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Berberine: Chemistry and Biological Activity

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Abstract

In the review, materials are generalized concerning the chemistry and pharmacological properties of phytogenous alkaloid berberine available under the conditions of Russia. Methods for berberine isolation from plant raw material as well as the biological activity of berberine and its synthetic derivatives are considered. The reactions of berberine and its hydrogenated derivatives occurring both with the conservation of protoberberine skeleton and with its transformation are considered in detail.

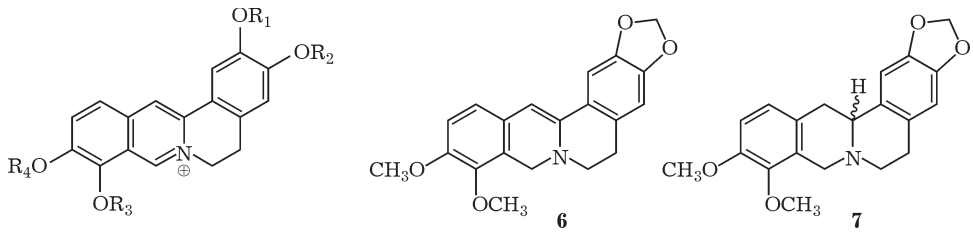
Key words: isoquinoline alkaloids, protoberberine alkaloids, berberine, dihydroberberine, lambertine, tetrahydroberberine, canadine, enamine, *Berberis*, *Phellodendron*, *Hydrastis*, antimicrobial activity, antibacterial activity, antifungal activity

Contents

INTRODUCTION

Isoquinoline alkaloid berberine **1** is one of widespread representatives belonging to the family of protoberberine alkaloids. This family includes also such alkaloids as jatrorrhizine **2**, columbamine **3**, palmatine **4**, coptisine **5** and hydrogenated derivatives such as lambertine **6**, canadine **7** as well as other related compounds (Scheme 1).

Various plant species containing protoberberine alkaloids were long since used in the traditional medicine of India, China, Tibet and Japan mainly as antimicrobial and antibacterial remedies. A wide experience of using in phytotherapy is accumulated for plants belonging to genus *Berberis* (barberry) those were used in the Japanese folk medicine against cholera and bacterial diarrhea [1], in the Indian folk medicine they were used for the treatment of leishmaniasis and malaria, as well as an abortive. Such properties of the barberry as choleretic, spasmolytic and haemostatic actions are considered to be connected with the specific activity of berberine. The barberry exhibits hemostatic action against metrorrhagia (uterine bleeding) and renal bleeding, reduces arterial blood pressure, weakens cardiac activity. It is used in the treatment of stomach and



1: $R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$
2: $R_1 = CH_3$, $R_2 = H$, $R_3 = R_4 = CH_3$
3: $R_1 = H$, $R_2 = CH_3$, $R_3 = R_4 = CH_3$
4: $R_1 = R_2 = R_3 = R_4 = CH_3$
5: $R_1 = R_2 = R_3 = R_4 = CH_2$

Scheme 1.

duodenal ulcer, against headache, stool retention *etc.* [2].

Of doubtless interest are recent data concerning berberine's hypocholesterolemic effects differing from the action of statins in the mechanism [3]. Modifications of the berberine molecule have allowed researchers to obtain its derivatives those exhibit valuable pharmacological properties. Besides barberry, other plant species containing berberine and other protoberberine alkaloids were widely used also in phytotherapy. So, *Phellodendron amurense* was used in Japan against dysentery, and *Corydalis* was used as an analgesic and spasmolytic agent against toothache. The goldenseal *(Hydrastis Canadensis)* was used as a tonic and anti-inflammatory agent as well as preparation for lowering blood pressure, anticatarral remedy, against the inflammations of gastrointestinal tract and of upper air passages.

Thus, one could consider the phytogenous alkaloid berberine accessible under the conditions of Russia to be an initial compound for obtaining pharmacologically promising agents. In this connection, it is necessary to emphasize the importance of generalizing the materials concerning chemistry and pharmacological properties of berberine. The present review in the most complete manner comparing to the works available in the literature [4–6] covers the aforementioned problem. The review is devoted to considering the reactions of berberine and its hydrogenated derivatives, occurring both with the conservation the protoberberine skeleton, and, oppositely, with its transformation. The reactions of other protoberberine alkaloids (as a rule, rather similar) are not presented in this paper. Methods for isolation of berberine from plant raw material and the biological activity of berberine and its synthetic derivatives are considered in brief. Synthetic methods based on acyclic precursors for obtaining protoberberine compounds are not discussed.

BERBERINE SOURCES IN THE NATURE AND THE METHODS OF ISOLATION

Berberine is produced by many plant species including the barberry *(Berberis)*, the meadow rue *(Thalictrum)*, the celandine *(Chelidonium)*, the goldenseal (*Hydrastis canadensis* L.), *Phellodendron amurense*, *etc.* [7, 8]. However, the main sources of berberine are presented by various barberry species (Asia) and goldenseal species (America). As the territory of the former Soviet Union is concerned, berberine was isolated from the rind of roots and young spears of barberry species such as *B. heteropoda* [9], *B. amurensis* [10], *B. sibirica* [11], *B. heterobotrus* [12], *B. thunbergii* [13]. For example, *B. sibirica* (Fig. 1) growing in the Karaganda Region contains 0.98 % of berberine in roots, and 0.14 % in young spears; in berberine leaves there is almost no berberine present [11]. Besides, obtaining the berberine from the cellular cultures of plant genera such as *Thalictrum*, *Coptis*, *Phellodendron* [14–22] is widely developed.

Classical techniques for berberine isolation are based on the extraction by alcohol in the neutral medium or with addition of acetic acid, the further removal of side substances and the precipitation of berberine as berberine chloride [12, 23], hydrosulphate [24, 25] or iodide

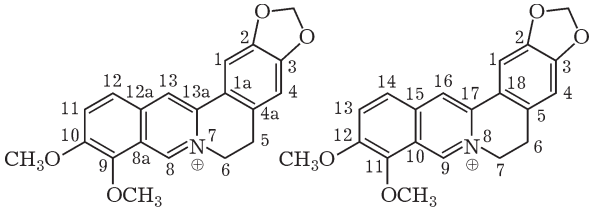
Fig. 1. Spears of the Siberian barberry (*Berberis sibirica*).

[26]. Modified extraction variants were also employed such as the procedure under the action of microwave radiation [27–29] or liquid extraction under pressure [30]. In order to isolate berberine, researchers used an ultrafiltration technique [31], chromatographic separation using macroporous [32] or ion-exchange resins [33, 34]. Physicochemical characteristics of berberine and other protoberberine alkaloids are generalized in the review [6].

CHEMICAL TRANSFORMATIONS OF BERBERINE AND ITS DERIVATIVES

It has engaged our attention in the analysis of the literature data, that there is certain confusion with the names of berberine derivatives. So, salts **1** were called either as berberine or as berberine chloride (sulphate, *etc.*) (Scheme 2). Compound **8** was called both as berberine, and as 8-hydroxydihydroberberine.

Therefore frequently it is difficult to establish, which of the alkaloid species was entered into a reaction, was it salt **1** or pseudo-base **8**. Compound **6** was called either as dihydroberberine or dihydrodeoxyberberine. Additional difficulties were contributed also by the use of various ways to number the atoms in the molecule in some articles. Below we are presenting contemporary (used by the authors of the review) and out-of-date systems of numbering the atoms in berberine molecule:

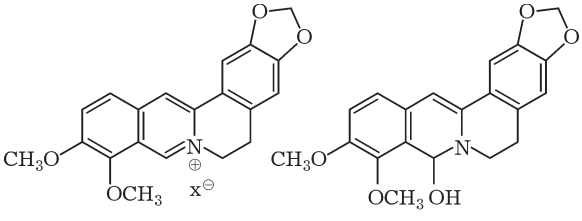


contemporary obsolete

Berberine

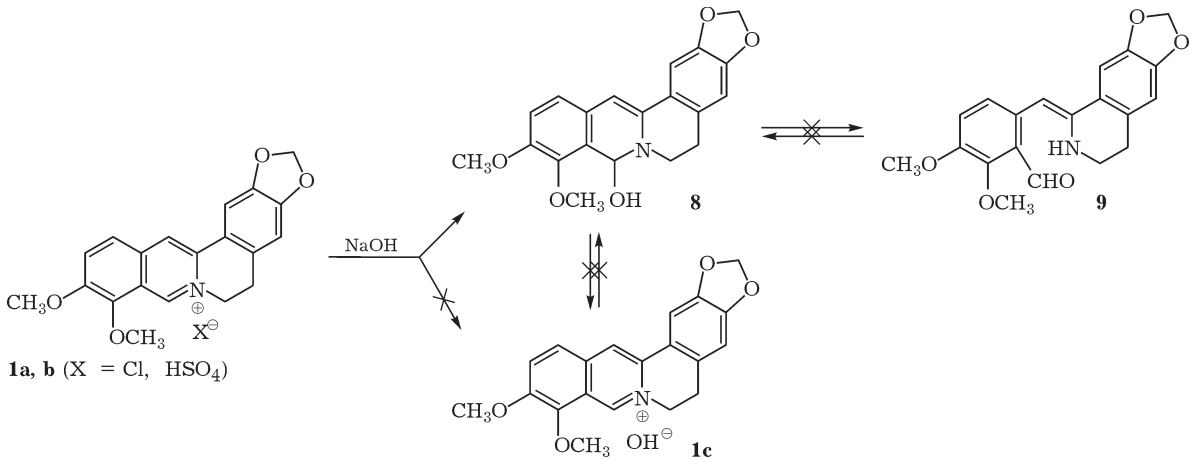
Nucleophilic addition to the isoquinolinium fragment. Nucleophilic addition to position **8** is inherent in the isoquinolinium systems of berberine salts. In the overwhelming number of papers, berberine was isolated as chloride **1a** or hydrosulphate **1b**, whereby their transformations under alkaline conditions (Scheme 3) have been investigated in detail. The treatment of berberine salts **1a**, **b** with alkali results in the formation of berberine **8**, instead of quaternary base **1c**. The process occurs in an aqueous ethanol environment at pH > 13 [35, 36]. In spite of the fact that in the case of isoquinolinium salts an equilibrium between the carbinol **8**, tertiary ammonium **1c** ($X = OH^-$) and aldehyde **9** forms could be realized, for the berberine the presence of such forms as **1c** and **9** was not confirmed [35, 37]. Berberine chloride under the action of alkali in CD_2Cl_2 results in the formation of berberine and its dimers (8R, 8′R) and (8R, 8′S) at a ratio of 10 : 2 : 1 [38]. Oxoberberine **10** is formed (with the yield of 46 %) in the reaction between berberine salts **1a,b** and hot aqueous alkali in air [46, 38] (Scheme 4).

Berberine **8**, obtained *in situ* from salts **1a**, **b** reacts with alcoholates and amines, to produce *O*-ethers **11** [39, 40] and nitrogenous compounds **12** [36, 41]. Acetone addition resulting in the formation of acetoneberberine **13** is worthy of a special attention [42–45]. In the alkaline environment, there is interaction between ber-

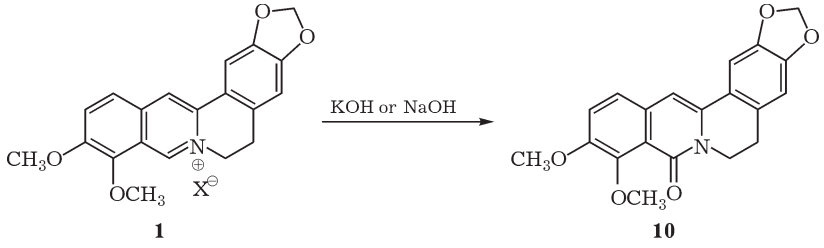


1 Berberine salts **8** Berberine

Scheme 2.

