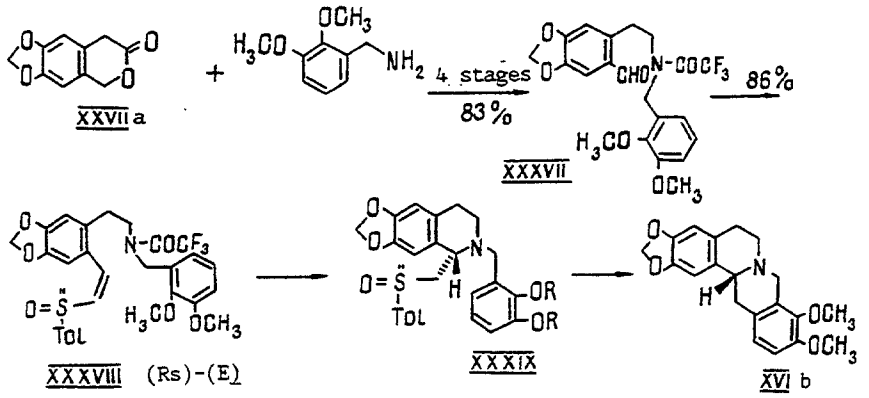
the substituted lactones (XXXIV) for the synthesis of the 13-methyl compounds (XXXVa) and of 8-methyl- and 8-phenylprotoberberines (XXXVI) [58].



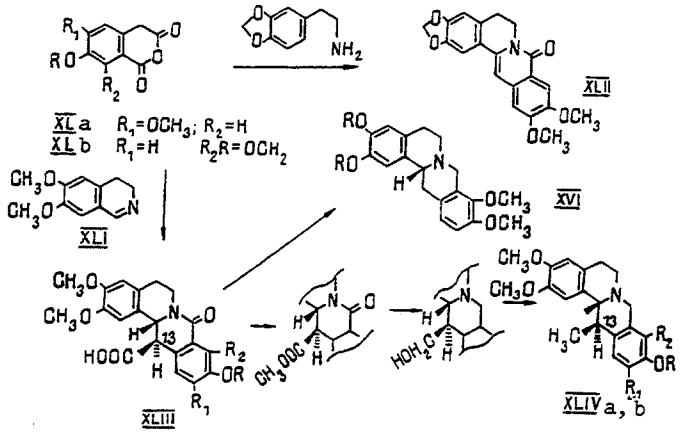


The 3-isochromanone (XXVIIa) can serve as the starting material for obtaining a chiral vinyl sulfoxide [59]. The interaction of (XXVIIa) with 2,3-dimethoxybenzylamine in boiling ethanol gave an amide which, on reduction with $LiAlH_4$ in THF yielded an amino alcohol. Treatment of the latter with trifluoroacetic anhydride followed by oxidation gave the aldehyde (XXXVII) in 83% yield. Compound (XXXVII) was olefinated with R-(+)-dimethylphosphorylmethyl p-tolyl sulfoxide by the Horner–Wittig method with the formation of the two vinyl sulfoxides (XXXVIII) [(Rs)–(E):(Rs)–(Z) 2:1]. Treatment of the mixture obtained with benzyltriethylammonium hydroxide gave a mixture of diastereomers with a predominance of (XXXIX), the intramolecular rearrangement of which under the action of trifluoroacetic anhydride gave (R–)-(+)-canadine (XVIb) (see scheme on following page).

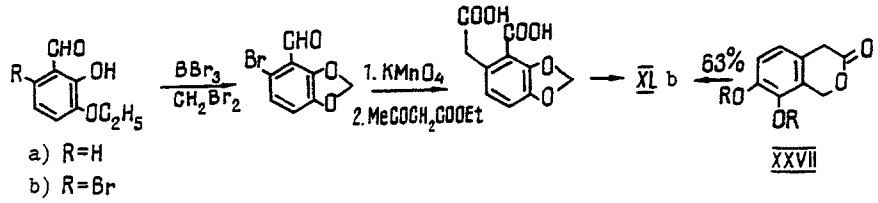
Investigations of Bischler–Napieralski cyclization using the homophthalic anhydrides (XLa) has continued. The condensation of the functionally substituted compounds (XLa) with β-phenylamine or with 3,4-dihydroisoquinoline (XLI) forms a route to the 8-oxo compound (XLII) or to the 13-carboxy-8-oxoprotoberberines (XLIII) [39, 60]. The reactions of (XLI) and (XLa) in chloroform at room temperature gives a mixture of cis- and trans-13-carboxy-2,3,10,11-tetramethoxy-8-oxotetrahydroprotoberberines with a predominance of the trans-



isomer (XLIII; R_1 and R_2 as in XLa). Boiling the latter in acetic acid leads to epimerization with the formation of the cis- isomer [39]. This method has also been used for obtaining 13-methyl-9,10-methylenedioxy-substituted protoberberines (XLIVb) by using the appropriately substituted phthalic anhydrides (XLb) [61-63].

