ISOLATION, ANALYSIS, AND SYNTHESIS OF EPHEDRINE AND ITS DERIVATIVES

A. N. Gazaliev, M. Zh. Zhurinov,
S. D. Fazylov, and S. N. Balitskii

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A review is given of methods for the isolation, quantitative determination, and modification of the ephedrine alkaloids, and advances in this field of natural compound chemistry are discussed.

Ephedrine was first isolated in 1987 from the Chinese species Ephedra sinica (Stapf.) and at the present time it is widely used in medical practice. In its pharmacological properties and structure, ephedrine is close to epinephrine (it stimulates the α- and β-adrenoreceptors and causes a contraction of the blood vessels, a rise in the arterial pressure, an expansion of the bronchi, an inhibition of intestinal peristalsis, a dilation of the pupils, and a rise in the level of sugars in the blood), but is less toxic [1-3]. The chemistry and pharmacology of ephedrine has been considered in detail in [2-5].

In the present review, information on methods for the isolation, identification, and modification of ephedrine during the last quarter-century is generalized, earlier work being cited only to confirm individual statements. The material in the paper is presented in the sequence determined by its title.

ISOLATION

Ephedrine and its isomer pseudoephedrine are found in various species of plants of the family Ephedraceae Dumort, which is widespread in moderate and subtropical zones. The genus Ephedra contains 67 species, of which 18 grow on the territory of the USSR [6, 7]. Until 1935, ephedrine was imported into the USSR from abroad. In domestic practice, preference is given to Ephedra equisetina (Mongolian ephedra) which contains about 2.5% of alkaloids and at the same time gives a large amount of vegetation from a single bush [6]. The percentage of the mixture of alkaloids in ephedras varies greatly according to the plant species, the time of collection, and the conditions of growth. In all species apart from Ephedra intermedia, ephedrine predominates, while in E. intermedia it is pseudoephedrine. Plants predominantly containing pseudoephedrine are not used in industry [8, 9].

Great work on finding of Ephedra species rich in ephedrine and suitable for the production of natural ephedrine has been carried out by the Soviet research botanist P. S. Massagetov. The method of obtaining ephedrine from a domestic ephedra was developed in 1934 in the All-Union Scientific-Research Institute of Pharmaceutical Chemistry (Moscow). Ephedrine and pseudoephedrine are present in the plants in the form of salts of various organic acids, because of which the methods for processing the plant raw material that are the usual ones for alkaloids are completely applicable in this case, as well [8, 10, 11]. Methods of extraction from the raw material have been considered in publications by various authors [12-16]. Dichloroethane, benzene, chloroform, toluene, chlorobenzene, amyl, ethyl, and isopropyl alcohols, and aqueous solutions of mineral acids of various concentrations have been tested as solvents. Use has also been made of the property of the ephedra alkaloids for undergoing steam distillation. This method eliminates the stage of freeing the alkaloids from impurities since the majority of them do not distill with steam, but extraction by this method takes a long time and does not give a certainty of completeness of extraction. The results of a comparative study of the influence of the nature of the solvent (ether, methanol, hot water) on the extraction of the alkaloids in commercial samples of ephedra herbage has been given in the literature [17]. The yield of ephedrine from extracts of the herbage amounted to 55-83%. The isolation of the total alkaloids from Ephedra vulgaris with 95% ethanol containing 0.5% of acetic acid has been described [18, 19]. The alkaloids

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have been extracted from Indian varieties of Ephedra by a mixture of three parts of ethanol and one part of chloroform in the presence of ammonia [20, 21]. In the process of developing a procedure for the quantitative determination of ephedrine and pseudoephedrine on their combined presence, the stage of extracting the total alkaloids from the herbage of Mongolian ephedra by various solvents has been investigated. The best proved to be chloroform made alkaline to pH 10.0-12.0 [22]. The extracted technical alkaloid was purified by recrystallization of its sulfate, oxalate, or hydrochloride from water or ethanol.

