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5,6-DIHYDROPYRIDIN-2(1H)-ONES AND 5,6-DIHYDROPYRIDINE-2(1H)-THIONES (REVIEW)

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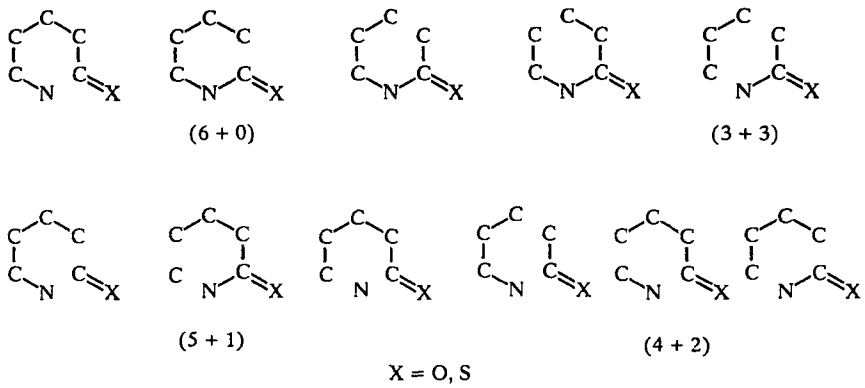
Data on methods for the production of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(H)-thiones and their biological activity are reviewed.

The chemistry of 5,6-dihydropyridin-2(1H)-ones began to develop toward the end of the last century, when the first representatives of this class compounds were obtained. In recent years significant growth in the chemistry of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones has been seen. This is due equally to their use as synthons for the production of more complex compounds, including those of natural origin, and to their characteristic biological activity. In spite of the large amount of information on the chemistry and biological activity of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones, until now no systematic review of these data has been published. In the present review the uncoordinated data on methods for the production of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones and their biological activity published up to the middle of 1997 are analyzed. The 3- and 4-hydroxy-5,6-dihydropyridin-2(1H)-ones, which exist in tautomeric equilibrium with 2,3- and 2,4-piperidinediones and also their sulfur analogs are not examined in this review.

We divided the methods for the production of the compounds under discussion into types, corresponding to the number of atoms of the initial fragments entering into the composition of the forthcoming heterocycle. We included the production of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones from derivatives of piperidine and other heterocycles in a separate section.



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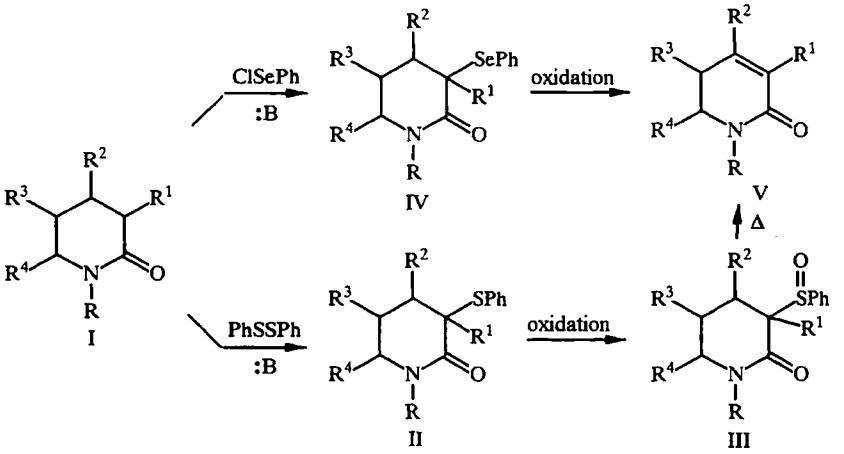
1. METHODS FOR THE PRODUCTION OF 5,6-DIHYDROPYRIDIN-2(1H)-ONES AND 5,6-DIHYDROPYRIDINE-2(1H)-THIONES

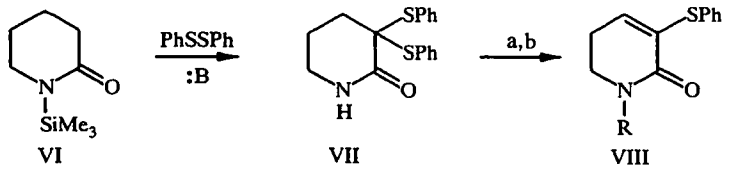
1.1. Synthesis of 5,6-Dihydropyridin-2(1H)-ones and 5,6-Dihydropyridine-2(1H)-thiones from Derivatives of Piperidine and Other Heterocycles

The most widely used method for the synthesis of 5,6-dihydropyridin-2(1H)-ones is the dehydrogenation of δ-valerolactams (I). In reaction with diphenyl disulphide [1, 2] or phenylselenyl chloride [3-11] in the presence of bases the δ-valerolactams (I) form the piperidones (II, IV). The oxidation of the sulfides (II) with *m*-chloroperbenzoic acid, sodium metaperiodate, or N,N,N-trimethylbenzylammonium metaperiodate leads to the formation of the sulfoxides (III), which are converted into the 5,6-dihydropyridin-2(1H)-ones (V) when heated in toluene or benzene in the presence of calcium carbonate. The sulfide (II) (R′ = H) can be alkylated at position 3 and only then is converted into the dihydropyridone (V) [12]. The selenides (IV) form the piperidones immediately during oxidation with hydrogen peroxide or *m*-chloroperbenzoic acid. The yields of compounds (V) amount to 80-90%.



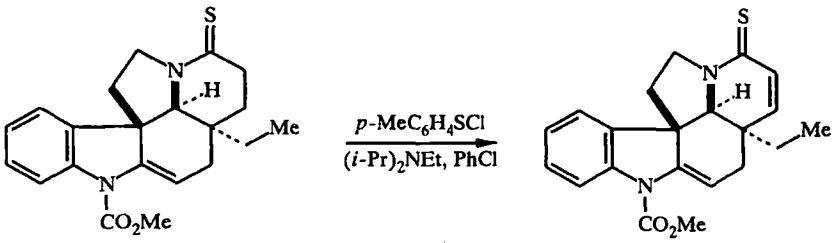
:B = NaH, LiN(*i*-Pr)$_2$, KN(SiMe$_3$)$_2$; R = Alk, CO$_2$Alk, CH$_2$OMe, CH$_2$CH$_2$OBn, Ts, *p*-O$_2$NC$_6$H$_4$, Bn; R^1 = H, Alk, CO$_2$Alk; R^2 = H, Ph; R^3 = H, Alk; R^4 = H, Alk

The reaction of compound (VI) with an excess of diphenyl disulfide leads to the disulfide (VII), which like the sulfide (II) can be converted into the dihydropyridone (VIII) [13].



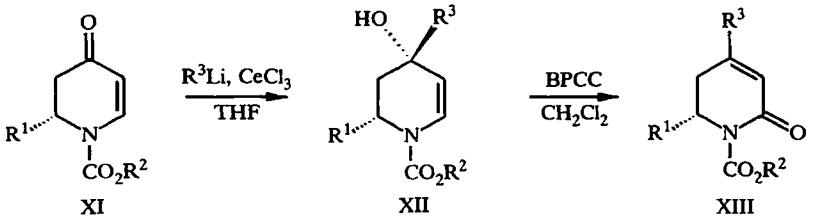
a LiBu or KN(SiMe$_3$)$_2$, RCl, THF, −78 °C; b 1. *m*-ClC$_6$H$_4$CO$_3$H, 2. C$_6$H$_6$, boiling ; R = PhSO$_2$, COOAlk

The dehydrogenation of piperidine-2-thiones can be realized in a single stage. By heating compound (IX) in chlorobenzene in the presence of p-toluenesulfinyl chloride with diisopropylethylamine the authors [14] obtained the 5,6-dihydropyridine-2(1H)-thione (X) with a yield of 86%. The 5,6-dihydropyridine-2(1H)-thiones can also be obtained by the sulfurization of 5,6-dihydropyridin-2(1H)-ones with Lawesson's reagent [15] or P_2S_5 [16].



IX X

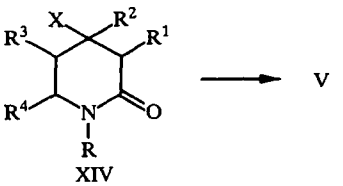
A two-stage method was recently developed for the synthesis of 5,6-dihydropyridin-2(1H)-ones from N-acyl-2,3-dihydro-4-pyridones (XI), which were first converted by reaction with organolithium compounds into 4-hydroxy-2-piperideines (XII). The reaction of compounds (XII) with bipyridinium chlorochromate (BPCC) leads to the formation of the 5,6-dihydropyridin-2(1H)-ones (XIII) [17] with yields of 50-70%. The use of the optically pure initial compounds (XI) in the reaction showed that the configuration of the carbon atom at position 6 of the heterocycles (XII) and (XIII) does not change.



