CHEMISTRY OF δ-ENAMINO LACTAMS (REVIEW)

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The known methods for the preparation of δ-enamino lactams are systematized. The principal trends of their utilization (for the preparation of pyridine derivatives and in the synthesis and establishment of the structures of various alkaloids, as well as steroid enamino lactams) are examined. Possible mechanisms for the syntheses of enamino lactams and their transformations and the isomerism of the position of the double bond are set forth.

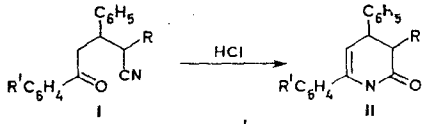
Nitrogen analogs of δ-enol lactones [1] – unsaturated lactams with a double bond in the vinyl position relative to the heteroatom (3,4-dihydro-2-pyridones and 6-alkylidene-2-pyridones) – differ in their chemical behavior from other lactams because of the presence of an enamino grouping in their chemical structures. The name "δ-enamino lactams" [2], which shows the presence of conjugation of the double bond with the heteroring nitrogen atom, reflects their general properties.

The accessibility and high reactivities of δ-enamino lactams make it possible to use them extensively for the preparation of diverse pyridine derivatives and in the synthesis and establishment of the structures of various alkaloids. Many studies have been devoted to the production of steroid δ-enamino lactams that have served as models for the study of the effect of the nitrogen atom in various rings of azasteroids on their physiological activity [2, 3]. The interest in this class of compounds is also the result of new data on the antioxidant properties and physiological activity of individual representatives [4-8].

The literature data on the chemistry of δ-enamino lactams is systematized for the first time in the present review.

Synthesis of δ-Enamino Lactams

Cyclization of δ-Keto Acids and Their Derivatives. The cycloisomerization of δ-keto nitriles under the influence of acidic reagents is an important method for the preparation of δ-enamino lactams. 3,4-Dihydro-2-pyridones II were synthesized in quantitative yields for the first time by saturation of solutions of diaryl-δ-keto nitriles I in chloroform with hydrogen chloride or bromide [9-11].



I II

R=CN, $COOCH_3$, $CONH_2$; R'=H, OCH_3, Cl

The possibilities of the utilization of cycloisomerization increased significantly after the introduction into synthetic practice of the cyanoethylation of ketones [12]; this procedure makes it possible to readily obtain the starting keto nitriles, and δ-enamino lactams with various structures [13-15], including bicyclic compounds, which were used in the synthesis of lycopodium alkaloids [15], were obtained from them. In addition to gaseous hydrogen halides, mineral and organic acids are used as catalysts of this reaction [16-26].

Lactams with a semicyclic double bond (IV) were obtained from cyanoethylated aliphatic-aromatic ketones III by the action of sulfuric acid:

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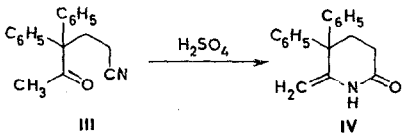
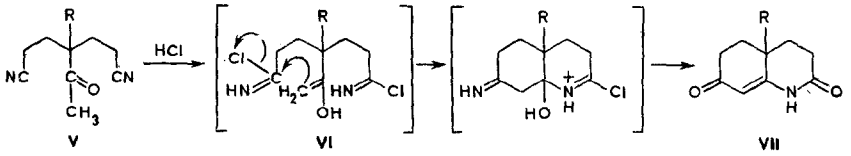


III IV

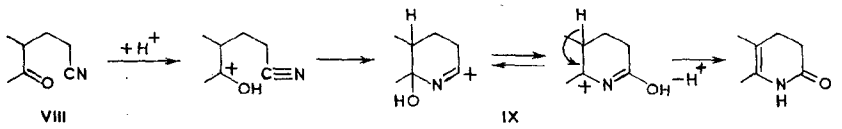
It is assumed that the reaction **proceeds through a** step involving the formation of imino halides VI, which then undergo cyclization via intramolecular addition of the imino group to the double bond of the enol form of the starting nitriles. Precisely this assumption is used to explain the conversion of bis(cyanoethylated) ketones V to two-ring enamino lactams VII, which were subsequently used in the synthesis of aspidospermine alkaloids [27-29].



