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SYNTHESIS OF 2,3-DIHYDROIMIDAZO[1,2-*a*]-PYRIDINES AND THEIR SALTS. (REVIEW)

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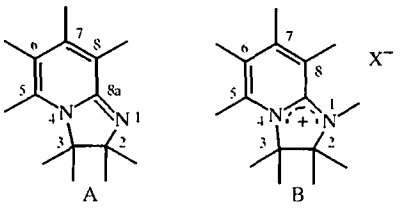
In the present review the published data on the nomenclature, structure, and synthesis of 2,3-dihydroimidazo[1,2-a]pyridines up to 1998 are reviewed.

The first information on 2,3-dihydroimidazo[1,2-*a*]pyridines appeared in the 1920s. In this series of compounds various dyes [1-17] (including photosensitive dyes [8-14]), optical data carriers [18], pesticides [5], fungicides [19], hypoglycemic agents [20], neuromuscular blockers [21], substances causing shrinkage of heart muscle [22], and compounds exhibiting antitumor [23-27], antiinflammatory, antipyretic, and analgesic activity [28-34] were synthesized. In recent years these compounds have found synthetic applications: 2-oxoimidazo-[1,2-*a*]pyridines and their salts are key intermediates in the synthesis of disubstituted maleic imides [35, 36] and anhydrides [36-42], while 3-oxoimidazo[1,2-*a*]pyridines are used as starting materials in the synthesis of N-(2-pyridyl)-α-amino acids and their esters [43].

Several reviews [44-47] on imidazo[1,2-*a*]pyridines have also described their 2,3-dihydro derivatives. However, both the methods and the properties of these compounds have been covered inadequately. The present review is devoted to the nomenclature, structure, and methods of synthesis of 2,3-dihydroimidazo[1,2-*a*]pyridines A and their salts B.



Compounds containing oxo group at positions 2 and 3 are also included.

1. NOMENCLATURE AND STRUCTURE OF 2,3-DIHYDROIMIDAZO[1,2-*a*]PYRIDINES AND THEIR SALTS

The nomenclature of imidazo[1,2-*a*]pyridines has changed significantly in the course of time [2, 16, 24, 46, 48, 49]. In the earlier papers the name 2,3-dihydropyrimidazole and the numbering in formula A1 were used for compounds A [48]. At the present time the atoms are usually numbered according to formula A, but there are exceptions (e.g., A2 [50]).

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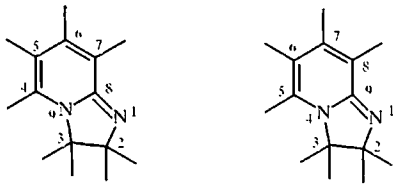
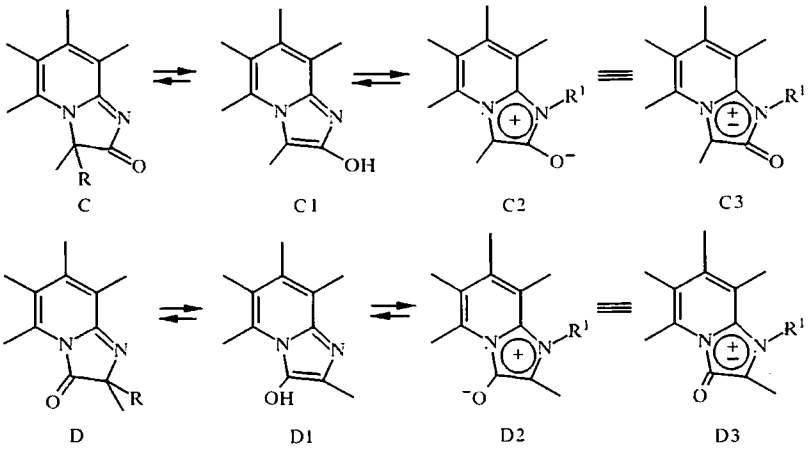


A1 A2

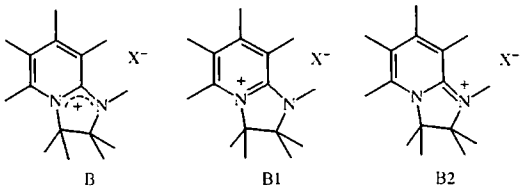
The 2-oxo and 3-oxo derivatives of 2,3-dihydroimidazo[1,2-*a*]pyridines C and D (R = H) can also exist in the enolic forms C1 and D1 respectively [51-54]. However, it follows from spectroscopic data [37, 38] that the structure of these compounds is reflected more accurately in formulas C2 (1H-imidazo[1,2-*a*]pyridinio-2-olate) and D2 (1H-imidazo[1,2-*a*]pyridinio-3-olate) (R^1 = H) [37-39, 55-59].



C C1 C2 C3

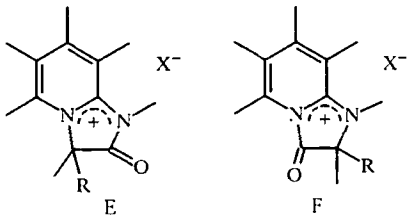
D D1 D2 D3

The salts of compound A are called 2,3-dihydroimidazo[1,2-*a*]pyridinium salts [60-62] or 2,3-dihydro(1H)-imidazo[1,2-*a*]pyridin-4-ium salts [62]. Their structure has been represented both by structure B [50, 61, 62] and by structure B1 [21, 37, 60, 62-74] or B2 [57, 65, 75].



B B1 B2

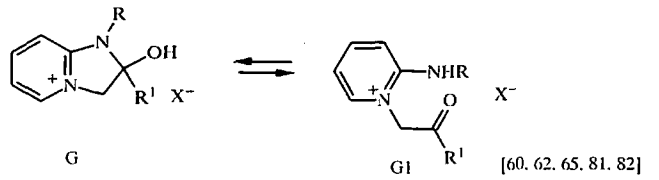
The oxo derivatives C and D also give 2-oxo(3H)imidazo[1,2-*a*]pyridinium salts E and 3-oxo(2H)imidazo[1,2-*a*]pyridinium salts F on alkylation or on treatment with mineral acids.



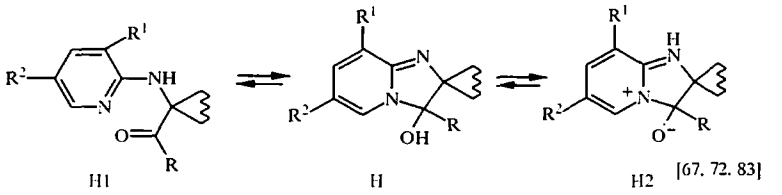
E F

The structures C3 and D3 formed in the course of the dehydration of compounds E and F (R = H, X = OH) have also been called 1-substituted 2- or 3-hydroxyimidazo[1,2-*a*]pyridinium anhydrohydroxides [76-79].

The structural features of imidazo[1,2-*a*]pyridines are also characterized by three effects: ring–chain tautomerism of 2- and 3-hydroxy derivatives (G-G1, H-H1), the formation of mesoionic compounds in the case of 2-oxo and 3-oxo derivatives (C2, C3, D2, D3), and the formation of zwitterions due to the basicity of the imidazole nitrogen atom $N_{(1)}$, such as H2 [50, 37, 80].



G G1 [60, 62, 65, 81, 82]



H1 H H2 [67, 72, 83]

It follows from the foregoing that there is no common nomenclature for the 2,3-dihydroimidazo[1,2-*a*]-pyridines, and it is consequently difficult to locate the data on compounds A and B, particularly in the earlier literature. In the present review we use the nomenclature according to the IUPAC rules and the Ring Index.

