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SYNTHESIS OF SOME ALKALOIDS USING THE ALLYL DERIVATIVES OF BORON (REVIEW)

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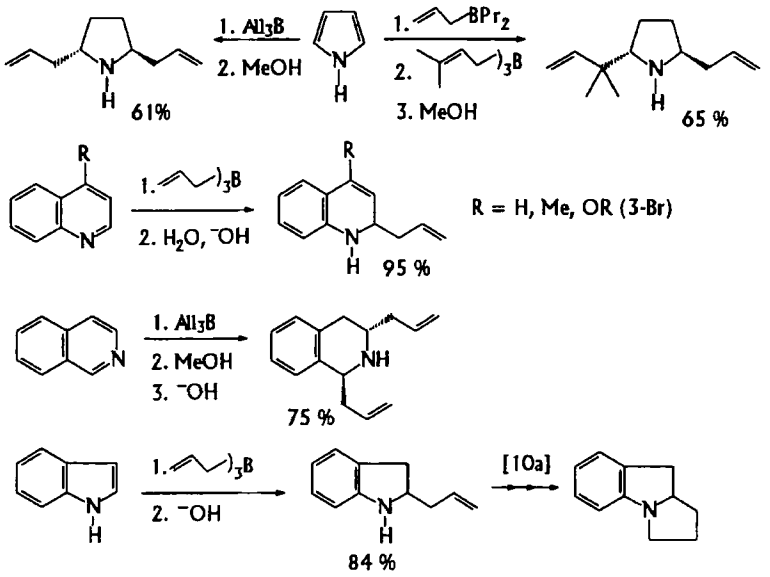
Data on the application of the allylic derivatives of boron for the synthesis of piperidine, indolizine, pyrrolizidine, and indole alkaloids are reviewed.

Alkaloids and their analogs have specific and often unique physiological activity and find use in practical and experimental medicine. At the same time many superactive alkaloids are produced by plants and animals in very small quantities, often insufficient even to study their biological action. Chemical synthesis therefore remains the only source for their production. Modern organic chemistry provides a rich arsenal of methods, the appropriate combination of which makes it possible to synthesize almost any natural compounds, including the most complex compounds. As a rule, however, such a synthesis was only carried out once on account of its laborious nature. The development of more perfect methods and general schemes for the synthesis of substances with various degrees of complexity therefore remains one of the important aims of organic chemists.

The chemistry of boron has made a substantial contribution to the development of the modern organic chemistry methodology [1-4]. In recent years various β,γ-unsaturated (allyl) derivatives of boron have been widely used in synthesis [1-7]. This is due to their high specific chemical activity, which is not characteristic for other types

Scheme 1



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of organometallic compounds [7-9]. Thus, allylboronation of compounds with C=O, C=S, C=N, C≡N, C=C, and C≡C multiple bonds [1-7] has become a standard reaction in organic chemistry.

Recently we discovered a series of reactions (Scheme 1) linking the chemistry of heterocyclic compounds and organoboron compounds on a new basis [10-14]. As found, pyrrole, indole, pyridines, isoquinoline, quinoline, and other aromatic nitrogen heterocycles undergo reductive mono- and *trans*-α,α'-diallylation under the action of allylboranes.

The addition of the allylboron fragment to all the heterocyclic systems is realized with allylic rearrangement through a six-center transition state [10-14] and is only characteristic of this type of organoboron compounds. In the case of pyrrole and indole the corresponding 3H-tautomers (imines), which are formed as intermediates in a consequence of the 1,3-hydrogen migration taking place under the influence of the organoborane, undergo allylboronation. These transformations and also the subsequently described transformations of the nitrogen heterocycles take place under mild conditions (20-100°C) and are not complicated by side processes.

The compounds obtained on their basis contain a NH group and double bonds, which can be functionalized by various methods.

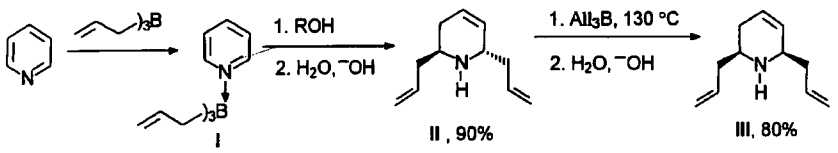
In the present paper we review data on the use of reductive allylboronation in the synthesis of certain alkaloids and their analogs. The aim is to attract heterocyclic chemists to these new reactions.

