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PYRIDINOPHANES (REVIEW)

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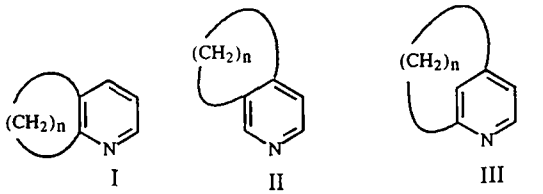
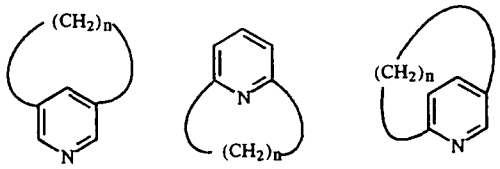
Methods for the production of o-, m-, and p-pyridinophanes containing only one pyridine ring and an all-carbon polymethylene chain are reviewed.

Pyridinophanes are bridged compounds of pyridines in which a polymethylene chain links the *o*- (2,3- and 3,4-), *m*- (2,4-, 3,5-, and 2,6-), and *p*- (2,5-) positions of the ring. All these forms are represented by structures (I-IV), where n is the number of links in the polymethylene chain [1, 2].

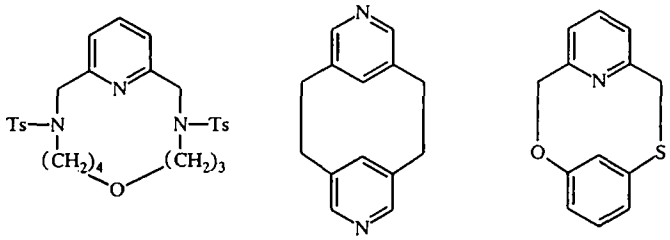


I II III



IV V VI

The carbon bridge can contain various heteroatoms [structure (VII)] and link several rings [structures (VIII) and (IX)].



VII VIII IX

Pyridinophanes are the nitrogen analogs of cyclophanes and form part of a large group of bridged heteroaromatic compounds, called heterophanes [1, 2]. At the present time, heterophanes containing the majority of nitrogen heterocyclic rings have been synthesized.

The chemistry of heterophanes has developed very quickly, and this is due to their growing practical significance. Some of the compounds have biological activity and complexing characteristics [3-6].

The amount of literature on the synthesis of pyridinophanes is fairly large. In the present review, we consider papers on the synthesis of pyridinophanes containing only one pyridine ring and an all-carbon polymethylene chain.

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1. NOMENCLATURE

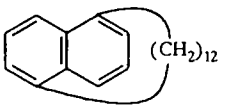
Interest in bridged compounds and the intensive growth in their number brought about a need to develop a special nomenclature for these compounds. The IUPAC nomenclature can be used for any macrocyclic compounds, but its use for complex bridged systems having substituents both in the ring and in the polymethylene chain becomes cumbersome and inconvenient. The main principles of the new "phane" nomenclature were set out in the book by Smith [1] and in papers by Voegtle and Neumann [7, 8]. The developers of the new nomenclature proposed a general terminology defining the whole range of bridged compounds.

It was proposed to use the "phane" fragment as a common root for the names of all bridged aromatic systems. The long-standing names for the bridged compounds of benzene, proposed by Cram [9, 10] and Schubert [11], were retained. As before, the name cyclophane is used for the bridged compounds of benzene. In order to define the structure of the bridged compound, prefixes to the word "phane," indicating the class of compound, were introduced.

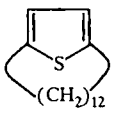
The basis of the names for bridged aromatic systems

Aromatic ring	Prefix	Full name of system
Acridine	Acridino-	Acridinophane
Anthracene	Anthraceno-	Anthracenophane
Benzene	Cyclo-	Cyclophane
Ferrocene	Ferroceno-	Ferrocenophane
Furan	Furano-	Furanophane
Naphthalene	Naphthaleno-	Naphthalenophane
Pyridazine	Pyridazino-	Pyridazinophane
Pyridine	Pyridino-	Pyridinophane
Pyrrole	Pyrrolo-	Pyrrolophane
Thiazole	Thiazolo-	Thiazolophane
Thiophene	Thiopheno-	Thiophenophane

The number in brackets before the main name is the number of atoms in the bridge; the point of addition of the bridge to the aromatic ring is indicated in parentheses placed between the main name and the brackets. The usual numbering of the aromatic ring is retained, and the carbon atoms linked by the bridge are given in parentheses. Thus, compound (X) is [12](1,5)naphthalenophane, while compound (XI) is [12](2,5)thiophenophane.

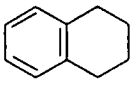


X

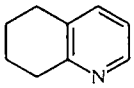


XI

This approach can also be used for *ortho*-bridged benzenes and other aromatic systems in which the bridge links adjacent positions of the ring. According to this principle, compound (XII) is called [4]orthocyclophane (better known as tetralin), and compound (XIII) is [4](2,3)orthopyridinophane.

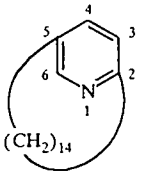


XII

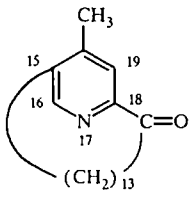


XIII

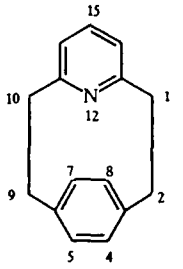
Examples of the naming of bridged compounds and the numbering of the structures



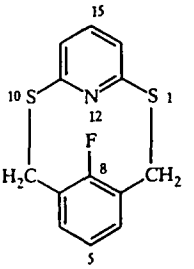
[14](2,5)Pyridinophane



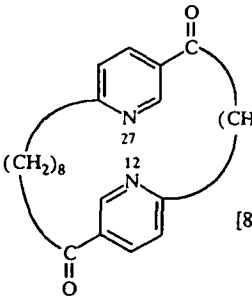
20-Methyl[14](2,5)-pyridinophan-1-one



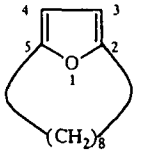
[2]Paracyclo[2](2,6)-pyridinophane



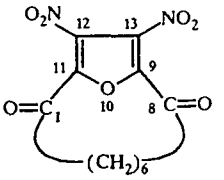
8-Fluoro-1,10-dithia[2]-metacyclo[2]pyridinophane



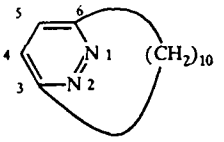
9,24-Dioxo[9,9]-(2,5)pyridinophane



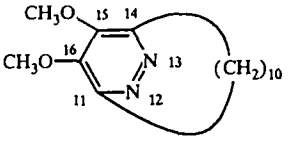
[8](2,5)Furanophane



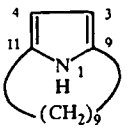
12,13-Dinitro[8](2,5)-furanophane-1,8-dione



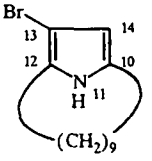
[10](3,6)Pyridazinophane



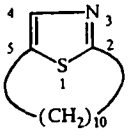
15,16-Dimethoxy[10]-(3,6)pyridazinophane