2. METHODS OF SYNTHESIS OF 2,3-DIHYDROIMIDAZO[1,2-*A*]PYRIDINES AND THEIR SALTS

Unsubstituted 2,3-dihydroimidazo[1,2-*a*]pyridine A was first obtained in 1935 [84], although its 2- and 3-hydroxy derivatives had been known earlier [48, 85-91].

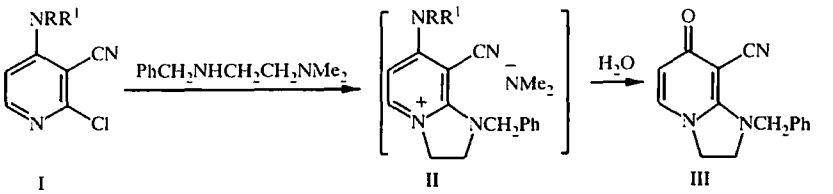
Methods for the production of 2,3-dihydroimidazo[1,2-*a*]pyridines can be divided into two main groups: syntheses based on pyridine derivatives; syntheses based on imidazole derivatives.

2.1. Syntheses Based on Pyridine Derivatives

2-Halopyridines and 2-aminopyridines and also 1-substituted pyridinium salts have most often been used for the synthesis of 2,3-dihydroimidazo[1,2-*a*]pyridines. These reactions can be subdivided in the following way according to the mechanism: intramolecular cyclization of 2-(β-X-ethyl)aminopyridines; alkylation and acylation of 2-aminopyridines followed by intramolecular cyclization; intramolecular cyclization of 1-substituted pyridinium salts and pyridinium ylides.

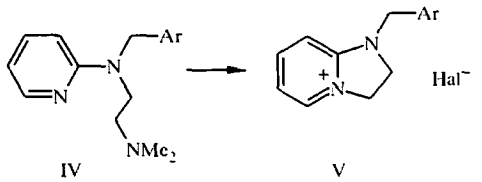
2.1.1. Intramolecular Cyclization of 2-(β-X-Ethyl)aminopyridines. 2-(β-X-Ethyl)aminopyridines are usually obtained from 2-halopyridines. Intramolecular alkylation or acylation at the nitrogen atom of the pyridine ring in N-(2-pyridyl) derivatives of ethylenediamine, ethanolamine, 2-haloethylamine, and aminoacetic acid leads to imidazopyridines.

Imidazopyridinium salts II are presumably formed as intermediates when 2-chloropyridines I are heated with N,N-dimethyl-N'-benzylethylenediamine in an autoclave at 190°C for 18 h, although only 1-benzyl-2,3-dihydro-8-cyanoimidazo[1,2-*a*]pyridin-7-one (III) was isolated [74].



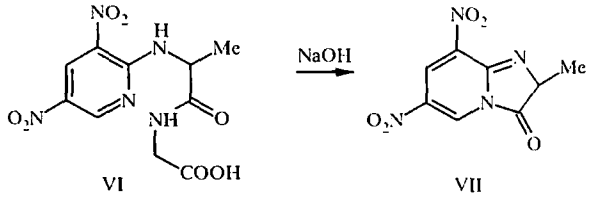
I II III

Intramolecular cyclization takes place in the course of dealkylation of N-(*p*-methoxybenzyl)-N-(2-pyridyl)ethylenediamine IV (Ar = C_6H_4OMe-4) with the formation of imidazopyridinium salt V (Hal = I, Ar = C_6H_4OH-4) [92]. Imidazopyridinium bromide V (Hal = Br) was obtained by heating the compound IV (Ar = Ph) with cyanogen bromide [93].



IV V

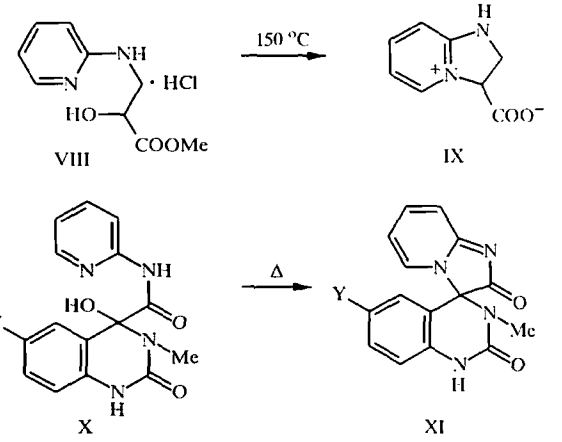
Spectrophotometric data show that imidazopyridine VII is formed during the alkaline hydrolysis of 3,5-dinitro-2-pyridylalanylglycine VI [94].



VI VII

Derivatives of N-(2-pyridyl)aminoethanol (of type VIII) are usually employed for the synthesis of 2,3-dihydroimidazo[1,2-*a*]pyridines. Dehydration of these derivatives gave the betaine IX [80] and the spiro compound XI [95].

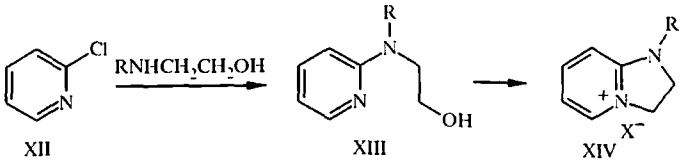
The analogous reaction is observed when N-(5-nitro-2-pyridyl)aminoethanol is heated with hydrochloric acid under pressure [84].



VIII IX

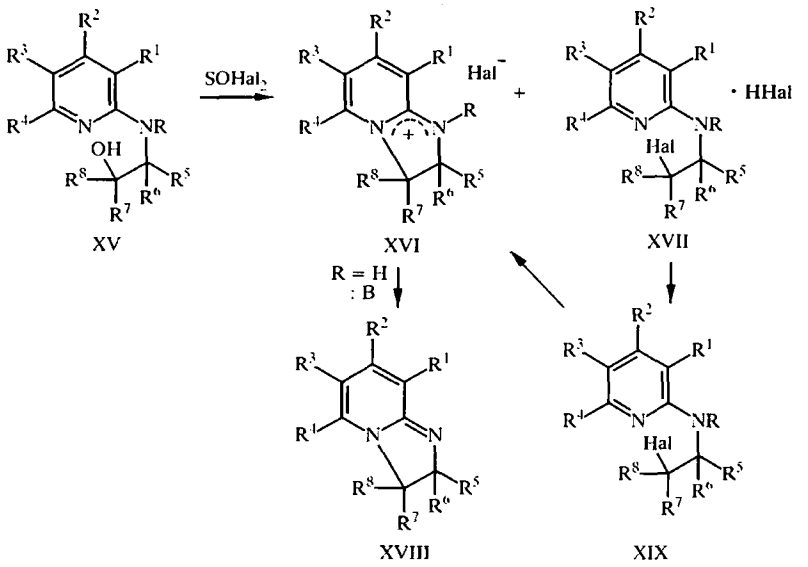
X XI

Phosphate [96], acetate [97], tosyl [24, 72] and mesyl [24, 73] derivatives of N-(2-pyridyl)aminoethanols readily form the products from intramolecular alkylation, i.e., imidazo[1,2-*a*]pyridinium salts. Thus, pyridines XIII, obtained from 2-chloropyridine XII, react with methanesulfonyl chloride or with triphenylphosphine to give 1-alkyl-2,3-dihydroimidazo[1,2-*a*]pyridinium salts XIV [73].



