SYNTHESIS AND CHEMICAL PROPERTIES OF 1,2-DIHYDROPYRROLIZINES (REVIEW)

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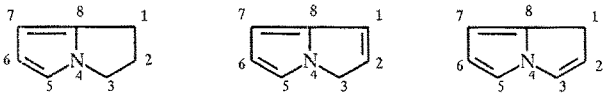
Known methods for the synthesis of 1,2-dihydropyrrolizines are presented in a systematized form. Literature data on the chemical properties of 1,2-dihydropyrrolizines are summarized and correlated; and synthetic, physiologically active substances belonging to this group of compounds are examined critically.

1,2-dihydropyrrolizines are bicyclic compounds consisting of two condensed five-membered rings with a common nitrogen atom; the rings formally contain two double bonds. The simplest dihydropyrrolizine (I) can be represented as a derivative of either 3H-pyrrolizine (II) or 1H-pyrrolizine (III).

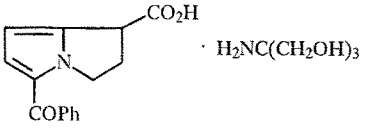


I II III

In the interest of brevity, we will regard the dihydropyrrolizines as derivatives of compound II, i.e., as 1,2-dihydropyrrolizines, omitting the designation "3H."

Derivatives of 1,2-dihydropyrrolizine became known in 1931 through studies of their synthesis [1]. Fifteen years later, an article appeared on the isolation of compounds of the dihydropyrrolizine series from a natural source [2]. The synthesis and properties of pyrrolizines were reflected in a review by Flitsch and Jones [3]. Unfortunately, their review left large gaps in the coverage of literature on the synthesis and properties of dihydropyrrolizines. In recent decades, dihydropyrrolizines formed from pyrrolizidine alkaloids in the human and animal organism have been the subject of intense study; and the data accumulated up to 1985 have been reviewed in [4].

The practical aspect of dihydropyrrolizine chemistry has been clearly recognized in recent years. Synthetic dihydropyrrolizines that are of interest as pharmaceuticals have been reported. The most important of these — ketorolac (IV), a nonsteroid analgesic — was the subject of a recent review [5].

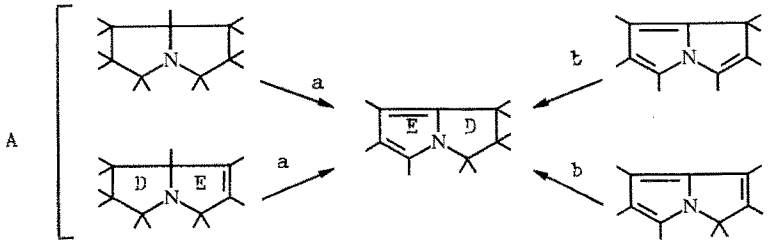


IV

The lack of any comprehensive analysis of the literature on dihydropyrrolizines has led us to systematize the very extensive, scattered data on the synthesis and chemical properties of these substances.

I. METHODS OF SYNTHESIS OF DIHYDROPYRROLIZINES

The strategy of most of the methods known for the synthesis of dihydropyrrolizines is expressed in three general approaches (A, B, C):



Institute of Biochemistry and Physiology of Plants and Microorganisms, Russian Academy of Sciences, Saratov. N. G. Chernyshevskii Saratov State University, Saratov. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 147-168, February, 1992. Original article submitted June 3, 1991.

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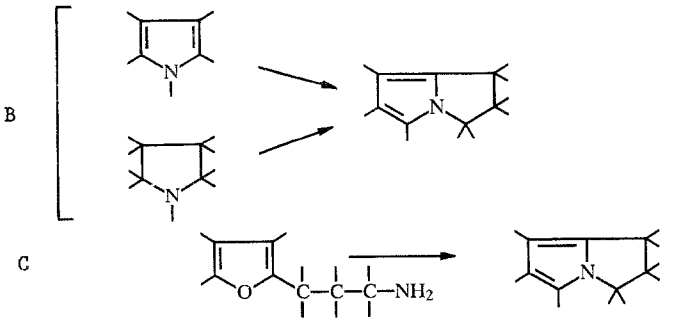


Formally, the simplest path to 1,2-dihydropyrrolizines is based on the use of the finished skeleton of the bicylic compound that exists in pyrrolizidines and dehydropyrrolizidines on the one hand, and in pyrrolizines on the other hand (type A methods). The conversions come down to dehydrogenation and oxidation (a) or to addition reactions at a multiple bond (b); the most extensive addition reaction is catalytic hydrogenation.

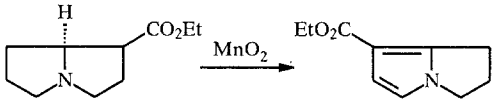
Type B methods are based on the use of compounds with pyrrole or pyrrolidine rings. The second five-membered ring is built into the compound as a result of intramolecular substitution and addition reactions, and also intermolecular cycloaddition reactions.

In type C syntheses, the key compounds are furans containing an aminoalkyl chain with the amino group in position 3 relative to the ring. They are converted to dihydropyrrolizines either through the intramolecular scheme of the Yur'ev reaction or through hydrolytic cleavage of the furan ring and a subsequent intramolecular reaction with participation of the amino group.

There are also other, less extensively used methods that do not fall into the general categories A, B, and C.

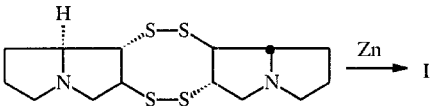
1. Change in Degree of Unsaturation of Compounds Having the Pyrrolizine Skeleton (Type A Methods)

1.1. Dehydrogenation and Oxidation of Pyrrolizidines and Dehydropyrrolizidines. Only a few instances of the conversion of pyrrolizidines to 1,2-dihydropyrrolizidines have been reported. For example, the ethyl ester of pyrrolizidine-1-carboxylic acid (V) is oxidized by manganese dioxide to the corresponding compound VI [6].