V VI VII

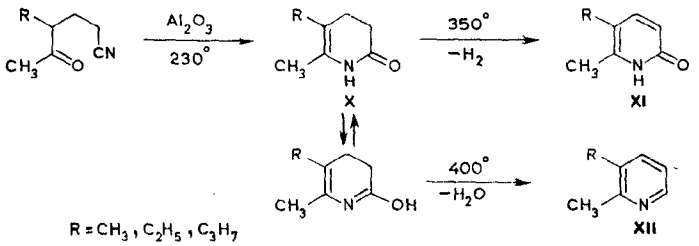
R = CH_3, C_6H_5, CH_2CH_2COOH, $CH_2CH_2OC_6H_5$

In fact, the formation of imino halides VI occurs under conditions of acidic cycloisomerization of keto nitriles [30] and explains the necessity for a high concentration of protons for carrying out the reaction, as well as the significant increases in the yields of cyclization products when electron-acceptor substituents are introduced in the α position relative to the keto group of the starting keto nitriles [31, 32]. From steric considerations, the concept of isomerization of δ-keto nitriles VIII under the influence of acids as a result of intramolecular electrophilic addition of the nitrile fragment to the **protonated carbonyl** group (a variant of the Ritter reaction*) [34, 35] with subsequent stabilization of cyclic carbonium ion IX and conversion to the enamino lactams is less likely:



VIII IX

The catalytic liquid-phase cycloisomerization of δ-keto nitriles over aluminum oxide at 220-230°C [36] gives relatively high yields of enamino lactams [37, 38]. At 350-400°C lactams X undergo partial dehydrogenation and dehydration to give the corresponding pyridones XI and pyridines XII [39]:



X XI XII

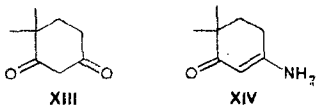
R = CH_3, C_2H_5, C_3H_7

Examples of the conversion of δ-**keto nitriles to** lactams under the influence of bases [14, 40-43] are known. Partial hydrolysis of the keto nitriles to the corresponding amides, which undergo subsequent cyclodehydrations to lactams [14] (see below), is possible when the reactions are carried out in aqueous media.

When hydrogen atoms are present in the ε position of the starting δ-keto nitriles, the yields of enamino lactams are reduced because of side condensation processes that take place

*The reaction of ketones with nitriles under the influence of acids was studied for the first time in [33].

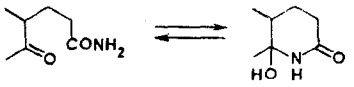
in acidic and alkaline media and lead to the formation of 1,3-cyclohexanediones XIII or their derivatives (XIV) [14, 42, 44]



XIII XIV

δ-Enamino lactams are often obtained from amides of δ-keto acids, which split out water upon heating [19, 45-51], under the influence of dehydrating reagents [52, 53] and acids and bases [5, 54], and even spontaneously on standing [48]. The ease of cyclization depends on the structures of the starting amides and catalysts [54].

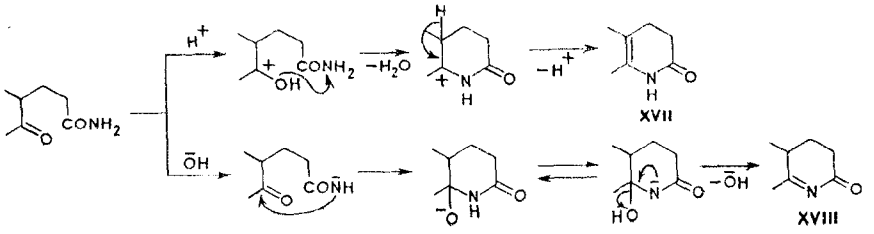
The possibility of the utilization of this reaction is determined by the accessibility of the starting keto amides, which can be obtained by incomplete hydrolysis of δ-keto nitriles [10, 11, 55] and by the action of ammonia and amines on esters of δ-keto acids and δ-enol lactones [1, 48, 56, 57]. In many studies the ease of dehydration [45-47, 52] is linked with the assumption of the existence of a tautomeric equilibrium between linear XV and cyclic hydroxy lactam forms XVI of the δ-keto amides.



XV XVI

Spectral studies have shown that amides of δ-keto carboxylic acids (like the δ-keto acids themselves [58-60]) generally have an open structure [61, 62]. However, they are converted to hydroxy lactams XVI under the influence of bases [42, 54, 63]. An increase in the rigidity of the chain between the carbonyl and amido groupings, for example, the presence of gem-dimethyl groups attached to one of the three sp^3-carbon atoms of this fragment (the Ingold–Thorpe effect) [42, 61] or replacement of two of them by a benzene ring [61, 62], also promotes stabilization of the ring forms. The existence of a tautomeric equilibrium between the cyclic and linear structures has been established for several amides of steroid δ-keto acids [56, 57].