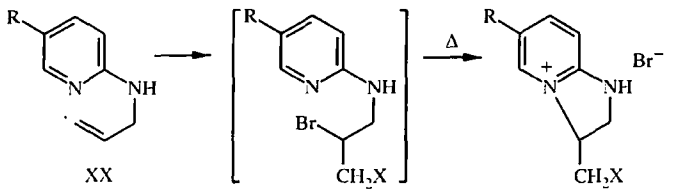
XII XIII XIV

Various N-(2-pyridyl)aminoethanols XV react with thionyl chloride to form the imidazopyridinium salts XVI [24, 84, 98-101], which give the bases XVIII when treated with alkali. At lower temperatures and with a smaller amount of thionyl chloride the chlorine derivatives XVII and XIX were isolated [98, 80, 101]. When heated or when treated with alkali, the 2-N-(β-haloethyl)aminopyridines (XIX) undergo cyclization to the salts XVI [24, 80, 98, 101-103].



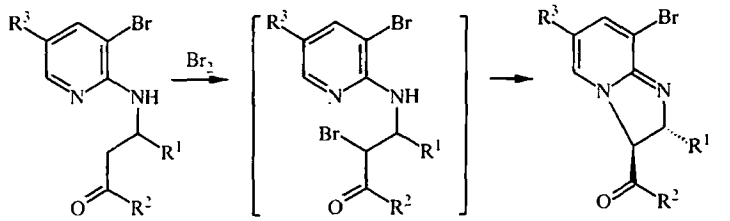
XV XVI XVII XVIII XIX

2-Allylaminopyridines XX and their salts can serve as the starting materials in the synthesis of imidazo[1,2-*a*]pyridines, since the reactions of these compounds with hydrobromic acid [84] or bromine [49] lead to the formation of 2-N-(β-bromoethyl)aminopyridines XXI, which on heating undergo cyclization to imidazopyridines XXII (X = H, Br).



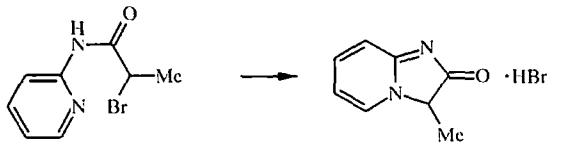
XX XXI XXII

It seems likely that *trans*-dihydroimidazopyridines XXV were produced through the analogous intermediate XXIV at the bromination of 2-alkylaminopyridine XXIII [104].



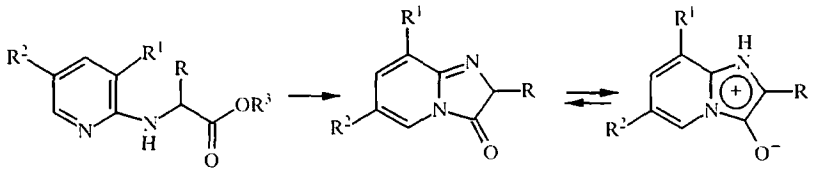
XXIII XXIV XXV

Thus, when heated, N-(2-pyridyl)haloacetamides undergo cyclization with the formation of the salts of 2-oxoimidazo[1,2-*a*]pyridines [40, 52, 91, 105-109]. For example, the compound XXVI is converted into imidazopyridinium hydrobromide XXVII even at room temperature [110].



XXVI XXVII

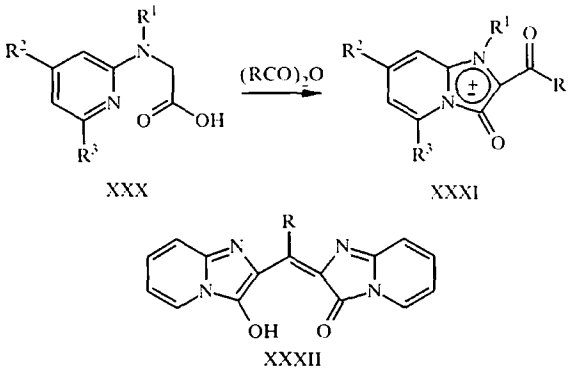
N-(2-Pyridyl)aminoacetic acid derivatives are the starting compounds in the synthesis of 3-oxoimidazo[1,2-*a*]pyridines. Thus, the compounds XXVIII (R^3 = H) undergo intramolecular acylation when treated with phosphorus trichloride and form 3-oxoimidazopyridines XXIXa [17, 94].



XXVIII XXIXa XXIXb

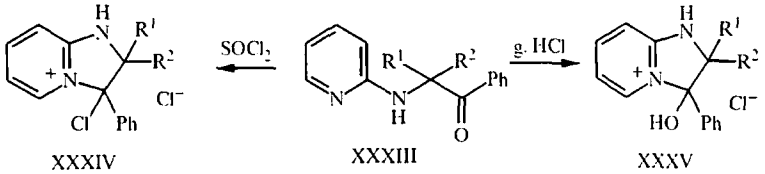
The cyclic compound XXIXa (R = Me) was also obtained by heating the ester XXVIII (R = Me, $R^1 = R^2 = H$, R^3 = Et) under vacuum, although this was not possible with other compounds (R = H, Ph) [52]. However, the mesoionic compound XXIXb (R = Ph, $R^1 = R^2 = H$) was isolated when the methyl ester XXVIII (R = Ph, $R^1 = R^2 = H$, R^3 = Me) was boiled in 5N hydrochloric acid and then treated with sodium carbonate [57].

N-(2-Pyridyl)aminoacetic acids XXX [77] and also their sodium salts [78] and hydrochlorides [17] gave imidazopyridines XXXI or XXXII (R = Me, R^1 = H) when heated with various carboxylic acid anhydrides.



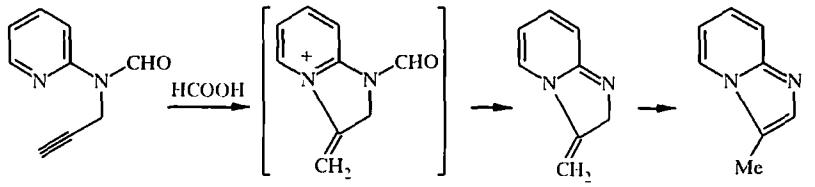
XXX XXXI XXXII

The formation of an electrophilic center at the β-position of the substituent at the exo-nitrogen atom of N-substituted 2-aminopyridines usually leads to intramolecular cyclization. For example, treatment of the keto derivative XXXIII with thionyl chloride gave imidazopyridinium chloride XXXIV, whereas treatment with hydrogen chloride gave the chloride XXXV [83, 111].



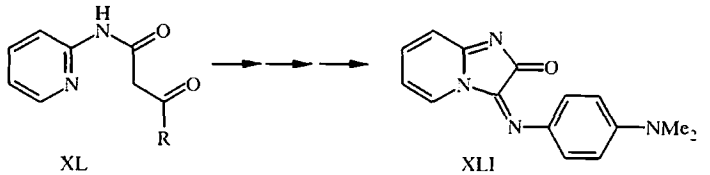
XXXIV XXXIII XXXV

It is suggested that when 2-aminopyridine XXXVI is heated with formic acid in absolute ethanol imidazopyridine XXXVIII containing an exocyclic double bond is formed through the intermediate XXXVII and is then stabilized to 3-methylimidazo[1,2-*a*]pyridine XXXIX [70].



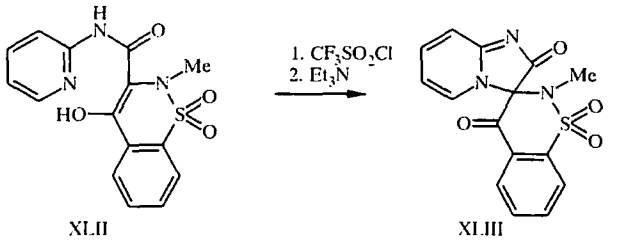
XXXVI XXXVII XXXVIII XXXIX

Azomethine XLI was obtained from 2-aminopyridine XL and N,N-dimethyl-*p*-nitrosoaniline through a series of transformations [112].