V VI (50%)

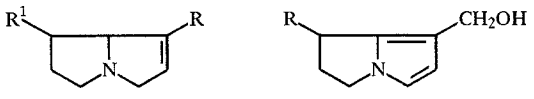
The saturated pyrrolizidine alkaloid cassipurine (VII), when distilled over zinc dust in a flow of hydrogen, is desulfurized, yielding 1,2-dihydropyrrolizine (I) [7].



VII

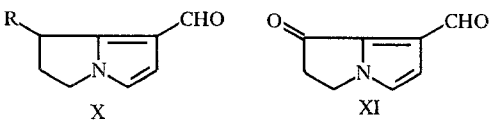
Microsomal enzymes of rat liver are capable of converting the saturated pyrrolizidine structure of alkaloids to the 1,2-dihydropyrrolizine structure [8, 9].

Much more extensive use is made of the conversion of dehydropyrrolizidines. Of the substances that have been studied, the simplest are the compounds VIII, containing either a 1-CH_2OH or 7-OH group, or both of these groups. They are readily oxidized by manganese dioxide [10-13], potassium permanganate [11], chloranil [11, 14, 15], or potassium nitrosodisulfonate [16] to the 1,2-dihydropyrrolizines IX-XI.



VIII
R=H, CH_2OH; R^1=H, OH

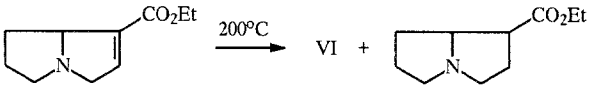
IX
R=H, OH



X XI

R=H, OH

Disproportionation of the dehydropyrrolizine derivative XII leads to the formation of compounds VI and XIII as the main reaction products [6]



XII VI XIII

A promising method is the conversion of dehydropyrrolizidines to dihydropyrrolizines by their direct oxidation to N-oxides with subsequent splitting out of water under the influence of carboxylic acid anhydrides [11, 17], iron(II) salts [17, 18], or o-chloranil [19], or by heating [17]. Extensive, careful studies have been made of the transformation of unsaturated pyrrolizidine alkaloids or their N-oxides to derivatives of 1,2-dihydropyrrolizines [10-14, 16-18, 20-24].

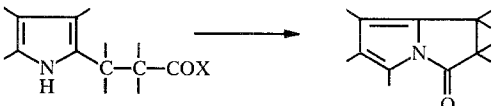
Unsaturated pyrrolizidine alkaloids, in the human or animal organism, and also in cultures of liver or lung tissue, are subject to enzymatic oxidation to the corresponding dihydropyrrolizidine derivatives [8, 9, 16, 20, 21, 25-34].

A subject that has been less studied is the synthesis of dihydropyrrolizidine pheromones in the organism of certain species of butterflies [35-40].

1.2. Hydrogenation of Pyrrolizines and Other Addition Reactions. A multiple bond of pyrrolizines that is localized in either the 1,2- or 2,3-position is very readily saturated under mild conditions by hydrogen with typical hydrogenation catalysts such as PtO_2 [41-43], Rh [6, 44-48], or Pd/C [49-52]. Another reaction that has been described is the electrochemical reduction of 1-amino-3H-pyrrolizine [53]. Compounds that have been brought into reaction include 3H-pyrrolizine [42, 44, 45], its homologs [45, 46, 52], homologs of 1H-pyrrolizine [46, 52], compounds with a carbonyl group [41, 49, 51, 54] or their derivatives [50], and esters of 3H-pyrrolizinecarboxylic acids [43, 47].

2. Syntheses Based on Compounds of the Pyrrole and Pyrrolidine Series (Type B Methods)

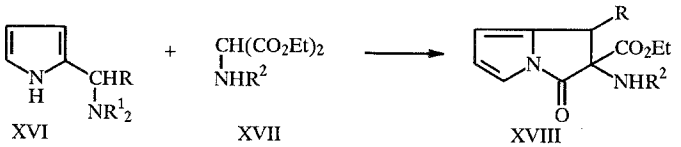
2.1. Intramolecular Acylation of Pyrroles and Cyclization of 2-(1-Pyrrolyl)propionitrile and Its Homologs. Cyclization of 2-(2-pyrrolyl)propionic acids and their derivatives XIV under the influence of acetic anhydride or polyphosphoric acid serves as a convenient method for obtaining 1,2-dihydropyrrolizin-3-ones XV.



XIV XV

In synthesizing compounds of the type of XV, the starting substances have included acids [49, 55, 56], anhydrides [49], and esters [57, 58].

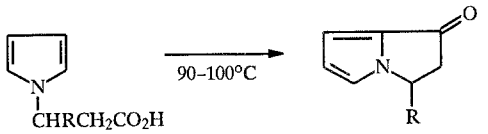
A related group of syntheses consists of conversions of pyrrole Mannich bases XVI, under the action of compounds XVII, into 2,2-disubstituted pyrrolizin-3-ones XVIII [57, 59-62].



XVI XVII XVIII

R=H, Me; R^1=Me, Et; R^2=CHO, Ac, COPh, $COCH_2Ph$

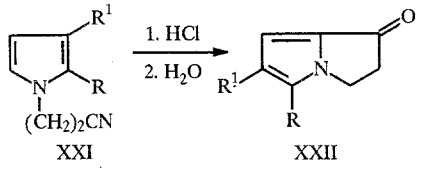
2-(1-Pyrrolyl)propionic acids XIX (R = Me, CH_2CO_2H) in the presence of polyphosphoric acid [63, 64] or phosphorus pentoxide [65] are converted to 1,2-dihydropyrrolizin-1-ones XX.



XIX XX

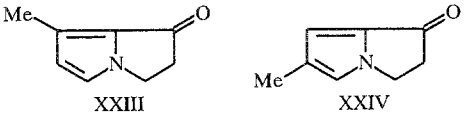
R=Me, CH_2CO_2H, CO_2Me

Intramolecular conversion of 2-(1-pyrrolyl)propionitriles XXI in accordance with the Houben—Hoesch synthesis scheme leads to compounds XXII with yields of 33-80% [1, 42, 63, 66-72].