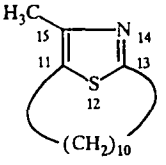
[9](2,5)Pyrrolophane



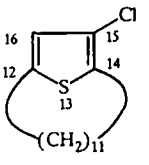
13-Bromo[9](2,5)pyrrolophane



[10](2,5)Thiazolophane



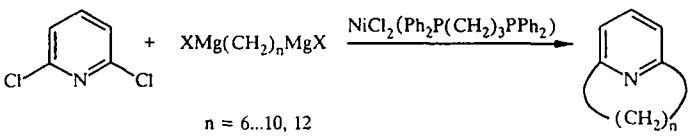
15-Methyl[10](2,5)thiazolophane



15-Chloro[11](2,5)thiophenophane

2. (2,6)PYRIDINOPHANES

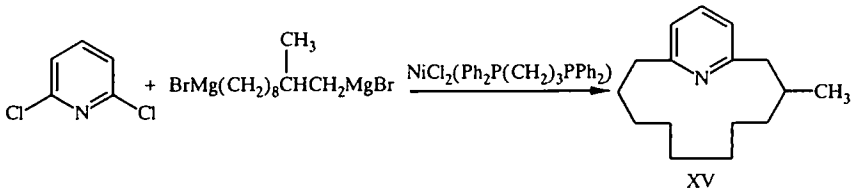
(2,6)Pyridinophanes can be synthesized by the cyclization of 2,6-disubstituted pyridines, by the aromatization of 1,5-bifunctional cyclic compounds, and by closure of the pyridine ring with the simultaneous formation of the bridge. Thus, the cross-coupling reaction of 2,6-dichloropyridine with the Grignard reagent in the presence of a nickel–phosphine complex [12, 13] gave [*n*](2,6)pyridinophanes (XIV) with yields of 10-33% in a single stage.



n = 6...10, 12

XIV

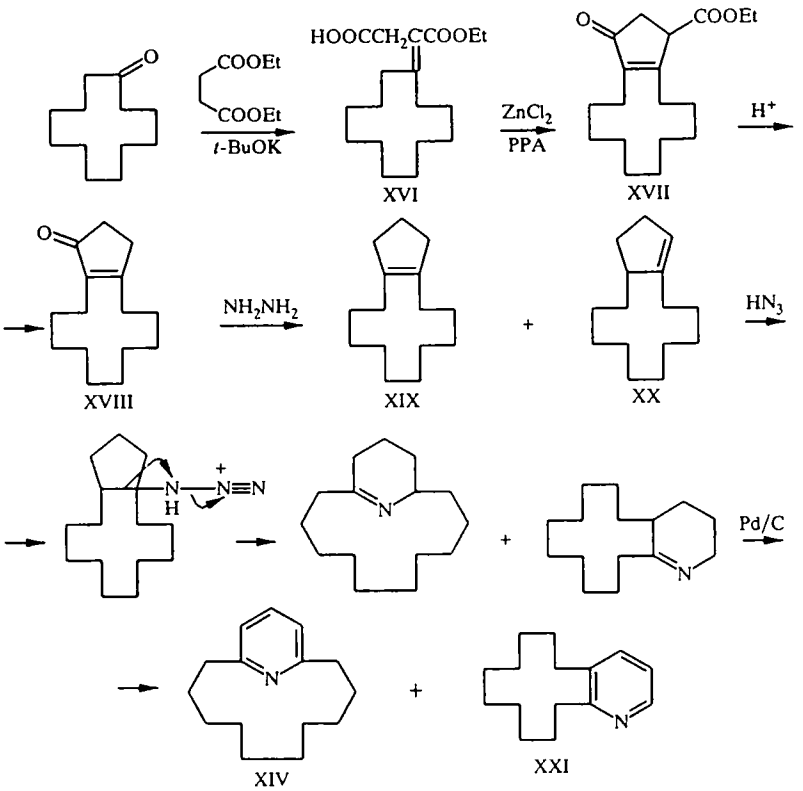
Of particular interest is the use [12] of this method for the production of the racemate of muscopyridine (XV) in a single stage. The *d*-form of this compound is the perfume component of natural musk isolated from the gland of the musk deer (*Moschus moschiferus*) [14].



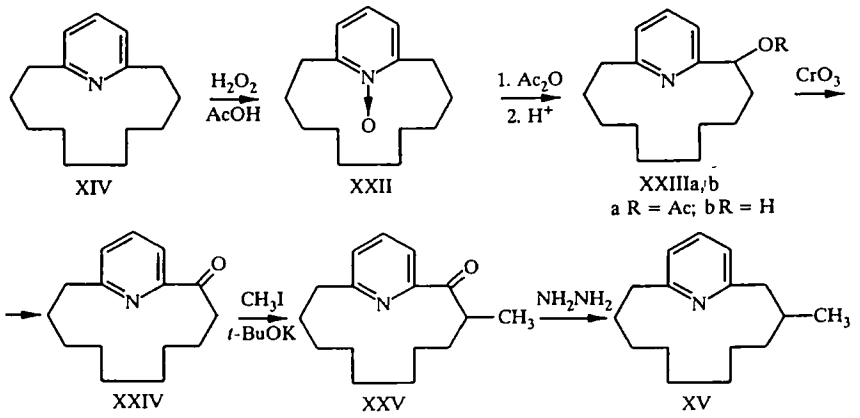
XV

The first full synthesis of muscopyridine was achieved in 1957 [15]. The Stobbe condensation of cyclododecanone with diethyl succinate gave the exocyclic carboxylic acid (XVI), which then underwent cyclization with zinc chloride in polyphosphoric acid to the δ-keto β,γ-unsaturated ester (XVII). Acid hydrolysis of the ester (XVII) with simultaneous decarboxylation gave the α,β-unsaturated ketone (XVIII). Kizhner–Wolff reduction of the obtained bicyclo[10.3.0]-1(12)-pentadecen-13-one (XVIII) gave the two isomeric olefins (XIX) and (XX), from which the trisubstituted olefin (XX) is formed with a 70% yield. The Schmidt reaction for compound (XX) and dehydrogenation at Pd/C gave [10](2,6)pyridinophane (XIV) and its 2,3 isomer (XXI).

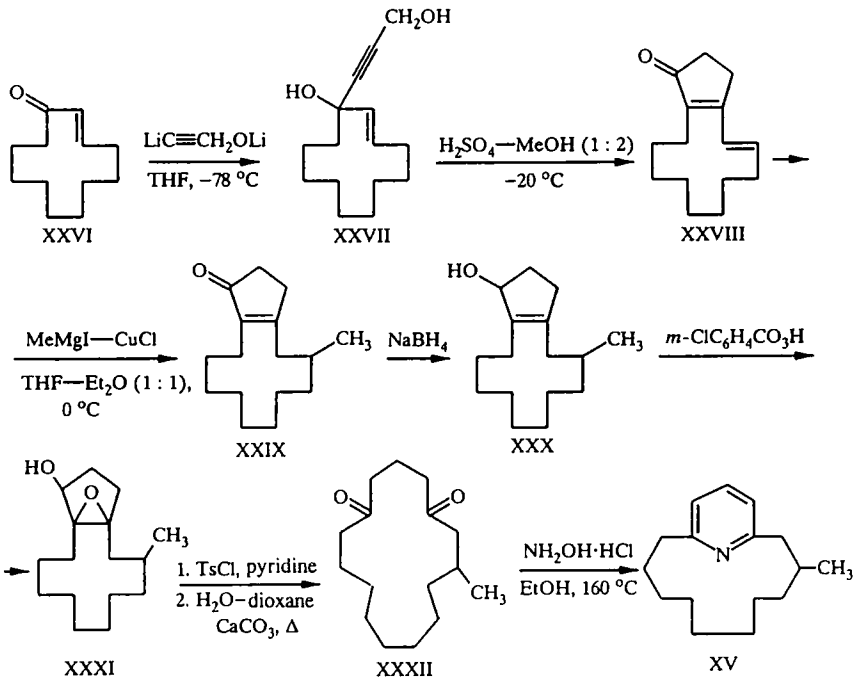
The transformation of (2,6)pyridinophane (XIV) into *dl*-muscopyridine was achieved in five stages. 2,6-Pyridinophane N-oxide (XXII) was acylated with acetic anhydride, and after hydrolysis of the acetoxy derivative (XXIIIa) the alcohol (XXIIIb) was obtained. Its oxidation with chromic anhydride in pyridine gave the ketone (XXIV), which was then methylated with methyl iodide in the presence of potassium *tert*-butoxide. Kizhner–Wolff reduction of the obtained ketone (XXV) led to *dl*-muscopyridine, which was then separated with di-*p*-toluoyl-*L*-tartaric acid.