XL XLI

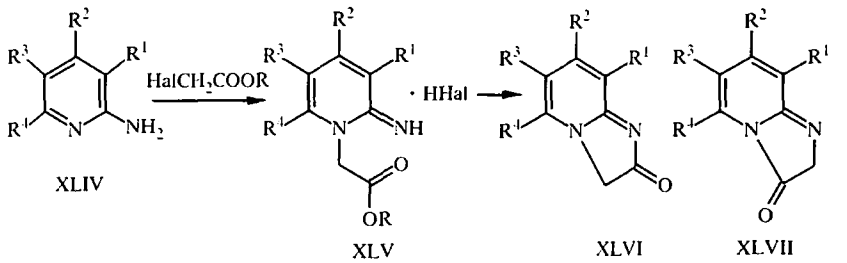
The spiro compound XLIII is formed in the reaction of pyroxycam XLII with trifluoromethanesulfonyl chloride [113].



XLII XLIII

2.1.2. Alkylation and Acylation of 2-Aminopyridines followed by Intramolecular Cyclization. The condensation of 2-aminopyridines with haloacetic acids, their esters and acid halides and also with α-halo ketones is the most widely used method for the synthesis of imidazo[1,2-*a*]pyridines. As known [45], the alkylation of 2-aminopyridines takes place mainly at the nitrogen atom of the pyridine ring except in cases where steric hindrance arise and the exo-nitrogen atom enters into the reaction. The acylation of 2-aminopyridines on the other hand usually takes place at the exocyclic nitrogen atom.

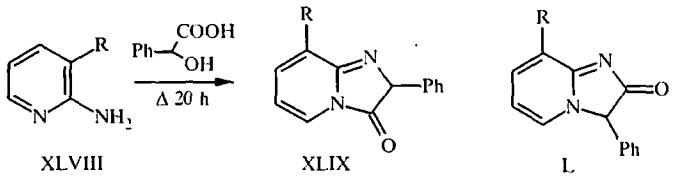
Many papers have been devoted to study of the reaction of 2-aminopyridines with haloacetic acids [48, 85, 87, 91, 114]. 2-Aminopyridines XLIV react with potassium or sodium salts of haloacetic acids in aqueous solution to form the corresponding (2-imino-1-pyridyl)acetic acids XLV (which can be isolated). When heated and treated with acid or alkali the latter undergo cyclization to 2-oxoimidazopyridines XLVI [1, 13, 63, 115-120].



XLIV XLV XLVI XLVII

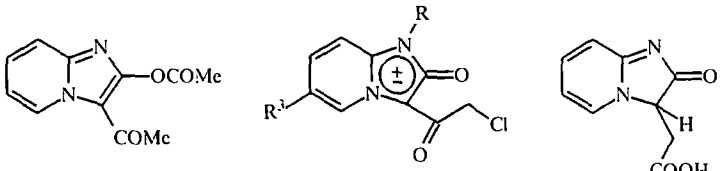
The above-mentioned investigations doubt the reactions of 2-aminopyridine with chloroacetic acid or chloroacetyl chloride described in 1924 [86] as leading to 3-oxoimidazopyridine XLVII.

The reaction of 2-amino-3-methylpyridine XLVIII (R = Me) with mandelic acid also gave oxoimidazopyridine, however its structure (XLIX) or (L) was not determined accurately [121].



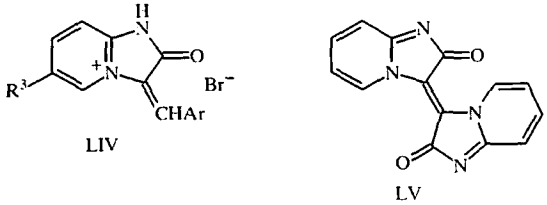
XLVIII XLIX L

When heated in acetic anhydride (2-imino-1-pyridyl)acetic acid (XLV) (R = H) forms diacetyl derivative of 2-hydroxyimidazopyridine (LI) [87]. When heated with chloroacetic acid or its anhydride N-substituted 2-aminopyridines give the mesoionic compounds LII [78]. 2-Oxoimidazopyridine LIII was obtained by the acylation of 2-aminopyridine with maleic anhydride [37, 38, 41].



LI LII LIII

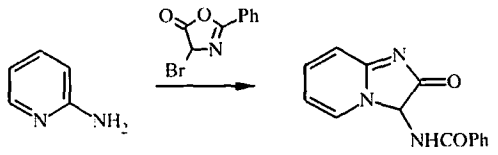
The reaction of 2-aminopyridines with the esters of α-halo carboxylic acids also takes place through the intermediate XLV with the formation of 2,3-dihydro-2-oxoimidazo[1,2-*a*]pyridines XLVI [1, 6, 8, 9, 48, 57, 91, 116, 117, 122] (if the reaction is carried out at room temperature, 2-iminopyridine can be isolated [117]). In the analogous reaction of 5-halo-2-aminopyridines XLIV (R^3 = I, Br) with ethyl bromoacetate the formed imidazopyridine XLVI without isolation is condensed with aromatic aldehydes, and the ylidene derivatives LIV are obtained [11].



LIV LV

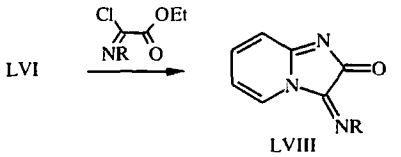
The reaction of diethyl 1,2-dibromomaleate with a twofold excess of 2-aminopyridine leads to the dimer of 2-oxoimidazopyridine LV [88].

4-Bromo-2-phenyloxazol-5-one reacts with 2-aminopyridine in the presence of alcohols with cleavage of the oxazolone ring and the formation of 3-benzoylamino-2-oxoimidazopyridine LVII [123].



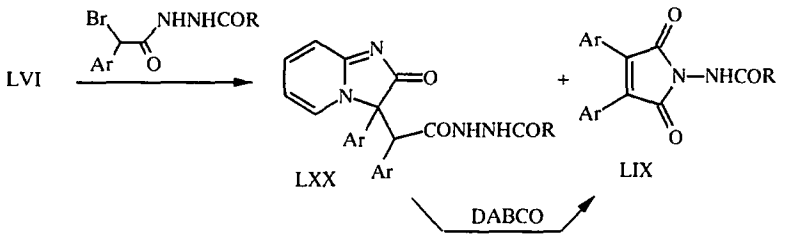
LVI LVII

In the reaction of 2-aminopyridine LVI with ethyl ester of hydroxyiminooxalyl chloride (R = OH) [124] or arylhydrazide of oxalic acid (R = NHAr) [125] 2-oxo derivatives LVIII are formed.

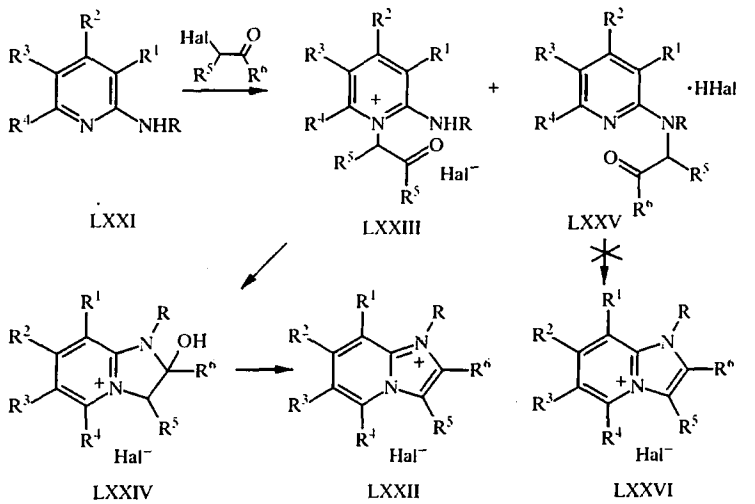


LVIII

The reactions of the amides [126] and hydrazides [35, 36] of haloacetic acids with 2-aminopyridines also give 2-oxoimidazopyridines. Thus, 2-aminopyridine with an excess of the α-halohydrazides of carboxylic acids forms a mixture of N-aminomaleimides LIX and 2-oxoimidazopyridines LXX. This reaction has been used for the production of N-aminomaleimides.