In industry, ephedrine is obtained mainly by extraction from the plant raw material with hot water in a diffusion battery by the countercurrent principle, but because of the short supply of the raw material, the demand for this drug is not being satisfied. A large amount of pseudoephedrine remains in the production wastes. Pseudoephedrine obtained as a by-product after the isolation of ephedrine from Mongolian ephedra can be recommended for medical practice as a broncholytic agent, but in amounts 2.5 times exceeding the corresponding dose of ephedrine [23]. The output of pseudoephedrine will enable the deficiency of ephedrine to be made up and will permit the use of Ephedra species rich in pseudoephedrine and a simplification of the production technology with elimination of the isomerization stage, which will give an increase in the volume of production by approximately 20% [24].

Many species of Ephedra (E. equisetina, E. intermedia, E. lomatolepis, E. strobelaceae, and E. fedtschenkoi) contain, in addition to alkaloids, a considerable amount of tannin substances, leucoanthocyanidins, flavone pigments, aromatic acids, and other compounds [25, 26]. In view of this, considerable interest is presented by the complex utilization of ephedras for obtaining some of these substances.

All the Ephedra species studied contain tannin substances of similar structure belonging to the products of the condensation of leucodelphinidin (delephinidol). The method of isolating the tannin from the spent ephedra juice (after the isolation of the alkaloids) consists in acidifying the isolated juice with sulfuric acid and filtering the precipitate. The tannin (ephedrotannide) is a highly tannidic product containing 50-56% of tannides that can be used for tanning sole leather in admixture with syntans and in the presence of sodium sulfite [27, 28].

The substance leucodelphinidin isolated from E. equisetina and the pigment prepared from it, delphinidin, on being tested for vitamin P effect showed an activity close to the activity of the catechins from tea leaves.

Under mild conditions (treatment with solvent without heating), it is possible to isolate from ephedras leucoanthocyanidins which, when their aqueous solutions are heated, are converted quantitatively into polymeric molecules. These consist of pulverulent amorphous substances decomposing on heating. The amounts of leucoanthocyanidins in ephedra species (in percentages) are: E. equisetina, 7.19; E. intermedia, 5.73; E. lomatolepis, 8.13; E. strobelaceae, 5.06; E. fedtschenkoi, 4.73 [25].

Gas-liquid and paper chromatography established that E. equisetina contained six phenolic acids: benzoic, p-hydroxybenzoic, cinammic, p-coumaric, vanillic, and protochatechuic [29].

The complex utilization of ephedras for obtaining alkaloids, leucoanthocyanidins, anthocyanidins, and tannides will undoubtedly promote an expansion of the raw materials basis of the preparation of drugs, food dyes, and high-quality tannins.

METHODS OF ANALYSIS

The total alkaloids in ephedra herbage are determined by a titrimetric method according to FS [Pharmaceutical Standard] 42-525-72 developed at the beginning of the 1940s and introduced almost without change into the new standardizing technical documentation for ephedra herbage. The method is characterized by the deficiencies of the majority of standard methods for determining total alkaloids in a raw material: poor reproducibility, lengthiness, and laboriousness. The amount of ephedrine in aqueous solutions is determined by the Kjeldahl method and by volumetric, gravimetric, and colorimetric methods based on the biuret reaction [5].

For the quantitative determination of ephedrine, the State Pharmacopoeia (Xth edition) recommends acid-base titration in nonaqueous media in the presence of mercuric acetate, but in this method it is the chloride anion that is titrated and not the ephedrine cation [2].

It can be determined colorimetrically from the coloration of a complex with copper sulfate or carbamate [3, 30, 31], by the direct titration of an ethanolic solution of ephedrine hydrochloride with a 0.1 N solution of caustic soda [32], and by argentometric titration in dimethyl sulfoxide [33] or in an aqueous solution of acetic acid [3]. The possibility has been shown of the conductometric titration of salts of the alkaloids in dimethyl sulfoxides [34]; the different solubilities of the oxalate can be used for the satisfactory separation and identification of ephedrine and pseudoephedrine [35]. Spectrometric and photometric methods for the quantitative determination of ephedrine have been developed [36-42]. Applicability of Beer's law is observed within the range of concentrations of ephedrine hydrochloride in solution of 0.0001-0.0006%. Titrimetric methods of determining ephedrine and norephedrine with the aid of cerium sulfate have been described [43] which are based on the complex-forming capacity of ephedrine with dyes (Bromophenol Blue, Bromothymol Blue, Bromocresol Green, etc.) selectively interacting with ephedrine in the presence of other substances. The proposed methods possess high accuracy and permit well-reproducible results to be obtained.