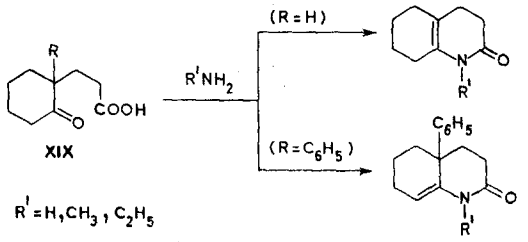
In the case of N-unsubstituted δ-keto amides, regardless of whether they exist in the cyclic or linear form, the formation of isomeric compounds with a double bond in the 5,6-position (3,4-dihydro-2-pyridones XVII) and in the 1,6 position (1,6-dehydro-2-piperidones XVIII) is possible during dehydration. It has been recently shown [5, 54] that the formation



XVII XVIII

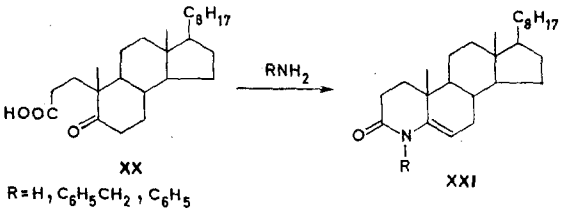
of one or another isomer depends on the dehydration catalyst. In the case of acidic catalysis the reaction leads to dihydropyridones XVII, whereas dehydropiperidones XVIII are formed in alkaline media.

δ-Enamino lactams are obtained by the action of ammonia and amines on δ-keto acids and their derivatives (δ-enol lactones and esters of δ-keto acids). The reactions are carried out under relatively severe conditions (heating under pressure or at elevated temperatures); this is necessary for the dehydration of the initially formed ammonium salts and amides of δ-keto acids. For example, 2-(β-carboxyethyl)cyclohexanone and its phenylated analog XIX were converted to the corresponding enamino lactams with endo- and exocyclic double bonds [64] upon heating with ammonia and amines in an autoclave:



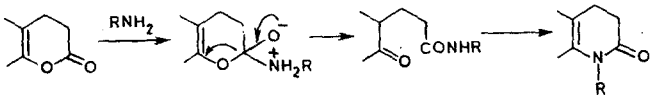
This reaction is widely used to obtain azasteroids in order to search for compounds with a definite spectrum of pharmacological activity [56]. The reaction of steroid δ-keto acids with ammonia and amines has served as a method for the selective inclusion of a nitrogen atom in the A, B, C, and D rings of the steroid system [2, 3, 65-69].

Thus azasteroids XXI with an A-lactam ring were obtained in almost quantitative yields by the action of ammonia [2, 65, 66] and amines [67] on δ-keto acid XX.



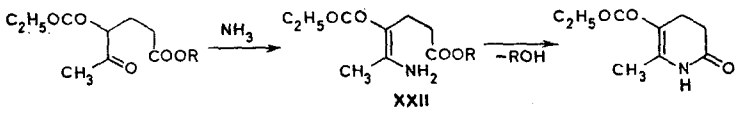
Steroid systems with B-, C- [3, 70-72], and D-lactam rings [73], as well as steroid sapogenins with a nitrogen atom in the C ring [74], were similarly synthesized.

The reaction of δ-enol lactones with ammonia and amines is a convenient method for the synthesis of δ-enamino lactams. Depending on the basicity of the nitrogen base and the structure of the lactone, the starting compounds react in the cold [49, 75-78] or upon heating [78, 79].



Amides of keto acids, which then undergo cyclization by the methods indicated above, are sometimes formed as a result of the reaction in [76]. The conversion of steroid δ-enol lactones to lactams under the influence of ammonia and amines has served for the synthesis of azasteroids [57, 65, 67].

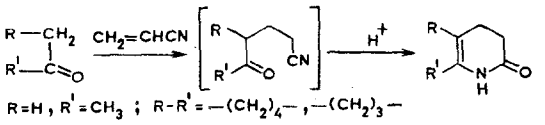
Enamino lactams are obtained by the ammonolysis of esters of δ-keto acids. The reaction proceeds through a step involving the formation of keto amides [49] or enamines XXII [80, 81]:



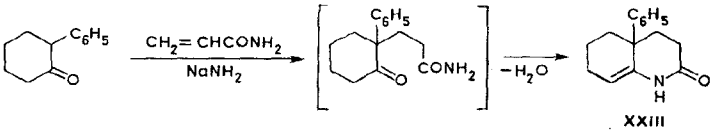
Preparation of δ-Enamino Lactams by Michael Condensation. The condensation of ketones (and their derivatives), β-diketones, and esters of β-keto acids with α,β-unsaturated acids and their nitriles, esters, amides, and acid chlorides is widely used for the synthesis of enamino lactams [82-93].

In addition, 3,4,6-trisubstituted δ-enamino lactams have been obtained by the reaction of **α,β-unsaturated ketones with** malonic acid derivatives [53, 93-97]. Both types of reactions lead initially to the formation of products of addition of the methylene component to the activated double bond of the acid or ketone; these products then undergo immediate cyclization.