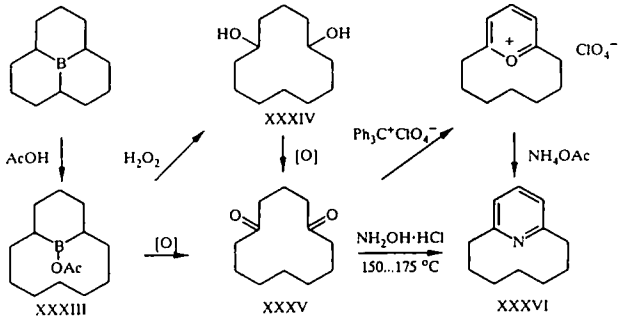
An alternative path to the racemate of muscopyridine was proposed in [16]. It included contrarotatory closure of the ring of the 3-hydroxypentadienyl derivative (XXVII) [the product from the addition of the dianion of propargyl alcohol to 2-cyclododecenone (XXVI)], leading to bicyclo[10.3.0]pentadeca-1(12),2-dien-13-one (XXVIII). The formation of the conjugated dienone (XXVIII) is regioselective, and the $C_{(2)}$ atom of 2-cyclododecenone is included in the five-membered ring. The selective 1,6-addition of the methyl group with methylmagnesium iodide in the presence of copper chloride leads to the cyclopentenone (XXIX).



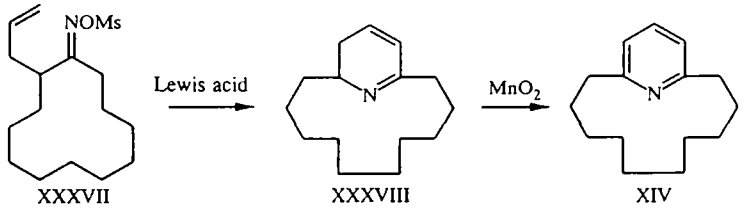
The transformation to the diketone (XXXII) was realized by the method described by Graham and Dreiding. The bicyclic cyclopentenone (XXIX) was reduced to the allyl alcohol (XXX), which was then oxidized to the epoxy alcohol (XXXI). Tosylation followed by solvolysis led to the diketone (XXXII). Its treatment with hydroxylamine hydrochloride in alcohol at 160°C in a sealed tube led to *dl*-muscopyridine (XV).



[7](2,6)Pyridinophane (XXXVI) was obtained earlier [17, 18] by cyclization of the diketone (XXXV) with hydroxylamine hydrochloride in an autoclave at 150-175°C. The required diketone (XXXV) can be synthesized by the oxidation of cyclododecane-1,5-diol (XXXIV) or B-acetoxy-13-borobicyclo[7.3.1]tridecane (XXXIII).



Significant successes by Japanese chemists in the use of new reagents for the Beckmann rearrangement made it possible to realize an original and effective approach to the synthesis of muscopyridine [19, 20]. It was established that the unsaturated sulfonates of ketoximes rearrange in the presence of alkylammonium reagents as Lewis acids to an iminocarbocation, which can undergo intramolecular alkylation to form the cyclic structure of 5,6-dihydropyridine. This result was used to develop a method for the *endo*(B)-*endo*-cyclization of 2-allyldodecanoxime mesylates — a key stage in the synthesis of muscopyridine. The conditions for the cyclization of the unsaturated imine to the pyridine (XXXVIII) and the choice of reagent were optimized for the case of 2-allylcyclododecanoxime mesylate (XXXVII), which is the starting compound in the synthesis of [10](2,6)pyridinophane (XIV).

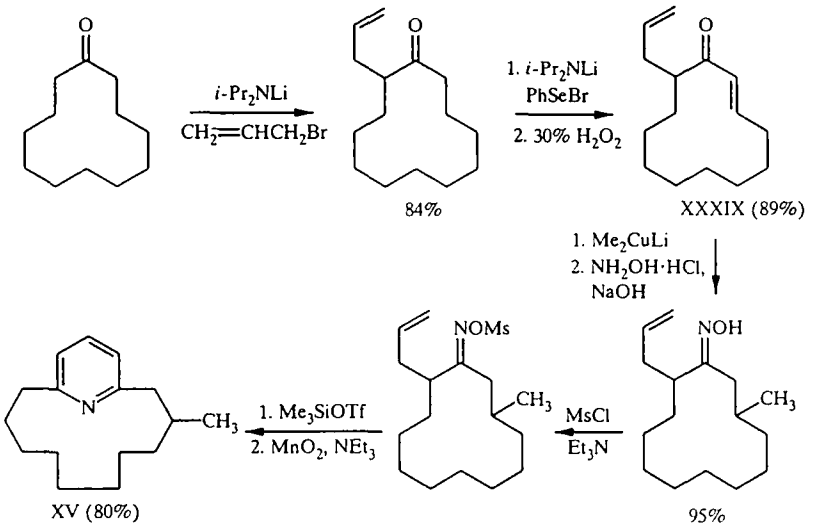


XXXVII XXXVIII XIV

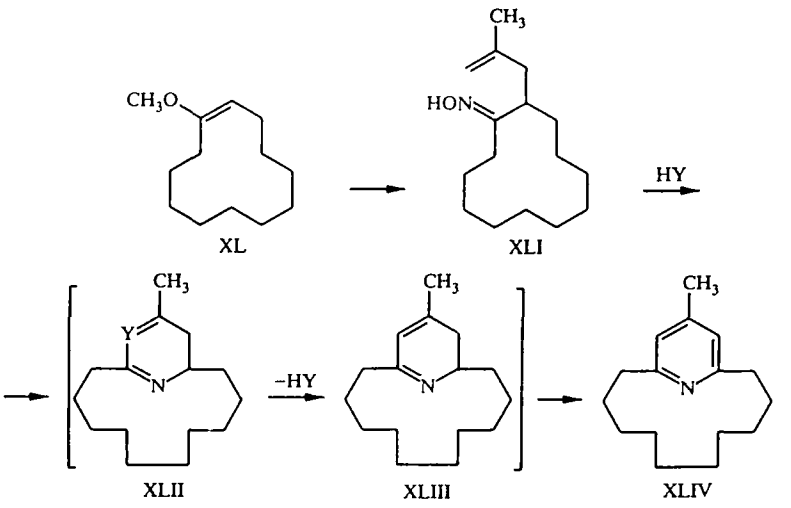
Conditions of cyclization and yields with the use of various Lewis acids [20]

Lewis acid (eq)	*T*, °C	Time, min	Yield, %
Et_2AlCl (1.1)	20	60	39
$SnCl_4$ (1.1)	0	40	65
Me_3SiI (1.1)	20	60	68
Me_3SiOTf (0.3)	20	150	55
Me_3SiOTf (1.1)	20	50	80

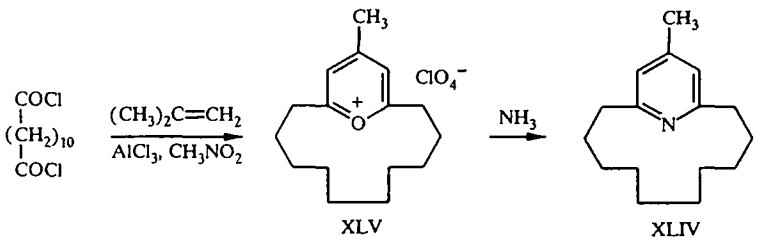
These results were used [19] in the synthesis of muscopyridine (XV) from cyclododecanone according to the scheme presented above. The methyl group of muscopyridine was introduced by the alkylation of the α,β-unsaturated ketone (XXXIX) with lithium dimethylcuprate.