The reaction of ephedrine with ninhydrin has been modified in such a way as to become suitable for quantitative analysis. The method can be used for the direct determination of medicinal preparations containing ephedrine. The absorption of the solution is measured at 570 nm [43, 44].

The oxidation of ephedrine to benzaldehyde by various oxidants is used for its quantitative determination. Spectrophotometric methods based on its oxidation by potassium periodate [45] or sodium periodate [46], by N-bromosuccinimide [47] and by potassium ferricyanide [48] have been developed.

The quantitative determination of ephedrine in the medicinal mixtures has not been adequately discussed in the literature. The methods proposed envisage, mainly, the extraction of ephedrine in the form of the base and its determination volumetrically. A method for the polarographic determination of ephedrine in various medicinal mixtures [49] gives good results. According to this method, the polarographically inactive ephedrine is converted quantitatively into benzaldehyde by oxidation with bromine at the boil, the aldehyde is then converted into the 2,4-dinitrophenylhydrazone, and the ephedrine content is determined from the amount of reagent consumed in the precipitation of the aldehyde. A gas-chromatographic method of analyzing a complex medicinal mixture containing ephedrine hydrochloride, phenobarbital, and theophylline has been investigated [50, 51]. A method has also been developed for its quantitative determination by PMR spectroscopy [52]. Ion-selective membrane electrodes were used in [53, 54] for the quantitative determination of ephedrine hydrochloride.

A large number of publications has been devoted to the development of methods for the separation and determination of optically active and racemic ephedrines. A method for separating a mixture of levorotatory and racemic ephedrines with a high proportion of the racemate by extraction with butyl acetate, in alkaline solution in the presence of 0.01-5% of a surface-active agent (nonionic or cationic) and without it, has been patented [55, 56]. Optically active and racemic ephedrines have been determined by high-performance liquid chromatography in the form of metal chelate derivatives [57, 58]. Another method for separating D,L-ephedrine into optically active isomers is carried out with the aid of the reaction with D-trans-2-benzoylaminocyclohexanecarboxylic acid [59]. Defects of the methods mentioned include the complexity of the apparatus required, their multistage nature, and their lengthiness.

An original method for the selective determination of ephedrine and D-pseudoephedrine or a mixture of them is based on the direct dependence of the specific rotation of the sum of the two alkaloids or their hydrochlorides (1-5% ethanolic solution) on the amount of each in the mixture [60]. The percentage contents of ephedrine (X_{eph}) and of D-pseudoephedrine (X_{ps}) are determined from the following formulae:

$$X_{eph} = \frac{52.8 - [\alpha]_{exp}}{56.8} \cdot 100,$$

$$X_{ps} = \frac{4 + [\alpha]_{exp}}{56.8} \cdot 100,$$

where $[\alpha]_{exp}$ is the specific rotation (1-5% solution) of the mixture of alkaloids under investigation.

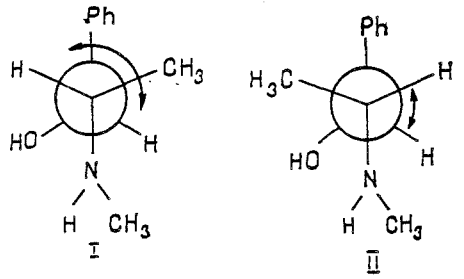
The method for the selective determination of ephedrine and D-pseudoephedrine permits the detection of ephedrine as an impurity in the drug deephedrine in an amount of up to 1% and is used for the stagewise control of its production [60].