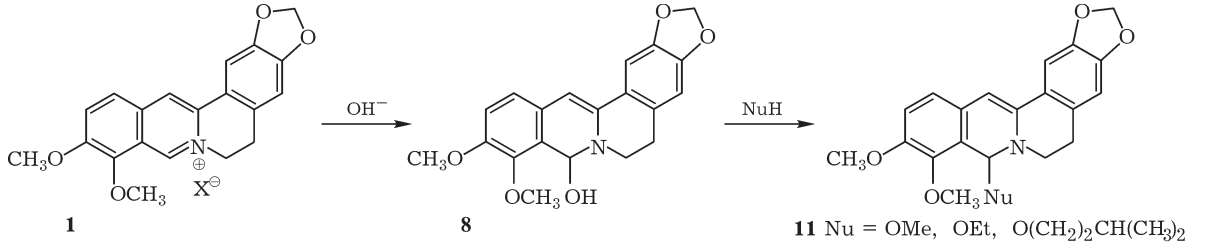


Scheme 3.

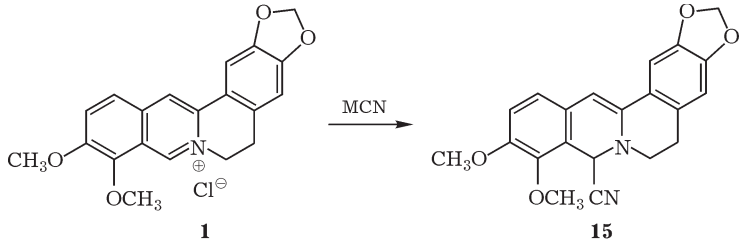


Scheme 4.

berine **1a, b** with chloroform to produce adduct **14**, therefore it is appropriate not to use chloroform in the process of extraction for the isolation of berberine alkaloids in alkaline media [39, 46] (Scheme 5). The interaction between berberine chloride **1** with cyanides results in nucleophilic addition with the formation of nitrile **15** [46, 47] (Scheme 6). Many works are devoted to the interaction between berberine salts **1** and Grignard reagents resulting in the

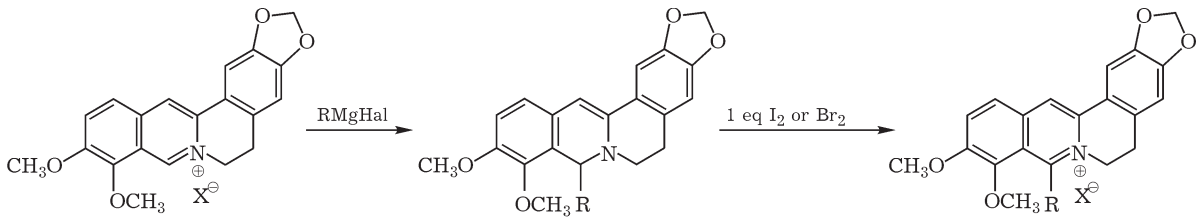


Scheme 5.



M = Na (89 %), K (95 %)

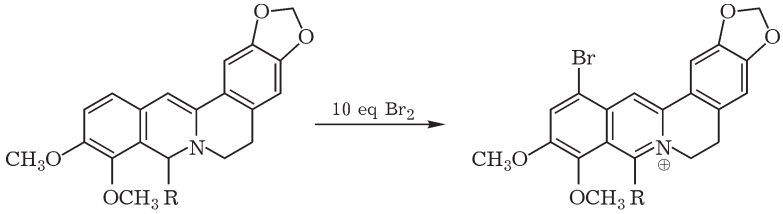
Scheme 6.



1 **16** **17**

R = Me, Et, Pr, CH_2=CH–CH_2, CH_2=CH–$(CH_2)_3$, Bu, C_6H_{13}, Ph, CH_2Ph, $CH_2C_6H_4$-*p*Br, CH_2=CH–CH_2–$SnBu_3$, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 1-naphtyl

Scheme 7.

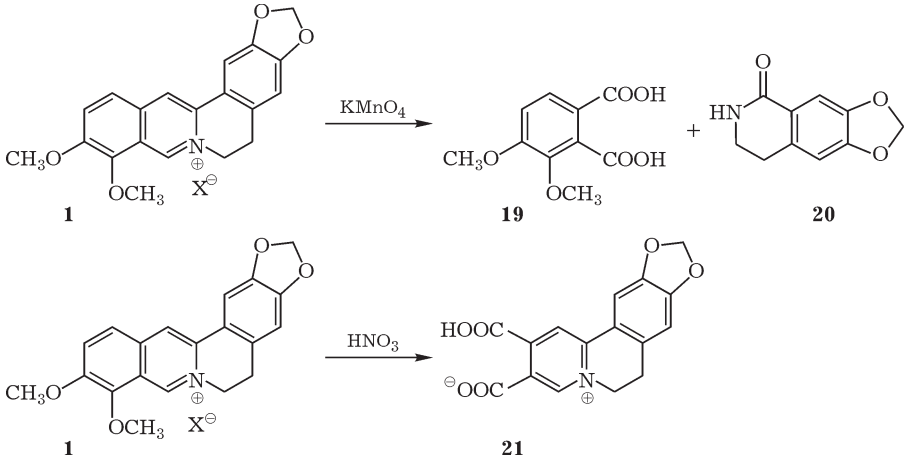


16 R = Me, Et, Pr, Bu, Hex, Ph **18**

Scheme 8.

formation of 8-alkyldihydroberberines **16** [48–59] (Scheme 7). This reaction is of important value since it allows obtaining C-8 substituted alkylberberines **17** *via* dehydration compounds 16 by the action of 1 eq of iodine [54, 55] or bromine [48]. An excess of bromine (10 eq) results in the formation of 12-bromo-8-alkylberberines **18** [48] (Scheme 8).

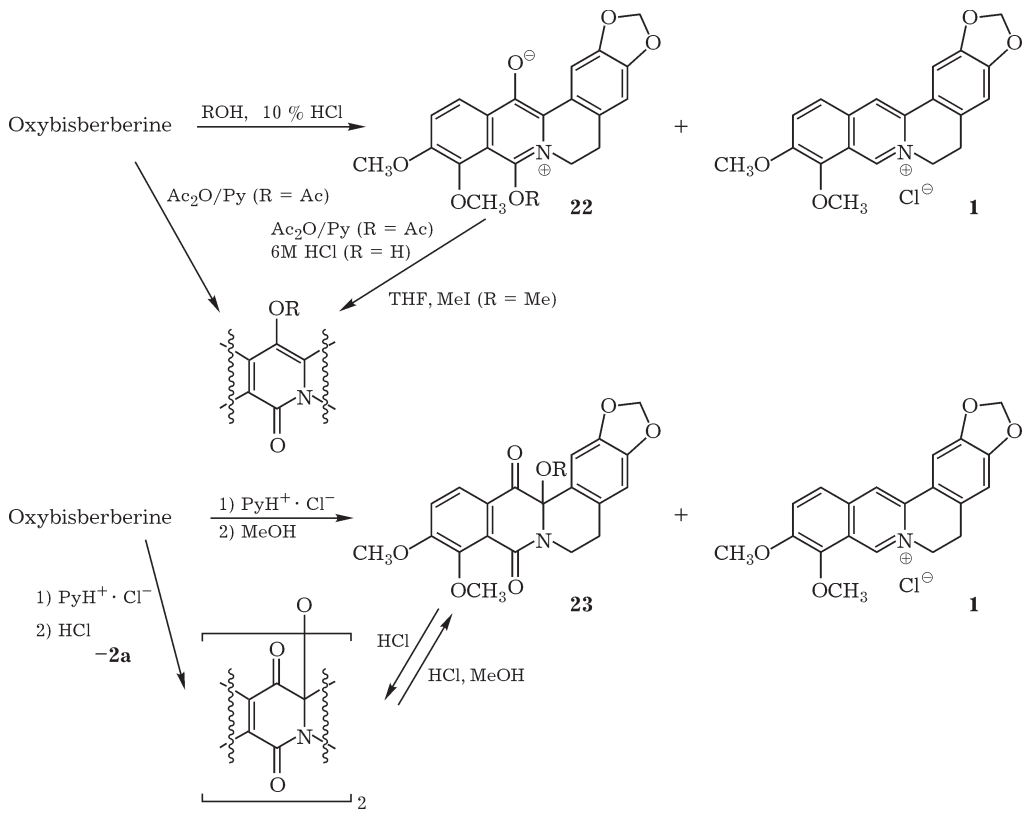
Oxidation reactions. Berberine **1** was subjected to oxidation by permanganate [60–62] and nitric acid [63, 64] with the formation of destruction products **19–21** (Scheme 9). The oxidation of berberine **1** by potassium ferrocyanide resulted in obtaining a dimeric compound such as oxybisberberine whose structure has not been established [65]. The dimer disproportionates with the formation of berberine **1** and oxyberberines **22**, **23** [65, 66] (Scheme 10). Photochemical oxidation of berberine **1** in methanol resulted in obtaining methoxyberberinephenolbetaine **24** [67], whereas under sensitized photooxidation in the presence of alcoholates or thiolates the formation of compound **25** is observed [68] (Scheme 11). Under photochemical process in acidic media there could a radical compound of methanol occur; the reduction of an intermediately formed iminium salt by sodium results borohydride results in the



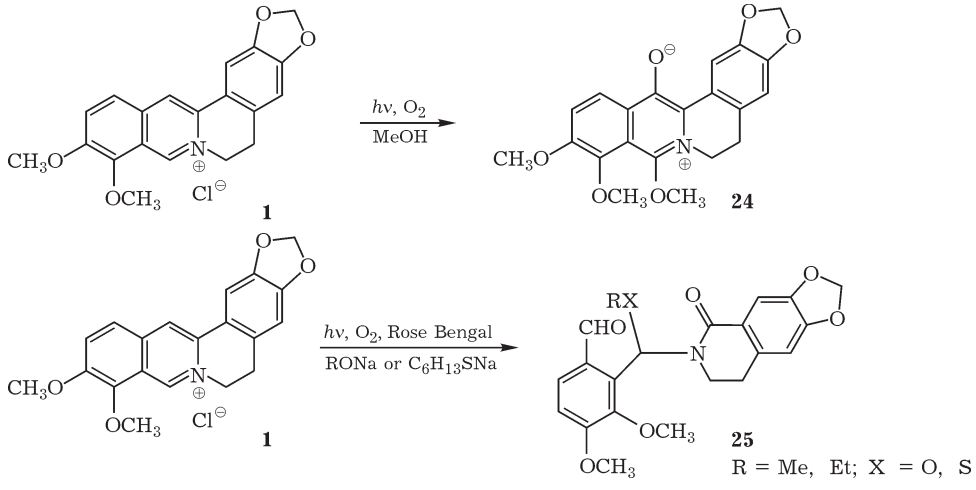
1 **19** **20**

1 **21**

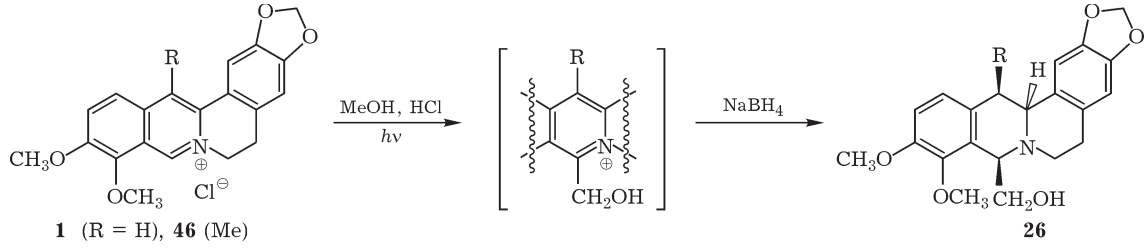
Scheme 9.