XI XII XIII

R^1 = Me, Ph, CH_2=CH$(CH_2)_3$; R^2 = Ph, Bn; R^3 = Me, Bu

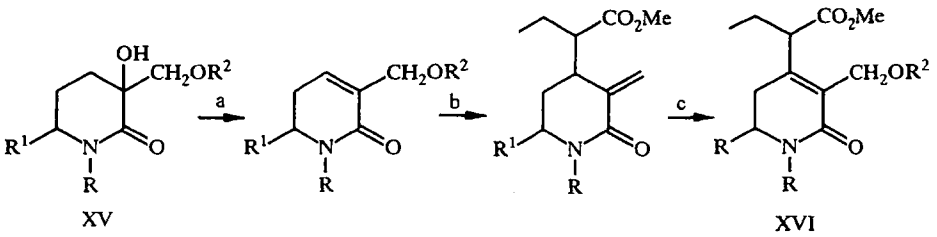
The 3-hydroxy-, 3-halogeno-, 4-hydroxy-, and 4-aminopiperidones and their derivatives have been used quite often for the synthesis of 5,6-dihydropyridin-2(1H)-ones [18, 19]. The dehydration of the 4-hydroxypiperidin-2-ones (XIV) (R = H, Alk; R^1 = OMe; R^2 = R^4 = H; R^3 = H, Alk; X = OH) takes place under the influence of acids and tosyl chloride, followed by treatment with a base or after heating with a mixture of acetic anhydride and sodium acetate [20-24]. 1,6-Dimethyl-4-(methylamino)-2-piperidone (XIV) is converted into 1,6-dimethyl-5,6-dihydropyridin-2(1H)-one after heating at 230°C [25]. The dehydrobromination of 3,4-dibromo-6-methyl-2-piperidone by diethylamine leads to 3-bromo-6-methyl-5,6-dihydropyridin-2(1H)-one [26].



XIV

R = H, Alk; R^1 = H, Br, OMe; R^2 = H, R^3 = H, Alk;
R^4 = H, Alk; X = OH, $NHCONH_2$, OAc, NHMe, Br

The dihydropyridone (XVI), used in the synthesis of the alkaloid camptothecin and its analogs, was obtained from 3-hydroxypiperidone (XV) [27, 28]. The yield at each stage amounted to 50-90%.

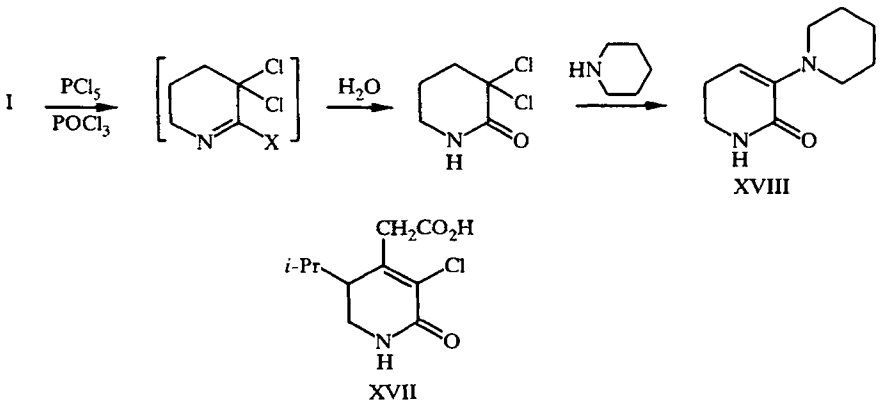


XV XVI

a 1. $SOCl_2$/PyH; 2. K_2CO_3/MeOH–H_2O; b $PrC(OMe)_3$, H^+; c 1. SeO_2/PhMe, Δ; 2. Ac_2O, H^+;

R = Me; R^1 = H, CO_2Me, Ph; R + R^1 = $(CH_2)_3$, $CH_2CH_2CHOR^2$; R^2 = H, Ac

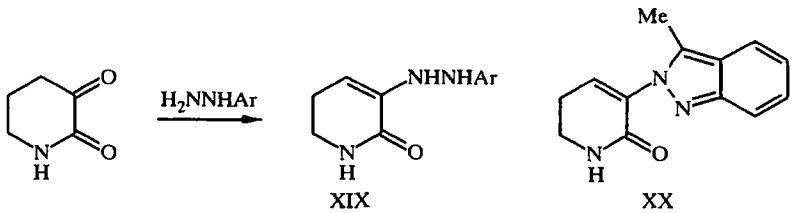
4-Carboxymethyl-5-isopropyl-3-chloro-5,6-dihydropyridin-2(1H)-one (XVII), which is an intermediate product in the synthesis of antihelminthic products, was obtained by heating 5-isopropyl-3,3-dichloro-4-ethoxycarbonylmethyl-2-piperidinone in water in the presence of barium hydroxide [29]. A method was developed for the production of the enamine (XVIII) (the starting compound in the synthesis of β-carbolins) on the basis of 3,3-dichloro-2-piperidone, formed during the reaction of unsubstituted valerolactam (I) with phosphorus pentachloride and phosphorus oxychloride [30].



XVIII

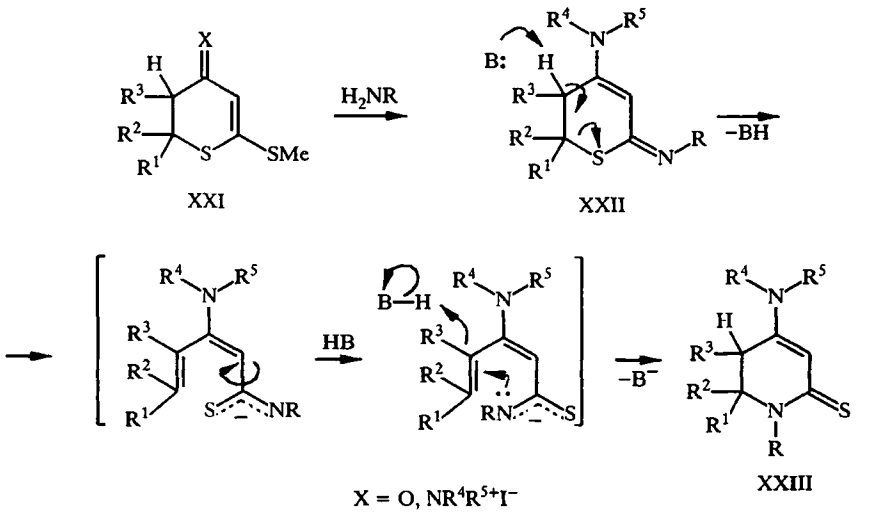
XVII

Under the conditions of the Fischer reaction 3-(alkylamino)-5,6-dihydropyridin-2(1H)-ones (XIX), obtained by the condensation of 2,3-piperidinediones [31] or enamines (XVIII) [30] with arylhydrazines, do not always form β-carbolins. In the presence of an acetyl substituent at the *ortho* position of the aryl ring in compounds (XIX) the main reaction product is the 5,6-dihydropyridin-2(1H)-one (XX) [32].



XIX XX

1-Alkyl-4-amino-5,6-dihydropyridine-2(1H)-thiones (XXIII) are formed as a result of the Dimroth rearrangement of 4-amino-2-alkylamino-5,6-dihydro-2H-thiopyrans (XXII). Thiopyrans (XXI) in a mixture with primary amines can also be used as starting compounds in this reaction [33].