XXI XXII

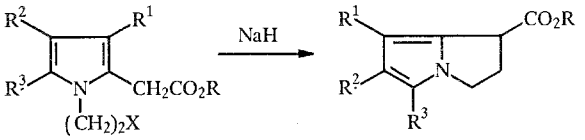
R=Me; R^1=H, Me



XXIII XXIV

In compound XXI, if R = H and R^1 = Me, a mixture of isomers is obtained.

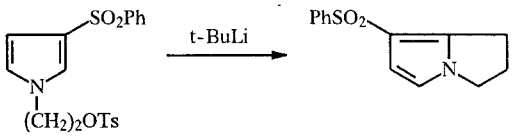
2.2. Intramolecular Alkylation and Arylation in Series of 1-Substituted Pyrroles. In a comparatively recent series of publications, it has been proposed that intramolecular alkylation in a series of 1-(2-X-ethyl-2-carbalkoxymethylpyrroles XXV should be used in the synthesis of derivatives of 1,2-dihydropyrrolizine-1-carboxylic acids XXVI with high yields [73-78].



XXV XXVI

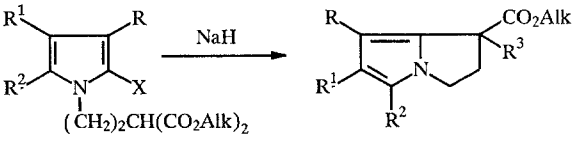
R=Me, Et; R^1=H, CO_2Me; R^2=H, Me, Et, $MeO(CH_2)_n$, (n=1-3), $PhCH_2$, Cl, Br; R^3=H, Me, Ph; X=I, OSO_2Me

Intramolecular alkylation in compound XXVII at the 2-position of the ring gives a 95% yield of the sulfone XXVIII [79].



XXVII XXVIII

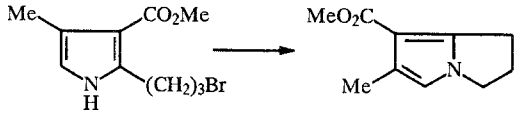
Similar to the reactions just described are the conversions of 1,2-disubstituted pyrroles XXIX into compounds XXX [80-85]



XXIX XXX

R = H, Cl, Br, Ts; R^1 = H, Alk, Cl, Br; R^2 = H, $COC_6H_4R^4$ (R^4 = H, Alk, F, Cl, Br), CO—R^5 (R^5 = 2-furyl, substituted 2-furyl, 3-furyl, 2-thienyl, substituted 2-thienyl, 3-thienyl, 2-pyrrolyl, 1-allyl-2-pyrrolyl); R^3 = H, CO_2Alk; X = Cl, Br, SO_2Me

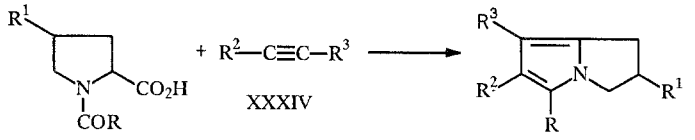
Compound XXXI in the presence of solid KOH and tris(dioxa-3,6-heptyl)amine is converted with good yield to the substituted 1,2-dihydropyrrolizine XXXII [86].



XXXI XXXII

2.3. Interaction of Proline and Its Derivatives with Acetylenic Compounds Containing an Activated Triple Bond. Treatment of proline with the methyl ester of acetylenedicarboxylic acid in acetic anhydride at 130°C gives 5-methyl-6,7-dicarbomethoxy-1,2-dihydropyrrolizine with a 76% yield [87]. A necessary condition for the synthesis of 1,2-dihydropyrrolizines starting with proline is N-acylation of the proline.

The reaction is general in character. As the pyrrolidine component XXXIII, proline and its derivatives have been used [87-106]. Substances used as the acetylenic component (XXXIV) of the process have included the dimethyl ester of acetylenedicarboxylic acid [87, 89-97, 100, 101, 105], the ethyl ester of propiolic acid [88, 98, 99, 107], and propargylaldehyde [103]. Substituted 1,2-dihydropyrrolizines XXXV were formed with good yields.



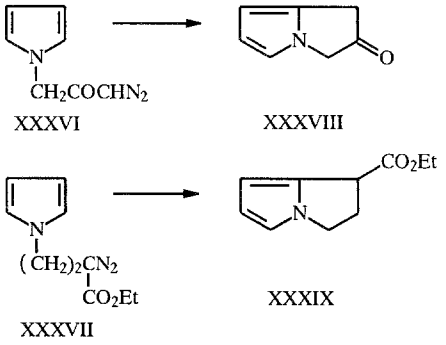
XXXIII XXXIV XXXV

R = H, Me, $(CH_2)_3CO_2Me$, $CH_2CH(Me)CH_2CO_2Me$, 3,4-di-ClC_6H_3, di-F-C_6H_3-, 2-furyl, 2- and 3-thienyl; R^1 = H, OH, O-acyl; R^2 = H, CO_2Me; R^3 = CO_2Me, CO_2Et, CHO

When the acetylenic component XXXIV is asymmetric (R^2 = H, R^3 = CO_2Et), the cycloaddition proceeds selectively, leading mainly to the isomer XXXV (R = R^2 = H, R^1 = H, CO_2H, R^3 = CO_2Et) with yields up to 90% [88, 98, 107].

The interaction of N-formylproline or proline in acetic anhydride with 2-chloroacrylonitrile gives the corresponding 7-cyano- and 5-methyl-7-cyano-1,2-dihydropyrrolizines [108].

2.4. Other Reactions Using Pyrrole and Pyrrolidine Compounds as the Starting Substances. Intramolecular carbenoid reactions of the pyrrole diazo compounds XXXVI and XXXVII are catalyzed by copper, copper ions, boron trifluoride, or copper(II) tetrafluoroborate, yielding compounds XXXVIII and XXXIX [109, 110].