1. STEREOSELECTIVE REDUCTIVE 2,6-DIALKYLATION OF PYRIDINE

In 1959 Topchiev and coworkers [15] showed that triallylborane, which is a strong Lewis acid, reacts with pyridine with the formation of the adduct I, which does not dissociate during vacuum distillation (bp 102°C). More recently the IR, Raman [16], and NMR spectra [17] of this compound have been investigated. It was also found that the complex I is not changed by prolonged heating at 160°C (20 h) [10, 11].

In 1991 we established [18] that treatment of the adduct I with alcohols, water, or R_2NH led to its complete rearrangement. *trans*-2,6-Diallyl-1,2,5,6-tetrahydropyridine II was obtained with an 80% yield [10-12, 18, 19] (Scheme 2).

Scheme 2



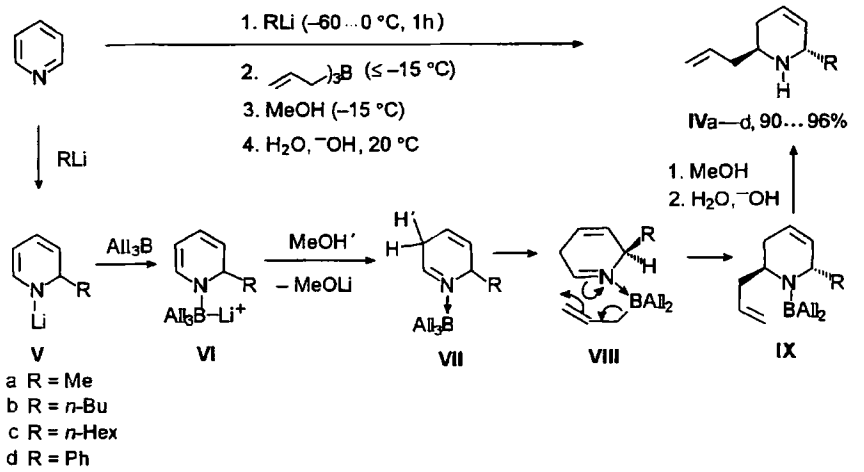
Trimethallylborane [20, 21] and tricrotylborane [10-12] react similarly with pyridine and its derivatives. The addition of allyl groups to the pyridine ring takes place with an allylic rearrangement [10-12].

This general stereospecific reaction, called reductive *trans*-2,6-diallylation of pyridines by allylboranes, takes place with destruction of the "aromaticity" of the pyridine ring and the formation of two new carbon–carbon bonds. The mechanism of the formation of *trans*-2,6-diallylated amines of type II and the dramatic role of the alcohol (or water) in the realization of the process (I → II) were discussed in [12, 20]. We then established that the *trans*-amines II are converted almost quantitatively into the corresponding *cis*-isomers III by heating with triallylborane (130-135°C) and subsequent deboronation with alkali [10-12, 20, 22].

On the basis of this reaction, however, it is only possible to obtain symmetrically 2,6-diallylated tetrahydropyridines and their hydrogenation products such as 2,6-dipropylpiperidines [10-12]. At the same time many natural alkaloids of the piperidine series contain different substituents at positions 2 and 6. It was therefore tempting to develop methods for the synthesis of both unsymmetrically *trans*- and *cis*-2,6-substituted tetrahydropyridines and then to use the "boron" methodology for the production of certain alkaloids and their analogs.

We found that the successive treatment of pyridine with the alkyl or aryl derivatives of lithium, triallylborane, methanol, and alkali gave 6-substituted 2-allylated tetrahydropyridines IV with the *trans*-arrangement of these two substituents [23-25] (Scheme 3).

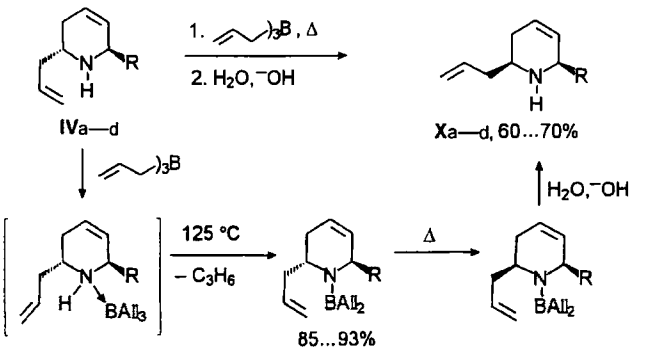
Scheme 3



All the operations were carried out in one flask. The method was based on a combination of the allylboronation with the well known 1,2-addition of organolithium compounds to pyridine [26, 27]. Treatment of the lithium product V formed from RLi and pyridine with triallylborane led to the at-complex VI, in which the B–N bond is easily cleaved by alcohol. The protolytic cleavage of the enamine VI takes place with a rearrangement of the allylic type; the proton adds at position 5 with the simultaneous migration of the double bond. The complex VII that forms immediately undergoes intramolecular allylboronation, while addition of the allyl fragment takes place stereoselectively in the *trans* position in relation to the existing group VIII. It is this stage that is responsible for the *trans* configuration of the final product. The obtained aminoborane IX is cleaved by alcohol, giving the *trans*-amine IV with one allyl group.