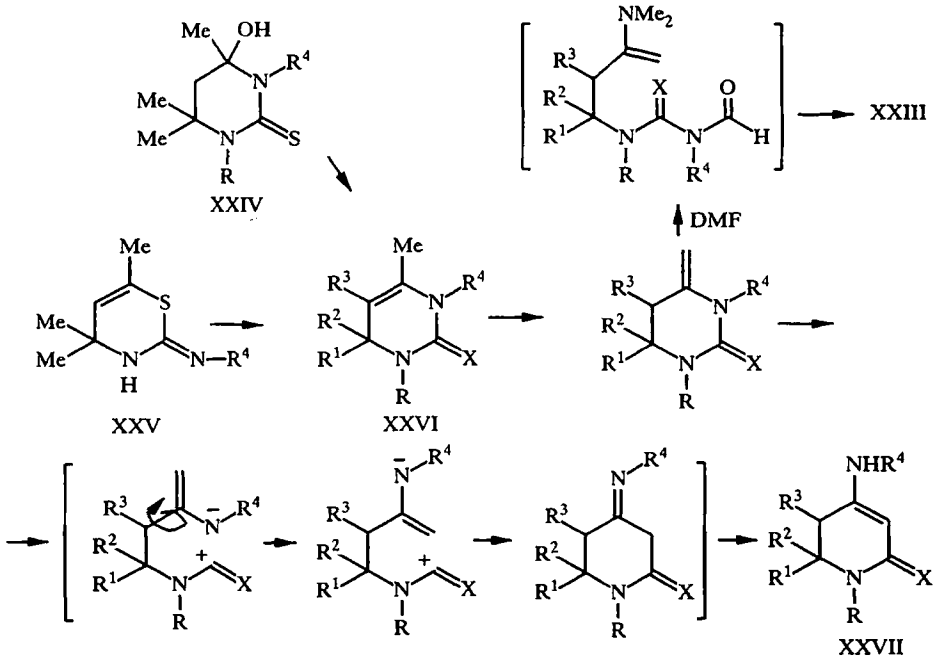


X = O, $NR^4R^5I^-$

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

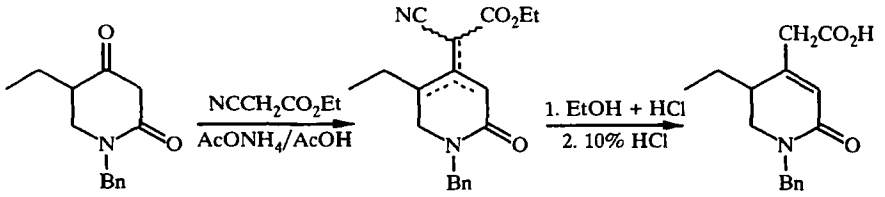
R^4 = H, Me, Et; R^5 = Me, Et, Bn, Ph; $R^4 + R^5 = (CH_2)_4$

When heated in DMF or methylformamide the tetrahydropyrimidin-2-ones and tetrahydropyrimidine-2-thiones are converted into 4-amino-5,6-dihydropyridin-2(1H)-ones and 4-amino-5,6-dihydropyridine-2(1H)-thiones (XXVII) through a stage involving the formation of enamine intermediates. Under the reaction conditions the 4-hydroxyhexahydropyrimidine-2-thiones (XXIV) undergo dehydration, while the thiazines (XXV) undergo a Dimroth rearrangement with the formation of tetrahydropyrimidinethiones (XXVI). This made it possible to obtain the 5,6-dihydropyridine-2(1H)-thiones (XXVII) starting from compounds (XXIV) and (XXV) [34, 35]. The recyclization of the tetrahydropyrimidinethione (XXVI) (R^4 = H, X = S) as a result of reaction with DMF, used as solvent, leads to the formation of the dihydropyridinethione (XXIII) ($R^4 = R^5$ = Me).



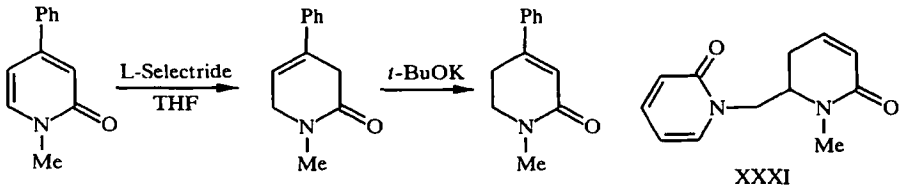
4-(Alkylamino)-5,6-dihydropyridin-2(1H)-ones (XXVII) (X = O) can also be obtained by the reaction of 2,4-piperidinediones with amines [36]. The reaction of 2,4-piperidinediones with ethyl orthoformate in the presence of catalytic amounts of p-toluenesulfonic acid leads to the formation of 4-methoxy-5,6-dihydropyridin-2(1H)-ones with good yields [37].

The dihydropyridin-2(1H)-one (XXX), which is used as the key synthon for the construction of certain benzoquinolizidinium alkaloids, was obtained from the piperidinedione (XXVIII) [23, 38]. The product (XXIX) from the condensation of the piperidinedione with cyanoacetic ester isomerizes during hydrolysis and decarboxylation of the substituent at position 4 of the heterocycle with the formation of the 5,6-dihydropyridin-2(1H)-one (XXX).



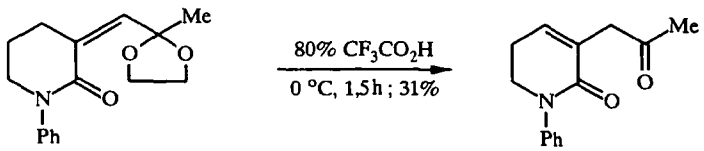
XXVIII XXIX XXX

The reaction of 1-methyl-2-pyridone with butyllithium gave a dimer [39], which was erroneously assigned the structure of substituted 5,6-dihydropyridin-2(1H)-one (XXXI). More recently it was established that the dimerization of 1-methyl-2-pyridone by the action of butyllithium led to the formation of 3,6-dihydropyridone, while the 5,6-dihydropyridone (XXXI) could be obtained by the isomerization of this compound in an aqueous solution of sodium hydroxide [40]. In [41] the reactions of 1-methyl-4-phenyl-2-pyridone with various reducing agents were investigated, and it was shown that its reaction with $LiB(Bu)_3H$ (L-Selectride) in THF led with a 99% yield to the corresponding 3,6-dihydro-2-pyridone, which isomerizes under the influence of potassium *tert*-butoxide to 1-methyl-4-phenyl-5,6-dihydropyridin-2(1H)-one. The isomerization of 3,6-dihydropyridine-2(1H)-ones to 5,6-dihydropyridones by the action of bases was reported in [38].



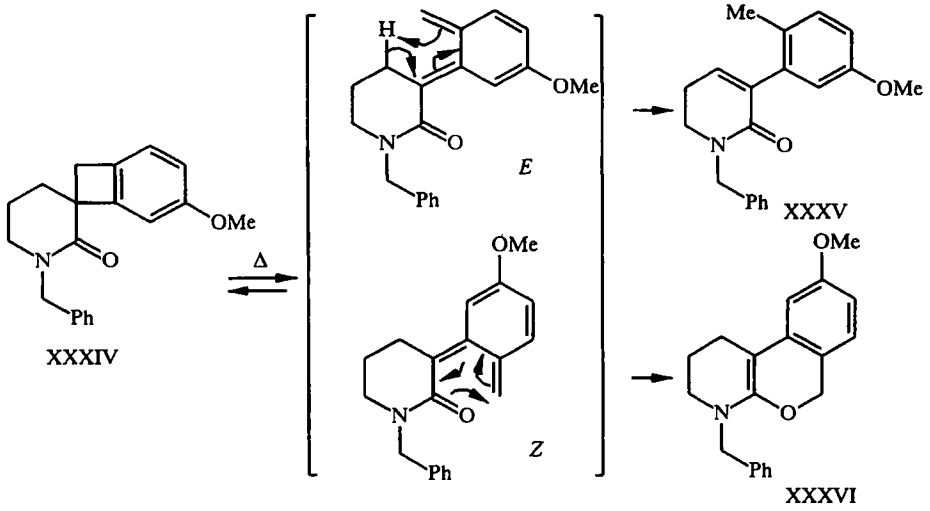
XXXI

3-Alkylidene- and 4-alkylidene-2-piperidinones can also be converted into 5,6-dihydropyridin-2(1H)-ones by the action of acids or bases [42-44]. For example, the isomerization of 3-alkylidene-2-piperidinone (XXXII) and cleavage of the dioxolane ring in trifluoroacetic acid have been used for the synthesis of compound (XXXIII) [43].

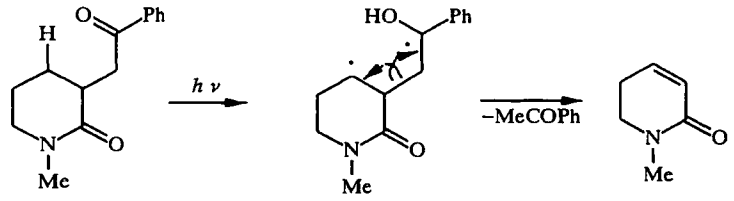


XXXII XXXIII

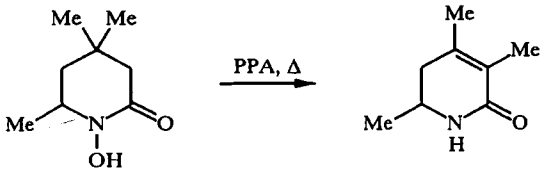
In [45] it was reported that the thermal cleavage of benzocyclobutane (XXXIV) led to two isomeric intermediates stabilized by electrocyclic closure of the pyran ring (intermediate "*Z*") and sigmatropic rearrangement (intermediate "*E*") with the formation of compounds (XXXV) and (XXXVI), obtained with an overall yield of 33% in a ratio of 3:1 respectively.