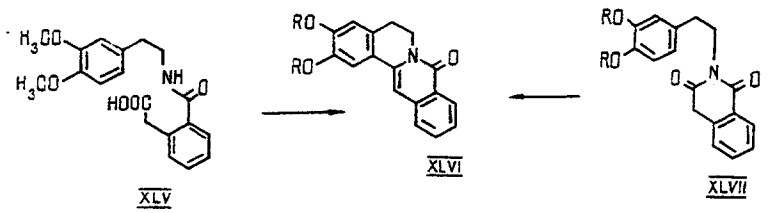


An effective route to such anhydrides (XLb, $R_2R = OCH_2$) has been proposed [64] that starts from 3-ethoxy-2-hydroxybenzaldehyde, which is an industrial waste, or from (XXVII) [65] by the following scheme



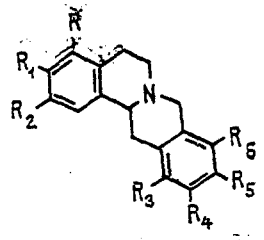
a) R=H
b) R=Br

It was found experimentally that the use of $POCl_3$ at the stage of the cyclization of (XLV) gave 2,3-dimethoxy-8-oxo-5,6-dihydro-dibenzo[a,g]quinolizine (XLVI) with a yield of not more than 35%. The use of polyphosphoric acid increased the yield of (XLVI) to 80%, while the phthalimide (XLXII) was cyclized under these conditions with a yield of 70% [66].



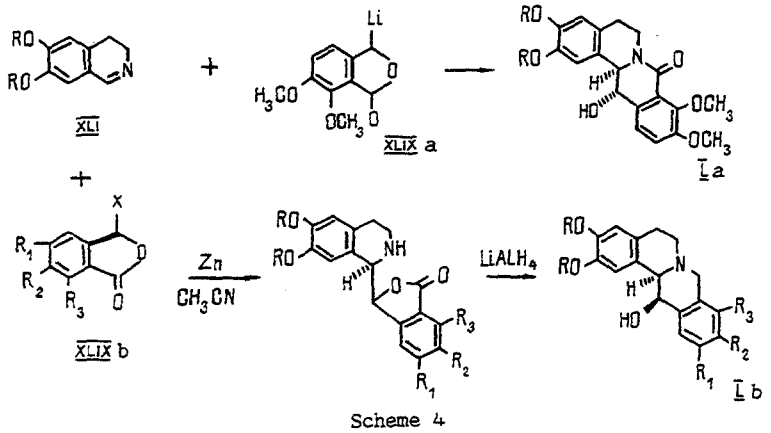
There is definite interest in synthesis via the condensation of the 3,4-dihydroisoquinoline (XLI) with the anion of the phthalide (XLIXa) (yield 65%, obtained from

TABLE 1. Synthesis of Tetrahydroprotoberberines Using Compounds (XXVII), (XXIX), and (XXX)



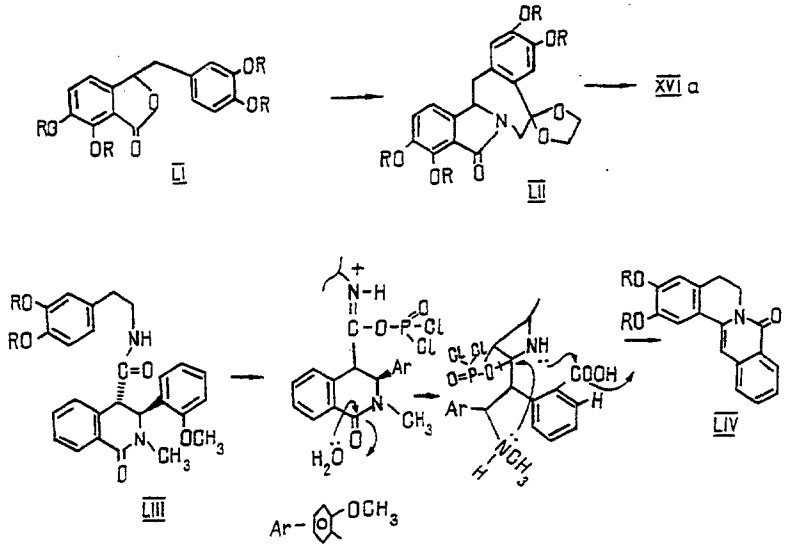
R	R_1	R_2	R_3	R_4	R_5	R_6	Literature
H	OCH_3	OCH_3	H	H	H	H	47, 57
H	"	"	H	OCH_3	OCH_3	H	47, 48, 57
H	"	OH	H	"	"	H	47, 57
H	"	"	H	H	"	H	47, 57
H	"	OCH_3	Br	OCH_3	"	OCH_3	47, 57
H	"	"	Br	H	"	"	
H	"	"	H	OCH	"	"	
H	"	"	H	H	"	"	42, 47, 55, 57
H	"	H	H	H	"	"	47, 57
H	OCH_2O		H	H	"	"	26, 55
H	"		H	H	H	"	52
H	"		H	H	OCH_3	H	52
H	OH	H	H	H	OCH_3	OCH_3	57
H	OCH_3	H	H	H	H	H	51
H	H	OCH_3	H	H	H	H	51
H	OCH_3	OCH_3	H	OCH_2O		H	47, 57
H	OCH_2O		H			H	57
H	OCH_3	OH	H	H	OCH_3	OH	47
H	OH	OCH_3	H	H	"	OCH_3	46
H	H	"	H	OCH_3	"	H	45
H	OCH_3	OH	H	H	OCH_2O		44
H	OH	OCH_3	H	H	"		44
H	OCH_3	"	H	H	"		55
H	OCH_2O		H	H	"		55
H	OCH_3	OCH_3	H	H	OCH_3	H	57
H	"	"	H	OCH_3	H	H	57
OCH_3	"	"	H	H	OCH_3	OCH_3	43
"	"	"	H	H	OCH_2O		43
"	"	"	H	OCH_3	OCH_3	H	43

6,7-dimethoxyphthalide and $(iso\text{-}Pr)_3NLi$ in tetrahydrofuran, to 13-hydroxy-8-oxotetrahydroprotoberberine (La) [62, 67] or with the 3-halophthalide (XLIXb) via a phthalidylisoquinoline to the tetrahydroisoquinoline (Lb) [30].