Like the *trans*-2,6-diallyl-1,2,3,6-tetrahydropyridines II [19, 20] (Scheme 2) the *trans*-amines IVa-d isomerize to the corresponding *cis* compounds Xa-d when heated with triallylborane at 140-190°C and subsequently deboronated with alkali [24, 28] (Scheme 4).

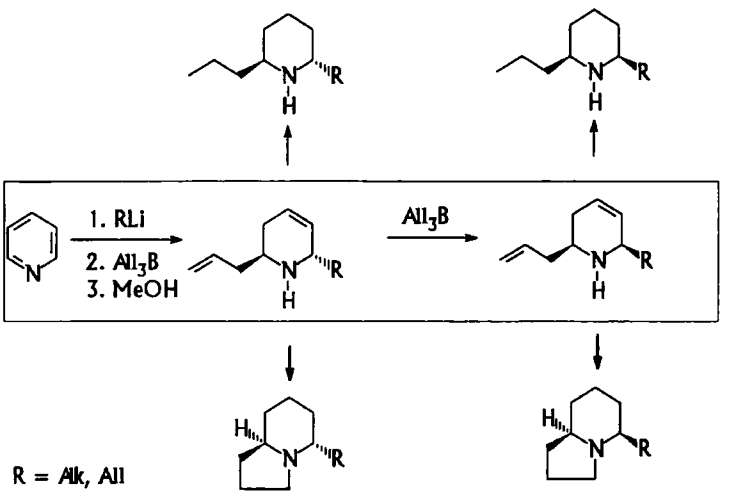
Scheme 4



	δ^{11}B, ppm	δ^{11}B, ppm
a R = Me	44.7 ($CDCl_3$)	43.1 ($CDCl_3$)
b R = *n*-Bu	49.9 (CD_3COCD_3)	48.9 (CD_3COCD_3)
c R = *n*-Hex	45.1 ($CDCl_3$)	43.8 ($CDCl_3$)
d R = Ph	45.4 ($CDCl_3$)	

On the basis of unsymmetrical reductive *trans*-2,6-dialkylation of pyridine (Scheme 3) we developed general methods for the stereoselective synthesis of 2,6-disubstituted piperidines [24] and 5-R-indolizidines [29] (Scheme 5).

Scheme 5



This methodology was used successfully for the synthesis of two alkaloids of the piperidine series [(±)-epidihydropinidine and (±)-dihydropinidine] and two alkaloids of the indolizidine series [(±)-indolizidines 167B and 209D]. Methods for the synthesis of these alkaloids and also their isomers and analogs are discussed further.

2. SYNTHESIS OF ALKALOIDS AND THEIR ANALOGS

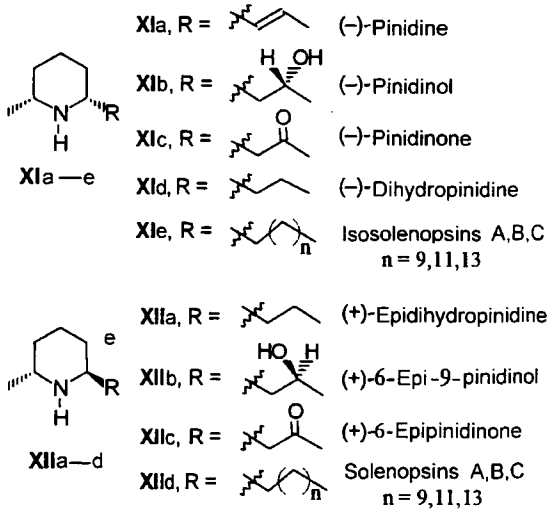
2.1. Synthesis of Piperidine Alkaloids and their Analogs

2,6-Disubstituted piperidine alkaloids are produced by many types of plants and insects and play an important role in their life processes. Thus, pinidine XIa, epidihydropinidine XIIa, and their derivatives XIb-d, XIIb,c were isolated from the needles, bark, and roots of certain types of pine and fir [30-34], e.g., *Pinus silvestris* L. and *Picea abies* (L.) Karsten, which are widely distributed in the European part of the Russian Federation. Pinidinone XIc was isolated from the ladybird beetle (*Cryptolaemus montrouziri*) [35] and Mexican bean weevil (*Epilachna varivestis*) [36]. The latter also produces dihydropinidine XId. Isosolenopsins and solenopsins A, B, and C XIb, XIId are components of the toxin of certain red ants (*Solenopsis geminata* and *Solenopsis invicta*) [37, 38].