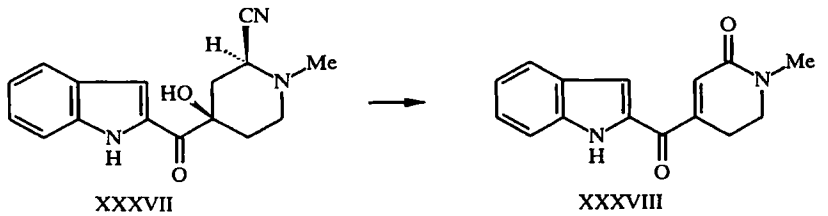
1-Methyl-5,6-dihydropyridin-2(1H)-one is formed as a result of the photochemical fragmentation of 3-(2-oxo-2-phenylethyl)-2-piperidinone [46].



An interesting rearrangement was discovered by Italian researchers. When N-hydroxy-4,6,6-trimethyl-2-piperidone was heated in polyphosphoric acid, 3,4,6-trimethyl-5,6-dihydropyridin-2(1H)-one was isolated with a high yield [47].



When heated in 80% acetic acid the indole derivative (XXXVII) gave a mixture of compounds, one of which was the dihydropyridone (XXXVIII) [48], isolated with a yield of 17%.

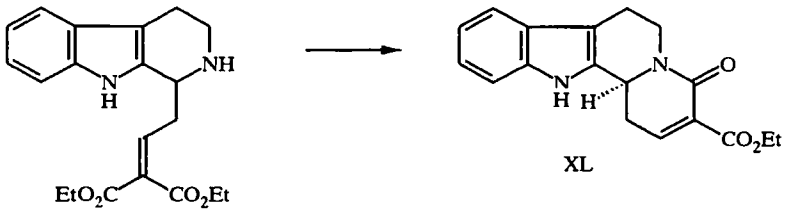


The method for the synthesis of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones based on the dehydrogenation of δ-valerolactams is the most universal in the presented series. It gives excellent results and makes it possible to obtain high yields of 3-alkyl-, 3-aryl-, and functionally 3-substituted 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones from commercially available starting materials. However, when it is necessary to obtain more complex 5,6-dihydropyridin-2(1H)-ones substituted at positions 4, 5, and 6, the method is restricted by the availability of the initial compounds.

1.2. (6 + 0) Methods of Synthesis

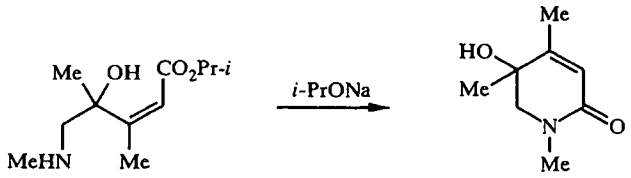
In this group of synthetic methods it is possible to single out two main methods for the construction of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones, i.e., intramolecular acylation of δ-amino acids derivatives and intramolecular condensation of N-3-oxoalkylamides and N-3-oxoalkylthioamides.

In [49] the dihydropyridone (XL) as the starting material for the synthesis of alkaloids of the indole series was obtained with a yield of 99% by heating the ester of the unsaturated dicarboxylic amino acid (XXXIX) in ethyl acetate.



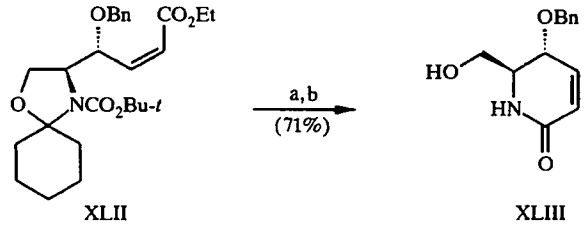
XXXIX XL

This method can also be used for the production of 5-hydroxy-substituted 5,6-dihydropyridin-2(1H)-ones. For example, 5-hydroxy-1,4,5-trimethyl-5,6-dihydropyridin-2(1H)-one is formed with a 70% yield during the cyclization of the unsaturated amino acid ester (XLI) by the action of sodium isopropoxide [50].



XLI

The intramolecular acylation of the δ-amino acids esters takes place without change in the configuration of the chiral center at the δ-position. This makes it possible to obtain the individual diastereomers of 5,6-dihydropyridin-2(1H)-ones from the respective initial compounds. After cleavage of the oxazolidine ring and removal of the protecting group at the nitrogen atom compound (XLII) is converted into the dihydropyridone (XLIII), which is a key synthon in the synthesis of azasugars and certain alkaloids of the piperidine series [51].



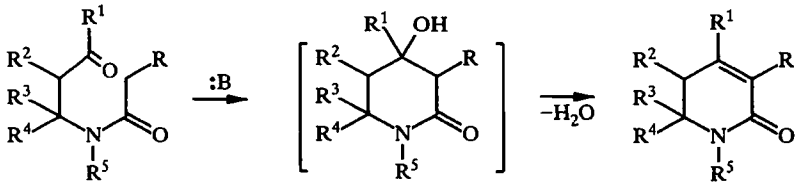
XLII XLIII

a Et_2O–H_2O–CF_3CO_2H, 1 : 1 : 3, 1h; b EtOAc, $NaHCO_3$, 15 h

It is clear that such cyclization is only possible for the *cis* isomers of the unsaturated δ-amino acids esters, the poor availability of which restricts the method.

N-3-Oxoalkylamides (XLIV), which have a mobile hydrogen atom at the α-position to the carbamoyl group, undergo cyclization to 5,6-dihydropyridin-2(1H)-ones under the influence of bases [52-57]. In [53, 54] the effect of electronic and structural factors on the rate of this reaction was studied, and it was shown that it depends on the effective size of the substituents in the N-3-oxoalkyl chain and on the acidity of the α-carbamoyl position of compounds (XLV). Increase in the acidity of the α-position with respect to the carbamoyl group, increase in the effective size of the substituents R^3 and R^4, and conversely decrease of the latter in the case of the substituents R^1

and R^2 facilitate cyclization of the N-3-oxoalkylamides (XLV). The cyclization of compounds (XLIV), having R = Ph and $R^1 + R^2 = (CH_2)_4$, leads to the isomeric derivatives of hexahydroisoquinolin-3(2H)-one, which differs in the position of the double bond in the ring [55].



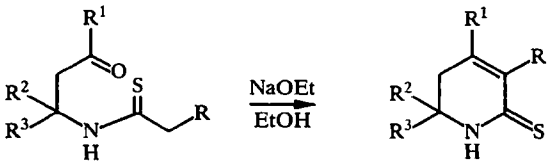
XLIV

R = Ar, Hetar; R^1 = Alk; R^2 = H, Alk; R^3 = H. Alk; R^4 = H, Alk, Ar; R^5 = Bn; $R^1 + R^2 = (CH_2)_3$; $R^2 + R^3 = (CH_2)_3$; $R^3 + R^4 = (CH_2)_5$

Under analogous conditions bis(2-benzyl-6-methyl-4-phenyl-4H-1,3-oxazinium) hexachlorostannate (XLV) is converted into 4-methyl-3,6-diphenyl-5,6-dihydropyridin-2(1H)-one [53]. During recyclization of the salt (XLV) to 4-methyl-3,6-diphenyl-5,6-dihydropyridin-2(1H)-one the oxazine ring is hydrolyzed with the formation of the corresponding N-3-oxoalkylamide (XLIV).

XLV

The cyclization of N-3-oxoalkylthioamides (XLVI) takes place under milder conditions than that of the analogous N-3-oxoalkylamides (XLV). This is due to the greater mobility of the hydrogen atoms at the α-thiocarbamoyl position. Here cyclization of the thioamides of aliphatic acids (XLVI) (R = H, Alk) becomes possible with the formation of not only 3-aryl- but also 3-H- and 3-alkyl-substituted 5,6-dihydropyridine-2(1H)-thiones (XLVII) [16, 58, 59].