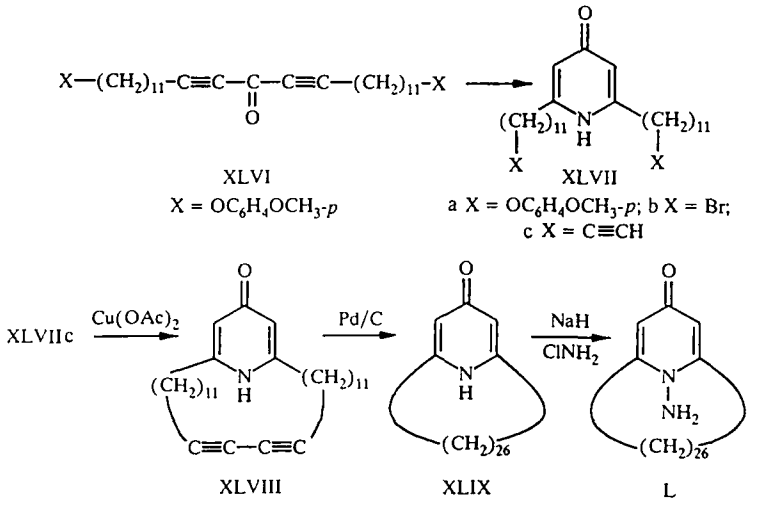
It should be mentioned that the papers [19, 20] were preceded by a report [21] on the synthesis of the isomer of muscopyridine (XLIV). 1-Methoxycyclododecene (XL) was converted into the active intermediate (XLII) by Beckmann rearrangement of the oxime (XLI). The intramolecular cyclization of the carbocation initiated under the conditions of the Beckmann rearrangement led to the formation of the dihydropyridine ring (XLIII), which was then oxidized to the pyridinophane (XLIV).



The same isomer of muscopyridine (XLIV) was obtained [22, 23] from the pyrylium salt (XLV), the synthesis of which was realized with a low yield by the diacylation of isobutylene with the corresponding acid dichloride in the presence of aluminum chloride.

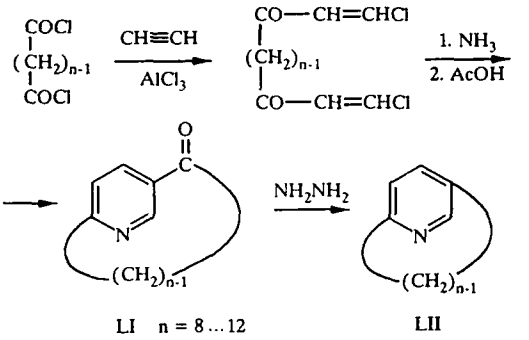


In [24] a method was proposed for the synthesis of N-amino[26](2,6)pyridonophane (L), which can be used as the starting compound for the production of catenane. Thus, in the presence of an alcohol solution of ammonia, the di(α-diynyl) ketone (XLVI) undergoes cyclization to the 4-pyridone (XLVII). Subsequent substitution of the terminal groups in the methylene chains by bromine and acetylene groups with hydrogen bromide and sodium acetylide leads to compound (XLVIIc). Copper acetate is used to link the terminal acetylene groups of compound (XLVIIc). Subsequent catalytic hydrogenation of compound (XLVIII) in the presence of palladium on carbon leads to the pyridone (XLIX). Its reaction with sodium hydride and chloramine gives the final N-amino-4-pyridone (L).



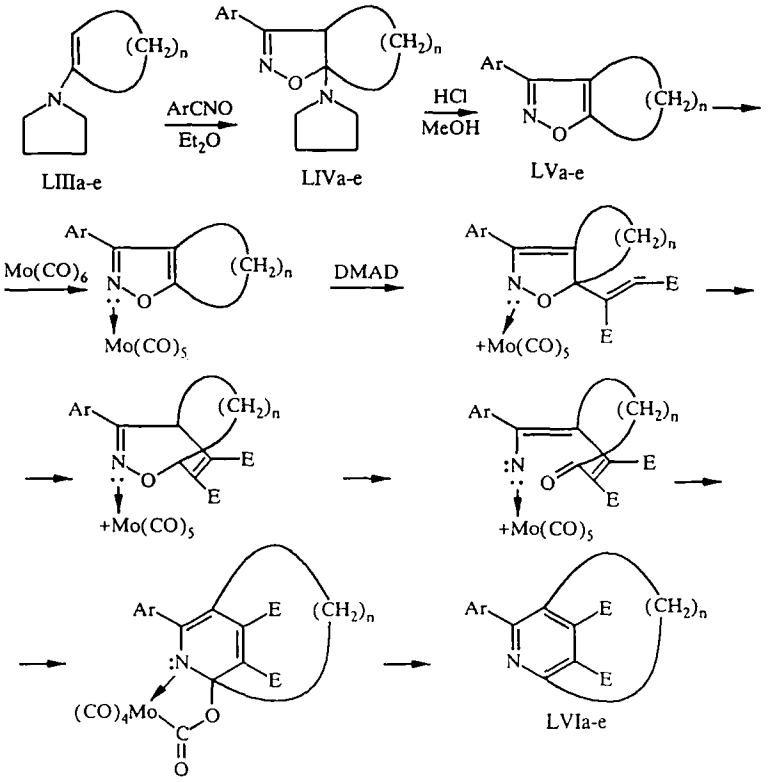
3. (2,5)PYRIDINOPHANES

In contrast to the carbocyclic analogs, there are few examples of the synthesis of (2,5)pyridinophanes. [n](2,5)Pyridinophanes with a carbon bridge (LII) were first obtained by Gerlach and Huber in 1968 [25] by the acid-catalyzed cyclization of bis(β-aminovinyl) diketones. The carbonyl group of the methylene bridge in the pyridinophane (LI) was reduced further by the Kizhner–Wolff method. The chemical properties and also the conformational stability were studied on the lower members of the series (LII) and, in particular, with n < 12 [26, 27].



LI n = 8...12 LII

More recently [28, 29], (2,5)pyridinophanes with a six-membered carbon bridge were synthesized by the cycloaddition of 3-aryl-4,5-polymethyleneisoxazole (LV) and dimethyl acetylenedicarboxylate in the presence of molybdenum hexacarbonyl. The addition of acetylenedicarboxylic ester was realized at the $C_{(4)}$ and $C_{(5)}$ atoms of the N-complex of isoxazole. Subsequent elimination of the oxygen atom led to the ring-substituted (2,5)pyridinophane (LVI). The initial isoxazole (LV) was obtained by the 1,3-dipolar addition of benzonitrile oxide to the enamine of the cyclic ketone (LIII).