Scheme10.



Scheme 11.

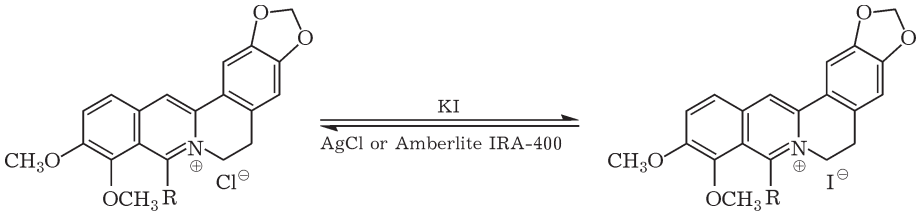


Scheme 12.

formation of tetrahydroberberines **26** [69] (Scheme 12).

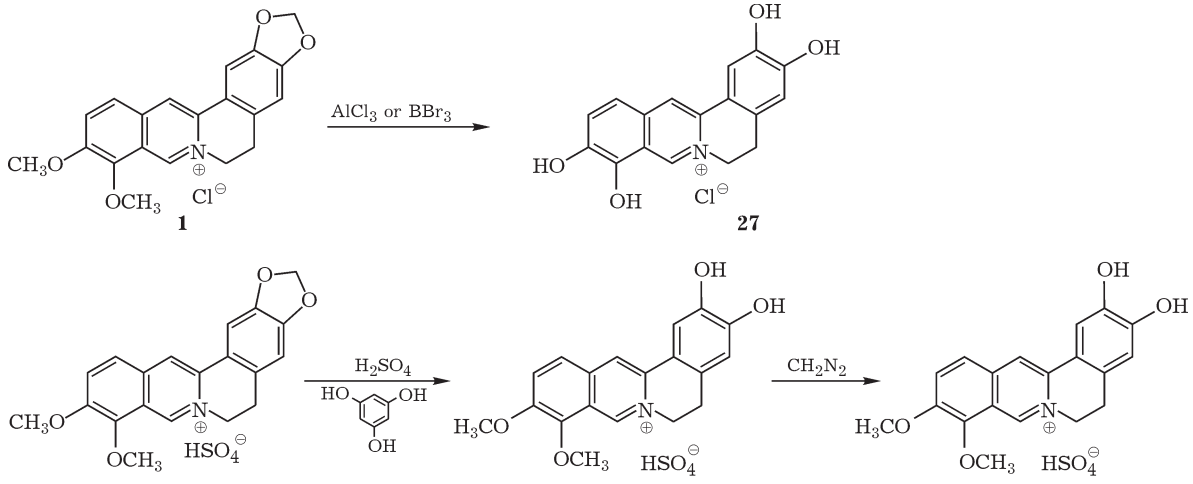
Other reactions. The anion exchange procedure in the chlorides of berberine **1** and 8-alkylberberine **17** was carried out under the action of KI [70], NaSCN or NaN_3 [71], as well as employing ion-exchange resins [48] (Scheme 13). Complete dealkylation of berberine **1** occurs under the action of aluminium chloride or BBr_3 with the formation of 2,3,9,10-tetrahydroxyprotoberberine **27** [72] (Scheme 14). The treatment by phloroglucinol in the acidic environment allows) selectively performing the dealkylation of 2,3-*O*,*O*-methylene group [73]. The subsequent methylation of hydroxyl groups (for example, using diazomethane) results in the formation of palmatine **4**. The pyrolysis of berberine **1** under vacuum [74, 91] or in the atmosphere of CO_2 [75] results in splitting selectively out the 9-*O*-methyl group with the formation of berberrubine **28** that has been used in the synthesis of dimeric berberine derivatives **29** (Scheme 15). The Reimer–Tiemann reaction resulted in obtaining 13-formyl-8-oxoderivative **30** [46] (Scheme 16). However, as it was already mentioned above, the present reaction instead of berberine **8**, resulted, to all appearance in the obtaining of 8-CCl_3-berberine derivative **14**.

Berberine **1** enters the cycloaddition reactions of different types, such as [1+2]-cycloaddition of dichlorocarbene with the formation of compound **31** [76] or [2+4]-cycloaddition of

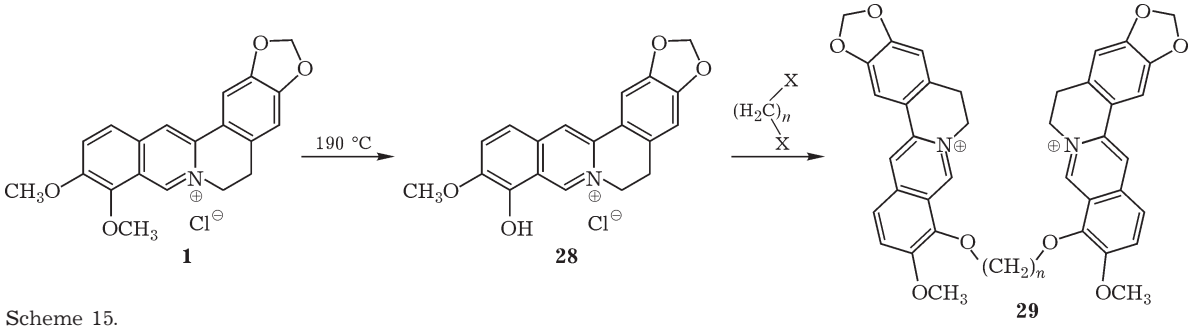


1 (R = H), **17** (R = Me, Et, Pr, Bu, Hex, Ph)

Scheme 13.

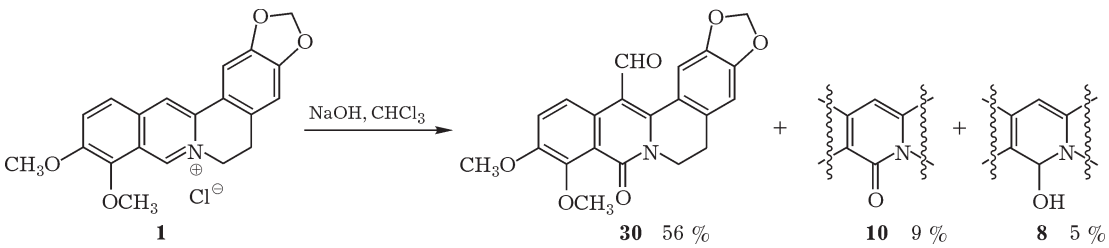


Scheme 14. **1** **27** **4**



1 **28** **29**

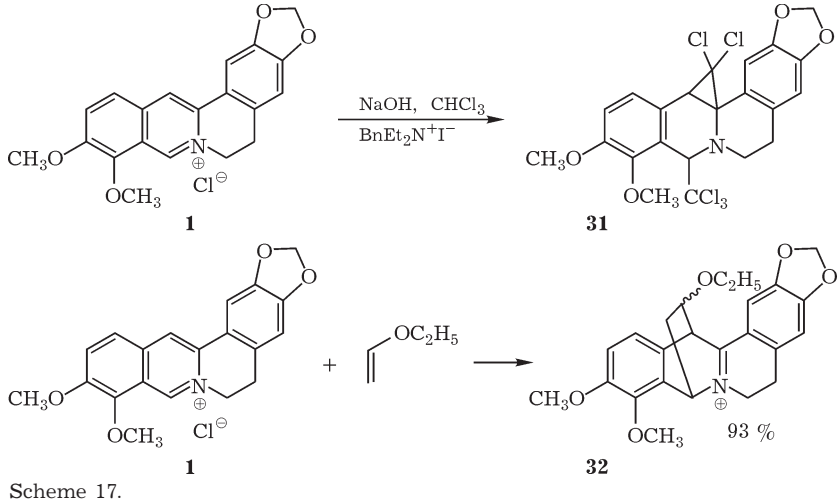
Scheme 15.



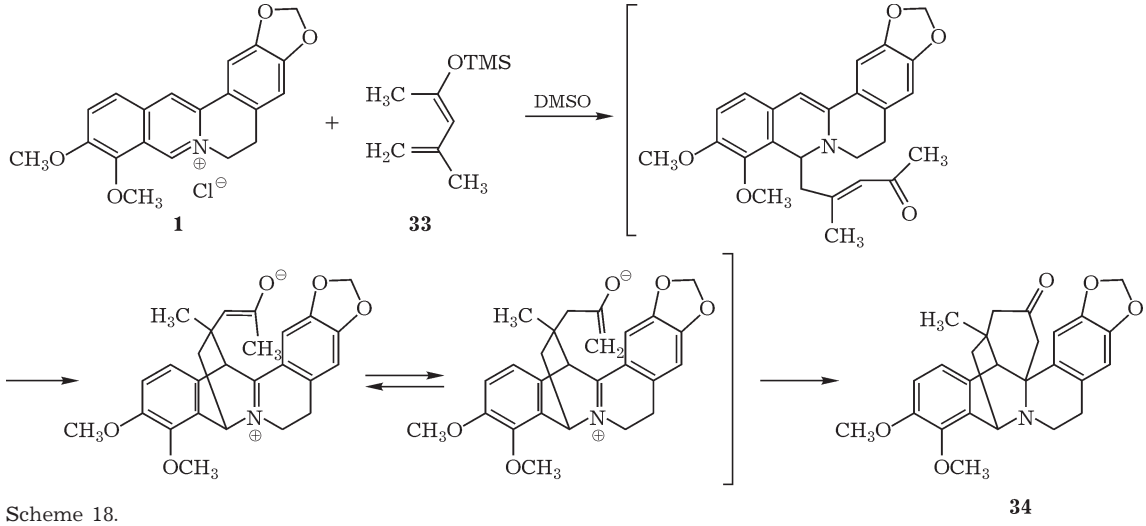
Scheme 16.

ethyl vinyl ether with the formation of adduct **32** [77] (Scheme 17). The interaction between berberine and 20-fold excess of siloxy diene **33** proceeds as a nucleophilic addition of diene to position **8** with the subsequent intramolecular addition according to Michael to form alkaloid karachine **34** (with the yield of 66 %) [78] (Scheme 18).