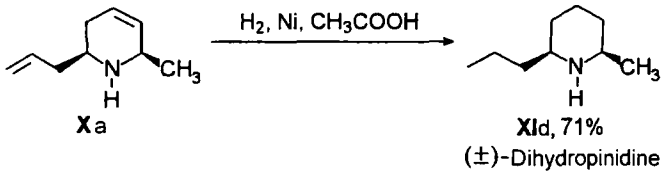
The aboriginals of North America added the needles and bark of certain types of spruce to improve the flavor of tea and also used various parts of coniferous trees for healing purposes (popular medicine). However, it was recently found that many piperidine alkaloids produced by conifers, including XIa-d, XIIa-c, have high teratogenic and embryotoxic activity [31]. Their biological function probably involves protection against species antagonists and foes.

Several methods have now been described for the production of such alkaloids [30-34, 36, 39-42], including some in the optically form [38, 43-49]. However, most of these methods are extremely laborious.

As starting material for the production of (±)-dihydropinidine XId we used *cis*-2-allyl-6-methyl-1,2,3,6-tetrahydropyridine Xa, obtained by the successive treatment of pyridine with methyllithium, triallylborane, methanol, and alkali [23, 24] (Scheme 3) followed by isomerization of the obtained IVa to Xa (Scheme 4).

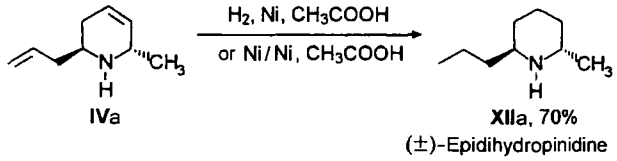


Hydrogenation of the amine Xa in acetic acid over Raney nickel in an autoclave (100°C, 100 atm H_2, 10 h) led to the desired alkaloid XId with a 71% yield.

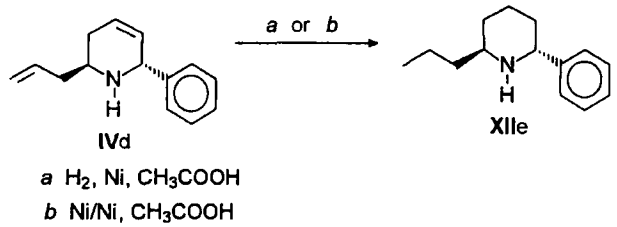


The alkaloid (±)-epidihydropinidine XIIa (*trans*-2-methyl-6-propylpiperidine) was obtained similarly from the *trans*-amine IVa [23, 24].

The alkaloid XIIa was also obtained with a yield of up to 95% by electrocatalytic hydrogenation of the amine IVa in a 10-fold excess of acetic acid at a nickel cathode, the surface of which had been modified with electrodeposited nickel (Ni/Ni) [50].

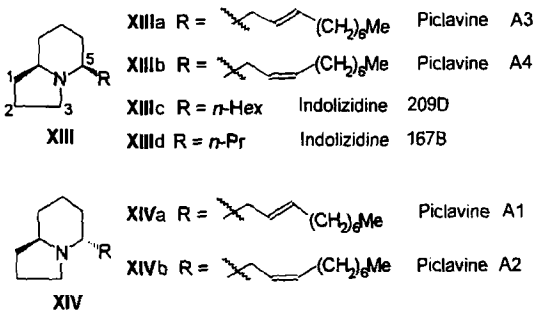


trans-2-Propyl-6-phenylpiperidine XIIe, the phenyl analog of epidihydropinidine, was synthesized by catalytic and electrochemical hydrogenation of *trans*-2-allyl-6-phenyl-1,2,3,6-tetrahydropyridine IVd [50].



2.2. Stereoselective Synthesis of Indolizidine Alkaloids and their *trans*-Analogs

A series (more than 20) of structurally similar indolizidine alkaloids – 5-substituted indolizidines XIII, XIV [51-55] and 5-R-8-methylindolizidines [56] (also known as bicyclic gephyrotoxins [53, 56]) – were found in the skin secretions of tree frogs of the *Dendrobatidae* family, widely distributed in Central America. They are blockers of neuromuscular transmission [53], and extracts of the skin of frogs were used by the indians from ancient times as poisons for arrows. The isomeric indolizidines – the piclavines A1-A4 XIIIa,b, XIVa,b – were isolated from extracts of sea squirts Tunicata (*Clavelina picta*) (marine Chlordata) [55]. The latter have antimicrobial activity against certain fungi and Gram-positive bacteria [55].