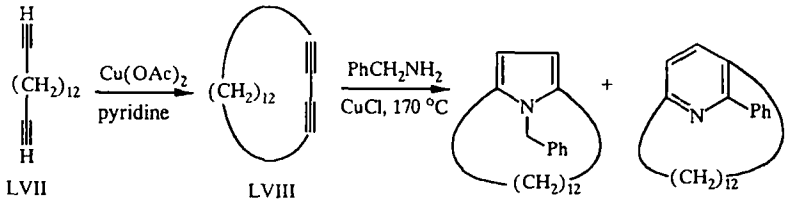
LIIIa-e LIVa-e LVa-e LVIa-e

E = CO_2CH_3; a n = 10, Ar = Ph; b n = 8, Ar = Ph; c n = 7, Ar = Ph; d n = 6, Ar = Ph; e n = 6, Ar = 4-ClC_6H_4

Yields (%) of the isoxazoline (LIV), isoxazole (LV), and [11](2,5)pyridinophane (LVI)

	Ar	[n]	LIV	LV	LVI
a	Ph	10	30	97	11
b	Ph	8	21	48	8
c	Ph	7	59	67	8
d	Ph	6	43	87	8
e	4-ClC_6H_4	6	56	57	5

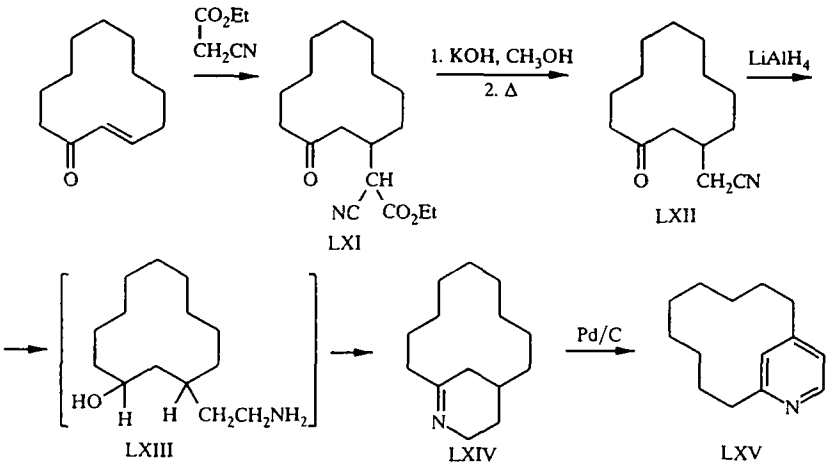
A relatively simple synthesis of 14-phenyl[12](2,5)pyridinophane (LX) was based on 1,14-cyclohexadecadiyne [30]. The cyclization of 1,14-hexadecadiyne (LVII) in the presence of copper acetate gave a 75% yield of 1,14-cyclohexadecadiyne (LVIII). When heated at 170°C with benzylamine and a catalytic amount of cuprous chloride, compound (LVIII) gave (2,5)pyrrolophane (LIX) and (2,5)pyridinophane (LX).



LVII LVIII LIX LX

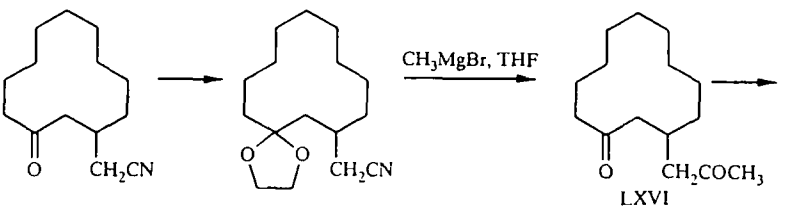
4. (2,4)PYRIDINOPHANES

In the literature there are only a few papers describing the production of (2,4)pyridinophanes. The Michael addition of ethyl cyanoacetate to cyclododecen-2-one gave the cyanoketo ester (LXI) [31]. Its subsequent alkaline hydrolysis and decarboxylation led to the ketonitrile (LXII). The reduction of the ketonitrile with lithium aluminum hydride took place with spontaneous cyclization of the obtained amino alcohol (LXIII) and gave the tetrahydropiperidine (LXIV), which was converted by catalytic dehydrogenation into [9](2,4)pyridinophane (LXV).

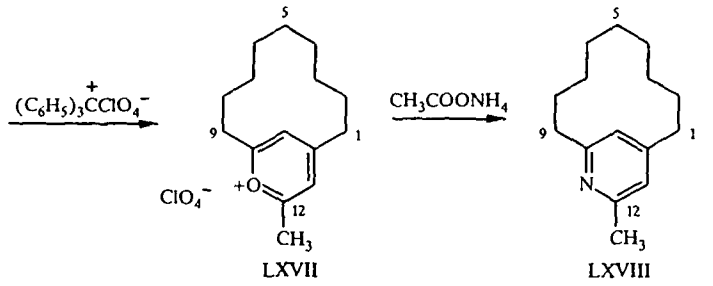


LXI LXII LXIII LXIV LXV

The synthesis of (2,4)pyridinophane (LXVIII) proposed by the same authors [32] involved treatment of the respective pyrylium salt (LXVII) with ammonium acetate in acetic acid. Triphenylmethylium perchlorate was used for the closure of the 1,5-diketone (LXVI) into the pyrylium salt (LXVII).

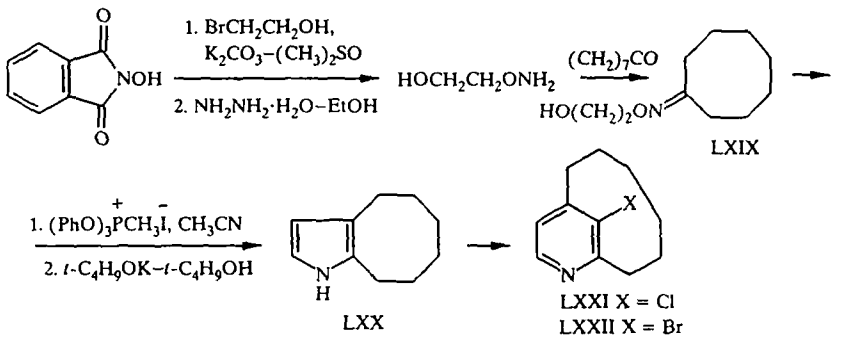


LXVI



LXVII LXVIII

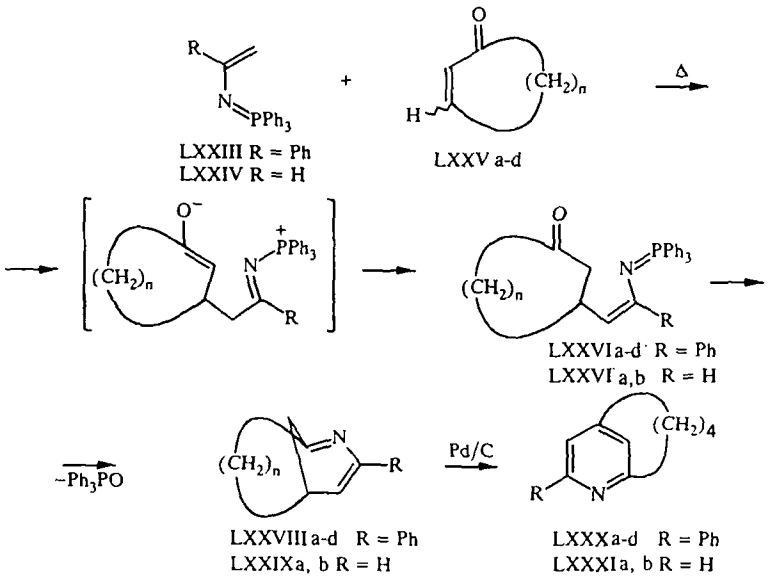
[6](2,4)Pyridinophanes (LXXI) and (LXXII) were obtained by treating 4,5,6,7,8,9-hexahydro-1H-cycloocta[8]pyrrole (LXX) with dichloro- and dibromocarbene respectively [33]. The initial [6](2,3)pyridinophane (LXX) was obtained by the successive treatment of cyclooctanone oxime (LXIX) with methyltriphenoxyphosphonium iodide and potassium *tert*-butoxide.