Characteristic for the majority of methods considered is good reproducibility and adequate accuracy in the determination. The methods described make it possible to choose the optimum procedure for the analysis of ephedrine in the light of concrete conditions.

SYNTHESIS OF EPHEDRINE AND ITS DERIVATIVES

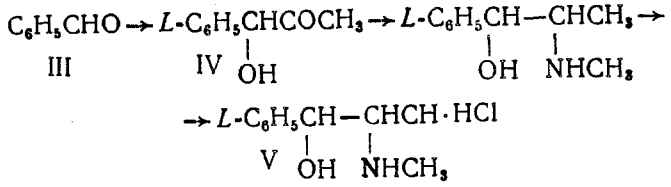
Until recently, ephedrine was obtained exclusively from a natural raw material – various species of Ephedra. However, the inadequate reserves of wild-growing ephedras has made it necessary to develop synthetic methods for obtaining ephedrine. These include the microbiological production of optically active ephedrine from benzaldehyde and a method for the synthesis of racemic ephedrine which is based on propionic acid or monochloroacetic acid, followed by the separation of the racemate into optical isomers.

The 2-methylamino-1-phenylpropan-1-ol molecule has two asymmetric carbon atoms, and therefore four optically active isomers and two racemates exist. The most commonly used isomers are ephedrine (the erythro isomer) (I) and pseudoephedrine (the threo isomer) (II), which are spatial isomers



The interconversion of these alkaloids was shown long ago. As early as 1906, Schmidt, in an attempt to prepare ephedrine racemate by boiling ephedrine with 25% hydrochloric acid, recorded the formation of pseudoephedrine. In this way, the practical possibility of converting ephedrine into pseudoephedrine and conversely was established. The interconversion of these alkaloids was studied in detail by Schmidt and Emde [61-63].

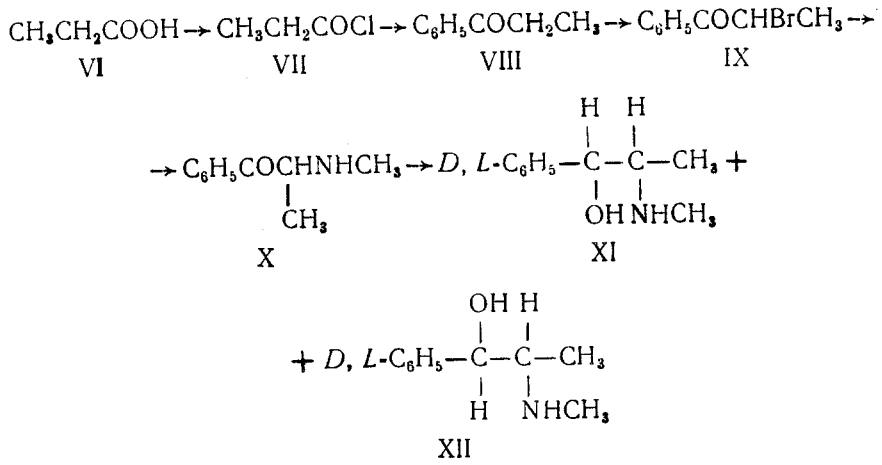
The first total synthesis of ephedrine and its isomers was achieved in 1925 by Späth from propionaldehyde, bromine, and phenylmagnesium bromide. The preparation of optically active ephedrine from benzaldehyde (III) is based on the biosynthesis of levorotatory phenyl acetyl carbinol (IV) as the result of the fermentation of molasses and sugar by yeast in the presence of benzaldehyde [64]. After the end of biosynthesis, 28-40% of (IV) is isolated and is converted by reductive methylamination in dibutyl ether with a platinum catalyst. The L-ephedrine base so obtained is converted into the hydrochloride (V).



Disadvantages of the method are the necessity for the large volume of the ether, the high demands on the purity of benzaldehyde, and the considerable consumption of a food raw material (the production of 1 kg of ephedrine consumes 9 kg of sugar, 64 kg of molasses, and 6 kg of yeast). In addition, L-phenyl acetyl carbinol is unstable and must be stored at low temperatures.