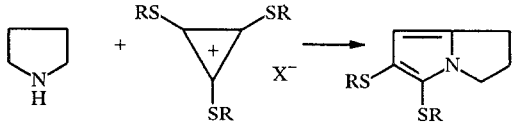


XXXVI XXXVIII

XXXVII XXXIX

The Dieckmann reaction with ethers of dicarboxylic acids proceeds smoothly, giving good yields of β-ketoacids of the dihydropyrrolizine series [111, 112].

From the products of pyrrolidine interaction with the cyclopropenium salt XL, the dihydropyrrolizine disulfide XLI is recovered with yields up to 59% [113-116].

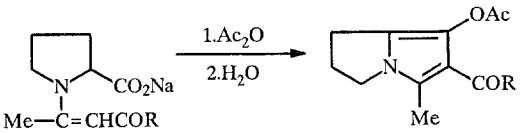


XL XLI

R = *t*-Bu

Alkyl- and phenyl-substituted 1,2-dihydropyrrolizines are formed with 17-47% yields by the interaction of Δ^1-pyrrolines with α-haloketones [117].

The enamines XLII are cyclized by the action of acetic anhydride, forming the substituted 1,2-dihydropyrrolizines XLIII [118].

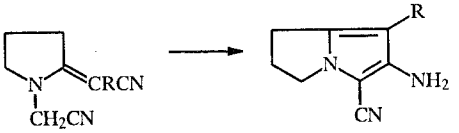


XLII XLIII (32...62%)

R=Me, OMe, OEt

A new method for the synthesis of compounds XLV was described recently, based on intramolecular Thorpe—Ziegler cyclization of the enaminonitriles XLIV under the action of BuONa or the diethylacetal of DMFA [119, 120].

If proline is introduced into the Maillard reaction, various acyl-1,2-dihydropyrrolizines may be formed, depending on the particular hydroxyaldehydes or (more specifically) carbohydrates that are used [121-127].



XLIV XLV (44...94%)

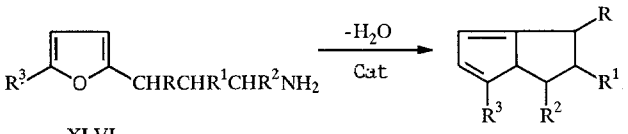
R=CO_2Et, $CONH_2$, CN

Vacuum pyrolysis of derivatives of Meldrum's acid and subsequent acylation of the conversion products leads to 5-R-6-acetoxy-1,2-dihydropyrrolizines (R = H, Me, Ph) [128] with 36-51% yields.

Reactions of formation of 1,2-dihydropyrrolizines from azafulvenes are described in [129-131].

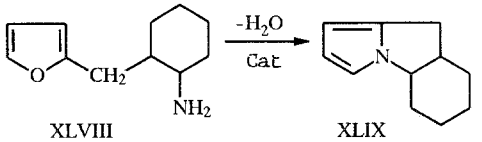
3. Intramolecular Conversions of Furan and Tetrahydrofuran Amines with Amino Group in Position 3 from Ring (Type C Methods)

In this group of methods for the synthesis of 1,2-dihydropyrrolizines, a particularly important reaction is the intramolecular catalytic gas-phase dehydration of furan amines with the amino group in position 3 from the ring. It is an intramolecular variant of the Yur'ev reaction [132-134] that was first described in 1947 [135]. The starting substance may be any one of a broad group of furan-series amines (XLVI, XLVIII) [67, 136-147].



XLVI XLVII

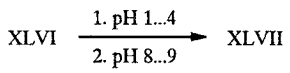
R=H, Me, Et, *i*-Pr; R^1=H, Me, Et; R^2=H, Me, *i*-Pr, *i*-Bu, *t*-Bu, Ph; R^3=H, Me



XLVIII XLIX

Materials employed as the catalyst (Cat) are γ-Al_2O_3 [67, 135, 138, 139, 141, 147], Al_2O_3 promoted with 5% ThO_2 [136, 137, 143], and a mixed catalyst consisting of 80% γ=Al_2O_3 and 20% ZrO_2 [142, 145, 146]. The most convenient catalyst from the preparative standpoint is evidently γ-Al_2O_3, with the reaction performed at 330-380°C. The yields of 1,2-dihydropyrrolizines XLVII and XLIX vary from 40 to 65%.

A liquid-phase version of the intramolecular conversion of furan amines to 1,2-dihydropyrrolizines has been accomplished under mild conditions [148].



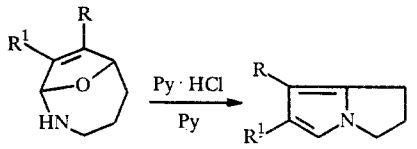
R=H; R^1=H, Me; R^2=H, Me; R^3=H, Me

This method, in the synthesis of compounds XLVII with a methyl group in position 5 (yields 35-40%), is preferable to the gas-phase synthesis, since it is simpler to carry out and gives the same yields, while the compounds that are obtained have higher purities.

1,2-Dihydropyrrolizines can be prepared in good yields from 2,5-dimethoxytetrahydrofuran amines by heating in propionic acid [149].

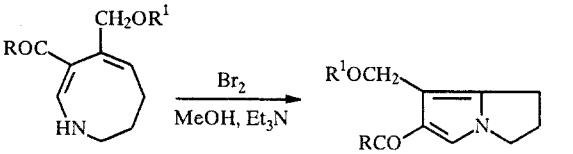
4. Other Reactions in Which the Starting Substances Are Not Pyrroles or Pyrrolidines

1,2-Dihydropyrrolizines that are functionalized in positions 6 and 7 (LI, LIII) are formed in the course of a transannular reaction of the corresponding hydroazocines (L, LII) [150, 151].