LXIX LXX LXXI X = Cl LXXII X = Br

[6](2,4)Pyridinophane (LXXI) was obtained by heating the pyridinophane (LXX) with a fourfold excess of sodium trifluoroacetate in absolute 1,2-dimethoxyethane. The bromine-substituted (2,4)pyridinophane (LXXII) was obtained by heating the same pyridinophane (LXX) with an excess of phenyl(tribromomethyl)mercury in absolute benzene [33].

A convenient synthesis of [4](2,4)pyridinophanes (n = 6-9) by the reaction of N-(1-phenylvinyl)iminotriphenylphosphorane (LXXIII) and N-vinyliminotriphenylphosphorane (LXXIV) with cyclic α,β-unsaturated ketones (LXXV) [34, 35] involves the Michael addition of the iminophosphorane (LXXIII) and (LXXIV) to the β-carbon atom of the unsaturated cyclic ketone (LXXV) followed by hydrogen transfer with the formation of the intermediates (LXXVI) and (LXXVII). The latter undergo an intramolecular aza-Wittig reaction, leading to the dihydropyridines (LXXVIII) and (LXXIX). Subsequent dehydrogenation at Pd/C catalyst leads to the production of (2,4)pyridinophanes (LXXX) and (LXXXI).



LXXIII R = Ph
LXXIV R = H

LXXV a-d

LXXVI a-d R = Ph
LXXVI a,b R = H

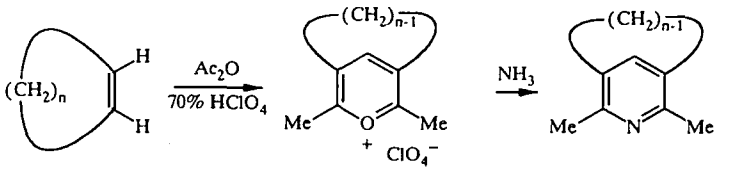
LXXVIII a-d R = Ph
LXXIX a, b R = H

LXXX a-d R = Ph
LXXXI a, b R = H

a n = 9, b n = 8, c n = 7, d n = 6

5. (3,5)PYRIDINOPHANES

There are no published data on preparative methods for the synthesis of (3,5)pyridinophanes. At the present time, two (3,5)pyridinophanes with carbon bridges containing seven [structure (LXXXIV)] and nine [compound (LXXXV)] methylene units have been synthesized from the respective pyrylium salts [36-38]. The initial pyrylium salts (LXXXII) and (LXXXIII) were obtained with yields of 1 and 3% respectively by the diacylation of cyclodecene and cyclododecene with acetic anhydride in the presence of perchloric acid.

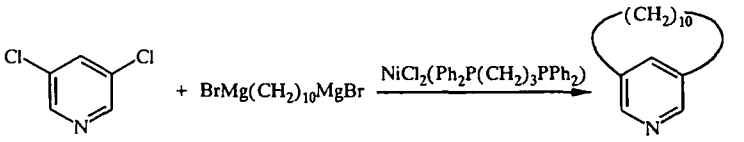


n = 8, 10

LXXXII n = 8
LXXXIII n = 10

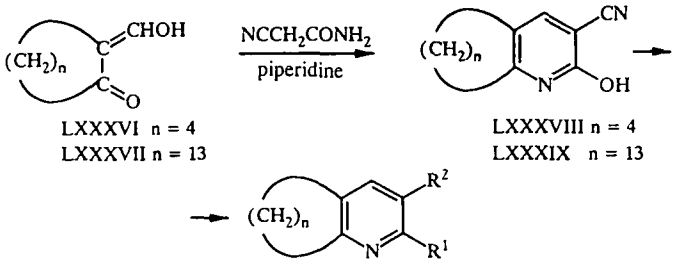
LXXXIV n = 8
LXXXV n = 10

The production of [10](3,5)pyridinophane, having a natural musk odor, by the reaction of 3,5-dichloropyridine with the Grignard reagent in the presence of a nickel–phosphine complex with a 23% yield has been patented [39].



6. (2,3)PYRIDINOPHANES

Pyridinophanes of this series were mainly synthesized by construction of the pyridine ring. Thus, (2,3)pyridinophanes (LXXXVIII-LXXXIX) were obtained by the condensation of 2-hydroxymethylenecyclohexanone (LXXXVI) and 2-hydroxymethylenecyclopentadecanone (LXXXVII) with cyanoacetamide in the presence of piperidine [40, 41].

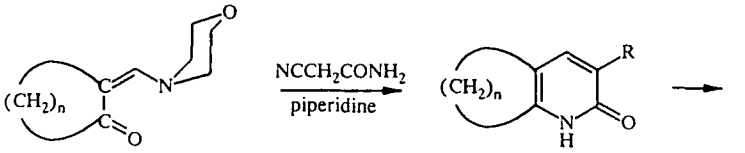


LXXXVI n = 4
LXXXVII n = 13

LXXXVIII n = 4
LXXXIX n = 13

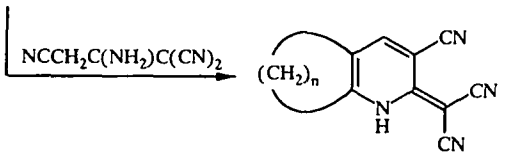
XC n = 4; R^1 = OH, R^2 = $CONH_2$; XCI n = 4; R^1 = OH, R^2 = COOH;
XCII n = 4; R^1 = OH, R^2 = H; XCIII n = 13; R^1 = OH, R^2 = H;
XCIV n = 13; R^1 = Cl, R^2 = H; XCV n = 13; R^1 = R^2 = H

The use of the β-enamino ketones (XCVI) in condensation with cyanoacetamide and malononitrile dimer leads to the production of 3-carbamoylpyridinophanes (XC-XCVII) and 3-cyanopyridinophanes (XCVIII) respectively [42].



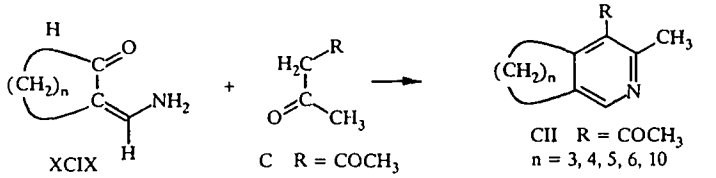
XCVI n = 3, 4, 5, 10

XC, XCI
XCVII R = $CONH_2$, n = 5, 6, 10



XCVIII n = 3, 4, 5, 6, 10

The cyclocondensation of the β-aminovinyl ketones (XCIX) with acetylacetone (C) and acetoacetic ester (CI) in the presence of ammonium acetate likewise gives (2,3)pyridinophanes (CII) and (CIII) respectively [43].