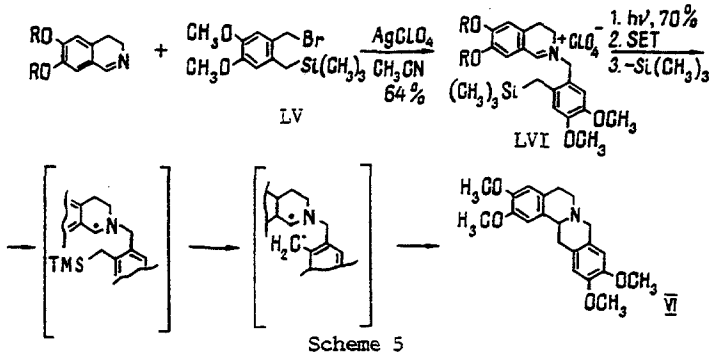
Scheme 4

Tetrahydropalmatine (XVIa) has been synthesized by a nine-stage process starting from 3-(3,4-dimethoxybenzylidene)-6,7-dimethoxyphthalide (LI) via compound (LII) in 16% yield [68, 69].



An unusual chain closure has been proposed by Kansal and Bhaduri [70] for 4-[(3",4"-dimethoxyphenylethyl)carbamoyl]-3-(2'-methoxyphenyl)-2-methyl-3,4-dihydro-1(2H)-isoquinolone (LIII), which gives 8-oxoprotoberberine (LIV) in 35% yield.

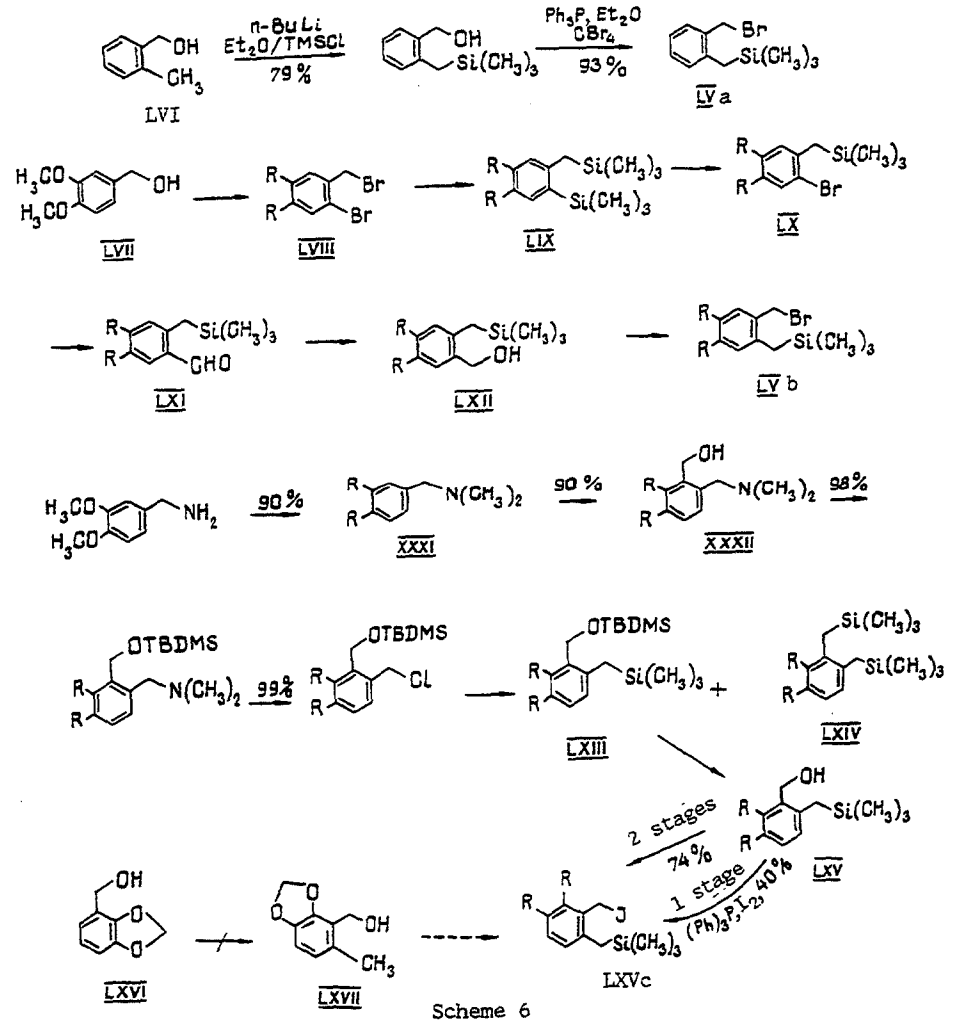
New approaches to the synthesis of the protoberberines have been proposed in a series of papers [71-79]. Their originality is based on the biradical cyclization of 2-(trimethylsilylxylyl)-3,4-dihydroisoquinoline salts (LVI in Scheme 5) obtained by the N-alkylation of 3,4-dihydroisoquinoline by substituted o-(trimethylsilylmethyl)benzyl halides. The irradiation of these salts leads to the formation of the tetracyclic protoberberine system, accompanied by the successive transfer of an electron, desilylation, and biradical coupling. The mechanism of this reaction is connected with intramolecular single-electron transfer (SET) from the side-chain of the arene in an excited state to a phenyl-conjugated iminium cation and the formation of a biradical [71]. The trasnfer of the electron is initiated