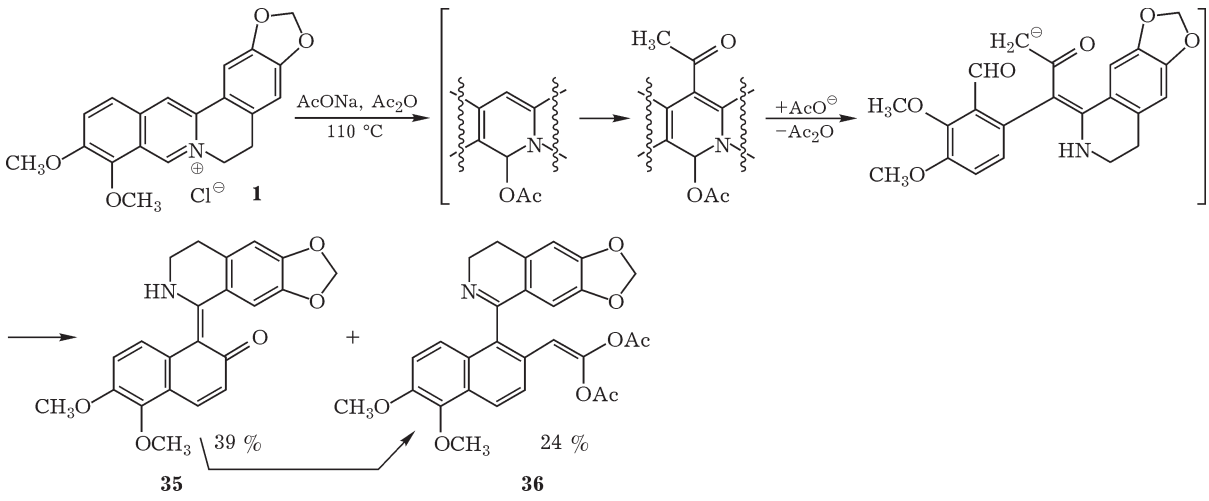
The interaction between berberine **1**, sodium acetate and acetic anhydride result in consecutive nucleophilic addition to position **8**, the acylation of enamine formed and opening the ring with the subsequent intramolecular aldol condensation resulting in the formation of naphthalene derivatives **35** and **36** [79] (Scheme 19). The interaction between berberine, sodi-



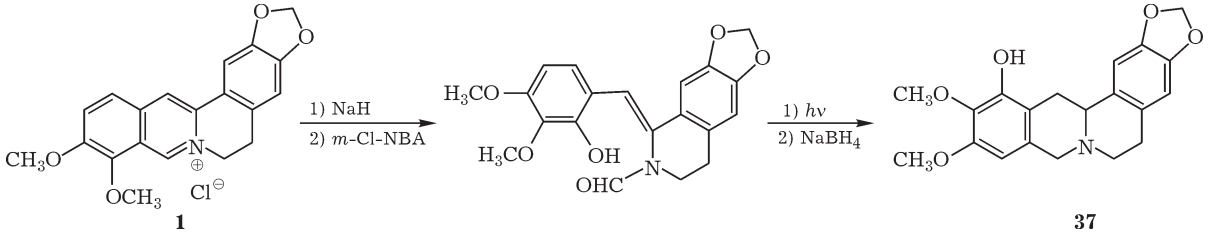
Scheme 17.



Scheme 18.



Scheme 19.

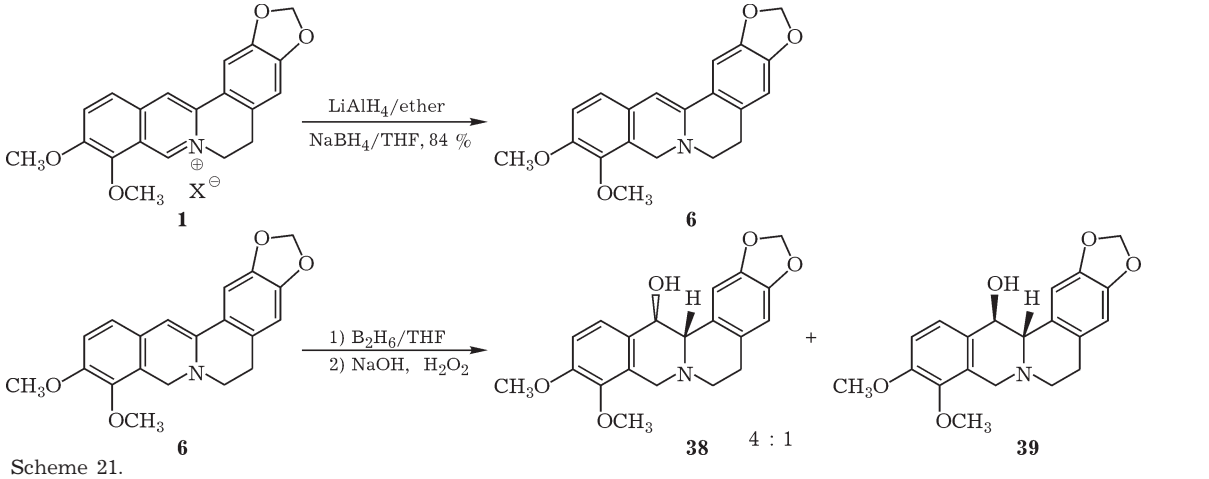


Scheme 20.

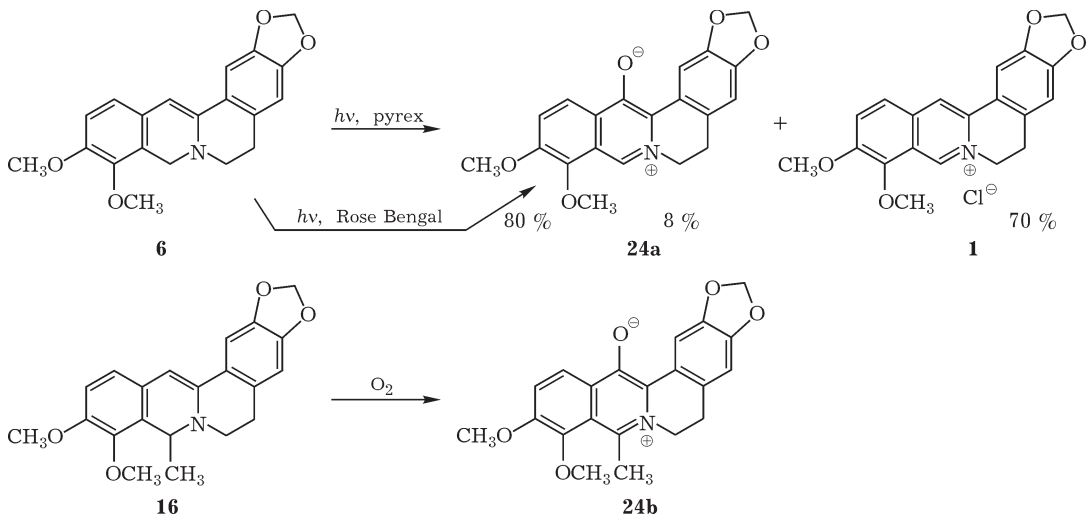
um hydride and *m*-Cl-NBA results in cleaving the isoquinolinium system. The photocyclization of the intermediate and the subsequent reduction by sodium borohydride result in the formation of pseudoberberine 37 [80] (Scheme 20).

Enamine derivatives of berberine

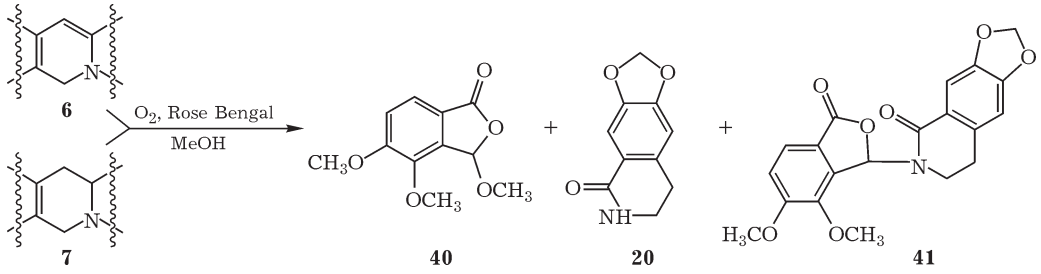
Dihydroberberine **6** was either isolated from plants belonging to genus *Glaucidium palmatum* (earlier *Hydrastis palmatum*) or obtained *via* the selective reduction of berberine **1** by borohydride in THF [81, 102] or by alumohydride in air [82, 89] (Scheme 21). The hydroboronizing of compound **6** results in the formation of *cis*- and *trans*-ophiocarpines **38**, **39** [81]. Sensitized photochemical oxidation of (Rose Bengal) dihydroberberine **6** [83] and of 8-methyldihydroberberine **16** [56] resulted in the



Scheme 21.



Scheme 22.



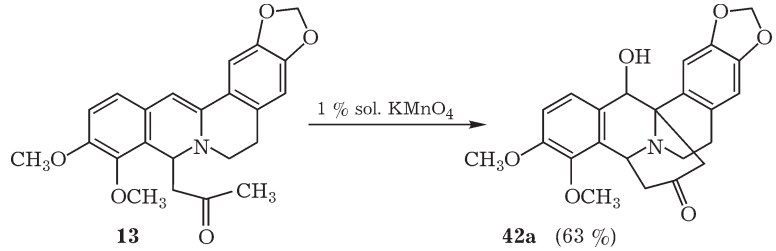
Scheme 23.

obtaining of berberinephenolbetaines **24a, b** as main products (Scheme 22). At the same time, according to [84], a similar photooxidation reaction involving both dihydroberberine **6**, and tetrahydroberberine **7**, results in the destruction with the formation of compounds **40**, **20**, **41** with the yields equal to 8, 18, 53 % and 14, 20 and 32 %, respectively (Scheme 23).

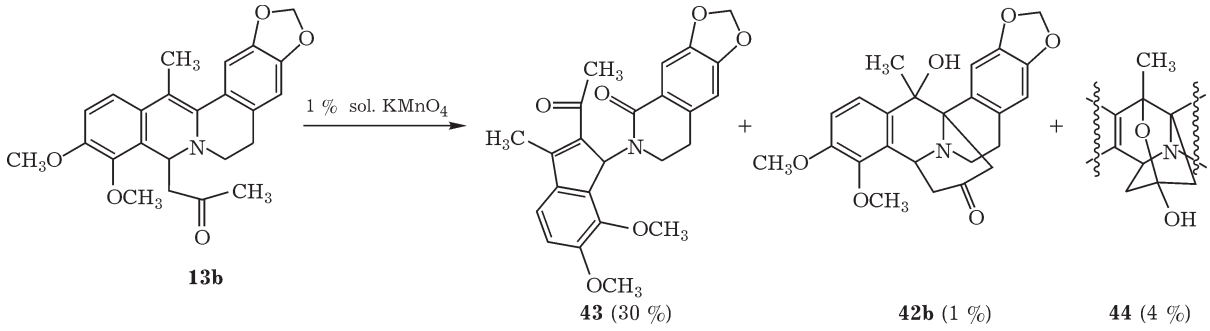
The oxidation of acetoneberberine **13** by 1 % $KMnO_4$ solution proceeds, to all appearance, *via* the dihydroxylation of double bond with the subsequent intramolecular aldol condensation. As a main product, neooxy acetone berberine **42a** has been isolated [85, 86] (Scheme 24). For the oxidation of 13-methylacetoneberberine **13b**, the main product is presented by a cleavage product of heterocycle **43**, in this case, one can observe forming only a small amount of compounds **42b**, **44** [87] (Scheme 25).

Dihydro derivatives of berberine **6**, **13** enter the reactions inherent in enamines [88]. So, the alkylation of compound **6** by alkylhalogenides results in producing immonium salts **45** [49, 89] (Scheme 26).

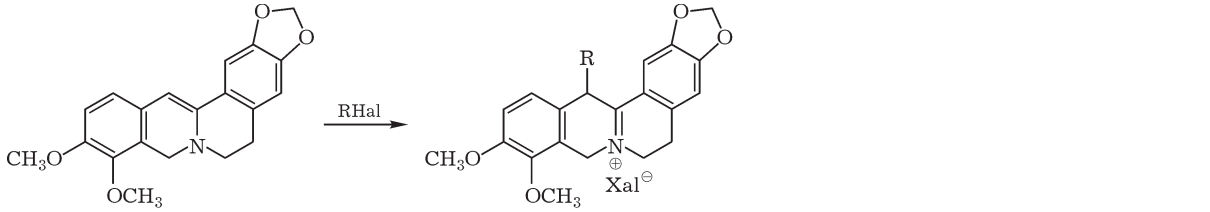
The condensation with aldehydes proceeding in an acetic acid solution represents an

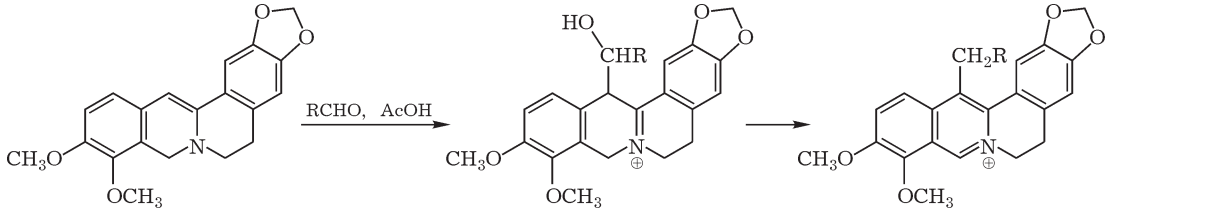


Scheme 24.