L LI

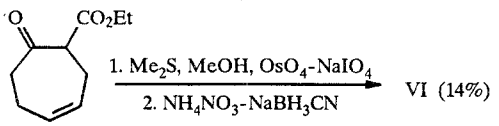
R = CO_2Me, CH_2OTHP; R^1 = CO_2Me, $COCH_2$(Me)CO_2-Bu-*t*; THP(tetrahydropyramyl); Py(pyridine)



LII LIII (37%)

R=CH_2CH(Me)CO_2Bu-t; R^1=THP

Two-stage conversion of compound LIV gives the ester VI [152].



LIV

II. CHEMICAL PROPERTIES

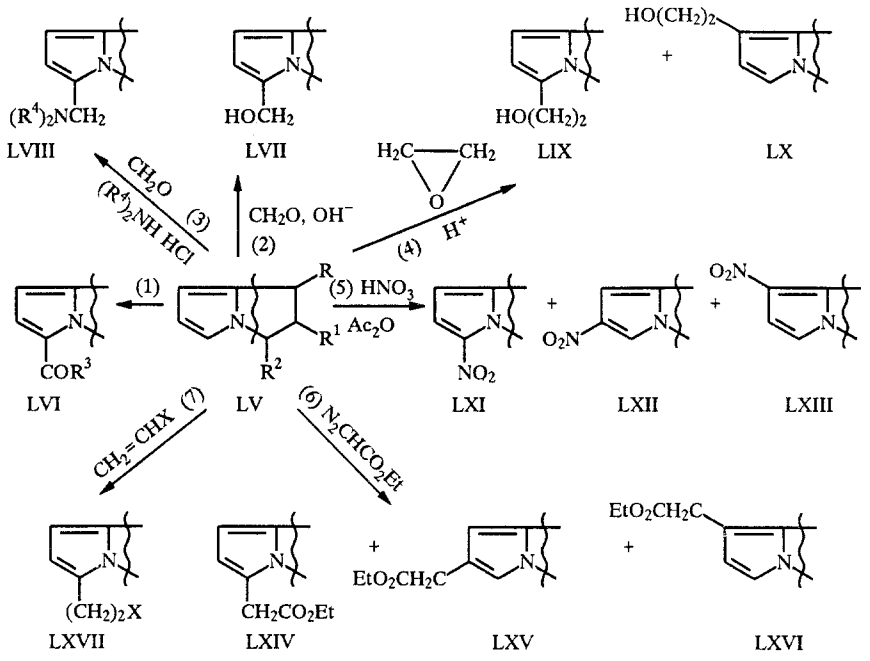
1,2-Dihydropyrrolizine (I), alternatively named as 1,2-trimethylenepyrrole, is the cyclic analog of 1,2-dialkylpyrroles. Therefore, we can obviously apply to compound I, its homologs, and derivatives with various functional groups the entire arsenal of chemical conversions that has been created in studying the simplest pyrroles [153, 154].

1. Substitution Reactions

In the scheme below we show various reactions of substitution (1, 3, 5) and substitutive addition (2, 4, 6, 7) that have been investigated for the dihydropyrrolizines LV with free positions on the pyrrole part of the double-ring system.

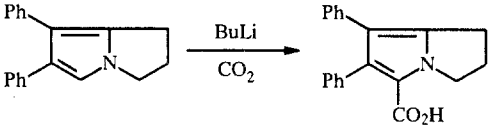
Acylation reactions (1) [6, 47, 73, 77, 143, 144, 155-157], oxymethylation reactions (2) [142-144, 158], Mannich reactions (3) [143, 159, 160], and substitutive addition of compounds with an activated multiple bond (7) [141, 161-165] in the case of the dihydropyrroplizines LV proceed in the same manner as the corresponding reactions of monocyclic pyrroles. Compounds LVI, LVII, LVIII, and LXVII with substituents in position 5 have been obtained with good yields. Acylation reaction, in particular the formylation of 1,2-dihydropyrrolizines having a methyl, phenyl, or substituted phenyl group in position 6, have been described

Scheme for substitution and substitutive addition reactions



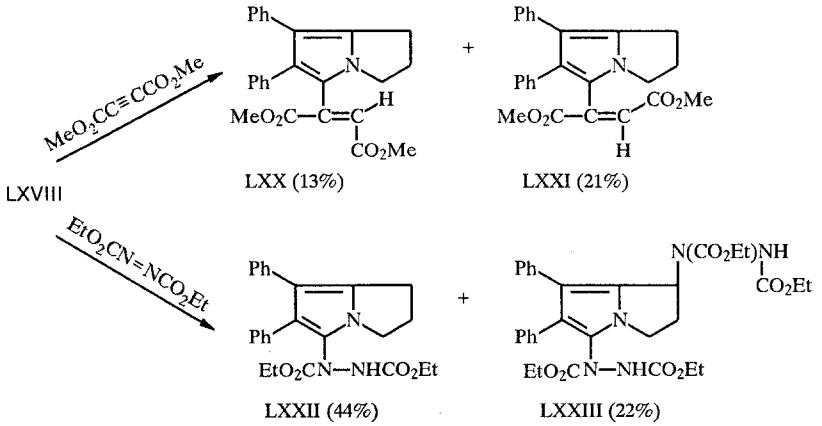
R, R^1, R^2 = H, Alk, CO_2H, CO_2Alk; R^3 = H, Alk, substituted Alk, Ar, substituted Ar; R^4 = Me, R^4 — R^4 = $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_2O(CH_2)_2$; X = CO_2H, CO_2Me, $CONH_2$, CN

in [117, 166]. With free positions 5 and 7, the formyl group enters only into position 5. If position 5 is occupied, the 7-formyl derivatives are formed. The formylation of 6,7-dicarbomethoxy-1,2-dihydropyrrolizine at a free position 5 was reported in [92]. Starting with compound LXVIII, the carboxylic acid LXIX has been synthesized [117].