Scheme 5

by irradiation. The photoinitiation of SET processes connected with desilylation and the formation of the corresponding benzyl radicals takes place very rapidly and, as a rule, excludes other reactions. The formation of a C–C bond from the biradical intermediate product gives the required substance. The use of silver perchlorate in the reaction of bromide (LV in Scheme 5) with 3,4-dihydroisoquinoline increases the yield of the product (LVI). Subsequent irradiation of acetonitrile solutions of the salt (LVI) by a mercury lamp (λ 270 nm) favors the selective irradiation of the chromophore of the phenyl-conjugated iminium ion, which leads to the tetracyclic product with a yield of 80%. Thus, photocyclization through the successive route of SET and desilylation leads to the construction of a C-piperidine ring. The key fragment in this scheme is the production of compound (LV) (Scheme 5). A method has been developed for the two-stage synthesis of the unsubstituted (trimethylsilylmethyl)benzyl bromide (LVa). For this purpose, the o-methylbenzyl alcohol (LVI in Scheme 5) was converted via lithiation and then trimethylsilylation, followed by replacement of the hydroxy group by bromine, into the required (LVa).

Synthesis of tetrahydroprotoberberines by scheme 5 has become competitive with the synthesis described above including Mannich and Bischler—Napieralski cyclizations, thanks to developments by certain authors [75, 76] who have proposed an alternative route for the synthesis of 2-(trimethylsilylmethyl)benzyl alcohol (LV) [sic] [77, 78].



Scheme 6

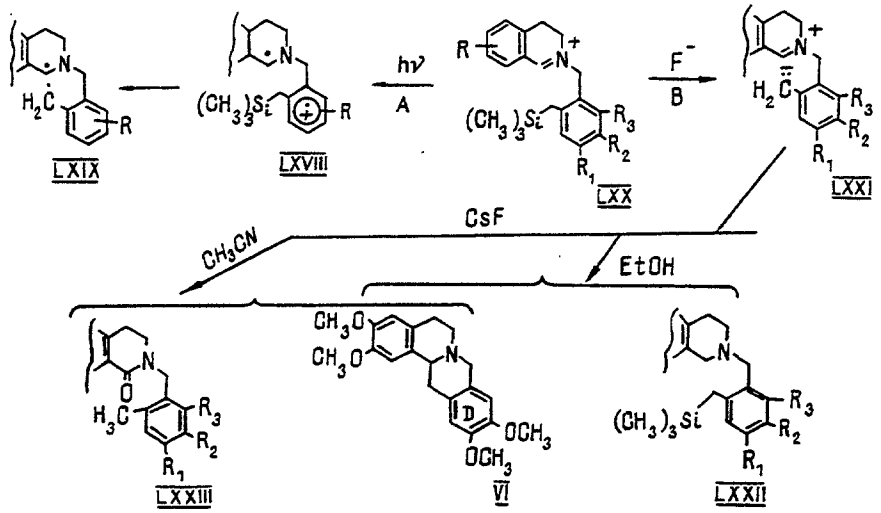
To obtain 10,11-dimethoxysubstituted protoberberines, the synthesis of 4,5-dimethoxy-2(trimethylsilylmethyl)benzyl bromide (LVb; R = OCH_3) has been converted from a two-stage to a six-stage one with an overall yield of 36% (scheme 6). In this case, veratryl alcohol was brominated to give 2-bromo-4,5-dimethoxybenzyl bromide (LVIII). The interaction of the latter, via the Grignard compound, with trimethylsilyl chloride (TMSCl) led to the bissilyl derivative (LIX). The aryl bromide (LX) can also be obtained directly from the dibromide by the selective formation of the monobenzyl Grignard compound followed by its treatment with TMSCl. However, in this process the bissilyl compound (LIX) is formed as a by-product. The lithium derivative of (LX), on formylation with dimethylformamide followed by reduction of the aldehyde (LXI) gives 4,5-dimethoxy-2-(trimethylsilylmethyl)benzyl alcohol, which is converted into the key bromide (LVb). N-Benzylation of dihydroisoquinoline by the bromide (LVb) takes place at 25°C in the presence of one equivalent of $AgClO_4$. It must be mentioned that this route for obtaining the salt (LXVI) proves to be more effective than by the Bischler—Napieralski reaction [79].

The preparation of the key compound (LXVc) in the synthesis of, for example, stilopinine containing substituents in positions 9 and 10 in ring D is extremely difficult, since it requires the introduction of four adjacent substituents into the aryl ring. Thus, all attempts to convert 2,3-methylenedioxybenzyl alcohol (LXVI) into its 6-methyl derivative (LXVII) were unsuccessful under the conditions described in [80].