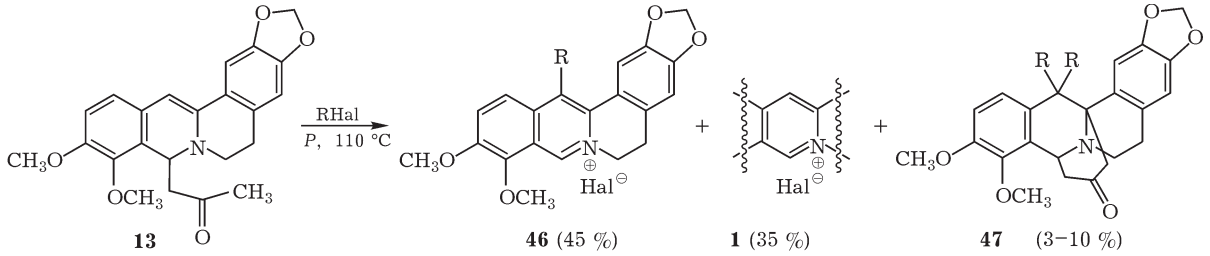


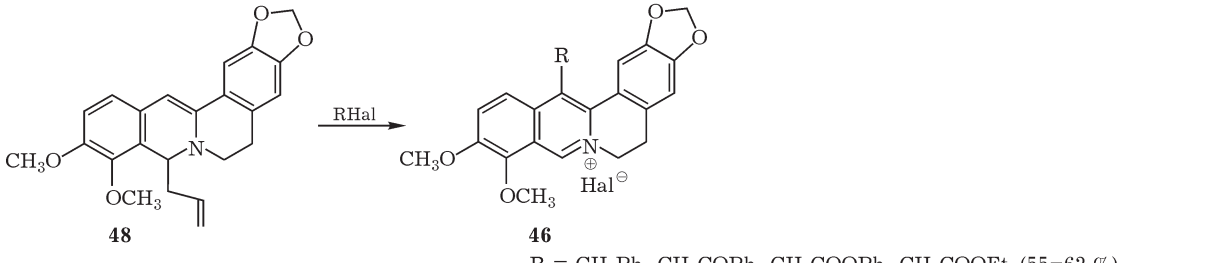
Scheme 25.





Scheme 26.

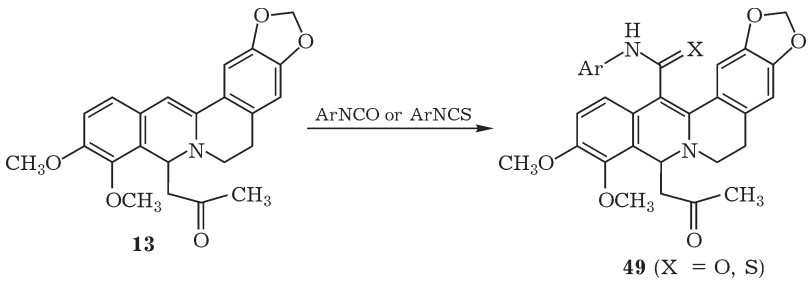




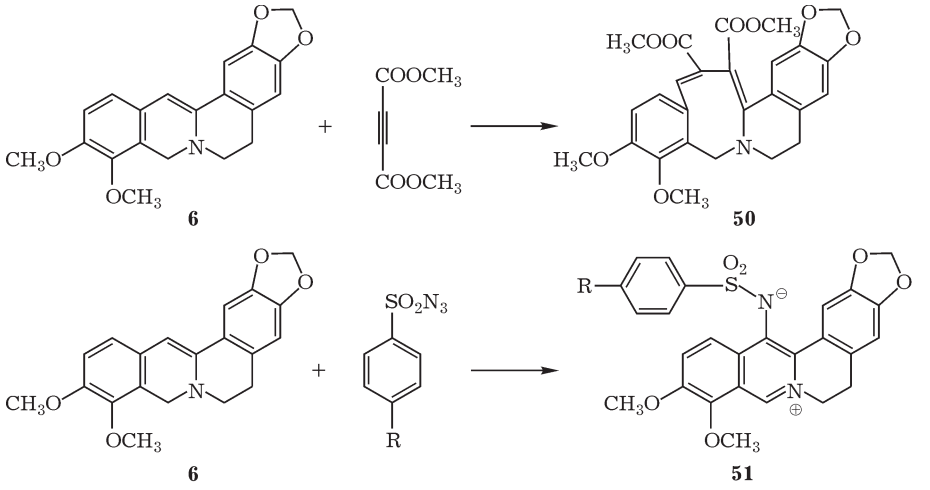
Scheme 27.

intramolecular oxidation-reduction reaction which results in the formation of 13-alkylberberine salts **46** [90, 47, 91, 92].

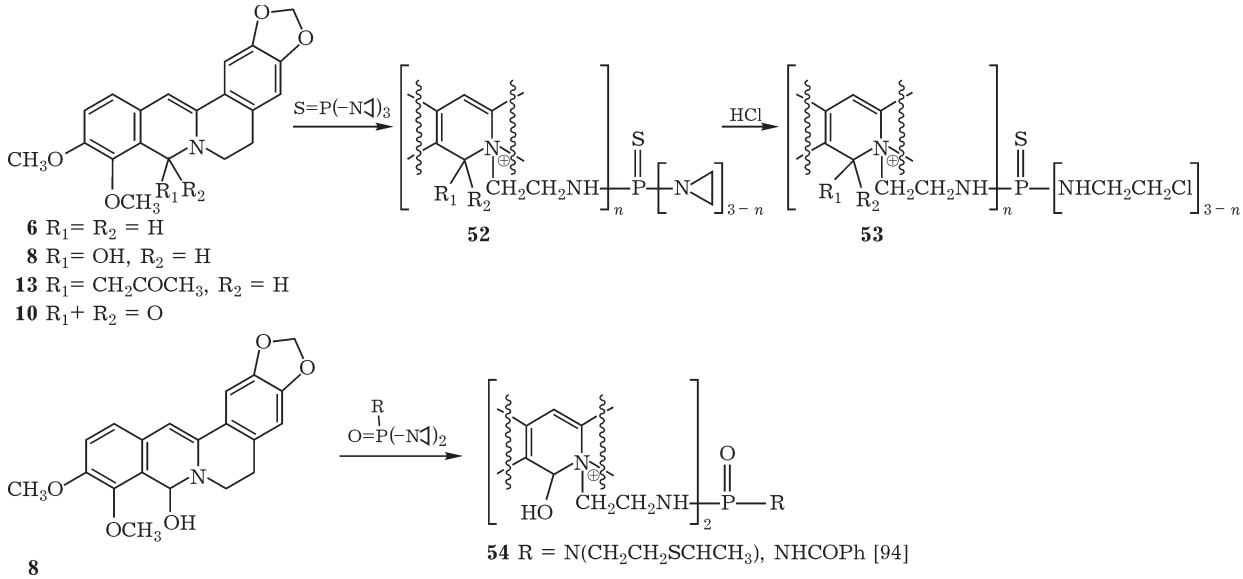
The alkylation of acetone berberine **13** is accompanied by the elimination of the acetone fragment with the formation of 13-alkylberberines **46**. In parallel a process proceeds whereby berberine salt **1** is formed [93, 89, 91, 42, 45] (Scheme 27). One of the minor products of acetoneberberine alkylation represents ketone



Scheme 28.



Scheme 29.



Scheme 30.

47. It is significant that the alkylation of 8-allyldihydroberberine **48** proceeds only with the formation of compounds **46** [59]. The interaction of acetoneberberine **13** with arylisocyanates and isothiocyanates allows one to obtain compounds **49** [49] (Scheme 28). The process of dihydroberberine **6** [2+2]-cycloaddition to dimethyl ether of acetylenedicarboxylic acid with the formation of compound **50** also represents a typical enamine reaction [49, 88] (Scheme 29).

The interaction between dihydroberberine **6** with arylsulphonylazides proceeds, to all appearance, through the [2+1]-cycloaddition of intermediately formed nitrene with the subse-

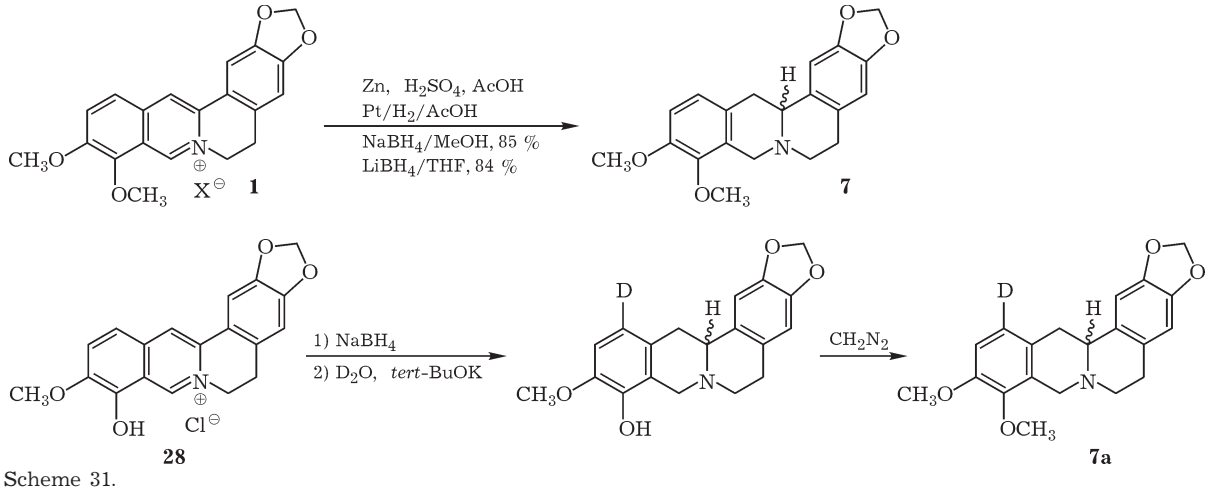
quent opening of the aziridiyne cycle and the formation of 13-substituted berberines **51**. Dihydroberberine **6**, berberine **8**, berberine acetone **13** and 8-oxoberberine **10** use to react with aziridine phosphamides and thiophosphamides with the formation of quaternary ammonium salts **52–54** [94, 95] (Scheme 30).

Tetrahydroberberine (canadine) and its derivatives

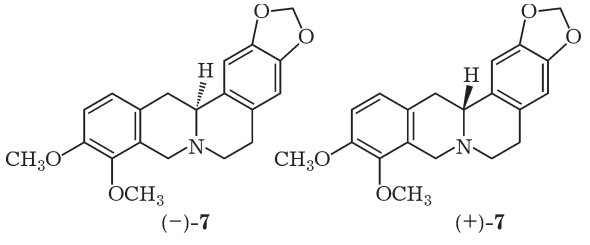
Tetrahydroberberine **7** was obtained from plants belonging to genus *Hydrastis Canadensis* as well as *via* the reduction of berberine **1** or dihydroberberine **6**. The reduction of berberine **1** was carried out using zinc in acidic media [23, 96, 97], by hydrogen on a catalyst [98–100], by sodium borohydride in ethanol or methanol [47, 101–104] (Scheme 31). The use of $NaB[^3H]_4$ or $NaB[^2H]_4$ has resulted in the obtaining of corresponding 8,13,13a-tritium [50] or 8,13a-deuterium derivatives of tetrahydroberberine **7** [105].