LXVIII LXIX

This same compound (LXVIII) enters into a reaction of substitutive addition with the dimethyl ester of acetylenedicarboxylic acid or azadicarboxylic ester [167].



LXX (13%) LXXI (21%)

LXXII (44%) LXXIII (22%)

In the first case, the isomeric adducts LXX and LXXI are formed with low yields, in the second case the adducts LXXII and LXXIII, the latter corresponding to addition at positions 5 and 1 [167].

The reaction of direct oxyethylation (reaction 4) of dihydropyrrolizines [168, 169] did not have any analogy in the pyrrole series. The interaction proceeds in the presence of proton-donor substances at 190-200°C. Yields of 33-65% have been reported for a mixture of 5- (LIX) and 7-(2-hydroxyethyl)-1,2-dihydropyrrolizines (LX) [168]. The positional selectivity of the oxyethylation reaction depends on the presence of a substituent in position 3, probably as a consequence of its steric influence on substitution in position 5.

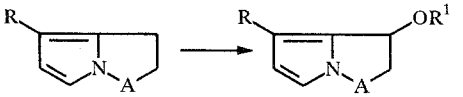
Nitration of 1,2-dihydropyrrolizines (reaction 5) gives the isomeric 5- (LXI), 6- (LXII), and 7-nitro-1,2-dihydropyrrolizines (LXIII) [170]. The positional selectivity in the nitration of 1,2-dihydropyrrolizine and its homologs with alkyl groups in positions 1 and 2 is analogous to what has been observed in the nitration of 1,2-dimethylpyrrole [171]. The introduction of an alkyl substituent into position 3 reduces the relative amount of isomers of the type of LXI [170].

In contrast to the reaction of pyrrole or N-methylpyrrole with the ethyl ester of diazoacetic acid, dihydropyrrolizines with this same reagent (reaction 6) give three isomeric reaction products (LXIV-LXVI). The same as in nitration, the ratio of isomers that are formed is influenced by a methyl group in position 3 [172, 173].

In 5,6-, 5,7-, and 6,7-diphenyl-substituted 1,2-dihydropyrrolizines, reactions with diazoacetic ester, carboxylation, and substitutive addition of methacrylate proceed at the free pyrrole position [174, 175].

Among reactions (4-6), nitration exhibits the lowest positional selectivity.

Almost no development work has been performed on the problem of functionalizing the "saturated" half of the bicyclic system. Interesting results in this direction were obtained in [176]. With the action of lead tetraacetate or tert-butyl perbenzoate on compound LXXIV, the derivatives LXXV were obtained (yields up to 44%) with a functional group in position 1 [176].

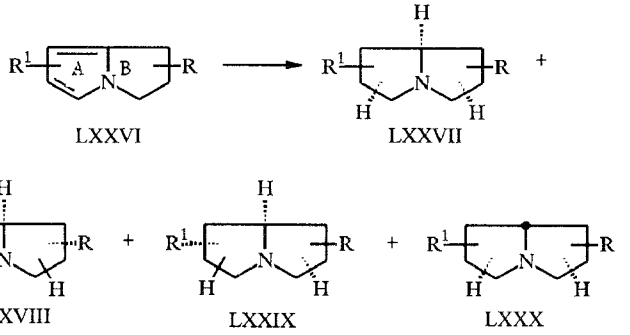


LXXIV LXXV

A=CO, CH_2; R=H, CO_2Me, CH_2OCH_2Ph; R^1=Ac, COPh

2. Reactions of Catalytic Addition of Hydrogen

The reaction of hydrogen addition to 1,2-dihydropyrrolizines, which is usually accomplished by catalysis, is one of the most important conversions of these compounds. By means of catalytic hydrogenation, the dihydropyrrolizines LXXVI can be converted to the pyrrolizidine-series compounds LXXVII-LXXX.



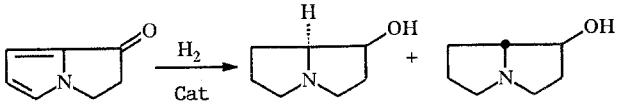
LXXVI LXXVII LXXVIII LXXIX LXXX

R=H, Alk, OH, CH_2OH; R^1=H, Alk, CH_2OH, $(CH_2)_2OH$, $(CH_2)_3OH$, CO_2Me, CO_2Et

Studies have been made of the hydrogenation of dihydropyrrolizine [7, 42, 44, 45, 140, 177] and its homologs [45, 139, 140, 146, 147, 177-183]. The conversion from dihydropyrrolizines to pyrrolizidines has been accomplished with a hydroxyl group in position 1 or 2 [70, 184], a hydroxymethyl group in position 1 or 5 [80, 185, 186], a β-hydroxyethyl group in position 5 or 7 [187], a 5-(3-hydroxypropyl) group in position 2, 5, 6, or 7 [188], or a carbalkoxyl group in position 2, 5, 6 or 7 [6, 43, 48, 88, 102, 104, 152], and also with two groups, for example 2- or 3-methyl and 5-hydroxymethyl [185, 186], or 3-methyl and 5-(3-hydroxypropyl) [188].

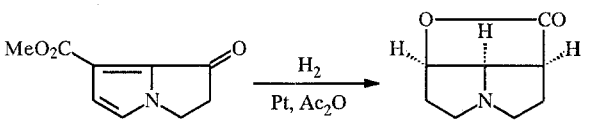
In all cases of hydrogenation under mild conditions, such that the secondary process of catalytic isomerization is eliminated, the principal products are pyrrolizidines with the *cis* configuration, of the type of LXXVII. In the hydrogenation of compounds containing substituents in ring A, higher stereoselectivity is observed than in the hydrogenation of compounds with substituents in ring B.

Hydrogenation of compound LXXXI under mild conditions apparently leads inevitably to both isomers LXXXII and LXXXIII [70, 184, 189, 190], of which the first is predominant [70, 190]. The assignment of the configuration of LXXXIII to the single isomer that was isolated in [184] is erroneous.