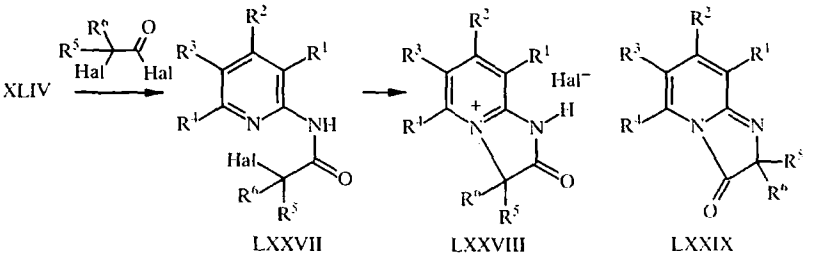


The reaction of 2-aminopyridines LXXI with α-halo ketones has been used since the twenties for the synthesis of imidazopyridines LXII. However, its mechanism for the case of 2-aminopyridine has been studied in greater detail only recently [81], when the PMR spectral data have shown that the main intermediate products were 1-alkylpyridinium salts LXXIII and 2-hydroxyimidazopyridines LXXIV. In most cases the salts are readily dehydrated (as a result of which their structure was erroneously described as the aromatic system LXXII [127]). They are nevertheless fairly stable and can be isolated [62, 65, 71, 81, 82].



In the case of 6-substituted 2-aminopyridines and secondary or tertiary alkyl halides the course of the reaction is complicated [128]. On account of the steric hindrance that arise here the alkylation can take place also (or mainly) at the exocyclic nitrogen atom with the formation of the intermediate LXXV, which cannot undergo cyclization to imidazopyridine LXXVI under the reaction conditions [128, 129].

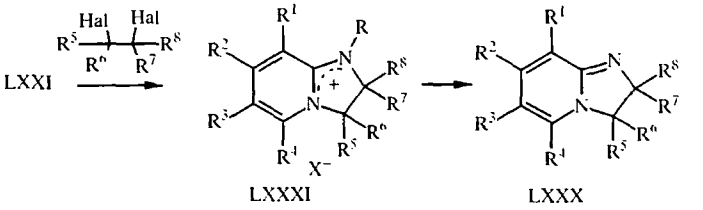
During the reaction of 2-aminopyridines XLIV with the halides of α-halocarboxylic acids acylation takes place first at the exocyclic nitrogen atom. It is then is followed by cyclization of the intermediate LXXVII at the nitrogen atom of the pyridine ring with the formation of the salts LXXVIII [1, 8, 38-40, 48, 52, 91, 105-107, 130-132]. Here 2-acylaminopyridines LXXVII can be isolated [40, 48, 52, 91, 105, 107].



LXXVII LXXVIII LXXIX

The reactions of 2-aminopyridines with phenyliminooxalic (R^5,R^6 = NPh, Hal = Cl) [133] and arylhydrazonooxalic (R^5,R^6 = NNHAr, Hal = Cl) [4, 134, 135] acid dichlorides in the presence of triethylamine proceed differently. The authors [4, 134] mention that aminopyridines enter into this reaction in the imino form, and acylation takes place at the cyclic nitrogen atom with the formation of 3-oxo derivative LXXIX.

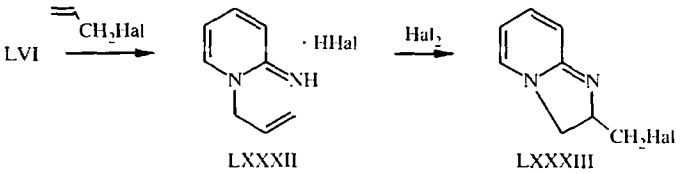
The alkylation of 2-aminopyridines with 1,2-bifunctional electrophiles has found widespread use in the synthesis of imidazopyridines. In the reaction of 2-aminopyridines with 1,2-dihaloalkanes followed by treatment with a base 2,3-dihydroimidazo[1,2-*a*]pyridines LXXX were obtained [19, 64, 102, 136]. In the reaction of 2-N-ethyl- and 2-N-phenylaminopyridines with 1,2-dibromoethane followed by treatment with sodium perchlorate the perchlorates LXXXI (R = Et, Ph, X = ClO_4) were obtained [61].



LXXXI LXXX

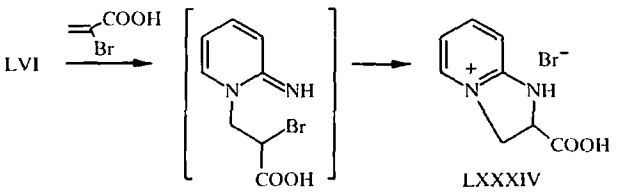
The reactions of 2-aminopyridines with derivatives of 1,2-diols [136] and halohydrins [116] take place in a similar way.

The reaction of 2-aminopyridine LVI with 3-halo-1-propene leads to alkylation of the pyridine nitrogen atom with the formation of salt of 1-allyl-2-aminopyridine LXXXII, which reacts with halogens with cyclization to the compound LXXXIII [137].



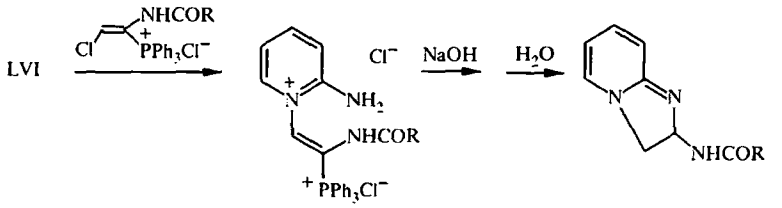
LXXXII LXXXIII

In reaction with 2-bromoacrylic acid 2-aminopyridine LVI forms imidazopyridinium salt LXXXIV [80, 138].



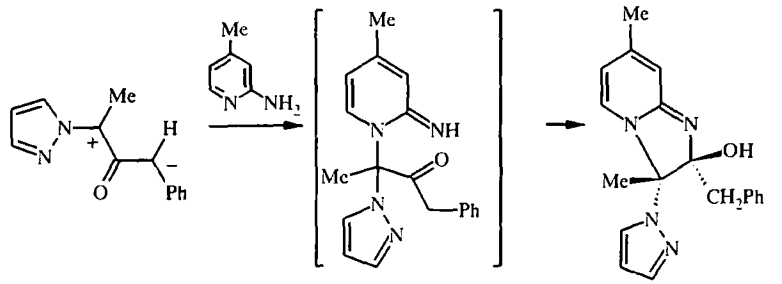
LXXXIV

The reactions of 2-aminopyridine LVI with 1-acylamino-2-chloroethenyltriphenylphosphonium chlorides give pyridinium chlorides LXXXV, which are capable of undergoing cyclization to imidazopyridines LXXXVI [139].



LXXXV LXXXVI

In the reaction of 2-amino-4-methylpyridine with the dipolar compound LXXXVII, formed in the reaction of methylphenylcyclopropenone with pyrazole, imidazopyridine LXXXVIII was isolated as one of the reaction products with a yield of 38% [140].