The reduction of berberrubine **28** by sodium borohydride with the subsequent deuteration and methylation by diazomethane allows one to obtain a deuterated analogue of tetrahydroberberine **7a** [75]. The diastereomeric cleavage of racemic tetrahydroberberine into (−) and (+) isomers **7** is possible for carrying out *via* the crystallization of salts with chiral (+)-di-O,O′-*n*-toluenyl-*D*-tartaric acid [47], (+)-10-camphor sulphonic acid (B-2-56) [104, 110] or α-bromocamphor sulphonic acid [106, 107] (Scheme 32).

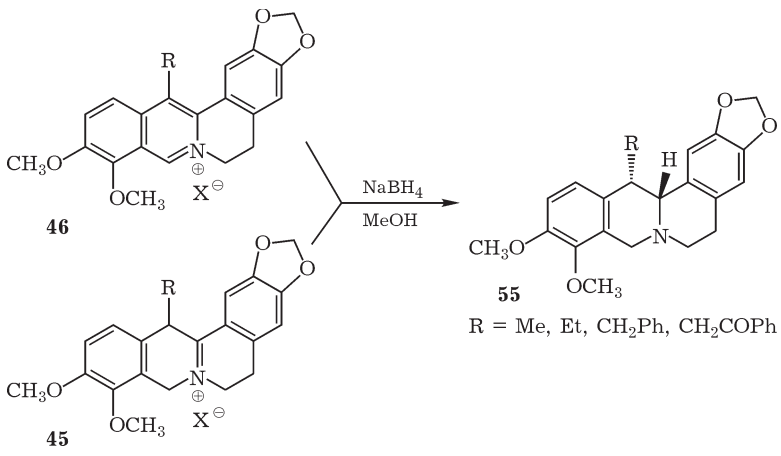
The reduction of 13-alkylberberines **46** or immonium salts **45** by borohydrides results in the formation of tetrahydroberberines **55** where an alkyl substituent at the position of the cycle and the proton at C-13a are *trans*-positioned with respect to each other [49, 89] (Scheme 33). Compounds **55** represent the analogues of the group of 13-methyltetrahydroprotoberberine alkaloids from the family Corydalis that includes the alkaloids such as lictricavine **56**, tetrahydrocorysamine **57**, corydaline **58**, mesotalictravine **59**, mesotetrahydrocorysamine **60**, mesocorydaline **61**, *etc.* (Scheme 34). 8-Alkyldihydroberberines **16** were reduced into 8-alkyltetrahydroberberines **62** by hydrogen on a cata-



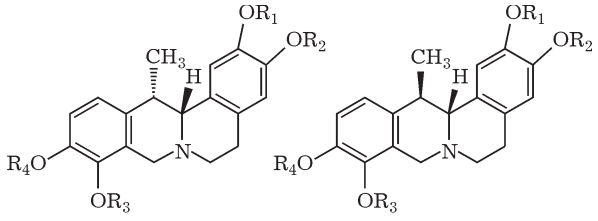
Scheme 31.



Scheme 32.

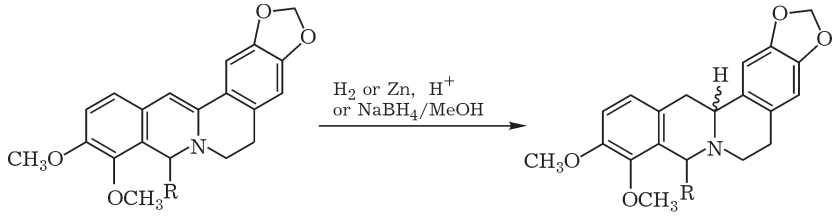


Scheme 33.



56 $R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$ **59**
57 $R_1 + R_2 = R_3 + R_4 = CH_2$ **60**
58 $R_1 = R_2 = R_3 = R_4 = CH_3$ **61**

Scheme 34.

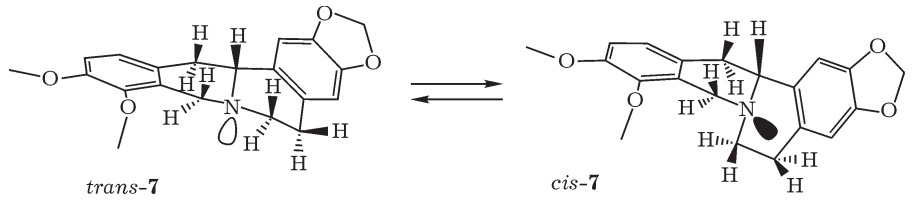


R = Et, Pr, CH_2Ph
$NaBH_4$: R = H, Me, CH_2Ph, *n*-BrC_6H_4

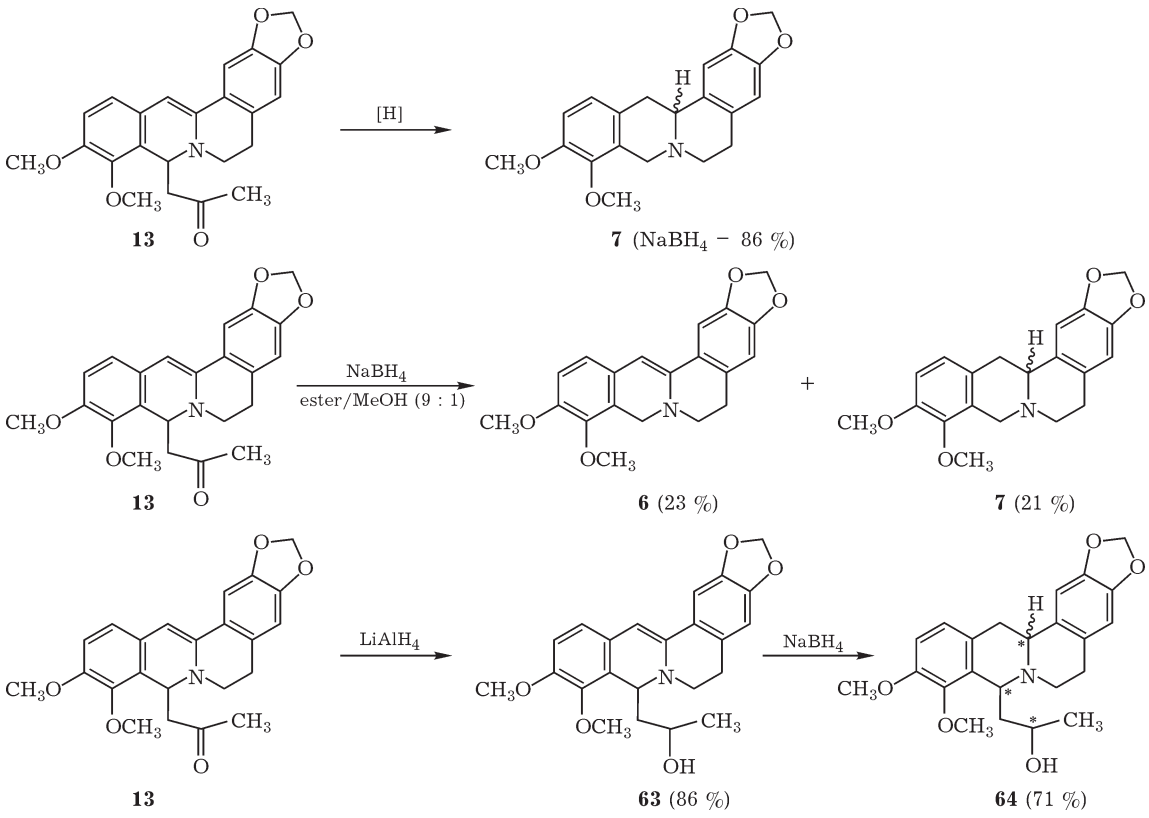
Scheme 35.

lyst [49, 54, 55, 57] or by borohydrides [102, 50, 52, 108] (Scheme 35).

The quinolizidine fragment of the tetrahydroberberine skeleton **7** exhibits the flexibility due to presence of nitrogen atom N-7 [7], however due to the two annulated aromatic cycles this structure is more rigid comparing to the structure of unsubstituted quinolizidine. As the result of a series of consecutive inversions of the nitrogen atom of and the conversion of cycles, the *trans*- and *cis*-conformers of tetrahydroberberine **7** are in equilibrium with respect to each other (Scheme 36). The comparative analysis of CD spectra for compound **7** with *trans*- and *cis*-*N*-methyl derivatives **66**, **67** demonstrates that tetrahydroberberine **7** is mainly in *trans*-conformation. The value of ΔG^0_{25} transition from the trans-forms to the *cis*-form amounts to 3 kJ/mol, which corresponds to the ratio for *trans*/*cis* conformers approximately



Scheme 36.



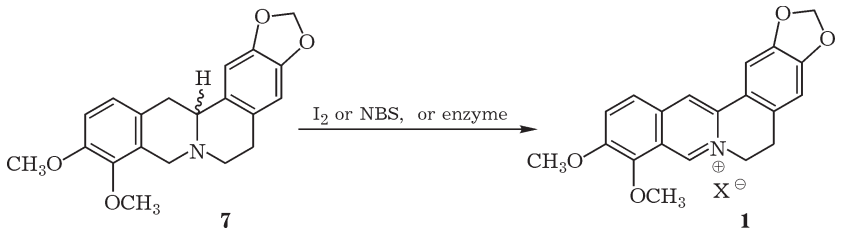
Scheme 37.

equal to 4 : 1 [8]. However, the introduction of substituents into the quinolizidine system including the nitrogen atom, can considerably make shift the equilibrium position shifted [109].

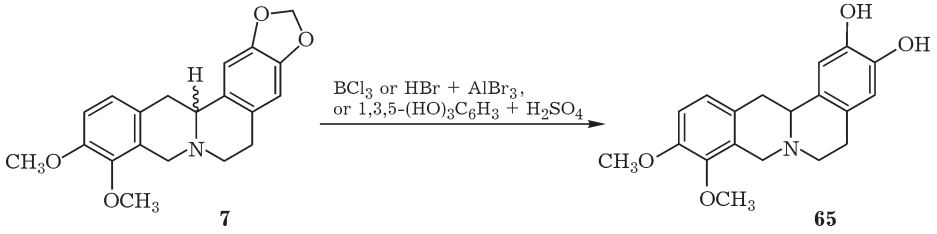
The reduction of acetoneberberine **13** by sodium in wet ether, by the amalgam of sodium, by aluminium isopropylate, by hydrogen on Pd/C catalyst, by $NaBH_4$ in methanol results in the abstraction of the acetone fragment with the formation of tetrahydroberberine **7** [102, 104] (Scheme 37). Sodium borohydride in the ether-methanol mixture (9 : 1) produces the mixture of dihydro- and tetrahydro compounds **6** and **7** with the yield amounting to 23 and 21 %, respectively [102]. Lithium alumohydride reduces acetoneberberine **13** to yield alcohol **63** [44] and after that it is possible to reduce double bond in the cycle by sodium borohydride with the formation of a diastereomeric mixture of substituted tetrahydroberberines **64** [102, 44].

Tetrahydroberberine **7** was oxidized to produce berberine salt **1** by the action of iodine [70], bromosuccinimide [111] or ensymatically [112–114] (Scheme 38). The removal methylene etherial group of tetrahydroberberine **7** with the formation of compound **65** was carried out by the action of BCl_3 [9], $AlBr_3$ + HBr [10], or by phloroglucinol in sulphuric acid [117, 118] (Scheme 39).