LXXXI LXXXII LXXXIII

The hydrogenation of compound LXXXIV proceeds stereoselectively; the lactone LXXXV is formed with a 40% yield [191].

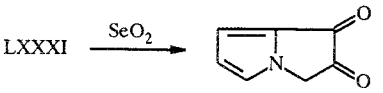


LXXXIV LXXXV

Among the hydrogenation catalysts investigated (Rh/Al_2O_3, Rh/C, Pt, Pd/C, Ni, Ru, Ni, promoted Ru) the 5% Rh/Al_2O_3 and Ru are apparently the best.

3. Reactions with the Participation of Functional Groups of Substituted 1,2-Dihydropyrrolizines

Detailed studies have been made of the conversions of dihydropyrrolizines with a carbonyl group in position 1, and also derivatives of these compounds [41, 42, 67, 68, 72, 111, 184, 192-196]. A methylene group adjacent to the carbonyl manifests its usual reactivity [68, 184, 197]. In compound LXXXI, it can be readily oxidized by selenium dioxide to a carbonyl group, and this leads to the formation of the α-diketone LXXXVI [192].



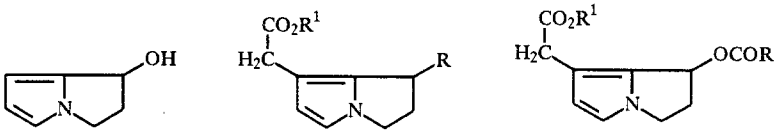
LXXXVI

Synthesis of derivatives of compound LXXXVI has been reported in [192, 193], and their properties have been described, in particular the electrochemical reduction of the dioxime of 1,2-dihydropyrrolizine-1,2-dione [53].

Reactions through a formyl group in position 5, 6, or 7 have been examined in [117, 143, 144, 161, 166, 198], [175], and [13], respectively.

Studies have been made of conversions involving carboxyl groups of their derivatives on the pyrrole ring [6, 74, 77, 92, 94, 95, 199], on the "saturated" half of the bicyclic system [47, 74, 200, 201], or in the composition of complex substituents [157, 162, 202]. The desulfurization of a disulfide of the dihydropyrrolizine series with Raney nickel catalyst proceeds in the usual manner [115, 203].

Reactions of alcohols have become the object of thorough study; here we refer to 1-hydroxy- (LXXXVII), 7-hydroxymethyl- (IX, R = H), and 1-hydroxy-7-hydroxymethyl-1,2-dihydropyrrolizines (IX, R = OH), and their esters with open and cyclic structures LXXXVIII and LXXXIX.



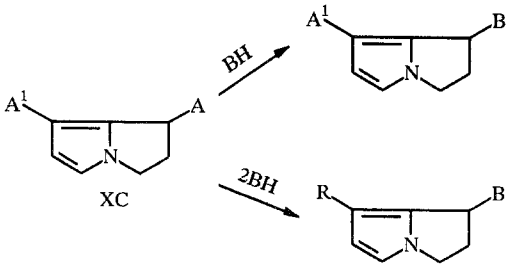
LXXXVII LXXXVIII LXXXIX

R = H, OH, O-acyl; R^1 = Alk, substituted Alk

R, R^1 = Alk, substituted Alk, or parts of a single macrocyclic system

These compounds manifest enhanced reactivities, and hence are unstable in storage [19, 22, 70, 184]. They change when stored in air [184], break down when water is present [17, 19, 22], and are extremely sensitive to acids, which cause oligomerization [99] and probably polymerization of the original substances [11, 16, 17, 19, 22, 204]. The 5-hydroxymethyl-1,2-dihydropyrrolizines behave analogously [142, 158].

A common property of compounds LXXXVII, IX, LXXXVIII, and LXXXIX is their capability for alkylating* in reactions with nucleophilic compounds B-H, as illustrated by the following general scheme:



A = H, OH, OOCAlk; A^1 = H, CH_2OH, $CH_2COOAlk$; R = H, CH_2-B, B = AlkO, AlkNH, Alk_2N

A hydroxyl group on a secondary carbon atom is more active than on a primary carbon atom; and for compound XC (A = OH, $A^1 = CH_2OH$), the reaction often proceeds only at the $C_{(1)}$ atom, i.e., the $C_{(7)}$ atom in the alkaloid numbering system, with preservation of the hydroxymethyl group [11, 20, 205-208]. The esters have a greater alkylating power than the alcohols [11, 17, 20, 22, 26, 209].

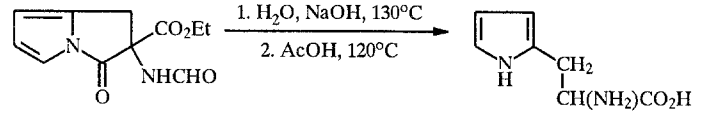
Detailed kinetic studies have been made of the alkylation of compounds XC [17, 99, 207]. It has been found that hydrolysis of the alkylating agent competes with the alkylation reaction [17, 207, 209]. The alkylation rate increases with increasing acidity of the medium [11, 210]. The reaction at the $C_{(1)}$ carbon atom proceeds through a S_N1 mechanism [17, 205, 206].

These compounds readily alkylate alcohols [11, 20, 22] and primary, secondary, and tertiary amines [22, 211]. Alkylation at the sulfhydryl group has been studied in the case of cisteine, glutathione [208], and a number of biologically important compounds [204-206, 208-210, 212-215].

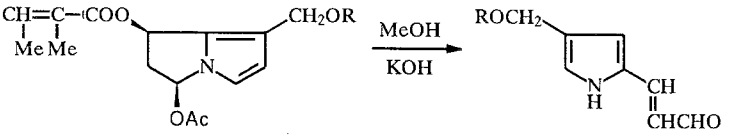
4. Other Reactions

Apart from catalytic hydrogenation, other reactions have been reported for the conversion of dihydropyrrolizines to other classes of compounds.