The most effective method of synthesizing (LVc) giving almost quantitative yields at all stages, apart from the Grignard reaction, proved to be a multistage route [71]. The

low yield at the Grignard stage is explained by the formation of a bissilyl by-product (LXIV) together with the required (LXIII). The benzyl alcohol (LXV) can be converted into the expected iodide (LXVc) by a one- or a two-stage process (Scheme 6). The subsequent alkylation of dihydroisoquinoline by the iodide (LXVc) in acetonitrile in the presence of $AgClO_4$ leads to a salt the photocyclization of which in ethanolic solution ($\lambda > 310$ nm) gives (+)-stilopine.

The influence of electron-donating substituents in the silylxylyl part of the molecule on the efficiency of photosynthesization has been investigated. The results obtained show that substituents have no fundamental effect on the rate of electron transfer but decrease the rate of desilylation of the intermediate diradical cations such as, for example, (LXV-III) through the back-transfer of an electron from (LXIX) (Scheme 7).



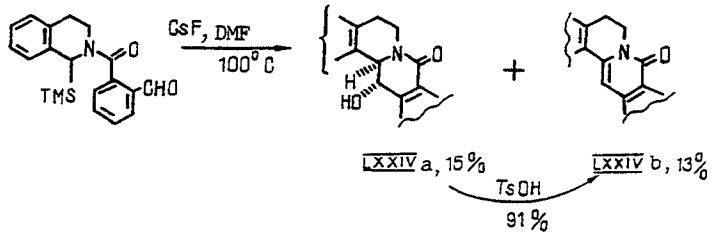
Scheme 7

Thus, an important step in this method is the cyclization of the biradical intermediate compound (LXIX) (route A, Scheme 7), and the method itself is promising in the creation of tetrahydroberberine systems.

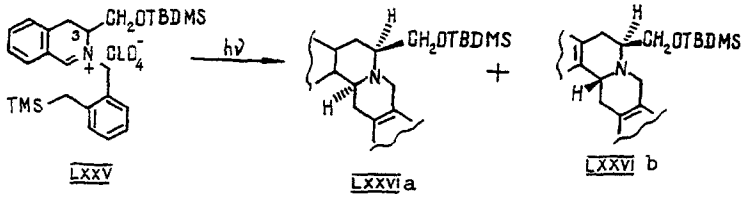
Close to the method described above is a route through the bipolar intermediate compound (LXXI) arising on the treatment of (LXX) with a fluoride ion (route B, Scheme 7). Thus, Japanese authors [79, 81] have reported that the salt (LXX), on treatment with CsF in alcohol at 80°C, gives xylopinine (VI, R = H) with high yield but is inert to CsF in boiling acetonitrile. However, other authors [71] succeeded in obtaining in acetonitrile not only (LXXIII) but also xylopinine (VI) and its analogs with yields of from 15 to 51%, depending on the substituents in ring D.

The formation of tetrahydroisoquinolines under these conditions takes place as the result of a disproportionation, including γ-deprotonation by fluorine, from the dihydroisoquinoline salts (LXX) with the formation of the tetraenamine (LXXI), on the transfer of hydride from which to the iminium salt a protoberberine is formed by route B [70]. At the present time, the factors determining the nature of the fluorine-induced reactions have not been finally elucidated.

The protoberberines (LXXIVa and b) have been obtained by using the introduction of a trimethylsilyl group into the isoquinoline part of the molecule [82, 83].

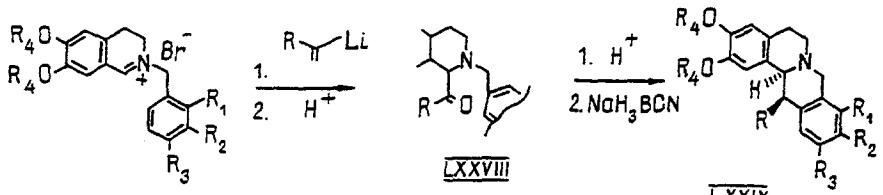


The method of photo-induced electron transfer (SET) permits the cyclization reaction to be performed in stereodirected fashion when, for example, the substituent $-CH_2OTBDMS$ (where TBDMS represents the tert-butyldimethylsilyl) is present in position 3. The irradiation (λ 270 nm) of (LXXV) formed the berberines (LXXVIa) and (LXXVIb) with a yield of 82%, their ratio depending on the solvent used and the reaction temperature and ranging from 1:1.3 to 1:6 [84a].



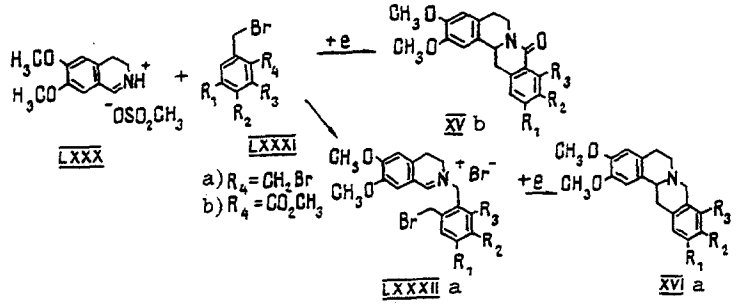
LXXV LXXVIa LXXVI b

The nucleophilic acetylation of a 3,4-dihydroisoquinolinium salt by a vinyllithium compound at −30°C in tetrahydrofuran solution followed by hydrolysis gives an 80% yield of the ketone (LXXVIII), which cyclizes under the action of conc. HCl and, after reduction with NaH_3BCN gives a tetrahydropseudoberberine (LXXIX) with a yield of 84% [85].