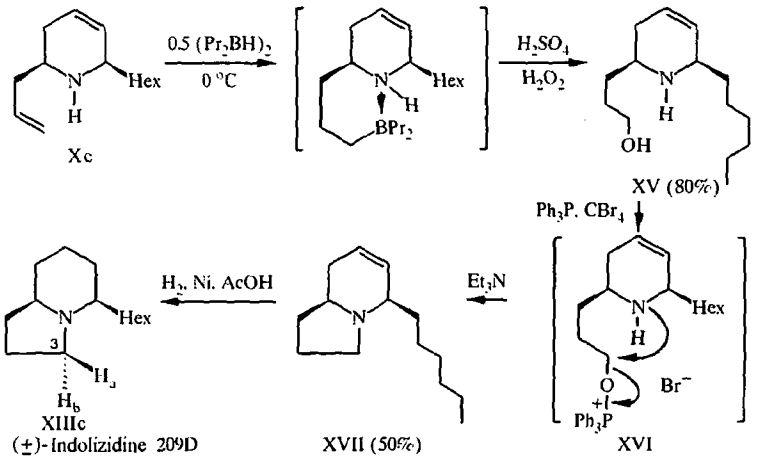


In recent years several special and general methods have been described for the production of bicyclic gephyrotoxins. Two compounds of this class – the indolizidines 167B XIIId and 209D XIIIc – were synthesized both in the racemic [57] and in the optically active forms (10-13 stages) [58-60].

We developed a new general method for the stereoselective construction of 5-substituted indolizidines XIII, XIV, based on the intramolecular cyclization of *trans*- II, IV and *cis*-2-allyl-6-R-1,2,3,6-tetrahydropyridines III, X (Scheme 5). The effectiveness of the method was demonstrated for the synthesis of the indolizidines 167B and 209D and also their *trans* isomers [29].

2.2.1. Synthesis of (±)-Indolizidine 209D and its *trans* Isomer. The *trans*- and *cis*-2-allyl-6-hexyl-1,2,5,6-tetrahydropyridines IVc, Xc respectively were used as starting materials for the production of the indolizidine 209D XIIIc and its isomer XIVc (R = C_6H_{13}) [29]. Hydroboronation of the *cis*-amine Xc with tetrapropyldiborane $(Pr_2BH)_2$ (2:1) in THF followed by oxidation with hydrogen peroxide in an acidic medium led to the alcohol XV (Scheme 6).

Scheme 6

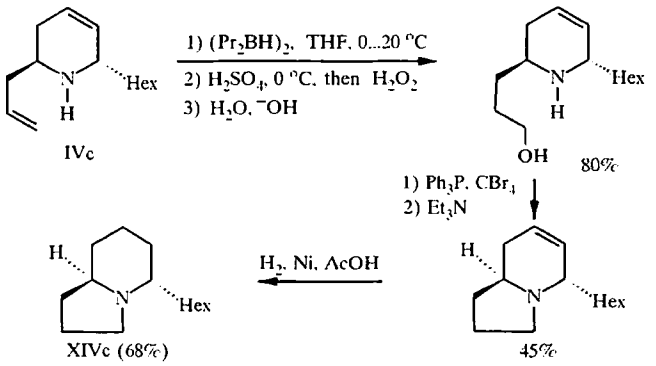


Under the influence of the Ph_3P/CBr_4 system [56] and then triethylamine [61] the amino alcohol XV undergoes intramolecular cyclization, giving *cis*-5-hexyl-1,2,3,5,8,8a-hexahydroindolizine XVII. The intermediate product of the cyclization process (closure of the five-membered ring) is the phosphonium salt XVI.

Hydrogenation of the unsaturated bicyclic compound XVII in acetic acid over Raney nickel in an autoclave (100°C, 100 atm H_2, 10 h) gave a 90% yield of the alkaloid (±)-indolizidine 209D XIIIc.