The preparation of enamino lactams by the direct **reaction of ketones** with acrylonitrile has been described [82]. The yields of lactams in this reaction depend substantially on the structures of the starting ketones:



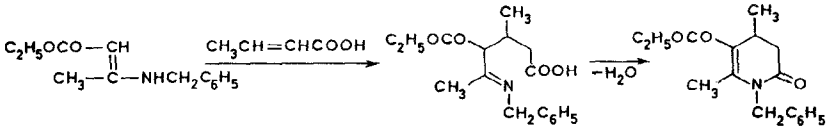
The reaction of ketones with acrylamide (carbamidoethylation), which was realized in the presence of strong bases, led to the formation of condensed enamino lactams XXIII in low yields (10-30%).



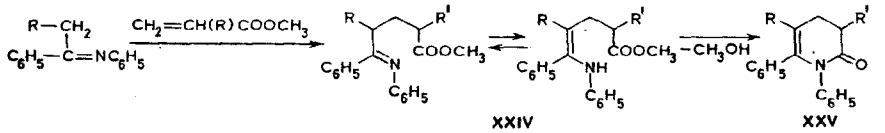
XXIII

It was found that the yields of lactams in this reaction could be increased by using the enamines [84, 85] or imines [85] of these ketones.

The enamino ketones are also converted to the corresponding lactams in the reaction with α,β-unsaturated acids [86] and their esters [87]:

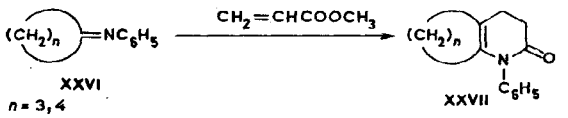


A method that consists in the addition of Schiff bases of **aliphatic**—aromatic ketones to esters [88] and nitriles [89] of α,β-unsaturated acids in the presence of aluminum chloride at 20°C with subsequent cyclization of the intermediately formed enamino esters XXIV was recently proposed for the synthesis of N-phenyl-3,4-dihydropyridones. Diverse N-phenyl lactams XXV were obtained in 60-85% yields by this method.



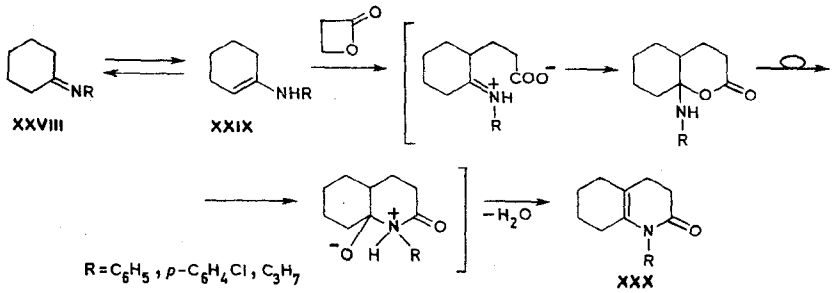
XXIV XXV

When this reaction is carried out with anils (XXVI) of cyclic ketones (without a catalyst) it gives lower yields of lactams XXVII [90].



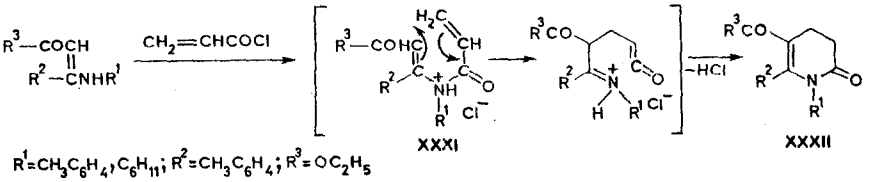
XXVI, n = 3,4 XXVII

A method for the synthesis of condensed lactams XXX, which consists in the reaction of imines (XXVIII) of cyclic ketones with β-propiolactone or α,β-unsaturated acids (acrylic, crotonic, and methacrylic acids), was proposed in 1980 [91]. Shabana and co-workers [91] propose the following scheme for the transformation, which includes the addition of propiolactone (or an unsaturated acid) to the double bond of isomeric enamine XXIX:

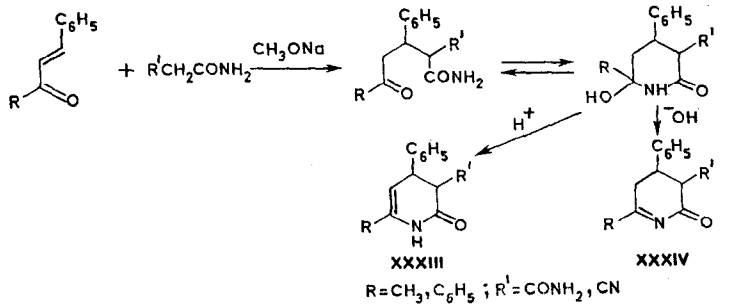


When cyclohexylidenepropylamine (XXVIII, R = C_3H_7) is used, the reaction proceeds unambiguously to give the corresponding lactam XXX (in 35-50% yield). However, mixtures of isomeric 2- and 4-quinoline derivatives are obtained when R = C_6H_5.