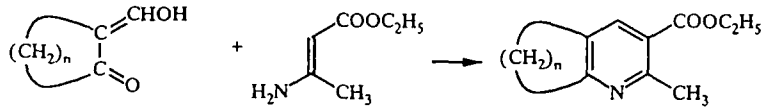


XCIX n = 3, 4, 5, 6, 10

C R = $COCH_3$
CI R = $COOC_2H_5$

CII R = $COCH_3$ n = 3, 4, 5, 6, 10
CIII R = $COOC_2H_5$ n = 3, 4, 5, 6, 10

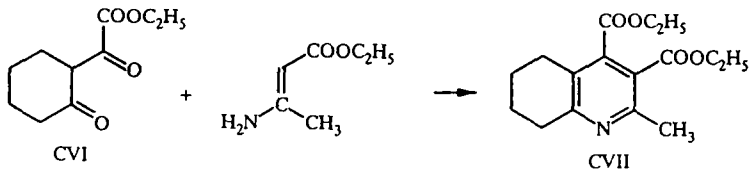
The pyridinophanes (CV) were obtained in the reaction of the hydroxymethylene ketones (CIV) with ethyl β-aminocrotonate [44, 45].



CIV n = 4, 5

CV n = 4, 5

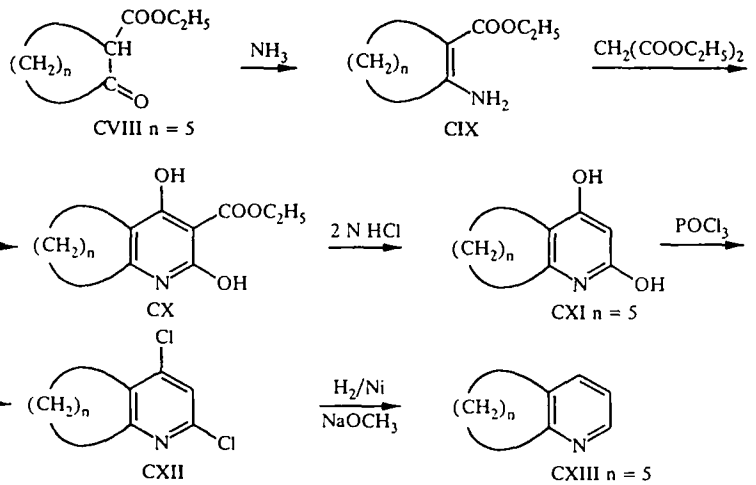
In reaction with β-aminocrotonic ester, the ethyl ester of oxalyl-2-cyclohexanone (CVI) gives the pyridinophane (CVII) [44].



CVI

CVII

The condensation of the enamine of the cyclic β-ketoester (CIX) with malonic ester in the presence of sodium ethoxide gave a good yield of the pyridinophane (CX) [46]. The initial β-ketoester (CVIII) was synthesized by the acylation of the ketone enolate with diethyl oxalate followed by decarbonylation. The hydroxyl groups in compound (CXI), obtained by hydrolytic decarboxylation of the pyridine (CX), were replaced by chlorine by heating with an excess of phosphorus oxychloride. Further catalytic hydrogenation of compound (CXII) led to the (2,3)pyridinophane (CXIII).



CVIII n = 5

CIX

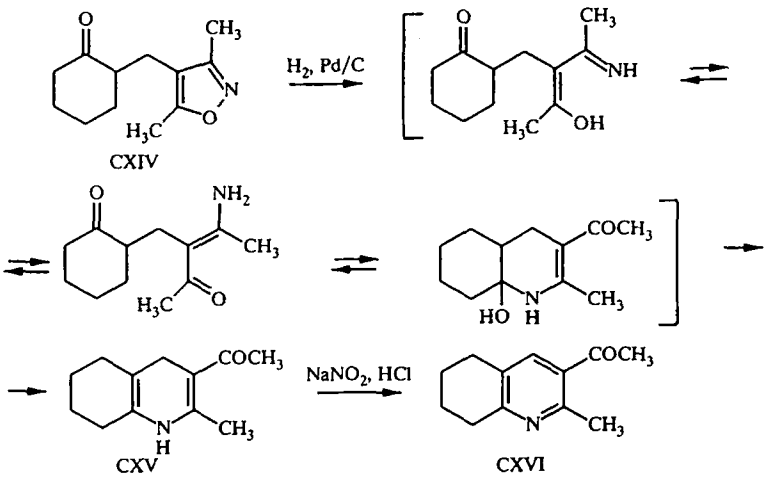
CX

CXI n = 5

CXII

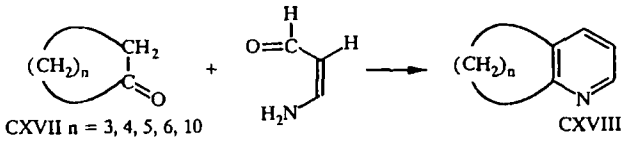
CXIII n = 5

The synthesis of the dihydropyridine (CXV) by the hydrogenation of 2-(3,5-dimethyl-4-isoxazolylmethyl)cyclohexanone (CXIV), obtained by alkylation of the cyclohexanone enamine with 4-chloromethyl-3,5-dimethylisoxazole, was described in [47]. Oxidation of the dihydropyridine (CXV) with sodium nitrate gave the pyridine (CXVI). It is possible that this transformation is common to isoxazole derivatives and may be useful for the synthesis of 2,3-pyridinophanes with polymethylene chains of various lengths.



CXIV CXV CXVI

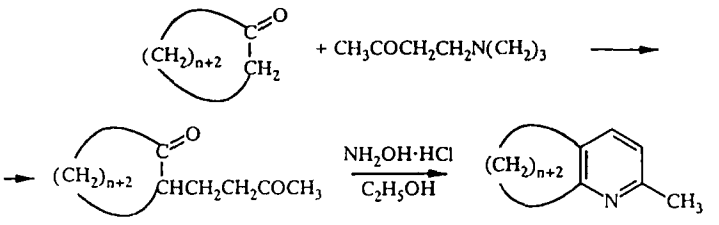
The starting material in a series of syntheses of (2,3)pyridinophanes is a cyclic ketone. Thus, the condensation of 3-aminoacrolein with the cyclic ketones (CXVII) at 120°C in the presence of a mixture of triethylamine and piperidinium acetate as catalyst gave the pyridinophanes (CXVIII) with yields of 60% [48, 49].



CXVII n = 3, 4, 5, 6, 10 CXVIII

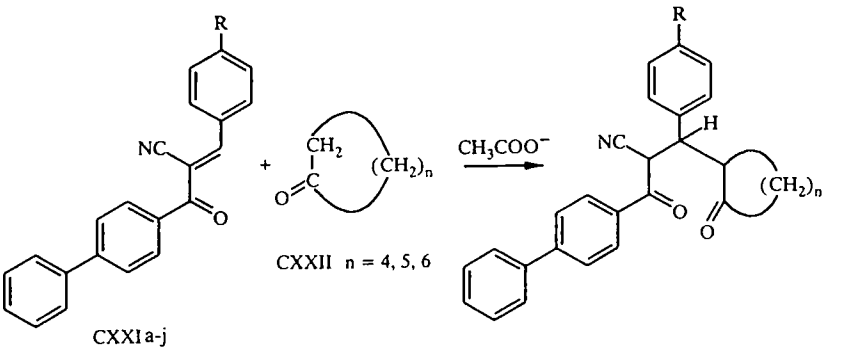
The production of (2,3)pyridinophanes by heating a mixture of a cyclic ketone, ammonia, and acrolein in the presence of aluminum silicate catalyst at 250°C [50] can be considered a modification of this method.