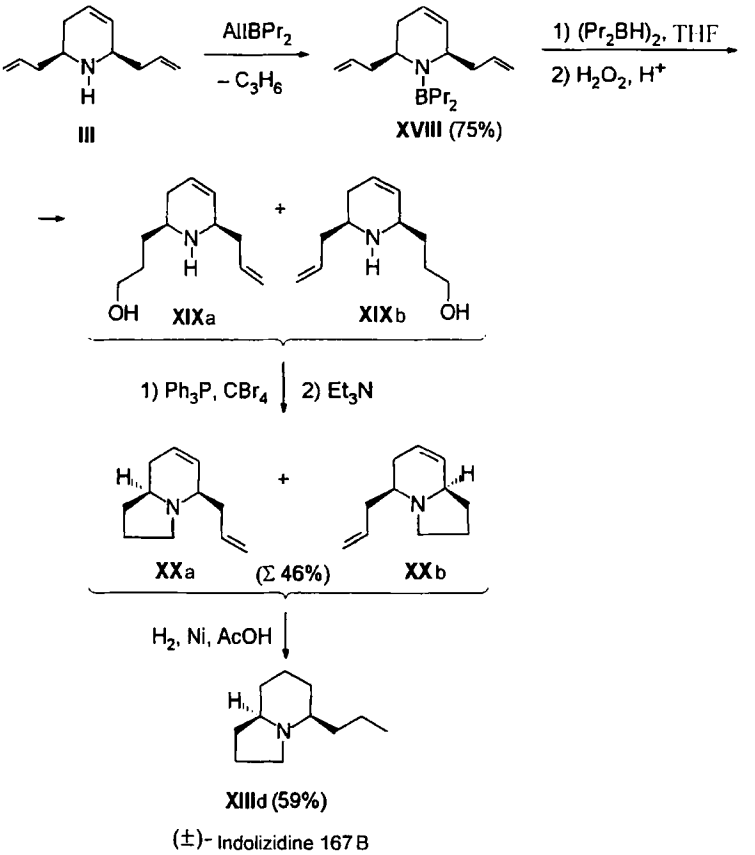
The *trans* analog of the indolizidine 209D – the bicyclic compound XIVc – was obtained similarly from *trans*-2-allyl-6-hexyl-1,2,3,6-tetrahydropyridine IVc (Scheme 7).

Scheme 7



2.2.2. Synthesis of (±)-Indolizidine 167B and its *trans* Isomer. The methodology for the construction of the five-membered ring described above was used for the synthesis of the indolizidine 167B XIIId and its *trans* isomer XIVd. The starting materials were *cis*- III and *trans*-2,6-diallyl-1,2,5,6-tetrahydropyridines II (Scheme 2).

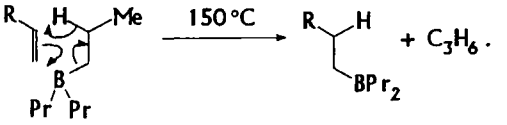
Scheme 8



During the synthesis of the alkaloid XIIId not the amine III but its N-dipropylboryl derivative XVIII, obtained with a 75% yield by heating compound III with allyl(dipropyl)borane at 130°C, was submitted to hydroboronation (Scheme 8).

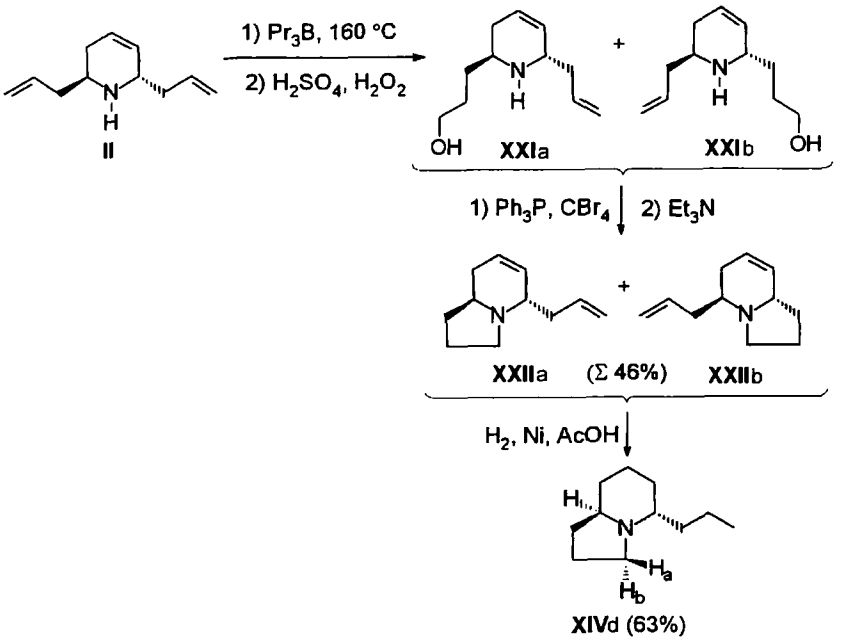
The hydroboronation of the aminoborane XVIII with tetrapropyldiborane (0.5 mole) followed by oxidation (sulfuric acid, hydrogen peroxide) led to a mixture of the isomeric alcohols XIXa, XIXb, which was treated successfully without separation by carbon tetrabromide, triphenylphosphine, and triethylamine. This resulted in the formation of a mixture of hexahydroindolizidines XXa, XXb (46%), the catalytic hydrogenation of which over Raney nickel gave to the (±)-indolizidine 167B XIIId (yield 59%).