It was recently shown that δ-enamino lactams with various structures can be obtained by the reaction of imines of ketones and monoenamines at β-diketones (or β-keto esters) with α,β-unsaturated acid chlorides. The authors assume that the initial step is N-acylation of the starting enamine by the acid chloride with subsequent cyclization of ketene salt XXXI as a consequence of [3,3]-sigmatropic rearrangement of the acylation product. The reaction makes it possible to obtain lactams XXXII with various substituents in the 1, 5, and 6 positions [92, 93]:



3,4,5-Trisubstituted 3,4-dihydro-2-pyridones were obtained in 40-75% yields [54, 94-97] in the condensation of unsaturated **aliphatic**—aromatic ketones with **malonic** acid derivatives in the presence of sodium methoxide [53, 54] or diethylamine [53]. Direct condensation products, viz., δ-keto amides, which, depending on the pH of the medium, were dehydrated to give the isomeric δ-enamino lactams XXXIII and XXXIV, were isolated when the reactions were carried out at room temperature [5]:

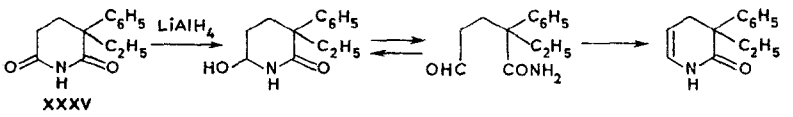


Both isomers are readily oxidized to pyridones when the reactions are carried out for a long time [5, 54, 96].

The reactions of arylidenecycloalkanones with malonic acid diamide and cyanoacetamide have been used for the preparation of 3,4-dihydropyridones with condensed rings [5].

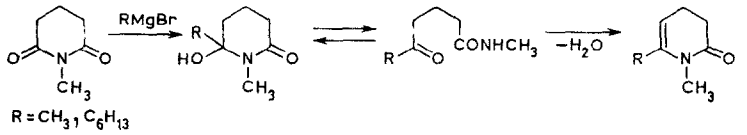
The reaction of α,β-unsaturated ketones with esters of cyanoacetic acid proceeds similarly [98, 99].

Other Methods of Preparation. The preparation of 3,4-dihydro-2-pyridones by the reduction of imides (XXXV) of substituted glutaric acids with lithium aluminum hydride [46, 100] has been described; for example, 3-ethyl-3-phenyl-3,4-dihydro-2-pyridone was obtained in 65% yield in the reduction of α-ethyl-α-phenylglutarimide [46]:

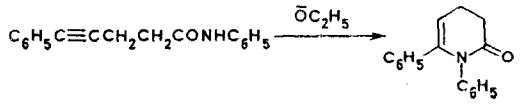


XXXV

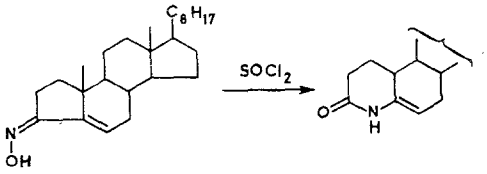
The N-methylimide of glutaric acid is converted to 3,4-dihydro-2-pyridones upon reaction with organomagnesium compounds [47].



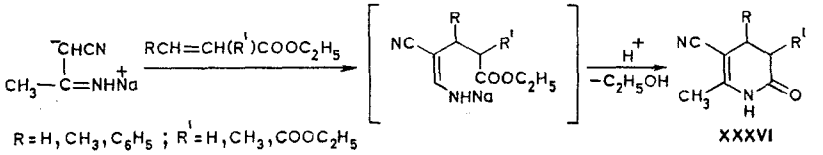
The cyclization of 5-phenylpentynoic acid anilide under the influence of sodium ethoxide was used to obtain 1,6-diphenyl-3,4-dihydro-2-pyridone [101, 102]:



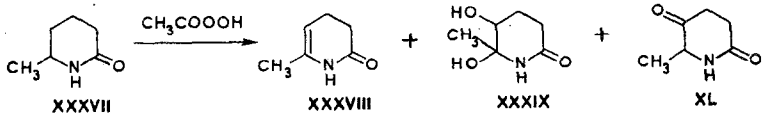
The introduction of a nitrogen atom in the A and D rings of the steroid system was realized by Beckmann rearrangement of oximes of unsaturated ketones of the cholestenone series [66, 73]:



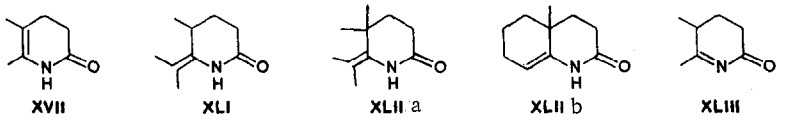
A general method, which consists in the reaction of esters of α,β-unsaturated acids with the sodium derivative of the acetonitrile dimer, has been proposed for the synthesis of substituted 3,4-dihydro-2-pyridones with a nitrile group in the 5 position (XXXVI, 60-70% yields) [103]:



The catalytic oxidation of 6-methyltetrahydro-2-pyridone (XXXVII) with peracetic acid led to dihydro-2-pyridone XXXVIII, together with diol XXXIX and its dehydration product XL [104].

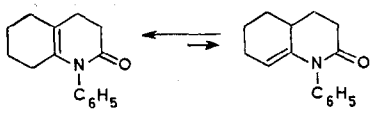


In the preparation of δ-enamino lactams by the methods described above the double bond may be found in the 5,6-position (the formation of 3,4-dihydro-2-pyridones) and also in the semicyclic position. In many of the papers cited above [13, 20, 64, 75-80] the authors assigned, without evidence, the 3,4-dihydro-2-pyridone structure (XVII) to the lactams obtained, although the structure of the starting compounds did not exclude the formation of lactams (XLI) with a semicyclic position of the double bond, as well as 1,6-dehydropiperidones XLIII [18, 53, 81, 96, 97, 99].



XVII XLI XLII a XLII b XLIII

An investigation of the structure of the lactams by IR and PMR spectroscopy showed that when the structural factors determine the possibility of the formation of both isomers equally probably, chiefly 3,4-dihydro-2-pyridones XVII are obtained [105] (in the cycloisomerization of δ-keto nitriles [24], the dehydration of amides of formyl and keto acids [46], in the cyclization of esters of δ-amino acids [81], and the aminolysis of δ-enol lactones [78]). Lactams with a semicyclic double bond (XLI and XLII) are formed primarily when there are two substituents in the 5 position (XLIIa) [14, 68-71, 83], i.e., when the formation of the XVII structure is impossible. However, the existence of an equilibrium for 1-phenyl-3,4,5,6,7,8-hexahydro-2-quinolone, which is shifted to favor dihydropyridine form XVII, was recently established by PMR spectroscopy [91]:

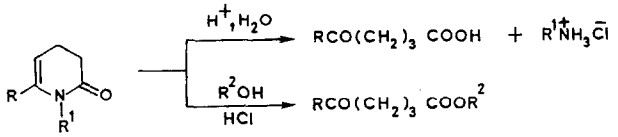


XVII XLII c

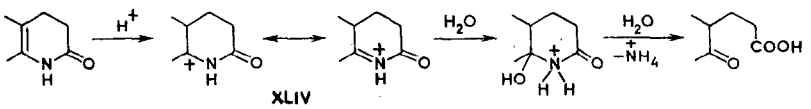
The formation of isomers XVII or XLIII in the dehydration of amides of δ-keto acids is determined by the character of the catalyst used and is due to the difference in the mechanisms of dehydration in acidic and alkaline media. The 3,4-dihydropyridine structure (XVII) was proven [54, 63] in conformity with the principle found for lactams obtained by acidic dehydration of δ-keto amides, to which the 1,6-dehydro-2-piperidone structure (XLIII) was previously erroneously assigned [53, 96].

Reactions of δ-Enaminolactams

In contrast to saturated lactams, the hydrolysis and alcoholysis of δ-enamino lactams is accompanied by removal of nitrogen [5, 18, 96, 99] by splitting out of ammonia or amine molecules. Both reactions, which proceed very readily under acidic catalysis conditions in the cold or upon refluxing, lead to opening of the lactam ring and the formation of δ-keto acids [5, 96, 99] and, correspondingly, to their esters [9, 10 , 102, 106]:



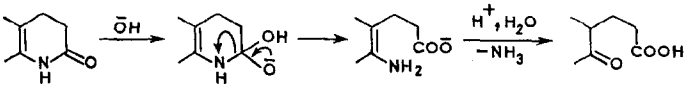
The greater ease of acidic hydrolysis and alcoholysis as compared with saturated lactams is due to the formation (as in the hydrolysis of enamines [107]) of conjugation-stabilized immonium ion XLIV, which upon subsequent hydration is converted to a keto acid:



XLIV

According to the data in [8, 9], δ-enamino lactams are resistant to the action of aqueous solutions of alkalis in the cold; however, it was later shown [5] that under these conditions they are readily oxidized to 2-pyridones.