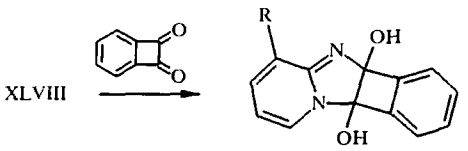


LXXXVII LXXXVIII

The alkylation of 2-aminopyridine with ethylene oxide gives 1-(β-hydroxyethyl)-2-iminopyridine [141], hydrochloride of which gives imidazopyridine hydrochloride XIV (R = H, X = Cl) when treated with thionyl chloride [84].

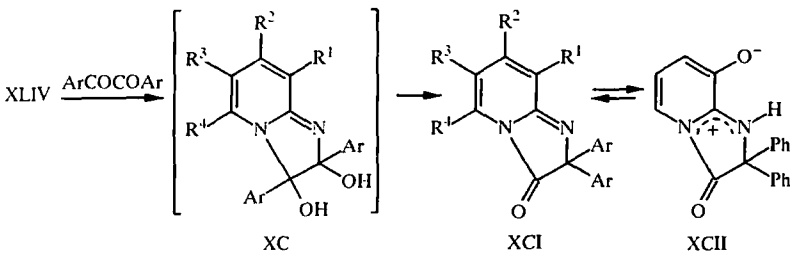
2-Oxoimidazopyridines of the C, C1, and C2 types were obtained in the reactions of the salts of 2-aminopyridines with chloroketene diethyl acetal [108] or with geminal dicyano epoxides [58]. Here 2-acylaminopyridines are formed as intermediate compounds.

The reactions of 2-aminopyridines with α-dicarbonyl compounds have also been used for the synthesis of imidazopyridines. Thus, 2-aminopyridines XLVIII (R = H, NH_2) form diols LXXXIX with benzocyclobutene-1,2-dione [142].



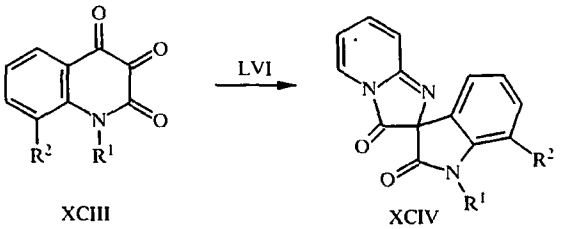
LXXXIX

2-Aminopyridines (XLIV) react similarly with benzil and its derivatives, but here the diols that form undergo pinacoline rearrangement, giving 3-oxoimidazopyridines XCI or, in the case of 2-amino-3-hydroxypyridine, the betaine XCII [50, 143, 144].



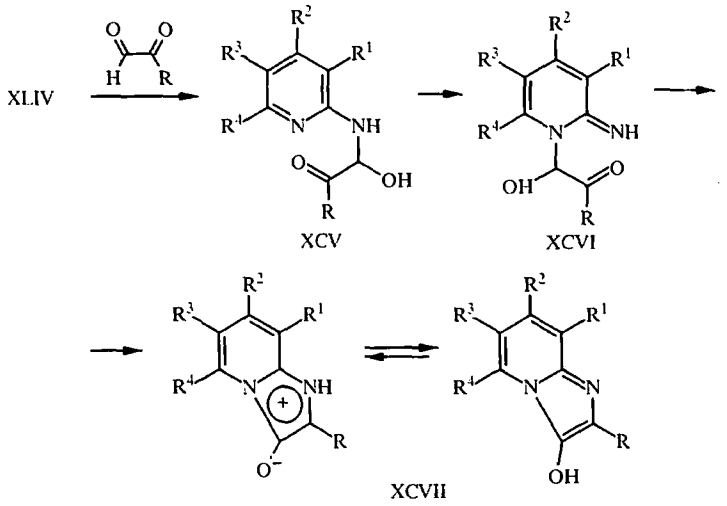
XC XCI XCII

The reaction of vicinal tricarbonyl compounds XCIII with 2-aminopyridine takes place with ring contraction and leads to the spiro derivatives of 3-oxoimidazopyridine XCIV [145].



XCIII XCIV

Investigations of the mechanism of the reaction of 2-aminopyridine with arylglyoxals [59] showed that 2-pyridylaminocarbinols, which can be isolated, are formed. However, if the heterocycle has sufficient nucleophilicity these compounds rearrange to the intermediates XCVI under the reaction conditions and then undergo cyclization. 2-Arylimidazopyridines XCVII were obtained in this way [55, 57, 59, 146, 147], while 3-hydroxy-2-methylimidazo[1,2-*a*]pyridine was obtained in the reaction of 2-aminopyridine with acetaldehyde [147].

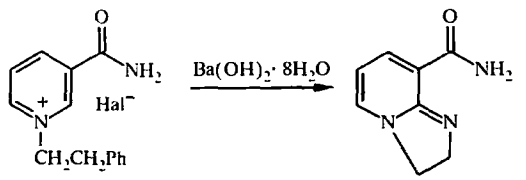


XCV XCVI XCVII

It is known that phenacyl bromide is transformed in reaction with 2-picoline 1-oxide into phenylglyoxal. The reaction of 2-aminopyridine 1-oxides with α-halo ketones can therefore be used as an alternative to the above-mentioned syntheses of 3-hydroxyimidazo[1,2-*a*]pyridines XCVII [3, 148].

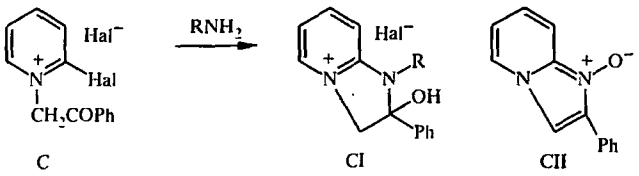
2.1.3. Intramolecular Cyclization of 1-Substituted Pyridinium Salts and Pyridinium Ylides. The intramolecular cyclization of 2-aminopyridinium salts is the most suitable method for the synthesis of imidazopyridines (see section 2.1.2), but other 1-substituted pyridinium salts can also be used.

The treatment of pyridinium salt XCVIII with $Ba(OH)_2 \cdot 8H_2O$ in methylene chloride leads to the formation of 8-carbamoyl-2,3-dihydroimidazo[1,2-*a*]pyridine XCIX [149].



XCVIII XCIX

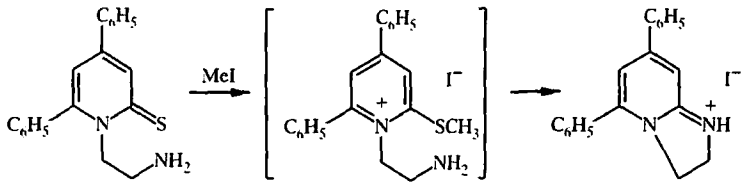
With primary amines pyridinium salt C (Hal = Br) gives imidazopyridinium bromides CI (R = Bu [60, 68], R = CH_2Ph [82]).



C CI CII

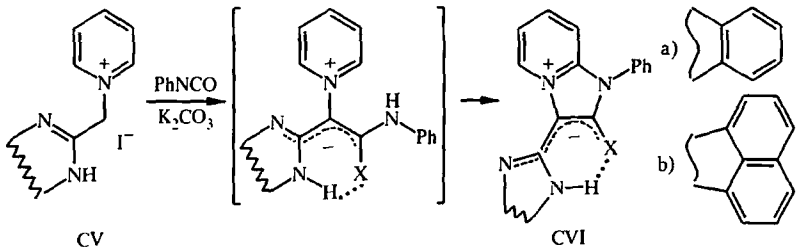
The salt C (Hal = Cl) reacts with hydroxylamine and gives N-oxide CII through the intermediate CI (R = OH, Hal = Cl) [66].