Tripropylborane was used as hydroboronating agent in the hydration of the double bond in the *trans*-amine II. This method was based on the ability of trialkylboranes to undergo transalkylation according to the scheme [1-3]:



A mixture of the amino alcohols was obtained as a result of heating the *trans*-diallyl compound II with tripropylborane (160°C, 20 h) and subsequent oxidation (sulfuric acid, hydrogen peroxide) (Scheme 9).

Scheme 9

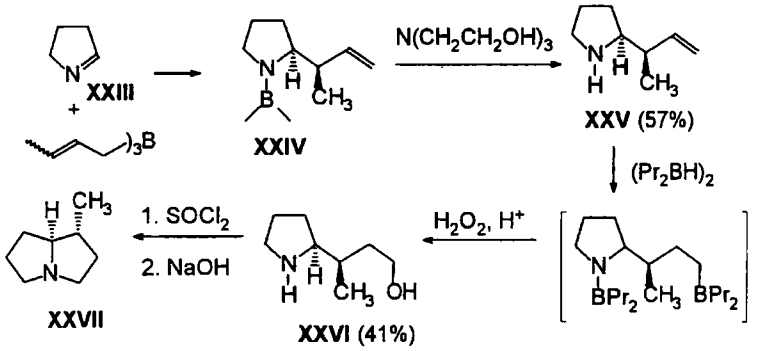


Standard cyclization (carbon tetrabromide, triphenylphosphine, and triethylamine) of the mixture of amino alcohols XXIa, XXIb led to a mixture of the isomeric bicyclic compounds XXIIa, XXIIb (46%), the hydrogenation of which gave (±)-*trans*-5-propylindolizidine XIVd.

3. SYNTHESIS OF (±)-PSEUDOHELIOTRIDANE AND (±)-CONIINE

Pseudoheliotridane is the necine base of the alkaloid trachelanamidine, produced by many plants, such as *Trachelanthus* Korolkovi, *Borraginaceae*, *Compositae*, *Leguminosae*, etc.

Scheme 10

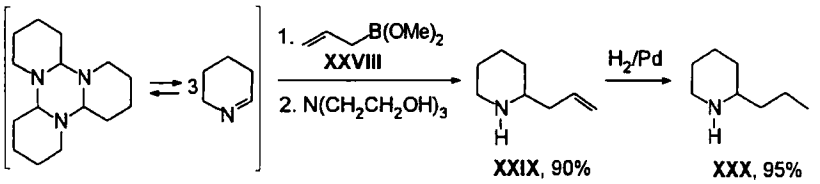


The key stage in the synthesis of this alkaloid (Scheme 10) is the crotylboronation of pyrroline XXIII. The addition of the crotyl fragment at the N=C bond is realized with rearrangement and leads to the aminoborane XXIV, in which the B–N bond is easily cleaved by the action of triethanolamine. As a result of the reaction, as shown in the Scheme 10, the essentially single diastereomeric adduct XXV is obtained (>93% pure) [62].

The hydroboronation of 2-(1-methylallyl)pyrrolidine XXV by one mole of tetrapropyldiborane gave a N,C-bisdipropylboryl compound, the oxidation of which in an acidic medium gave the amino alcohol XXVI. Subsequent direct cyclization of 2-(3-hydroxy-1-methylpropyl)pyrroline XXVI under the action of thionyl chloride gave (±)-pseudoheliotridane (1-methylpyrrolizidine) XXVII with a yield of 60%.

The alkaloid coniine (2-propylpiperidine) is produced by water hemlock (poison hemlock, *Conium maculatum*). One of the simplest methods for its production is based on the allylboronation of the 1-piperideine trimer by allyl(dimethoxy)borane XXVIII [63] (Scheme 11).

Scheme 11

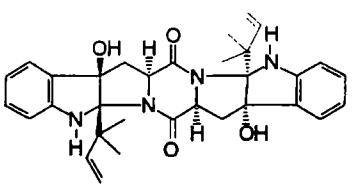


At room temperature and in boiling dichloromethane allylboronation takes place slowly and is only complete after a few days, but the limiting stage of this process is evidently the formation of the monomer of 1-piperideine from the trimeric compound. The hydrogenation of the 2-allylpiperidine XXIX obtained in this way (90%) led to (±)-coniine XXX (95%).