The production of racemic ephedrine from propionic acid (IV) is done by the following scheme [65]. With the aid of phosphorus trichloride, (VI) is converted into propionyl chloride (VII) from which, by the Friedel–Crafts reaction in benzene, propiophenone (VIII) is obtained. The latter is brominated to α-bromopropiophenone (IX) which, without isolation,

is converted by the action of methylamine into α-methylaminopropiophenone (X). On the catalytic hydrogenation of (X) with palladium on carbon or with Raney nickel, a mixture of racemic ephedrine (XI) and racemic pseudoephedrine (XII) is formed, from which (XI) is isolated in the form of the hydrochloride.



Compound (XI) is separated into optical isomers, and pseudoephedrine is isomerized, giving an additional amount of (XI).

The disadvantages of the method include the use of propionic acid, which is in short supply at the present time and is fairly expensive, and also the formation, as an intermediate in the production process, of the α-bromoketone (IX), which is a powerful lachrymator.

The production of racemic ephedrine from monochloroacetic acid takes place through the reductive methylamination of benzoylacetyl and the isolation of (XI) from the resulting mixture of ephedrine and pseudoephedrine in the form of the sparingly water-soluble oxalate (XIII). Alkalinization of the mother solution with caustic potash leads to the isolation of (XII). On boiling with an ethanolic solution of hydrogen chloride, the hydrochloride of (XI) is formed with a yield of about 50% on the benzoylacetyl; the yield of (XII) is 13-15% [66, 67].

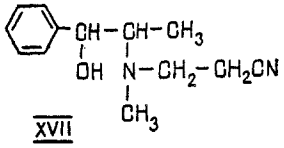
To obtain L-ephedrine, the racemic (XI) is separated into optical antipodes with the aid of dibenzoyl-D-tartaric acid (XIV). The hydrochloride of racemic (XI) and the sodium salt of (XIV) are used for the separation, whereupon the sparingly soluble D-ephedrine dibenzoyl-D-tartrate (XV) separates from the aqueous solution, and the salt of L-ephedrine (V) remaining in the solution is subsequently converted into the base and then via the hydrochloride into the pharmacopoeial product.

From the salt (XV) are regenerated the acid (XIV) and D-ephedrine (XVI). The latter is subjected to racemization by heating with sodium ethanolate at 190-195°C. The resulting mixture of racemic ephedrine (XI) and racemic pseudoephedrine (XII) is separated through the oxalates.

D,L-Pseudoephedrine is isomerized under the same conditions as we used for the racemization of D-ephedrine, and in this case, also, a mixture of racemic ephedrine and pseudoephedrine is obtained. The yield of D,L-ephedrine with allowance for the pseudoephedrine obtained after isomerization amounts to about 50% [64].

At the present time, natural sources alone cannot completely satisfy the demand for drugs, and therefore a considerable part of them is obtained by modifying natural compounds.

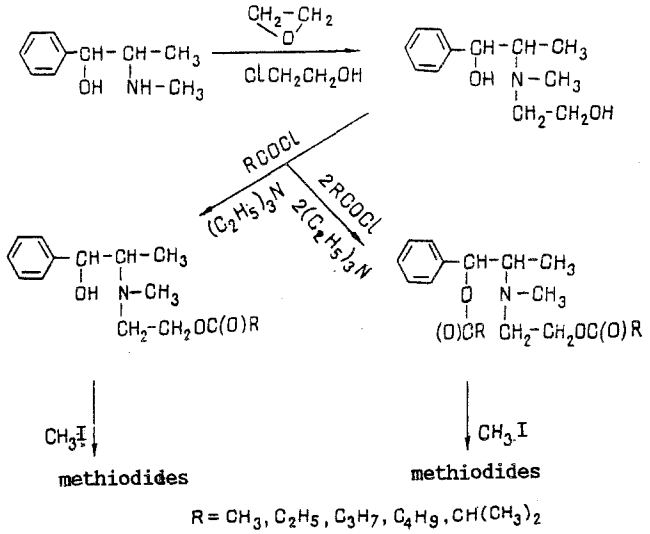
A method has been patented for obtaining ephedrine cyclohexylsulfamate, which is used in bronchial asthma and possesses a sweet taste [68]. With 6-phosphogluconic acid is obtained the salt diephedrine 6-phosphogluconate [69]. On interaction with 36% formalin in 84% HCOOH, D,L-ephedrine hydrochloride gives D,L-methylephedrine hydrochloride, which possesses an antiasthmatic action [70]. A method has been proposed for obtaining N-(β-cyanoethyl)ephedrine (XVII) which is based on the condensation of ephedrine with acrylonitrile [71].