When they are heated with alkaline solutions, lactams undergo ring opening to give δ-keto acids (upon subsequent acidification) [41]:



The hydrogenation of enamino lactams was carried out in the presence of platinum and palladium catalysts [3, 73, 108] (in the cold) and was not accompanied by hydrogenolysis of the lactam ring. Thus, for example, the hydrogenation of azasteroids with B- and D-lactam rings over Pt/C proceeded with the formation of the corresponding steroid piperidones in 60-85% yields [3, 73].

The dehydrogenation of δ-enamino lactams with an endocyclic double bond is a well-known method for the preparation of pyridones [19, 22]. Although the ability of enamino lactams to undergo spontaneous oxidation was noted in [5, 96, 98], in synthetic practice oxidizing agents or dehydrogenation catalysts are used for this purpose.

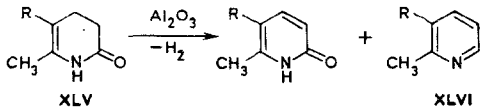
The oxidation of δ-enamino lactams with hydrogen peroxide or benzylideneindandione in an alkaline medium [5], as well as with chromium trioxide in acetic acid [5, 63], was recently proposed for the preparative production of 2-pyridones. The reactions are catalyzed by traces of benzoyl peroxide or UV light, which indicates a radical mechanism for the oxidation. In addition, it has been shown that the rate of dehydrogenation of 3,4-dihydro-2-pyridones with these oxidizing agents is higher than the rate of dehydrogenation of isomeric lactams with a double bond in the 1,6-position (XLIII) [5].

The use of sulfuric acid for the dehydrogenation of 5,6-cyclohexano-3,4-dihydro-2-pyridone gave good results. However, a change in the size of the ring condensed with the lactam ring and other structural factors have a pronounced effect on the yields of pyridones [19].

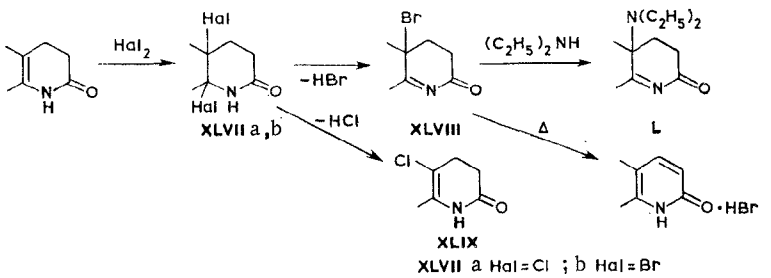
The oxidation of 3,4-dihydro-2-pyridones with nitrous acid [9-11] cannot serve for the preparative production of 2-pyridones.

The usual dehydrogenation reagents, viz., sulfur, N-bromosuccinimide, and palladium on charcoal, have been used successfully for the preparation of pyridones from lactams [22, 23, 38, 40].

The vapor-phase catalytic dehydrogenation of 3,4-dihydro-2-pyridones XLV over Al_2O_3 at 360-400°C is accompanied by a side process, viz., dehydration, as a consequence of which the corresponding pyridines XLVI are formed along with 2-pyridones [39] (see above).

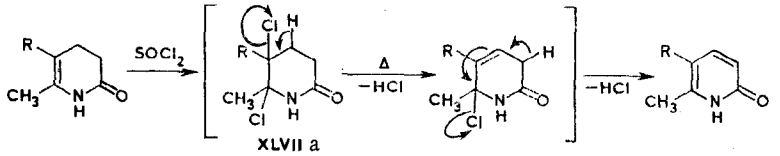


Electrophilic addition to the double bond of δ-enamino lactams has been studied in the case of chlorination and bromination [13, 109-111]. 3,4-Dihydro-2-pyridones readily add chlorine and bromine to give 5,6-dihalo-3,4-dihydro-2-pyridones XLVII, which, depending on the conditions, may split out one or two molecules of hydrogen halide. In the case of partial dehydrohalogenation (treatment with water in the cold) a halogen atom is split out from the 6 position to give 5-halo-1,6-dehydro-2-piperidones XLVIII [13] or 5-halo-3,4-dihydro-2-pyridones XLIX [110]. Extremely reactive bromo lactams XLVIII are hydrolyzed when they are heated with water, undergo isomerization to 2-pyridone hydrobromides [13] during distillation, and undergo nucleophilic exchange of the halogen atom to give 5-dialkylamino-1,6-dihydro-2-piperidones L [112].