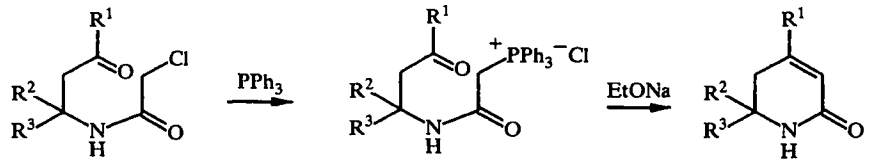


XLVI XLVII

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

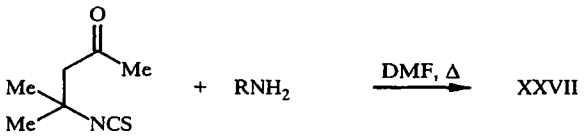
The method for the synthesis of 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones based on the cyclization of N-3-oxoalkylamides also has its limitations. In spite of the fact that the initial N-3-oxoalkylamides and N-3-oxoalkylthioamides are accessible by many methods [16, 58-60] their cyclization only becomes possible when the acidity of the α-position in relation to the carbamoyl group is higher than the acidity of the α-carbonyl position. This makes it impossible to obtain 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones from the N-3-oxoalkylamides of aliphatic acids (XLV) (R = H, Alk) and the thioamides of aliphatic acids containing an aldehyde group (XLVI) (R^1 = H).

Recently it was shown that 5,6-dihydropyridin-2(1H)-ones can be synthesized by an intramolecular Wittig reaction, which makes it possible to remove these limitations. The triphenylphosphonium salts, obtained from N-3-oxoalkylchloroacetamides by the action of sodium ethanolate, are converted into 5,6-dihydropyridin-2(1H)-ones with high yields [61].

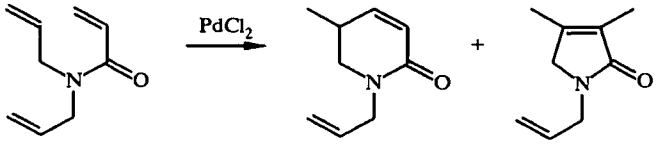


R^1 = Me, Ph; R^2 = Me, Ph; R^3 = H, Me

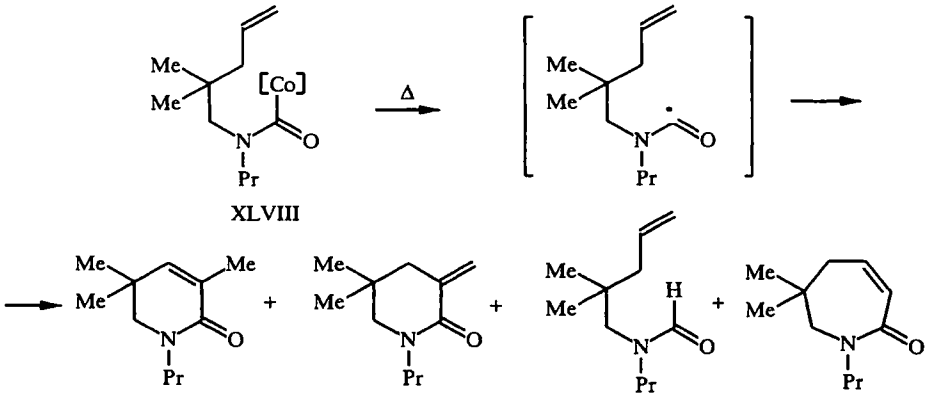
Not only pyrimidinethiones (XXIV-XXVI) but also their precursors 1,3-isothiocyanato ketones can be used for the synthesis of 4-alkylamino-5,6-dihydropyridine-2(1H)-thiones (XXX). Under the conditions for the recyclization of compounds (XXVII-XXIX) the 1,3-isothiocyanato ketones in a mixture with amines form compounds (XXVII) (R = R^3 = H, R^1 = R^2 = Me, R^4 = Ph, X = S) [32].



In the presence of palladium chloride N,N-diallylacrylamide is converted into 1-allyl-5-methyl-5,6-dihydropyridin-2(1H)-one and 1-allyl-3,4-dimethyl-5,6-dihydropyrrol-2(1H)-one [62]. The total yield of the obtained compounds amounts to 35%.



When the organocobalt compounds (XLVIII) are heated in toluene, homolytic cleavage of the carbon—metal bond occurs, and a mixture of substances containing 3,5,5-trimethyl-1-propyl-5,6-dihydropyridin-2(1H)-one is formed [63, 64].

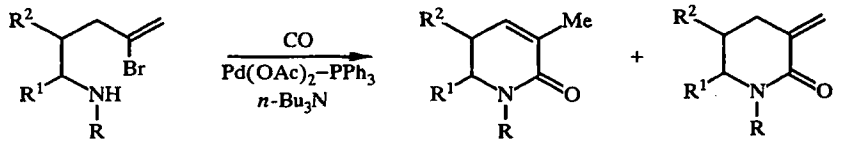


XLVIII

1.3. (5 + 1) Methods of Production

5,6-Dihydropyridin-2(1H)-ones were obtained in a mixture with the isomeric 3-alkylidenepiperidin-2-ones by the carbonylation of the amines (XLIX) in the presence of catalytic amounts of palladium acetate and triphenylphosphine [65]. The yields of the 5,6-dihydropyridin-2(1H)-ones amounted to 27-80%.

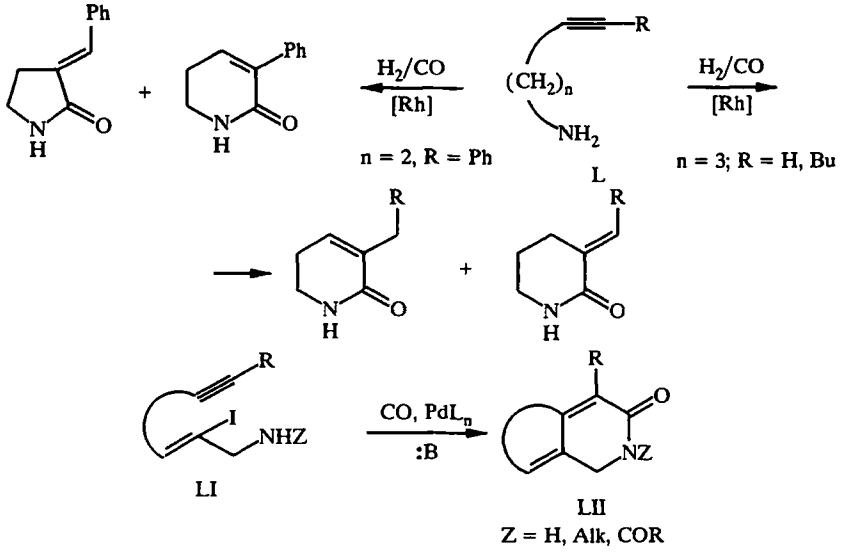
The reaction of the γ-alkynylamines (L) (n = 3) with hydrogen and carbon monoxide in the presence of rhodium catalysts also leads to a mixture of 5,6-dihydropyridin-2(1H)-ones and 3-alkylidenepiperidines. The



XLIX

R = Bn; R^1 = H; R^2 = H, Me; R + R^1 = $(CH_2)_3$; R^1 = $(CH_2)_3$; R^1 + R^2 = $(CH_2)_4$

β-alkynylamine (L) (n = 2, R = Ph) is transformed under these conditions into a mixture of 3-benzylidene-2-pyrrolidone and 3-phenyl-5,6-dihydropyridin-2(1H)-one in a ratio of 3:2 with an overall yield of 80% [44]. The 5,6-dihydropyridin-2(1H)-ones (LII) annellated with carbocycles were obtained by the carbonylation of compounds (LI) in the presence of palladium catalysts [66].