XVII

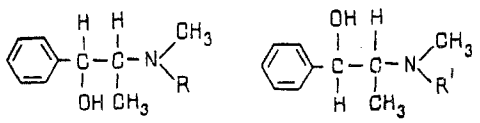
Cephedrine (XVII) is an antidepressant similar to the tricyclic antidepressant. With cephedrine, thymoleptic action is combined with a stimulating effect.

Out of a large group of ephedrine and pseudoephedrine derivatives studied, a broad spectrum of properties of effective inhibitors from a specific substrate of acetylcholinesterase to a highly effective reversible inhibitor of butyrylcholinesterase has been revealed [72]. In the pseudoephedrine derivatives a lengthening of the acyl radical led to a considerable increase in efficiency with respect to butyrylcholinesterase. The opposite relationship was observed for the ephedrine derivatives: a sharp fall in efficiency with an increase in the size of the acyl radical. In the case of acetylcholinesterase, the structure-efficiency relationships were qualitatively similar for the two series of compounds. The change in the properties of the compounds studied is apparently connected with differences in the structure of the diastereomeric analogs of ephedrine and pseudoephedrine. The substances investigated were synthesized by the interaction of N-(β-hydroxyethyl)ephedrine with carboxylic acid chlorides in the presence of triethylamine.



More detailed information on the anticholinesterase properties of the ephedrine and pseudoephedrine esters studied is contained in a monograph [72].

Ephedrine and pseudoephedrine have been condensed with acrylamide [74], and with methyl isocyanate and isothiocyanate and the previously undescribed compounds N-(N'-methylcarbamoyl)ephedrine (XVIII) (yield 98%), N-(N'-methylthiocarbamoyl)ephedrine (XIX) (yield 97%), and N-(N'-methylthiocarbamoyl)pseudoephedrine (XX) (yield 83%) have been obtained [75]:

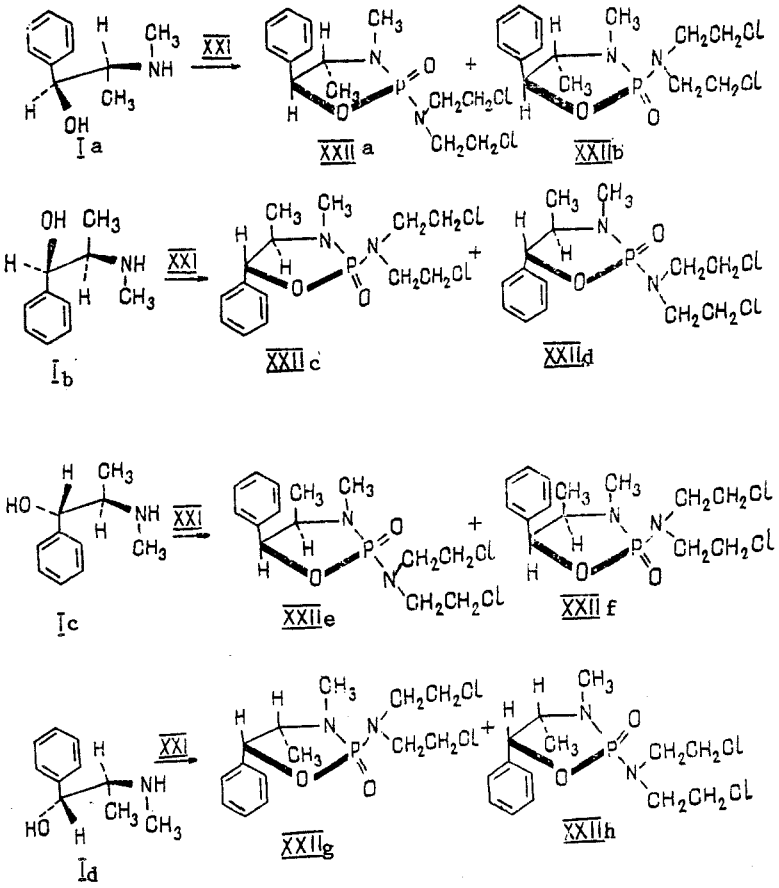


XVIII. R = CONHCH3
XIX R = CSNHCH3

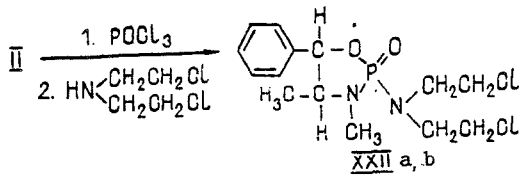
XX. R' = CSNHCH3

Structural isomerism is one of the most important factors determining the selective action of the substances, and it is widely used in the search for effective synthetic drugs.

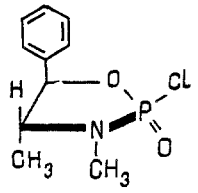
All the theoretically expected spatial isomers of the corresponding phosphoramidates of D,L-ephedrine and D,L-pseudoephedrine were obtained by the interaction with N-bis(β-chloroethyl)phosphoramidic dichloride (XXI) [76]. Here, each of the four isomers of ephedrine gave two diastereomeric compounds differing in the form of the crystals, melting point, and angles of rotation of the plane of polarization but having the same composition and the same molecular mass. The same racemates were obtained on the interaction of racemic D,L-ephedrine and D,L-pseudoephedrine with N-bis(β-chloroethyl)phosphoramidic dichloride (XXI).



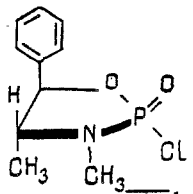
Compound (XXII) was also obtained via the intermediate formation of the 2-chlorooxazaphospholidine (XXIII) from D-pseudoephedrine and phosphorus oxychloride followed by the replacement of the chlorine by a N-bis(β-chloroethyl)amine residue [77]. In this case, only one isomer of 2-[bis(β-chloroethyl)amino]-3,4-dimethyl-2-oxo-5-phenyl-2,1,3-oxazaphospholidine (XXIIb) was obtained.



It may be assumed that the reason for the stereospecific occurrence of the reaction is steric hindrance on the interaction of a molecule of the amine with a molecule of one of the 2-chlorooxazaphospholidine isomers (XXIIIa) and (XXIIIb). These compounds (XXII) and (XXIII) are the first representatives of optically active organophosphorus compounds in which, in addition to the asymmetric phosphorus atom, there are two asymmetric carbon atoms.



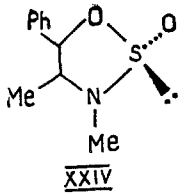
XXIIIa



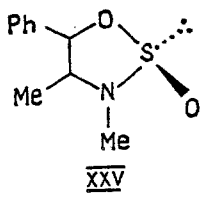
XXIIIb

Questions of the synthesis and stereochemistry of 1,3,2-oxazaphospholanes from (−)-ephedrine and (+)-pseudoephedrine are discussed in [78-82].

An asymmetric synthesis of chiral sulfoxides has been developed. The reaction of ephedrine with thionyl chloride gives a mixture of products (XXIV) and (XXV) in 60% yield [83].