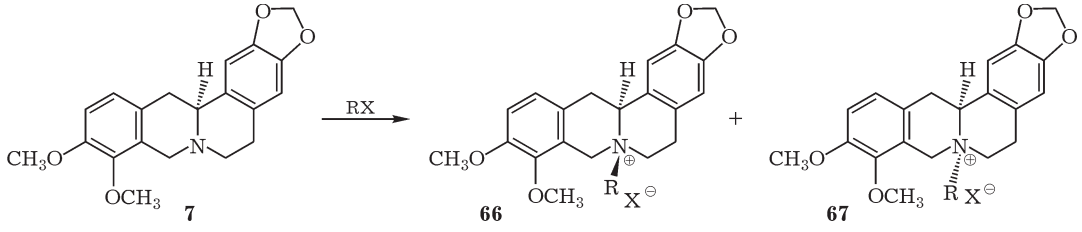
The interaction between tetrahydroberberine **7** and alkylhalogenides resulted in obtaining qua-



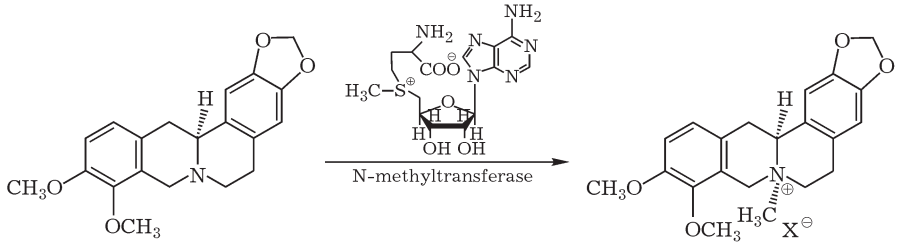
Scheme 38.

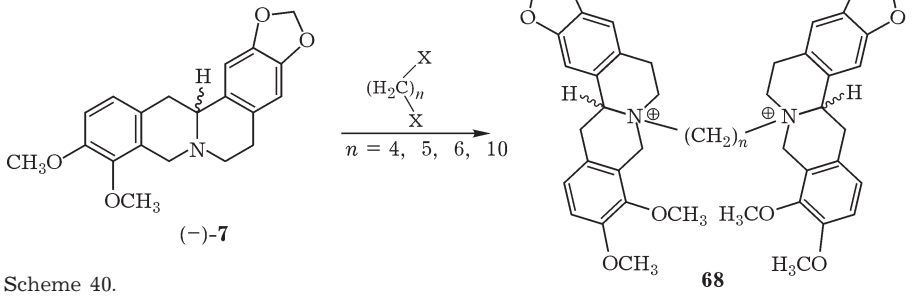


Scheme 39.



R = Me, Et, $PhCH_2$, 4-$CH_3OC_6H_4CH_2$:

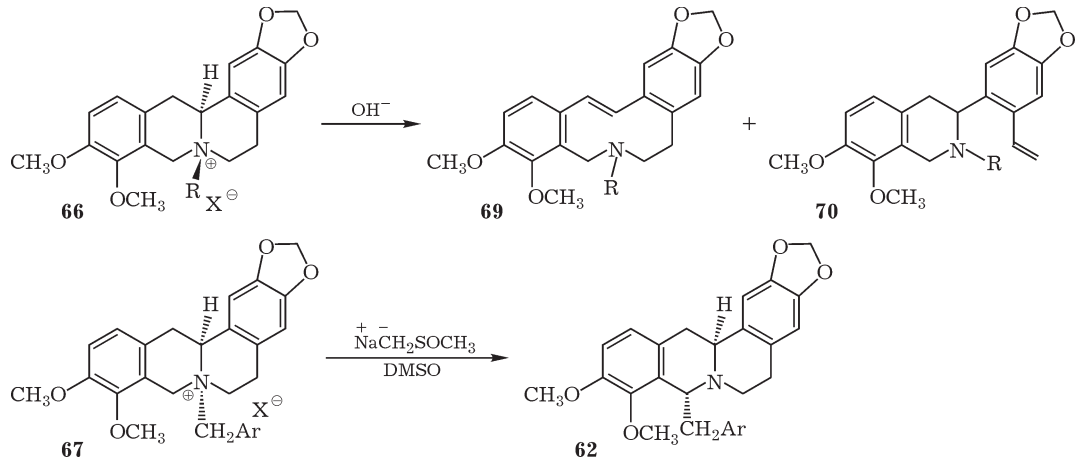




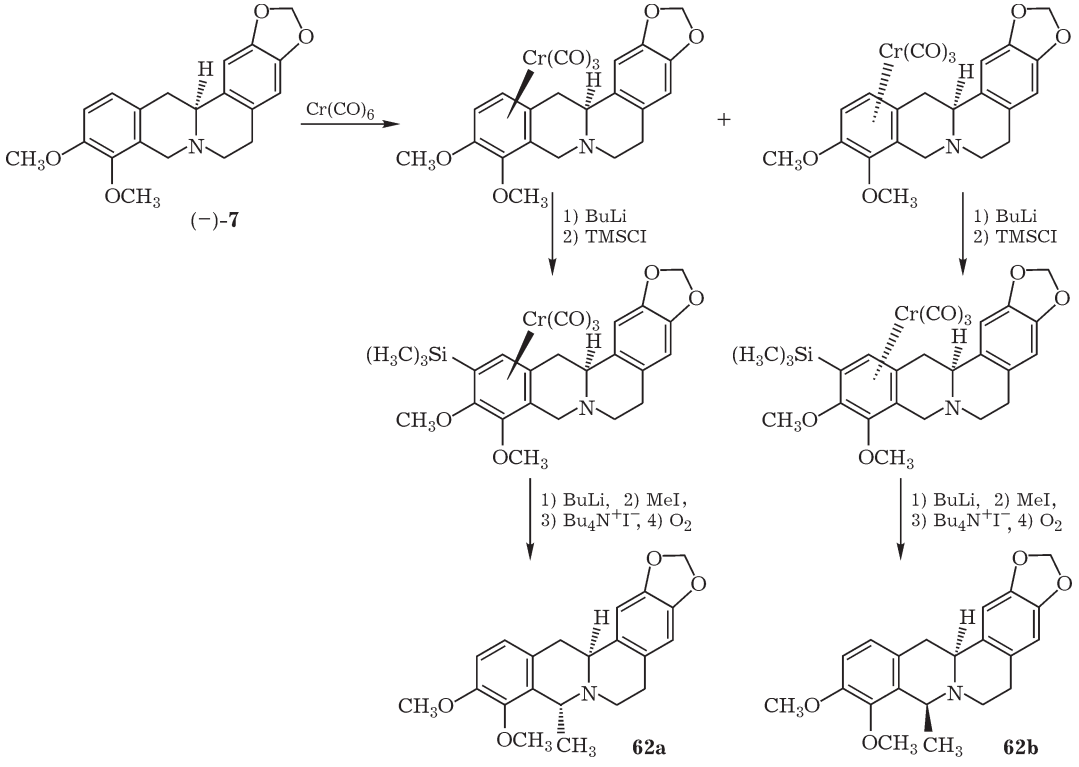
Scheme 40.

ternary ammonium salts [96, 105, 119, 101, 104] those represented a mixture of *trans*- and *cis*-isomers **66**, **67** (Scheme 40). The ratio between the isomers depends on the nature of an alkylation agent. So, the methylation by methyl iodide results in the formation of the mixture of *trans*- and *cis*-isomers **66**, **67** at a ratio of 75 : 25. This indicates that the trans-isomer **66** is formed from the *trans*-conformer of tetrahydroberberine **7**, and the *cis*-isomer **67** if formed from the *cis*-conformer of compound **7** [110]. The alkylation by benzyl bromides results in the prevailing of *cis*-isomer **67** (for R = $PhCH_2$ the ratio *trans*/*cis* = 8 : 84) [11].

Selective methylation with the formation of pure *cis*-isomer **67** could be carried out with the use of *S*-adenosyl-*L*-methionine and *N*-methyltransferase [121]. Bis-ammonium salts **68**



Scheme 41.

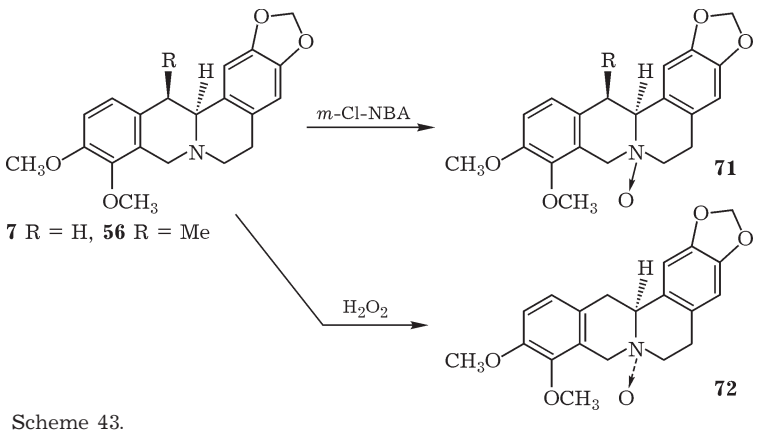


Scheme 42.

were obtained with lower yields [122]. The *N*-alkyl salts **66**, **67** obtained can either decompose with the formation of elimination products according to Hoffmann **69**, **70** [120, 105, 101] or undergo rearrangement according to Stevens under the action dimsyl sodium in DMSO with the formation of 8-substituted tetrahydroberberines **62** [120] (Scheme 41).

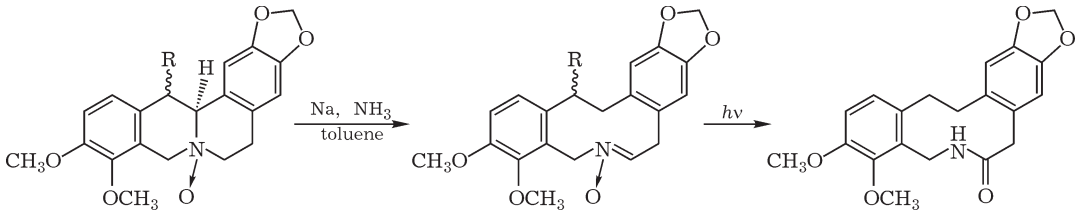
The stereoselective alkylation to position 8 was performed by the metallation of the complex of (−)-tetrahydroberberine **7** with chromium carbonyl [52] (Scheme 42). The oxidation of tetrahydroberberine **7** or 13-methyltetrahydroberberine **56** by metachloroperbenzoic acid results in forming the *trans*-isomer of *N*-oxide **71** as the main product, whereas *cis*-isomer **72** was present only in trace amounts [47, 123, 124] (Scheme 43). The *cis*-isomer of *N*-oxide was obtained with the yield of 9 % *via* the oxidation by hydrogen peroxide [47].