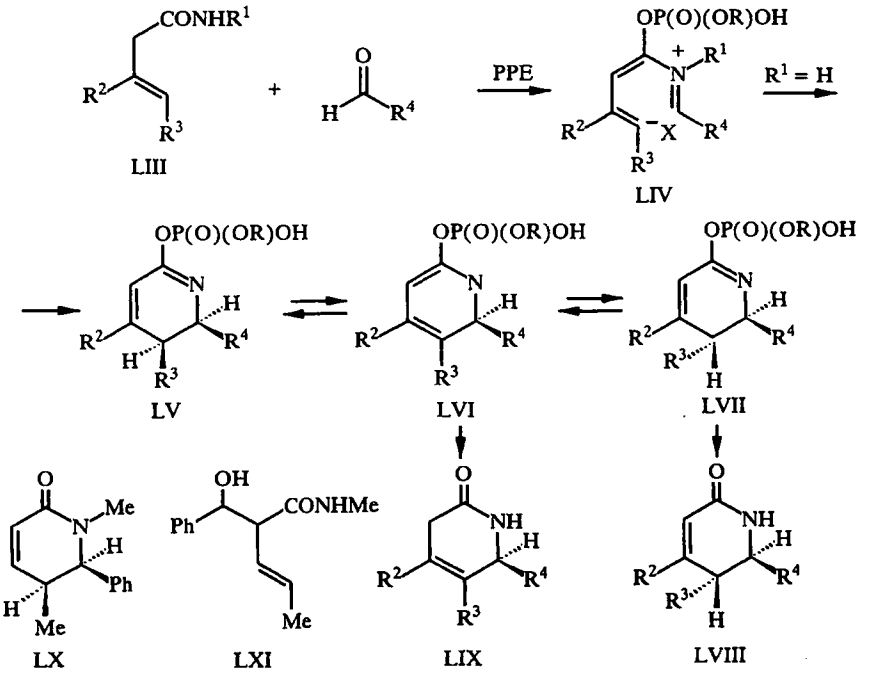


LI

LII

Z = H, Alk, COR

A method was recently developed for the production of 6-aryl-5,6-dihydropyridin-2(1H)-ones [67, 68] by the condensation of the β,γ-unsaturated acids amides (LIII) with aromatic aldehydes in polyphosphoric acid,



LIII

LIV

LV

LVI

LVII

LX

LXI

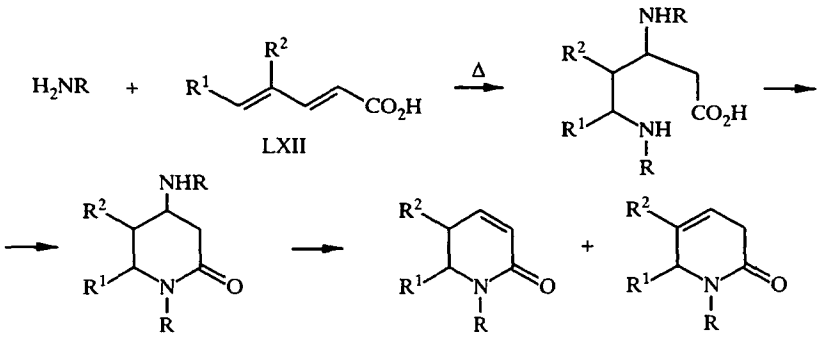
LIX

LVIII

R^1 = H, Me, Bn; R^2 = H, Me, Et; R^3 = H, Me; R^4 = Ar

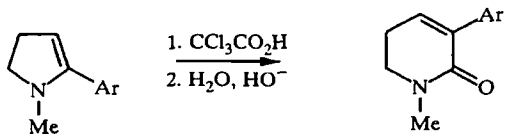
polyphosphoric esters, or $MeSO_3H$—P_2O_5. The reaction takes place as electrocyclic closure of the ring in the intermediate (LIV) (R = H) and leads to *cis*-5,6-disubstituted 5,6-dihydropyridin-2(1H)-one derivatives (LV), which are in equilibrium with compounds (LVI) and (LVII). The latter are converted into the *trans*-5,6-substituted 5,6-dihydropyridin-2(1H)-ones (LVIII) or 3,6-dihydropyridin-2(1H)-ones (LIX) after treatment by the aqueous solution of the base. Isomerization does not occur in the case of the N-substituted amide (LIII) (R^1 = Me; R^2 = H, R^3 = Me, R^4 = Ph), and the reaction products are *cis*-1,5-dimethyl-6-phenyl-5,6-dihydropyridin-2(1H)-one (LX) and compound (LXI). The yields of the 5,6-dihydropyridin-2(1H)-ones (LVIII) amount to 30-95%.

The reaction of sorbic acid and its homologs (LXII) with amines or ammonia has been studied by many investigators [22, 26, 69-72]. The reaction takes place when the initial compounds are heated at 180-200°C in an autoclave and gives a mixture of 5,6-dihydropyridin-2(1H)-ones and their isomeric 3,6-dihydropyridin-2(1H)-ones. Cinnamic acid enters into an analogous reaction [70]. At the same time, only 5-ethyl-3,6-dihydropyridin-2(1H)-one was isolated as a result of the condensation of the acid (LXII) (R^1 = H, R^2 = Et) and ammonia [73]. As a rule the yields of the 5,6-dihydropyridin-2(1H)-ones are low.



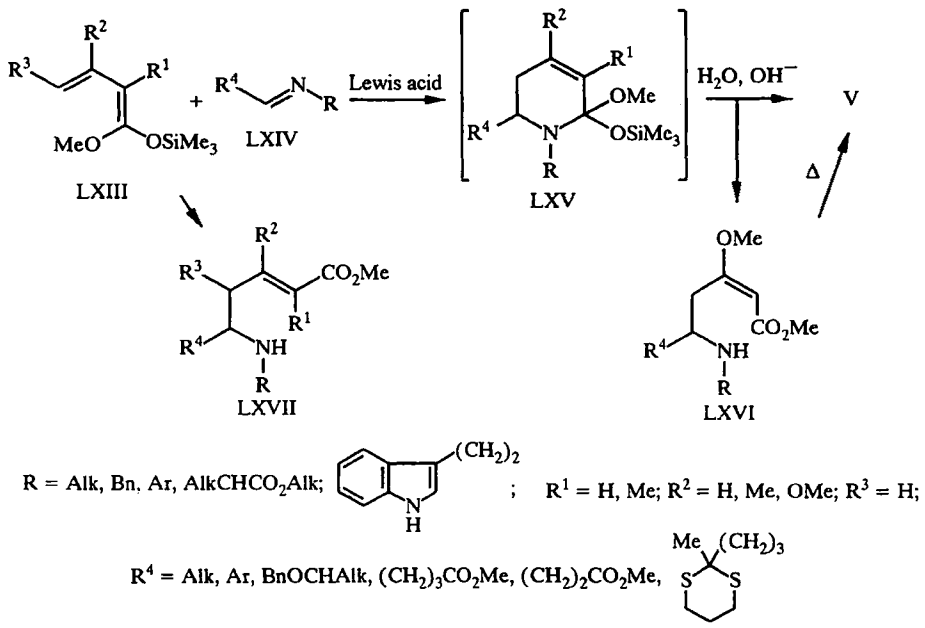
R = H, Alk, Ar; R^1 = H, Me, Ph; R^2 = H, Et

The reaction of N-methyl-5-aryl-2,3-dihydro-1H-pyrroles and trichloroacetic acid followed by hydrolysis of the reaction mixture gave 3-aryl-5,6-dihydropyridin-2(1H)-ones, which have been patented as herbicides [74].

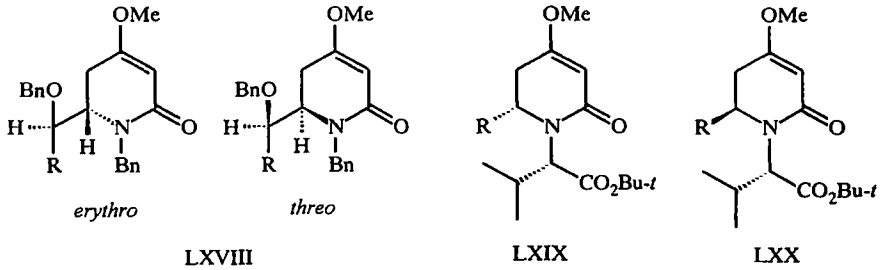


1.4. (4 + 2) Methods of Synthesis

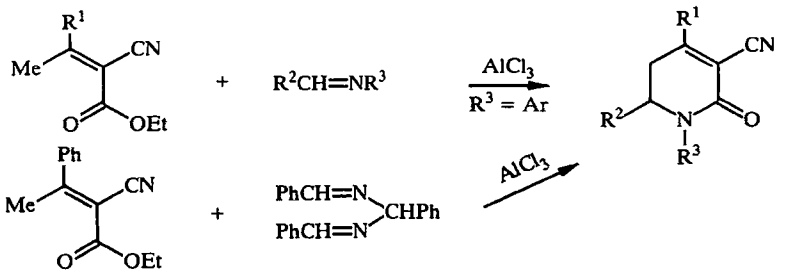
The hydrolysis of the adducts from the cycloaddition of (LXV), Danishevkii's diene (R^1 = H, R^2 = OMe) (LXIII), and the imines (LXIV) leads to the formation of the 5,6-dihydropyridin-2(1H)-ones (V) and the δ-amino acids esters (LXVI), which can be converted into dihydropyridones by heating in toluene [75-79]. The products of the reaction of 1-methoxy-1-trimethylsilyloxy-1,3-butadienes (R^1, R^2 = H, Me) (LXIII) with imines (LXIV) are the 5,6-dihydropyridin-2(1H)-ones (V) and the δ-amino acids esters (LXVII), formed as a result of nucleophilic addition of the imine (LXIV) at the γ-position of the diene (LXIII) [80]. In this case the regioselectivity of the reaction depends substantially on the nature of the substituents R^1 and R^2. In the case of R^1 = Me and R^2 = H the main product is the acyclic compound (LXVII), and conversely when R^1 = H and R^2 = Me the main product is the dihydropyridone (V). The reaction takes place in the presence of Lewis acids at reduced temperature. As a rule the overall yields of compounds (V, LXVI) and compounds (V, LXVII) are high.