1,2-Dihydropyrrolizines with an oxygen function at the $C_{(3)}$ carbon atom, for example compounds XCI and XCIII, are susceptible to cleavage of the "saturated" ring to form the substituted pyrroles XCII [62] and XCIV [216].



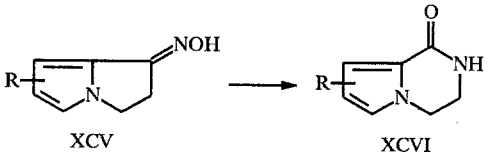
XCI XCII (18%)



XCIII XCIV

R = unsaturated acyl group

Oximes of the dihydropyrrolizine series XCV, when heated with polyphosphoric acid, undergo the Beckmann rearrangement to the pyrrolopyrazines XCVI [217, 218].

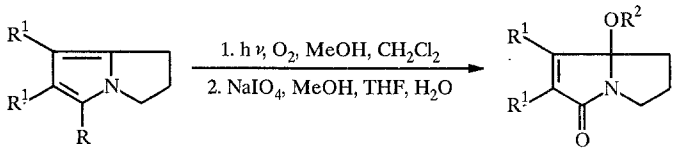


XCV XCVI

R=H, NO_2

*The term is generally accepted in the chemistry of dihydropyrrolizines and pyrrolizidine alkaloids, but it is not entirely accurate.

Oxidation of compound I or 6,7-diphenyl-1,2-dihydropyrrolizines (XCVII) by singlet oxygen in the presence of methanol [219, 220], or oxidation of compound XCVII by sodium periodate in the presence of methanol and water [221], is accompanied by simultaneous addition of the elements of methanol or water and the formation of the unsaturated ketones XCVIII.

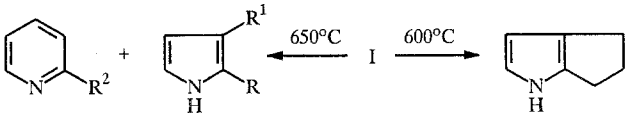


XCVII XCVIII

R=H, CH_2OH; R^1=H, Ph; R^2=H, Me

Examples have been reported of the use of functional groups present in the pyrrole part of the bicyclic system to close a new ring and obtain derivatives of pyrimido[4,5-f]pyrrolizines [222] and benzopyrrolizines that are related to Mitomycin A [223].

Pyrolysis of 1,2-dihydropyrrolizine (I) gives a mixture of breakdown products, among which the rearranged compound XCIX, 2- and 3-methylpyrrole, and pyridine bases have been detected [67, 138].

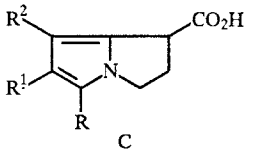


XCIX (9%)

R=H, Me; R^1=H, Me; R^2=H, Et, CH=CH_2

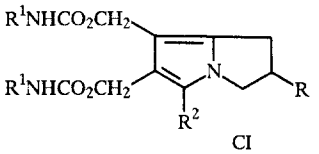
III. SYNTHETIC, PHYSIOLOGICALLY ACTIVE COMPOUNDS AND PHARMACEUTICALS

Depending on their structure, derivatives of 1,2-dihydropyrrolizine may manifest various types of physiological activity. Among the substances that have been studied for biological effects, we can distinguish two major groups of compounds: group C (ketorolac and its analogs and their derivatives through the carboxyl groups), and group CI (see structural formulas below). Compounds of the first group have shown merit as analgesics [47, 75, 76, 82, 83, 224-231], antiinflammatory agents [47, 73, 76, 82, 83, 200, 225-237], myorelaxants [76, 82, 83], inhibitors of thrombocyte aggregation [82, 231], fibrinolytics [82], temperature-lowering substances [76, 83, 226], and drugs for the treatment of glaucoma and conjunctivitis [238].



C

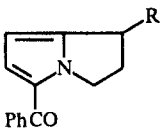
R_1 = substituted phenyl, ArCO; R^1 = H, Me, Cl, Br, substituted phenyl; R^2 = H, Cl, Br, CO_2Me



CI

R = H, OH, Me_2NHCOO; HO_2CCH_2COO; R^1 = Me, Et, i-Pr, C_6H_{11}; R^2 = F- or Cl-substituted phenyl, 2-furyl, and 2- or 3-thienyl, 2-$R^3C_5H_3N^+MeI^-$ (R^2 = F, Cl)

The group selected as Ar in these compounds may be Ph [47, 82, 200, 224, 233, 234, 236], substituted phenyl [47, 73, 75, 82, 83], furyl or thienyl [82, 226], substituted thienyl [82], pyrrolyl [236], substituted pyrrolyl [76, 82, 225, 229], or 1,2-dihydropyrrolizin-5-yl and substituted 1,2-dihydropyrrolizin-5-yl [230]. Derivatives of C acids — esters [225] and thioesters [200, 234] — probably owe their antiinflammatory action to conversion to the free acids as a result of hydrolysis in the organism [200]. Antiinflammatory properties have also been manifested by compounds that are similar in structure, in which there is a propenyl or acetonitrile group in position ' of the bicyclic system — compound CII [235].



CII

R = CH_2-CH = CH_2, CH_2COMe

Compounds of the second group CI are of interest as representatives of a new class of anticancer substances [93, 100, 105, 106, 239-244]. They have carbamate functions and are alkylating agents; this is evidently responsible for their activity. The simplest derivatives of dihydropyrrolizines IX and X have antiviral and antineoplastic activity and also the ability to suppress immunity [14].

On the basis of 1-carboxy-6-acyl-1,2-dihydropyrrolizines, substances have been patented for the treatment of microvascular complications associated with diabetes [245]. Other derivatives of dihydropyrrolizines have been proposed as cardiovascular preparations [246], inhibitors of thrombocyte aggregation [197, 247], antiinflammatory agents [167, 247-249], and analgesics [69, 247, 249].

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*As in Russian original; text indicates that the date may be 1946 — Translator.

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