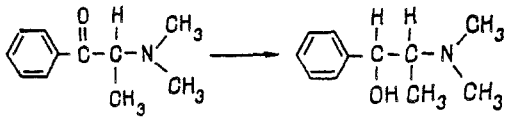


XXIV



XXV

By reducing the corresponding aminoketone (XXVI) with the optically active complex of $LiAlH_4$ and a quina alkaloid, the physiologically active erythro-N-methylephedrine (XXVII) has been synthesized [84]. The maximum yield of the erythro-aminoalcohol was achieved when ethanol was added in an amount of 0.05 mole per 1 mole of $LiAlH_4$.



XXVI XXVII

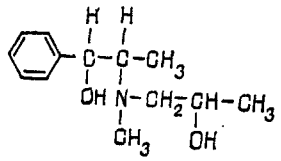
Syntheses of the oxazolidines obtained by the reaction of (−)-ephedrine with aromatic aldehydes and their absolute configurations have been considered [85, 86].

With the development of physical methods of investigation, the possibility has appeared of a deepened study of the mechanism of the transformations of ephedrine and its derivatives and of the directed performance of chemical transformations. The interrelationship of the electrochemical activity and chemical structure of ephedrine and of compounds related to it has been studied by the method of oscillographic polarography. It was established that ephedrine, methylephedrine, dexphenmetrazine, amphetamine, and phentermine in a concentration of 10^{-4} M and norephedrine in a concentration of 10^{-3} M depolarize a dropping mercury electrode, which is shown by the appearance of jags on the cathodic part of the curves between −1.3 and −1.5 V. The depolarization of the electrode is due to the absorption on the surface of the electrode, but the close depolarization potentials of the compounds studied do not permit their individual identification. Only a partial correlation is observed between the depolarizing activity and the hydrophobic properties of these compounds. The presence of a carboxy, and particularly, of a phenyl group strongly suppresses electrochemical activity. The presence of a hydroxy group in the side chain has no appreciable influence on the capacity for causing a depolarization effect [87]. The preparative electrolysis of aqueous solutions of ephedrine leads to the formation of benzaldehyde, methylamine, and formaldehyde [88].

The electronic structures of biogenic amines have been investigated by photoelectron spectroscopy. The interpretation of the results obtained is based on a comparison of the ionization potentials of ephedrine and of related aromatic compounds. Such a comparison of model compounds shows that interaction through the space between the unshared pairs and the π-electron system of the phenyl ring is negligibly small [89, 90].

It is known that many aminoalcohols obtained from alkaloids possess a direct physiological action [91]. Furthermore, a study of the conformational states for such classes permits the dependence of biological activity on structure to be investigated.

Results have been given of the PMR spectroscopy of the aminoalcohols (XXVIII) and (XXIX) obtained from ephedrine and pseudoephedrine by condensing the initial substances with propylene oxide [92].



XXVIII

The conformational states of nitrosamines of the alkaloids ephedrine and pseudoephedrine [93] and of their N-β-chloroethyl derivatives [94] have been studied with the aid of PMR spectroscopy. It has been established that the conformational states of the latter have changed only slightly in comparison with the initial bases and their predominant conformations in solutions have been suggested.

A quantum-chemical calculation of the ephedrine molecule by the SCF MO LCAO method in the MINDO/3 approximation has shown that a substantial influence on the distribution of reaction centers in them is exerted by the unshared pair of electrons of the nitrogen atom; this is localized almost completely in the highest occupied molecular orbital, which weakens the mobility of an electron at the nitrogen atom in comparison with the nearest atoms. The electronic structure of the ephedrine molecule has been established by the optimization of its geometry [95]. The dipole moments of the molecules of twenty phenylethylamine derivatives have been calculated with the aid of the methods of quantum mechanics. The results obtained permit the influence of various structural elements on the basic and hydrophobic properties of the molecules to be evaluated.

Thus, a considerable amount of a material has accumulated on the biological activity, methods of identification, structural investigation, and the transformations of ephedrine and its derivatives. Analysis of literature information shows the high promise of investigations in the field of the synthesis of new highly effective pharmacologically active ephedrine derivatives.

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