LXXVII LXXVIII LXXIX

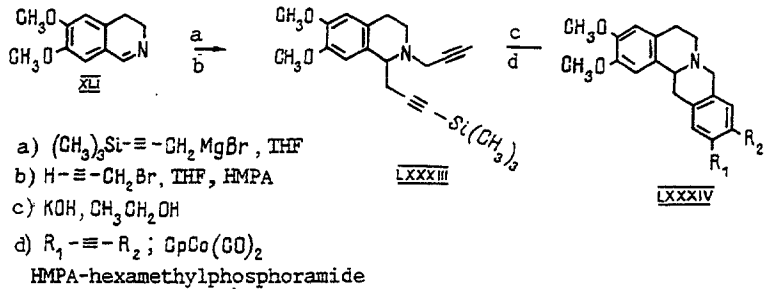
An effective annelation of the iminium salt (LXXXIIa), prepared from (LXXX) and α,α'-dibromo-ortho-xylene (LXXXIa) [86] by electroreduction to the tetrahydroberberines (XVIa) (R = H) (or to the amides (XVb) if (LXXXIb) is used) has been proposed (LXXXVII). In this way, a number of derivatives of (XV) were obtained with high yields (70-94%).



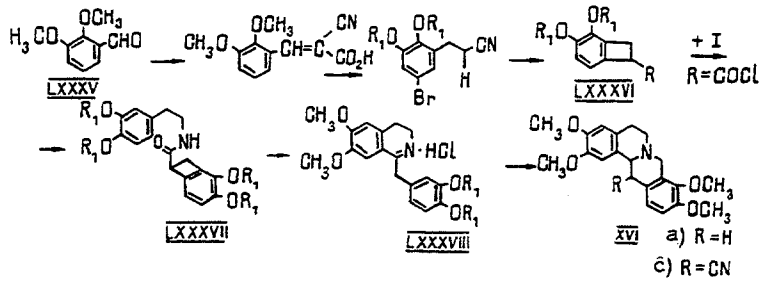
LXXX LXXXI XV b LXXXII a XVI a

An original synthesis of the protoberberine system was achieved in [88]. The authors formylated homoveratrylamine with methyl formate followed by cyclization in the presence of $POCl_3$ to 6,7-dimethoxy-3,4-dihydroisoquinoline (XLI) with 89% yield. The reaction of the latter with the Grignard reagent obtained from 3-bromo-1-trimethylsilylpropyne followed by N-propargylation gave (LXXXIII) with an overall yield of 35%. Saponification with alcoholic alkali followed by cocyclization with bis(trimethylsilyl)ethyne catalyzed by η^5-cyclopentadienyldicarbonylcobalt [$CpCo(CO)_2$)] gave the expected tetrahydroprotoberberine (LXXXIV) with 93% yield (see scheme on following page).

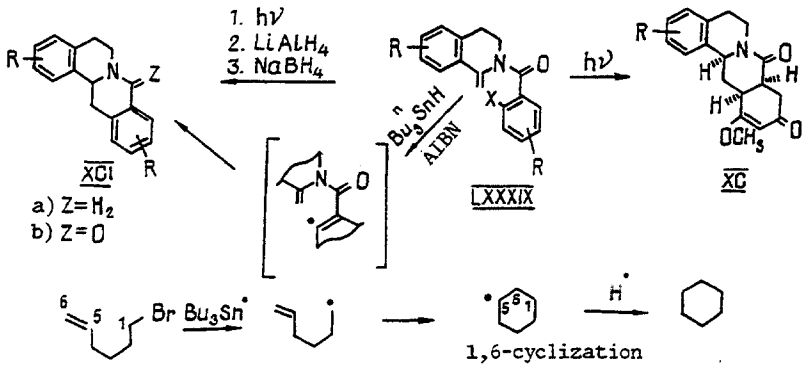
Individual papers have been published on the synthesis of tetrahydroberberines by thermolysis [89] and photolysis [90-94], using methods developed previously. Thus, the benzocyclobutene (LXXXVI), synthesized from 2,3-dimethoxybenzaldehyde (LXXXV) by Knoevenagel condensation followed by sodium tetrahydroborate reduction, decarboxylation, bromination, and cyclization by the method of Bunnet and Skorcz [90], was condensed with the amine (I) in 92% yield. The Bischler–Napieralski reaction of the amide (LXXXVII) so obtained gave



the 3,4-dihydroisoquinoline (LXXXVIII), which, on heating to 160°C followed by reduction with sodium tetrahydroborate, yielded tetrahydropalmatine (XVIa, R = H) [89] or 13-cyanoprotoberberine (XVIc, R = CN).