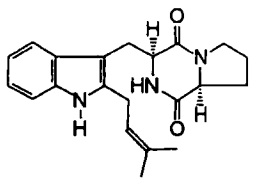
With the use of suitable chiral allyl derivatives of boron it is possible to obtain both enantiomers of coniine.

4. SYNTHESIS OF GYPSETIN AND TRYPROSTATIN B

Danishefsky and coworkers used prenylboronation as one of the key stages in the synthesis of gypsetin [64] and tryprostatin B [65].



XXXI (gipsetin)



XXXII (tryprostatin B)

Gypsetin XXXI was isolated recently from *Nannizzia gypsea* var. *incurvata* IFO 9228 and, supposedly, regulates the content of cholesterol in the human organism.

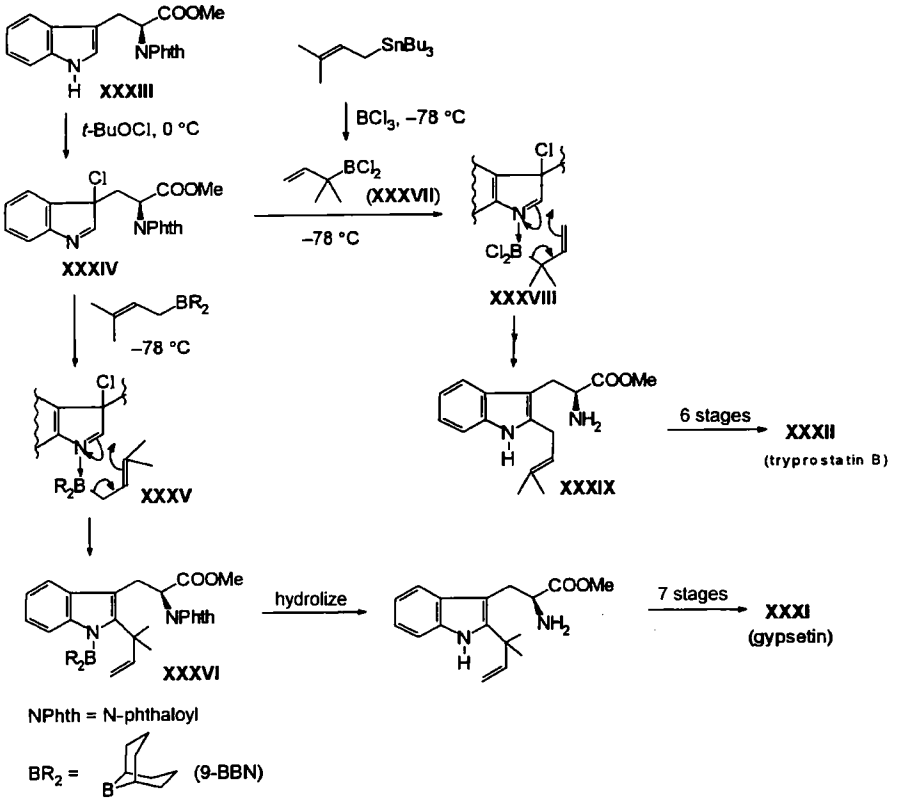
Tryprostatin B XXXII was isolated from the fungi *Aspergilles fumigatus* (type BM 939); according to existing data, this indole derivative inhibits cell division and can be used for the treatment of certain types of cancer.

The molecule of tryprostatin B XXXII contains a "normal" prenyl group at position 2 of the indole fragment, whereas the molecule of gypsetin XXXI contains two "inverted" prenyl groups. The most important stages of the synthesis of these alkaloids in terms of the present review are presented in scheme 12.

The precursors of these compounds, i.e., the indole derivatives XXXVI and XXXIX were obtained by prenylboronation of 3-chloroindolenine XXXIV, generated *in situ* by treatment of N-phthaloyl-L-tryptophan methyl ester XXXIII with *tert*-butyl hypochlorite at 0°C.

9-Prenyl-9-borabicyclo[3.3.1]nonane was used to introduce the "inverted" 1,1-dimethylallyl group. As expected [5], its reaction with the imine XXXIV takes place with rearrangement (XXXV, arrow) and leads to the aminoborane XXXVIa. Hydrolysis of the latter with cleavage of the B–N bond gives the indole compound XXXVI, which is converted into gypsetin XXXI in seven stages.

Scheme 12



The introduction of a "normal" prenyl group is realized by means of the allyl dichloroborane XXXVII, generated from tributyl(prenyl)tin and BCl_3. Its reaction with the indolenine XXXIV, which also takes place with rearrangement XXXVIII, led (after hydrolysis) to the indole derivative XXXIX. Tryprostatin B XXXII was obtained from the latter in six stages [60].

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