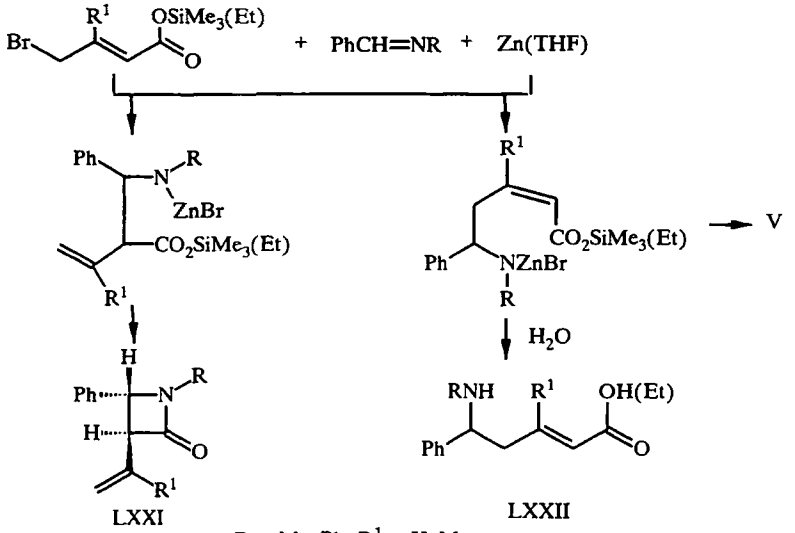
The method gives good results for the production of 4-methoxy-5,6-dihydropyridin-2(1H)-ones. Study of the reaction of the imines (LXIV) (R^4 = PentCHOBn, *i*-PrCHOBn, *t*-BuCHOBn; R = Bn) with the Danishevskii's diene showed that the reaction is diastereoselective with preference as a rule for the *threo* isomer of the dihydropyridone (LXVIII) [78]. The overall yield of the diastereomers of (LXVIII) varies in the range of 10-75%, while the content of the *threo* isomer in the reaction products in a number of cases amounts to 99%. The asymmetric synthesis of 4-methoxy-5,6-dihydropyridin-2(1H)-ones (LXIX) and (LXX) was realized from the amines obtained from aromatic or aliphatic aldehydes and valine *tert*-butyl ester. The ratio of the diastereomers (LXIX):(LXX) amounted to 97:3-92:8 [77]. Among the large number of Lewis acids used in this reaction the best results were obtained with diethylaluminum chloride.



The condensation of 3-aryl-2-cyanobuten-2-oic esters with Schiff bases and hydrobenzamide in the presence of aluminum chloride leads to 3-cyano-5,6-dihydropyridin-2(1H)-ones with yields of 20-60%. The 3-arylbuten-2-oic acid ethyl esters without a cyano group at the α-position do not react with Schiff bases under these conditions [81].

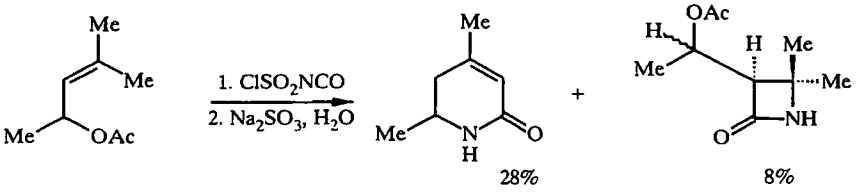


Under the conditions of the Reformatsky reaction the esters of γ-bromocrotonic and γ-bromo-β-methylcrotonic acids with benzylidenemethylamine or benzylideneaniline in the presence of zinc form the β-lactam (LXXI), the 5,6-dihydropyridin-2(1H)-one (V), and the δ-amino acid or its ester (LXXII). The yields of compounds amount to 55% [82].

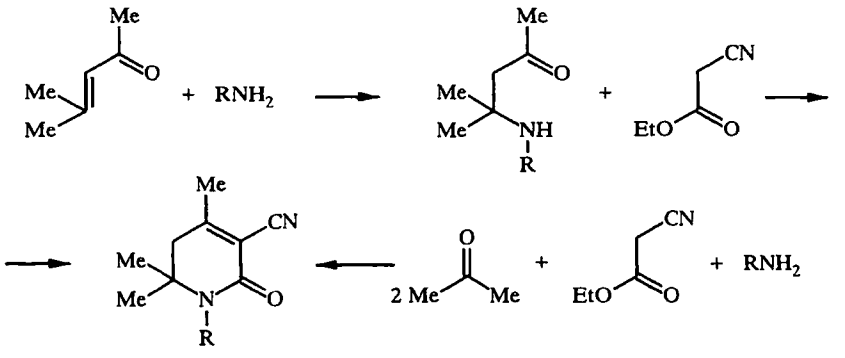


LXXI LXXII

3,6-Dimethyl-5,6-dihydropyridin-2(1H)-one was obtained with a yield of 28% as a result of the reaction of 1,3-dimethyl-2-butenyl acetate and chlorosulfonyl isocyanate [83].

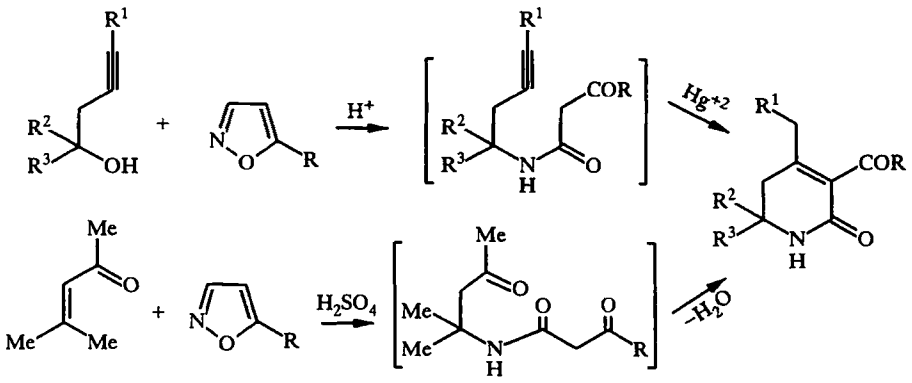


One of the oldest methods for the synthesis of 5,6-dihydropyridin-2(1H)-ones is the condensation of 1,3-aminoketones with ethyl cyanoacetate. This reaction was studied in 1893 by Guareschi [84] for the case of diacetoneamine and its N-substituted derivatives. The 1,3-aminoketones can be prepared beforehand or in the reaction process from mesityl oxide and amines or from amines and acetone [85].



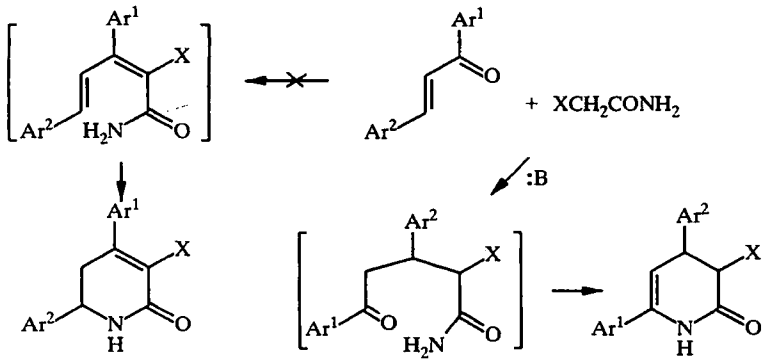
1.5. (3 + 3) Methods of Production

3-Acyl-5,6-dihydropyridin-2(1H)-ones were obtained by the reaction of 5-substituted isoxazoles with mesityl oxide in sulfuric acid [86] or with substituted 3-butyn-1-ols in an acidic medium in the presence of mercury salts [87].