The reductive photocyclization [91] of the dimethoxy-substituted enamide (LXXXIX) (X = H, scheme 8), which is readily synthesized from 6,7-dimethoxy-1-methyl-3,4-dihydroquinoline and 3,5-dimethoxybenzoyl chloride, gave, in the presence of sodium tetrahydroborate in a mixture of benzene and methanol, a tetracyclic lactam, which, without purification, was subjected to acid hydrolysis to form cis-(XC) (44%) and the trans-methoxyenone (XVI) or was reduced successively with $LiAlH_4$ and $NaBH_4$ to (XCIa) [92, 93].

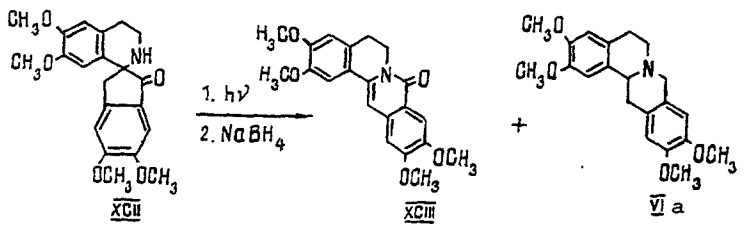


Scheme 8

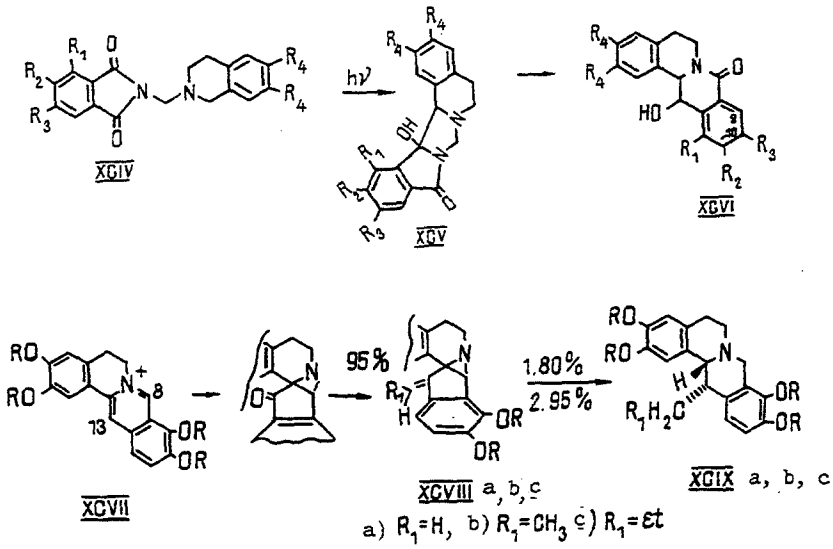
A method has also been proposed for aryl radical-induced 1,6-cyclization which enables (XCIb) to be obtained with a yield of 20% starting from (LXXXIX; X = Br), using n-Bu_3SnH and, as catalyst, 2,2'-azoisobutyronitrile (AIBN) [94]. The mechanism of the 1,6-cyclization reaction is given in Scheme 8.

The synthesis of tetrahydroprotoberberines is effected from the spirobenzyloisoquinolines (XCII) by photocyclization with 35-40% yield [95]. The presence of vitamin C increases the yield of the desired product (VIa) to 75-82% and correspondingly lowers the formation of the 8-oxo compound (XCIII) to 94% (see scheme on following page).

The Mannich base (XCIV), on irradiation with a mercury lamp in benzene solution, gives the pentacyclic product (XCV) treatment of which with aqueous HCl (2 M) leads to the protoberberine skeleton (XCVI) with a yield of 28-70%. The presence of substituents lowers the yield of the desired product. At the same time, approximately twice as much of the



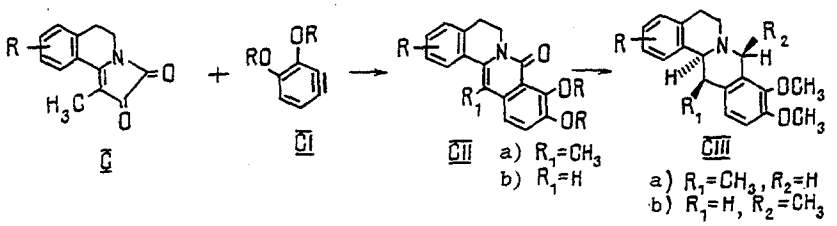
10,11-dimethoxy-containing isomer is formed as of the 9,10-substituted isomer – for example, the 13-hydroxy-8-oxoxylopinine (XCVI; R_1 = H, R_2 = R_3 = R_4 = OCH_3, 35%) [96].



Definite interest is aroused by the search for methods of synthesizing 8- and 13-methylprotoberberines. An effective method has been proposed by the authors of a series of papers [3, 97]. The quaternary salt (XCVII) was reduced with $LiAlH_4$ and was then oxidized with m-chloroperbenzoic acid followed by the isomerization of the 8,14-cycloberberine (XCVIII), which, with the aid of a photochemically induced electrocyclic reaction followed by sodium tetrahydroborate reduction, was converted with high yield into the 13-methylprotoberberine (XCIXb).

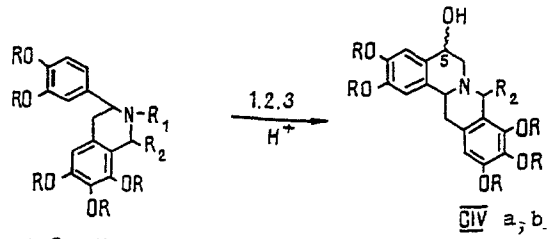
The cyclization of the isoquinolinopyrrolinedione (C) with the aryne (CI) [98] obtained from anthranilic acid, gives, after reduction of the (CIIa), (±)-corydaline (CIIIa).