During the alkylation of pyridinethione CIII with methyl iodide in anhydrous benzene at room temperature the imidazopyridinium salt CIV was obtained with a 48% yield [75].



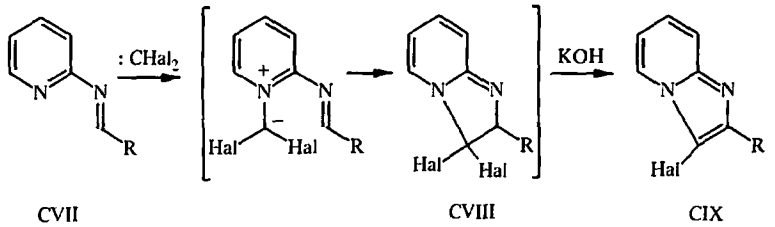
CIII CIV

Pyridinium ylides containing the second nitrogen atom in the necessary position can be used in the synthesis of imidazopyridines. During the reaction of pyridinium salts CV with phenyl isocyanate or phenyl isothiocyanate betaines CVIa with yields of 15% (X = O) and 54% (X = S) or ylide CVIb with a yield of 66% (X = S) were obtained [150, 151].



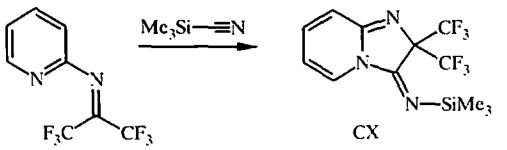
CV CVI

In the reaction of pyridine CVII with dihalocarbene imidazopyridine CIX was obtained probably through the formation of the intermediate CVIII [152].



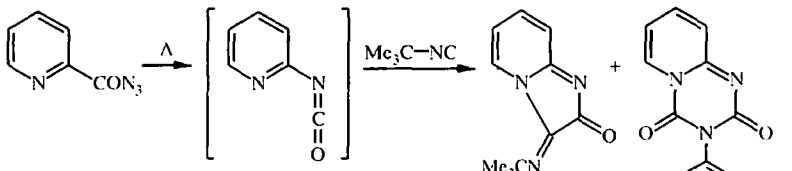
CVII CVIII CIX

2.1.4. Reactions of Other Pyridine Derivatives. The formation of the imidazopyridinium system CX is possible in reaction of the heterocyclic diene CXI with trimethylsilyl cyanide. The reaction takes 24 h at room temperature [153].



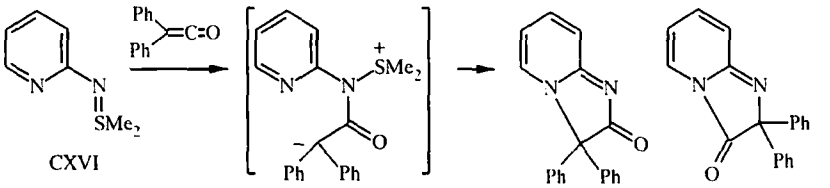
CXI CX

2-Pyridyl isocyanate CXIII formed when the azide CXII is heated reacts with *tert*-butyl isocyanide to form a mixture of imidazopyridine CXIV and triazine CXV [154].



CXII CXIII CXIV CXV

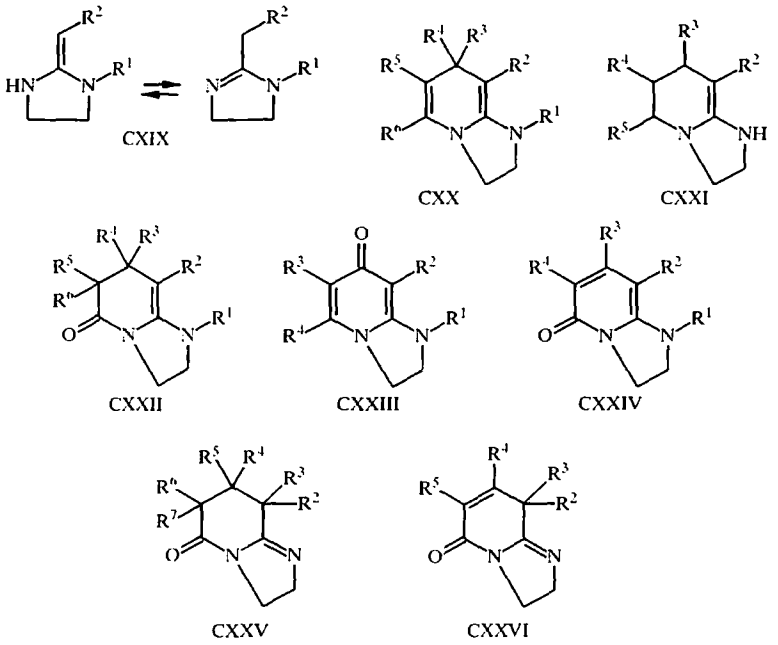
The compound obtained from 2-pyridylsulfimide CXVI and diphenylketene was originally assigned the structure of CXVII [131]. This was later rejected, and it was established that 2-oxoimidazopyridine CXVIII is formed.



CXVI CXVIII CXVII

2.2. Syntheses Based on Imidazole Derivatives

Derivatives of imidazolidine (CXIX), which can exist in the form of both ketene aminal and amidine, are 1,3-binucleophiles and have often been used in the synthesis of N-bridged heterocycles [155]. Their reactions with α,β-unsaturated ketones and aldehydes [156-160] give 1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridines CXX or 1,2,3,5,6,7-hexahydroimidazo[1,2-*a*]pyridines CXXI, and with aromatic aldehydes [158] they form imidazopyridones CXXII. 1,2,3,7-Tetrahydroimidazo[1,2-*a*]pyridin-7-ones (CXXIII) were obtained from the compounds CXIX in reactions with β-keto esters [161] or diketene [162]. The partly hydrogenated imidazo[1,2-*a*]-pyridin-5-ones (CXXII, CXXIV-CXXVI) were obtained in the reactions of the compounds CXIX with acrylic acid esters [163-169] or acetylenemono(di)carboxylic acid esters [163-167, 170-172], with the imidazolides of α,β-unsaturated carboxylic acids [168], and with acryloyl chloride [168]. In addition, imidazo[1,2-*a*]pyridin-5-ones (CXXII, CXXV) were obtained from the compound CXIX and β-keto esters [173], aldehydes [158], diketene [174], and cyclopropenone [175].

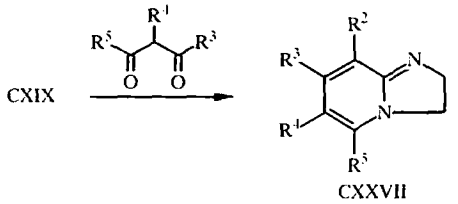


CXIX CXX CXXI

CXXII CXXIII CXXIV

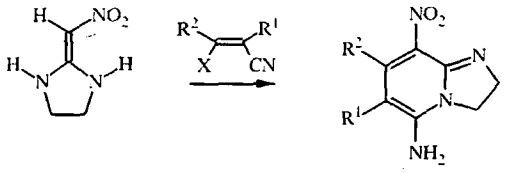
CXXV CXXVI

The condensation of 1,3-dicarbonyl compounds with imidazolines CXIX (R^1 = H) gives 2,3-dihydroimidazo[1,2-*a*]pyridines CXXVII [173, 176].