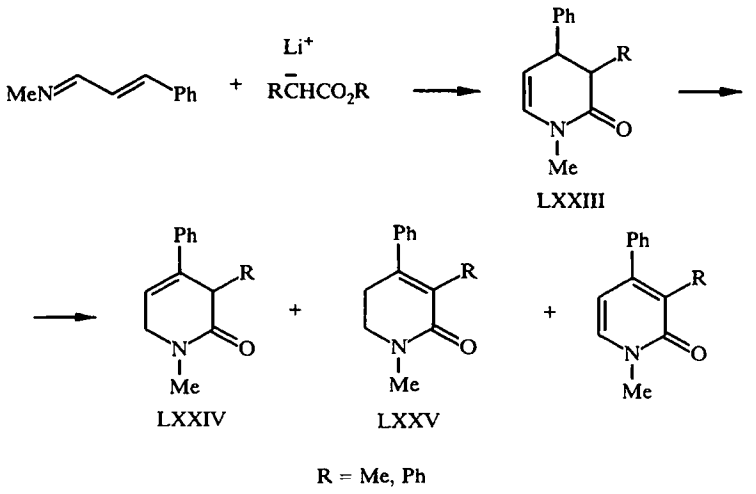
R = Me, Ph; R^1 = H; R^2 = H, Me, Et, *i*-Bu;
R^3 = Me, Et, *i*-Bu, *t*-Bu, Ph; $R^2 + R^3 = (CH_2)_n$; n = 4–7

In [88-91] the products from the reaction of chalcones with the cyanoacetic and arylacetic acid amides were erroneously assigned the structure of 5,6-dihydropyridin-2(1H)-ones. In more recent investigations [92-94] it was established that at the first stage the reaction takes place as Michael addition of the cyanoacetic and arylacetic acid amides to the chalcones followed by closure of the obtained adduct into the 3,4-dihydropyridin-2(1H)-one.



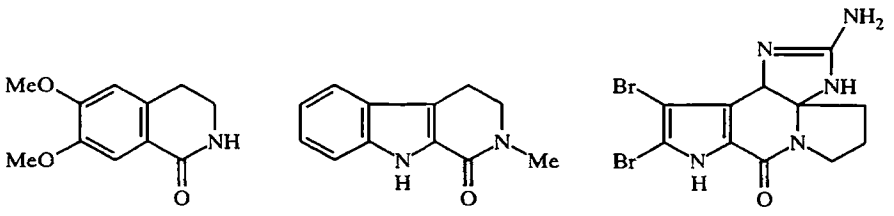
X = Ar, CN

Azodienes react in a similar way with the enolates of esters [95]. At room temperature the main reaction products are 3,4-dihydropyridin-2(1H)-ones (LXXIII), while at elevated temperatures they are the three isomeric dihydropyridin-2(1H)-ones (LXXIII-LXXV) and 2-pyridone. When heated the initially formed 3,4-dihydropyridin-2(1H)-one (LXXIII) isomerizes to 5,6- and 3,6-dihydropyridin-2(1H)-ones. The yields of the 5,6-dihydropyridin-2(1H)-ones (LXXV) amount to 10-20%.

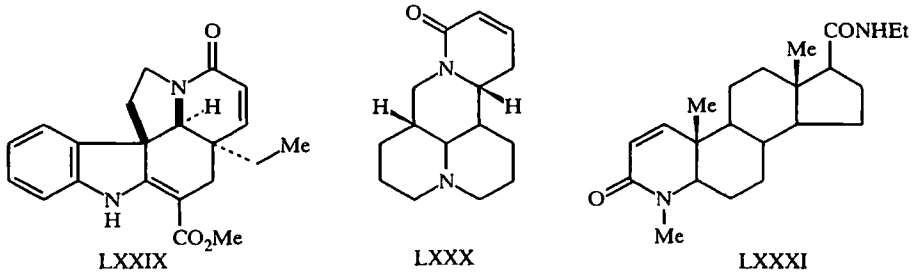


2. THE BIOLOGICAL ACTIVITY OF 5,6-DIHYDROPYRIDIN-2(1H)-ONES AND THEIR NATURAL REPRESENTATIVES

5,6-Dihydropyridin-2(1H)-ones are 2-oxo derivatives of 3-piperideines, the physiological activity of which is well known [96]. They are metabolites of 3-piperideines [5], formed during the chemical cleavage of certain alkaloids [19, 97, 98]. Alkaloids in which the dihydropyridone and aromatic rings are condensed are well known. Among them it is possible to include strychnocarpine (LXXVII) [99], dibromoisofakelline (LXXVIII) [100, 101], corydaldine (LXXVI) [102], and other alkaloids [103]. It is quite likely that the 5,6-dihydropyridine ring is formed in plants as a result of the oxidation of the frequently encountered piperideine fragment or as a result of the oxidative degradation of more complex heterocyclic structures, such as benzoquinolines [102]. The formation of 5,6-dihydropyridin-2(1H)-ones as intermediates during the chemical oxidation of 3-piperideines was reported in [104, 105].

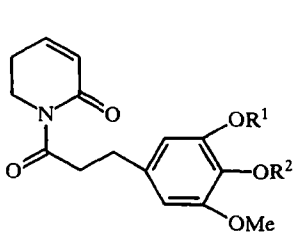


The structural fragment of 5,6-dihydropyridin-2-one is also encountered in lupin and indole alkaloids, such as sofocarpine (LXXX) [106], 8-oxotabersonine (LXXIX) [14], and in the azasteroid (LXXXI) [107].



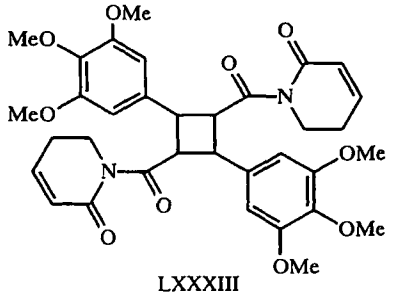
At the present time a considerable number of natural compounds for which the 5,6-dihydropyridin-2(1H)-one fragment forms the structural base have been found. Above all it is necessary to include among such

compounds the alkaloids isolated from plants of the *Piperaceae* family — piplartine (LXXXIVb) [106-114], piplartine-dimer (LXXXIII) [110, 114, 115], pipermesistine (LXXXV) [116], and also (LXXXIIa, b) [113, 115] and (LXXXIIIa, c) [113, 114]. Compounds (LXXXVI) and (LXXXVII) were isolated from the marine sponge *Halichondria melanodocia* [117].

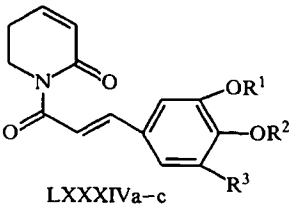


LXXXIIa,b

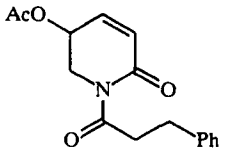
a $R^1 = R^2 = Me$; b $R^1 + R^2 = CH_2$



LXXXIII

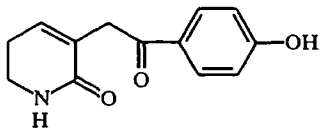


LXXXIVa–c

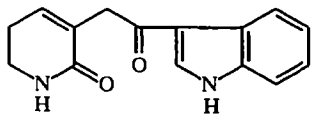


LXXXV

a $R^1 = R^2 = Me$, $R^3 = H$; b $R^1 = R^2 = Me$, $R^3 = OMe$; c $R^1 + R^2 = CH_2$, $R^3 = OMe$



LXXXVI



LXXXVII

The range of biological activity in 5,6-dihydropyridin-2(1H)-ones is very wide and varied. Piplartine (LXXXIVb) is an effective product for the treatment of asthma and chronic bronchitis [112], while the synthetic analogs of the azasteroid (LXXXI) inhibit 5α-reductase and are used in the treatment of diseases sensitive to androgens, such as common acne, seborrhea, and alopecia [118-120]. 3-Acetyl- and cyano-5,6-dihydropyridin-2(1H)-ones have analgesic, antipyretic, and antiinflammatory activity [121]. Among this series of compounds substances that inhibit HIV protease [122, 123] and phosphodiesterase [124, 125], have antiviral and antibacterial activity [52, 122-125], are effective as tranquillizers and muscle relaxants [126, 127], and plant growth regulators [128, 129] have been found. Recently substances active toward the AIDS virus were found among these compounds [122-125]. 3-Aryl- and 3-heteroaryl-substituted 5,6-dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones have been used as herbicides [5, 57, 74, 128].

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