N-oxide **71** under the action of sodium in ammonia passes into nitrone **73** which rearrang-

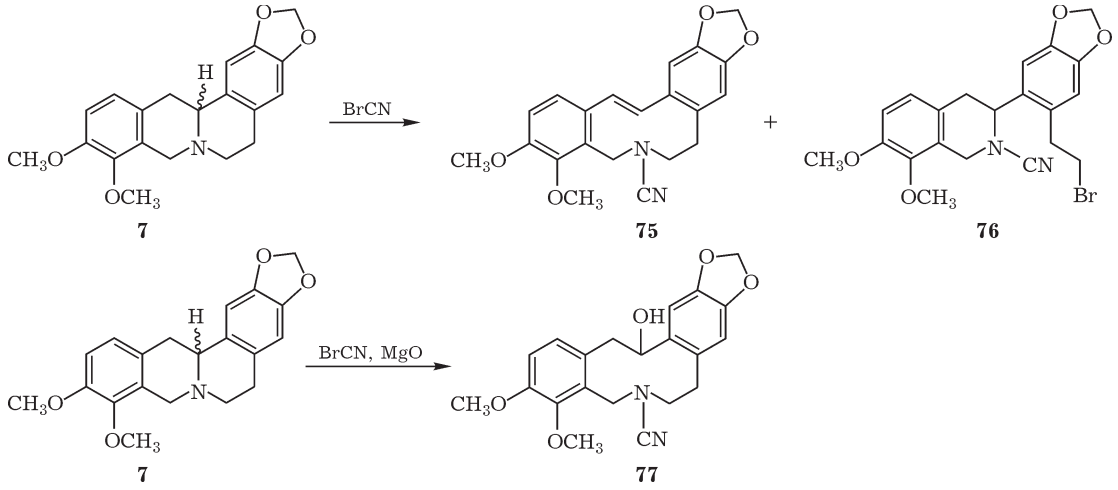


7 R = H, **56** R = Me

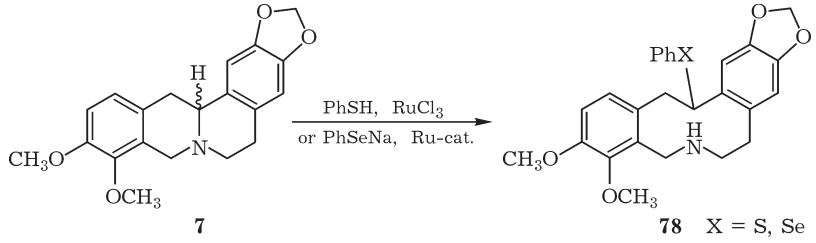
Scheme 43.



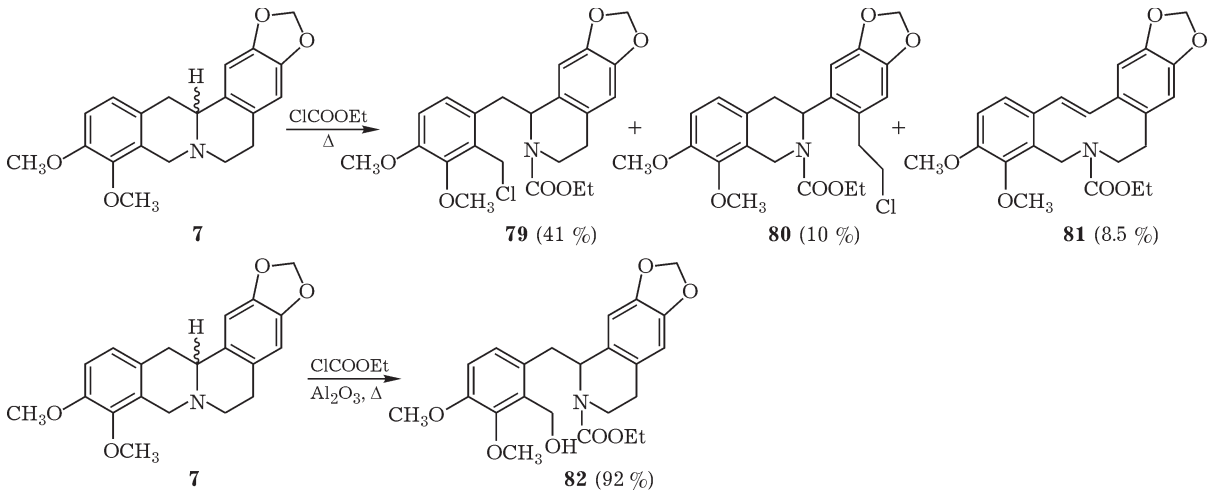
Scheme 44.



Scheme 45.



Scheme 46.



Scheme 47.

es into amide **74** with a low yield [124] (Scheme 44). The interaction between tetrahydroberberine **7** and bromocyan resulted in obtaining the elimination products according to Hoffmann **75–77** [101, 105, 125] (Scheme 45). In the case of the catalysis by the salts of ruthenium, the tetrahydroberberine **7** reacts with thiolates and selenolates with the formation of secondary amine **78** [126, 127] (Scheme 46). The acylation of tetrahydroberberine **7** by ethyl chloroformate results in the formation of a complex mixture of products **79–81** [128–130] (Scheme 47). At the same time, performing this reaction with the addition of aluminium oxide results in obtaining an individual product such as compound **82** [70].

BIOLOGICAL ACTIVITY OF BERBERINE AND ITS DERIVATIVES

Berberine chloride **1** belongs to the 2nd class of toxic substances. It's mid-death doze level (LD_{50}) in the case of intraperitoneal introduction amounts to 50 mg/kg for mice [131], whereas for berberine **8** this parameter is equal to 22 mg/kg [94]. Dihydroberberine **6** and oxoberberine **10** exhibit a lower toxicity level: LD_{50} = 190 and 240 mg/kg, respectively. Notwithstanding the fact that berberine-containing plants have found application as antimicrobial and antibacterial remedies, berberine itself exhibits a low activity in this connection. So, this substance appeared ineffective against gram-negative bacteria. Its minimal inhibiting concentration (MIC) amounts to, mg/L: for *Candida albicans* 500, for *E. coli* > 2000 [90], for *Bacillus subtilis* 500, for *Salmonella enteritidis* 250 [132], for *Pseudomonas aeruginosa* >1000, for *Streptococcus faecalis*, *Streptococcus sanguis* (ATCC 10556) this parameter is equal to 500 [133]. Berberine is ineffective also against *Serratia liquefaciens*, *Citrobacter* MFBF, *Providentia stuardii* [134].

As far as gram-positive bacteria are concerned, berberine demonstrates a slightly greater activity. For *Staphylococcus aureus* (X) the MIC value amounts to 250 mg/L [90], for *Fusobacterium nucleatum* (ATCC 25586) 15.6 mg/L [135]. Berberine inhibits the growth of hazardous intestinal bacteria *Clostridum perfringens* (ATCC 13124), *Clostridum paraputrificum* (ATCC 25780), with no influence upon lactic bacteria *Bifidobacterium bifidum* (ATCC 29521), *Bifidobacterium longum* (ATCC 15707), *Bifidobacterium adolescents* (ATCC 15073), *Lactobacillus acidophilus* (JCM 1028) and *Lacto-bacillus casei* (ATCC 14916) [136].

The introduction of alkyl substituents in the molecule of berberine increases to a considerable extent antimicrobial and antibacterial activity of berberine. So, for 13-alkylsubstituted berberines **46** the activity against *Staphylococcus aureus* increases in the sequence R = Me < Et < Pr < Bu < Hex. 13-Hexylberberine exhibits a 64-fold against *S. aureus* (X) (MIC = 3.91 mg/L) and 128 times higher efficiency against *S. aureus* ATCC 3061, (MIC = 7.82 mg/L) as

compared to berberine [90, 136, 93, 137]. 8-Alkylsubstituted berberines **17** demonstrate a sligtly greater activity in comparison with 13-substituted derivatives, however the highest and universal activity have demonstrated by 12-bromo-8-alkylberberines **18**.

The most active compounds in this series are presented by 12-bromo-8-hexylberberine and 8-butylberberine inhibit well even gram-negative bacteria. So, the activity of 12-bromo-8-hexylberberine exceeds that for berberine itself by 64 times in the action against *Staphylococcus aureus* (MIC = 3.9 mg/L), by 256 times in the action against *Bacillus subtilis* (3.9 mg/L), by 128 times in the action against *Salmonella enteritidis* (3.9 mg/L), by 32 times in the action against *Candida albicans* (15.6 mg/L) and by 16 times in the action against *E. coli* (125 mg/L) [48.] Such compound as 8,13-dibenzyl berberine derivative 83 demonstrates *in vitro* antistaphylococcal activity (MIC = 0.48 mg/L), but exhibits no activity *in vivo* [49]. Berberine-ethyleneamide **53** is active against *Staphylococcus mutant* 209 UF-2 (0.0035 mg/L) [94].

Enamine **49** exhibits antifungal activity *in vitro* against *Trichophyton interdigitale* (MIC = 125 mg/L) [49]. 13- and 8,13-substituted berberines demonstrate antifungal activity against *Candida*, *Epidermophyton* [138].

Berberine is efficient against some plasmodia species of malarial mosquito such as *Plasmodium falciparum*: IC_{50} = 0.968 μmol/L for strain K1 [139], 0.08 μmol/L for strain K39 and 1.98 μmol/L for strain V1/S [140]. Against other plasmodia species, berberine is less efficient: IC_{50} = 141 and 148 ng/mL for strains D-6 and W-2, respectively; berberine exerts no effect on *P. berghei* [141].

Berberine is used for the treatment of cardiovascular diseases as a hypolipidemic agent [142]. So, with administering berberine within three months the content of cholesterol in patients decreased by 29 %, that of triglycerides was reduced by 35 % and the content of LDL-cholesterol decreased by 25 % [3].

N-Alkyl derivatives of tetrahydroberberine **66** are efficient as an antiarrythmic agent [143], there are data concerning their antihyperglycemic activity (R = CH_2Ph): the content of sugar in blood decreases by 146 mg/dL [96]. Berberine exhibits a capability of lowering temporarily the blood pressure *via* the inhibition of acetylcholinesterase [1].

Berberine inhibits monoaminooxidase (MAO, the enzyme destroying neurotransmitter norepinephrine) not so efficiently: K_i = 110 μmol/L, IC_{50} = 126 μmol/L [144].

The berberine citotoxicity (IC_{50}) against various kinds of tumours was studied: Dalton limphoma of ascitic cancer cells: >1000 mg/L, cells L929: 40 mg/L [145], HeLa cells of human uterine cancer: 7.2 mg/L, IC_{100} = 74.6 mg/L; adenocarcinoma of human uterine neck >20 mg/L [146]. The cells of lines HT 29, LoVo, LoVo/Dx of human rectal carcinoma: 1.90 mg/L; human nasopharyngeal carcinoma of KB: 7.32 μmol/L [139]. The cells L1210 of mouse leukaemia: 3.5 mg/L, IC_{100} = 32.2 mg/L [147], L1210/CDDP 0.4 mg/L, L1210 0.37 mg/L [148].

Berberine exhibits a dose-dependent anticarcinogenic activity, reducing the death level of animals with entwined sarcoma by 60, 53 and 33 % at the dozes of 5, 2.5 and 0.5 mg/kg, respectively [149].

For berberine, an antiprofilerative activity in the inhibition of cancer cells keratinocytes (IC_{50} = 30 μmol/L) has been revealed *in vitro* [150], apoptosis-stimulating action with respect to HeLa of human uterine cancer cells at the doses of 100 and 150 mg/L [147].

The introduction of berberine derivatives in the molecule of well-known antineoplastic preparation thiophosphamide resulted in obtaining derivatives those also exhibit antineoplastic activity. The greatest activity was demonstrated by berberine ethyleneamide **53**; at a dose of 25 mg/kg the level of tumour inhibition amounted to 80–100 %, for Crocker sarcoma this parameter was equal to 66 % [94]. As one of the variants of anticarcinogenic and antineoplastic therapy, studies were performed concerning the binding of berberine and its derivatives with DNA. For the series of dimeric derivatives, the greatest binding level has been demonstrated by compound **29** with n = 3 [74].

CONCLUSION

Thus, berberine is a phytogenous alkaloid available for obtaining in the territory of Russia; the methods of its isolation are well-de-

veloped. Reduction and oxidation reactions, the reaction of nucleophilic addition to the isoquinolinium system of berberine and electrophilic addition to the enamine system of dihydroberberines are studied in most detail. The fact that berberine and its derivatives exhibit antimicrobial, antibacterial, antifungal activities, as well as hypolipidemic and antineoplastic activities allows considering the berberine as an attractive object for chemical transformations with the purpose of directed amplifying its native biological activity.

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