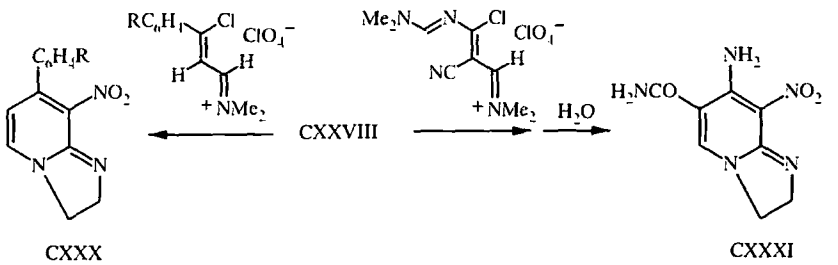
CXIX CXXVII

The reactions of imidazolidine CXXVIII with various derivatives of acetonitrile, leading to the formation of 2,3-dihydroimidazo[1,2-*a*]pyridines CXXIX, have been described [177, 178].



CXXVIII CXXIX

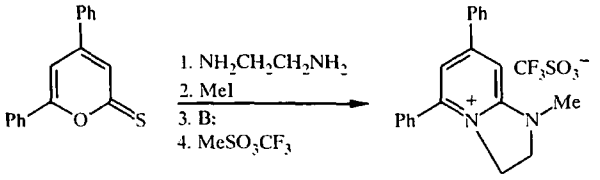
2,3-Dihydroimidazo[1,2-*a*]pyridines CXXX, CXXXI are formed during the reaction of nitroenamine CXXVIII with 3-chloro-2-propeniminium salts, which serve as 1,3-dielectrophiles [178].



CXXX CXXVIII CXXXI

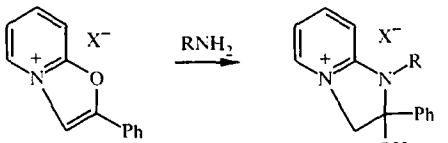
2.3. Other Methods

Other heterocyclic compounds, such as pyranthiones or oxazolo[3,2-*a*]pyridinium salts, have been used as starting materials for the synthesis of 2,3-dihydroimidazo[1,2-*a*]pyridines. 2,3-Dihydroimidazo[1,2-*a*]pyridinium salt CXXXIII was obtained in the reaction of 4,6-diphenylpyran-2-thione CXXXII with ethylenediamine followed by methylation [69].



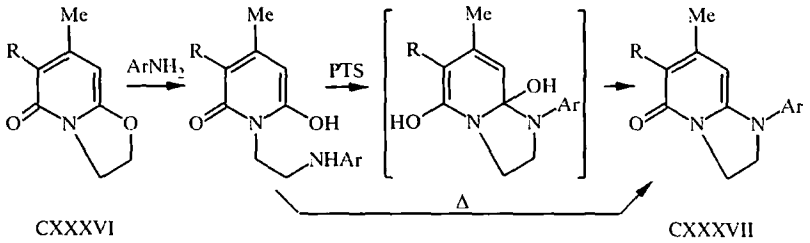
CXXXII CXXXIII

When heated with amines oxazolo[3,2-*a*]pyridinium salts CXXXIV give imidazopyridinium salts CXXXV [60, 68].



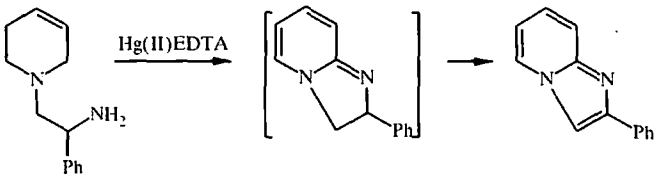
CXXXIV CXXXV

When oxazolo[3,2-*a*]pyridones CXXXVI are heated to 180°C with an excess of arylamine, imidazopyridines CXXXVII are formed [179].



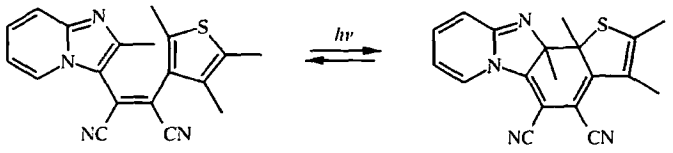
CXXXVI CXXXVII

The cyclodehydrogenation of 1-substituted 1,2,3,6-tetrahydropyridine CXXXVIII, which clearly takes place *via* the formation of 2,3-dihydroimidazo[1,2-*a*]pyridine CXIX, gave imidazopyridine CXL [180].



CXXXVIII CXIX CXL

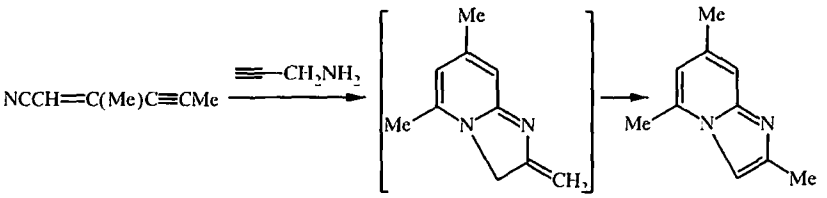
The electrocyclic reaction of arylethene CXLI gives the derivative of 2,3-dihydroimidazo[1,2-*a*]pyridine CXLII [18].



CXLI CXLII

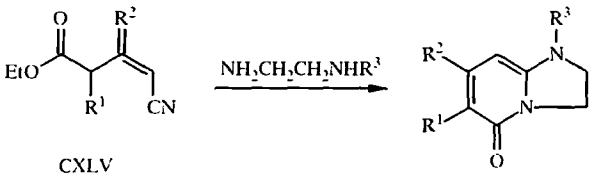
There are some examples of the synthesis of imidazopyridines from acyclic compounds.

2,5,7-Trimethylimidazo[1,2-*a*]pyridine CXLIII was obtained by heating 2-methyl-1-cyanopent-1-en-3-yne with propargylamine. 2,3-Dihydroimidazo[1,2-*a*]pyridine CXLIV with an exocyclic double bond is presumably formed during this reaction and then rearranges to imidazopyridine CXLIII [181].



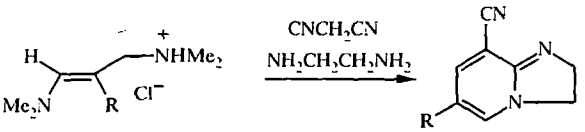
CXLIV CXLIII

The reaction of the cyano esters CXLV with various ethylenediamines gave a series of imidazopyridones CXLVI [29].



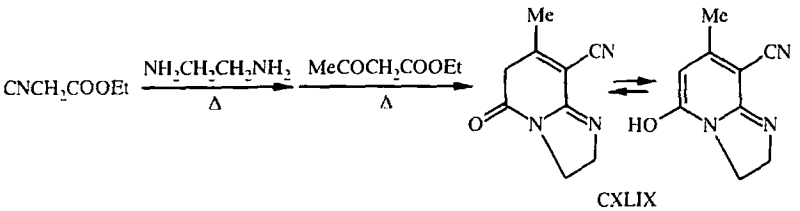
CXLV CXLVI

The synthesis of bicyclic system from three acyclic components, realized in the reaction of the 1,3-dielectrophile CXLVII with ethylenediamine and malononitrile in the presence of triethylamine, leads to the formation of imidazopyridine CXLVIII [22].



CXLVII CXLVIII

Imidazopyridinone CXLIX was synthesized by the reaction of ethyl cyanoacetate with ethylenediamine followed by heating the mixture with acetoacetic ester [7].



CXLIX

From the methods for the synthesis of 2,3-dihydroimidazo[1,2-*a*]pyridines and their salts discussed above the methods involving the construction of the imidazole ring from pyridine derivatives are most widely used.

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