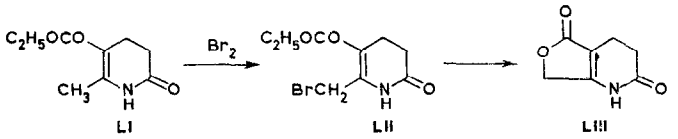
Splitting out of two molecules of hydrogen halide from 5,6-dialkyl-substituted lactams XLVII, which was accomplished by thermolysis [109] or by the action of bases [13], leads to the formation of 2-pyridones. The thermolysis of dichlorides XLVIIa is used for the preparative production of 2-pyridones. The process is realized directly from 3,4-dihydro-2-pyri-

dones by chlorination with sulfuryl chloride and subsequent dehydrochlorination without the liberation of dichlorides [109], just as has been described for the oxygen analogs [1]. Under these conditions a chlorine atom is first split out from the 5 position of dichloride XLVIIa.



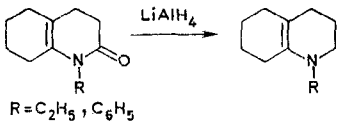
XLVII a

Allylic bromination of δ-enamino lactams with N-bromosuccinimide (NBS) was observed for 3,4-dihydro-2-pyridones LI, the double bond of which is deactivated with respect to electrophilic addition [23, 113]. Thus, bromomethyl lactam LII, the structure of which was proved by spectral means and also by the production of lactono lactam LIII from it, was obtained from 6-methyl-5-carbethoxy-3,4-dihydropyridone (LI) [108, 113].

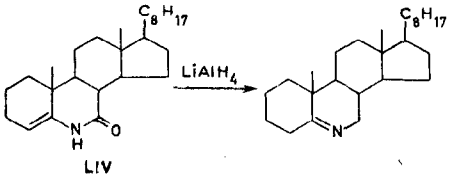


LI LII LIII

Reduction of the carbonyl group to give tetrahydropyridine derivatives occurs when N-substituted enamino lactams are treated with excess lithium aluminum hydride [78, 114, 115]:



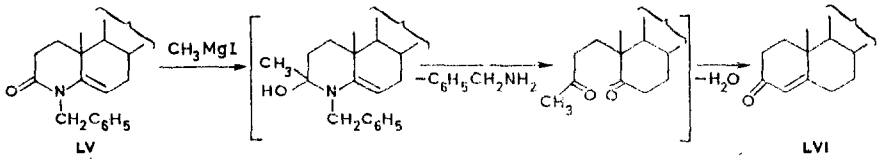
Azasteroid LIV with an N-unsubstituted lactam ring undergoes isomerization with migration of the double bond, together with **reduction of the** carbonyl group, when it is treated with lithium aluminum hydride [3, 115].



LIV

The reaction of the simplest δ-lactams with lithium aluminum hydride proceeds ambiguously [78].

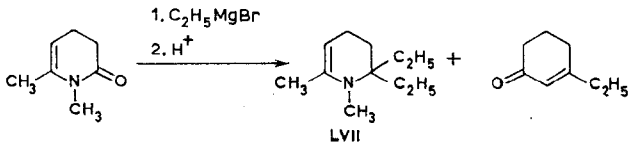
The reaction of enamino lactams with organomagnesium compounds (in a ratio of 1:1) leads to 1,5-diketones (via a crotonic condensation scheme). For example, cyclohexenone LVI was obtained in 50% yield in the reaction of azacholestenone LV with methylmagnesium iodide [68]:



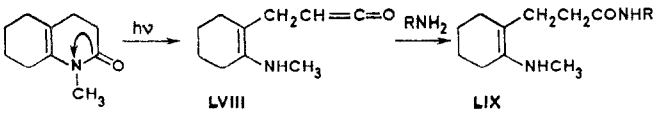
LV LVI

This synthetic method has been used for the construction of a cyclohexene ring in the steroid series just as this has been realized by the reaction of δ-enol lactones with organomagnesium compounds [1].

The addition of 2 moles of an organomagnesium compound to 1,6-dimethyl-3,4-dihydro-2-pyridone led to tetrahydropyridine LVII, along with 3-ethyl-2-cyclohexenone (via the scheme described above) [116].



In the photolysis [117] of δ-enamino lactams, which was studied in the case of 1-methyl-5,6-cyclohexano-3,4-dihydro-2-pyridone, one observes cleavage of the 1,2 ring bond to give enamino ketene LVIII (identified in the form of enamide LIX).



Enamino lactams are alkylated by dimethyl sulfate [27] and benzyl chloride [15] only at the nitrogen atom, in contrast to enamines, for which preferred alkylation of the α-carbon atom of the enamino grouping is characteristic.

The oxidation of azaprogesterone (with an A ring in the form of an enamino lactam) with phenylsulfurous acid was recently studied in order to obtain new azasteroids that have biological activity [118].

Papers in which new methods for the preparation of enamino lactams [119, 120] were proposed and their condensation with aldehydes was described [121] were published while this paper was being prepared for publication.

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