Jahangir et al. [99a], having treated 8-oxoberberine (CIIb) with methyllithium, obtained an exomethylene compound which, in an acid medium, was transformed into an iminium salt the reduction of which with sodium tetrahydroborate gave a mixture of (R)- and (S)-8-methylcanadines (CIIIb) in a ratio of 1:3). The stereodirected synthesis of (–)-(8R)-methylcanadine was achieved through the selected monocomplex-formation of (–)-(8R)-canadine with $Cr(CO)_3$ [99].



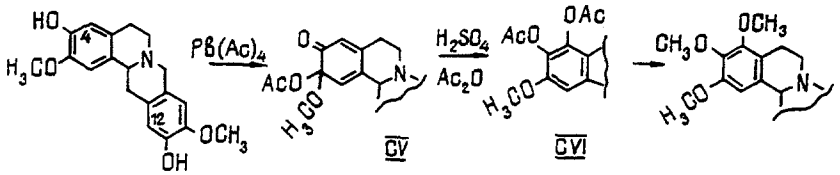
A route to hydroxy-substituted protoberberines depends on the position of the hydroxy group. Thus, the 5-hydroxyprotoberberines (CIV) has been synthesized from a 3-aryltetrahydroisoquinolines (R_1 = H) by N-alkylation (with glycidol – 2,3-epoxypropan-1-ol) and

oxidation by sodium periodate to the corresponding aldehyde, followed by cyclization in 6 M HCl [100]. At the same time, a hydroxy substituent can be introduced into position 4 by oxidizing a tetrahydroprotoberberine with lead tetraacetate to an ortho-quinol acetate followed treatment with concentrated sulfuric acid and acetic anhydride to give the diacetate (CVI); the analogous reaction may take place at position 12 [101].

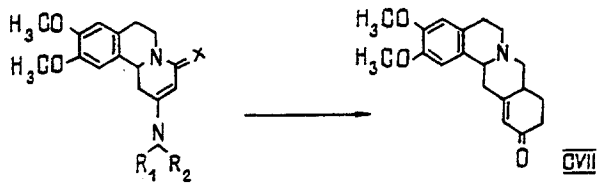


CIV a, b

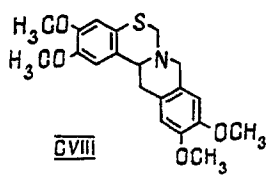
A new method has been proposed for synthesizing in 84% yield the enones (CVII), which are key intermediates in the synthesis of alkaloids of the berberine series [102] via the reduction with lithium tetrahydroaluminate of an enaminolactam followed by treatment with methyl vinyl ketone [103].



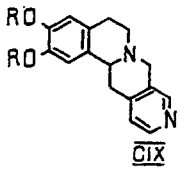
CV CVI



CVII



CVIII



CIX

Syntheses have been performed of analogues of tetrahydroprotoberberine – for example, thieno analogues and thio analogues such as (CVIII) [104, 105], corresponding analogues of benzopyridoquinolizidine bases [106].

Thus, a considerable amount of material has accumulated in the literature on the investigation of methods of synthesizing tetrahydroprotoberberines, but their high biological directivity is leading to a continuous search for more effective and simpler methods of synthesis.

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12. Japanese Patent No. 115706/72, 113706/72; Japanese Patent Application Nos. 51-12034, 47-116547.
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DIMERIC STILBENES OF THE WOOD OF Maackia amurensis

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Dimeric stilbenes have been isolated from the wood of Amur maackia for the first time. Two of them have been identified as the known scirpusins A and B. The structure of a new dimeric stilbene with a dioxane linkage, which has been called maackinin, has been established. The PMR and ^{13}C NMR spectra of the substances isolated have been studied in detail.

We have previously reported on the isolation from alcoholic extracts of the hardwood of Amur maackia Maackia amurensis Rupr. et Maxim. of isoflavonoids – formononetin, genistein, and retusin – and two stilbenes – resveratrol and piceatannol [1] and also of an isoflavonostilbene, which was called maackiasin [2]. The substances were designated as M-1, M-2, M-3, M-4, M-5, M-6, respectively.

We have continued the study of the chemical composition of an ethyl acetate fraction of the alcoholic extract of maackia wood and have isolated another three substances, M-7, M-8, and M-9. They proved to be related compounds, and on the basis of spectral properties and other physicochemical characteristics they have been identified as dimeric stilbenes. Oligomeric stilbenes have apparently not hitherto been detected in representatives of the genus Maackia not in the closely related genera Cladrastis and Sophora. At the same time, Japanese scientists have recently found two trimers of the stilbene resveratrol – (–)-α-viniferin and (+)-α-viniferin – in an extract of the roots of the plant Caragana chamalagu, a representative of another legume genus (Caragana) [3].

Since oligomeric hydroxylated stilbenes exhibit a high biological activity, their chemical structure is peculiar, and their functions in plants are not completely clear, we have found it necessary to preface an account of the experimental results with a short review of the literature relating to this group of natural polyphenols.

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