The Michael condensation of cyclic ketones with a Mannich base (4-dimethylamino-2-butanone) as source of methyl vinyl ketone [45] gave the 1,5-dicarbonyl compounds (CXIX). With hydroxylamine, the latter underwent cyclization to the (2,3)pyridinophane (CXX).



CXIX n = 3, 4, 5 CXX

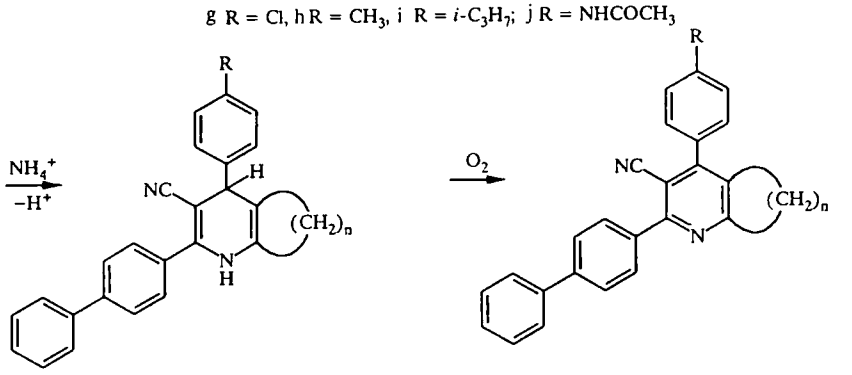
With ammonium acetate as catalyst in the reaction of 4-R-benzylidene-4-phenylbenzoylacetonitrile (CXXI) with cyclic ketones (CXXII) it was possible to realize a one-pot synthesis of the 1,4-dihydropyridines (CXXIII) [51]. The obtained 1,4-dihydropyridines (CXXIII) were oxidized to the pyridinophanes (CXXIV-CXXVI) by atmospheric oxygen.



CXXII n = 4, 5, 6

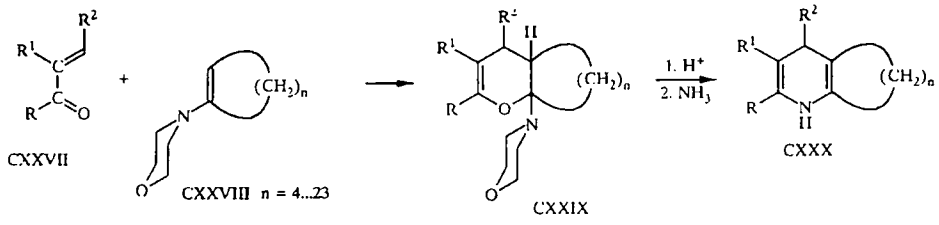
CXXI a-j

a R = NO_2, b R = H, c R = OC_2H_5; d R = $N(C_2H_5)_2$, e R = OCH_3, f R = F;
g R = Cl, h R = CH_3, i R = *i*-C_3H_7; j R = $NHCOCH_3$



CXXIII CXXIV b-i n = 4; CXXV a-d n = 5; CXXVI a-g n = 6

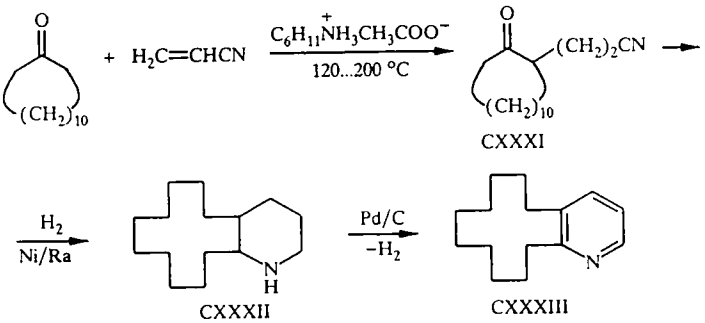
A development of this method is the use of the enamines of cyclic ketones (CXXVIII) in condensation with unsaturated ketones (CXXVII) for the production of 4H-chromenes (CXXIX). They are the starting materials in the synthesis of biologically active 1,4-dihydropyridines (CXXX) [52].



CXXVII CXXVIII n = 4...23 CXXIX CXXX

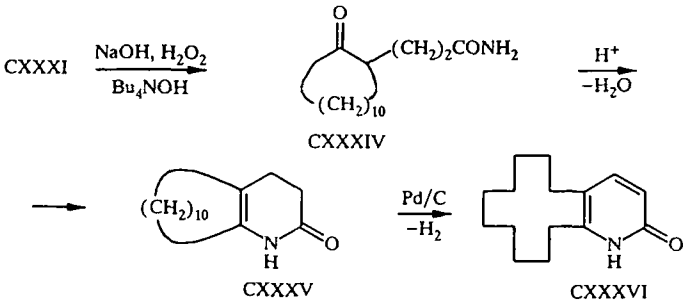
R = H, Me, Ph; R^1 = H, NO_2, CN, alkylsulfonyl, acyl, cycloalkylsulfonyl R^2 = H, Alk, Ph, $PhCH_2$

Hydrogenation of the oxonitrile (CXXXI) over Raney nickel [53] leads to the quantitative formation of 2,3-cyclododecenopiperidine (CXXXII), which is dehydrogenated smoothly over Pd/C to 2,3-cyclododecenopyridine (CXXXIII). The initial oxonitrile (CXXXI) was obtained by the cyanoethylation of cyclododecanone with acrylonitrile.

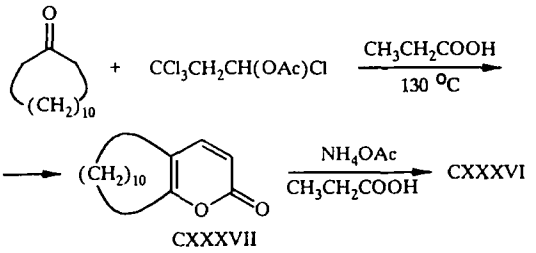


CXXXI CXXXII CXXXIII

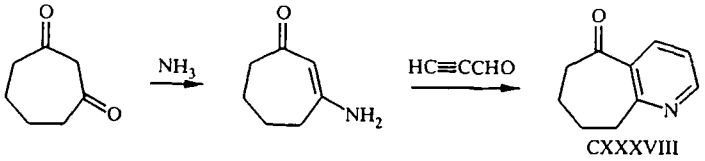
The same paper [53] describes the synthesis of the pyridine (CXXXVI) by two methods. The alkaline hydrolysis of the nitrile (CXXXI) under the conditions of phase-transfer catalysis in the presence of hydrogen peroxide leads to the formation of 3-(2-oxocyclododecyl)propionamide (CXXXIV). This compound easily undergoes cyclization with the elimination of water under the influence of catalytic amounts of p-toluenesulfonic acid to derivatives of 3,4-dihydropyridone (CXXXV). 2,3-Cyclododecenopyridone (CXXXVI) is formed quantitatively during the dehydrogenation of the pyridine (CXXXV) over Pd/C.



A second approach to the synthesis of the pyridone (CXXXVI) involves the reaction of cyclododecanone with 1,1,1,3-tetrachloro-3-acetoxypropane with the formation of the α-pyrone (CXXXVII) and its transformation by the action of ammonium acetate into the (2,3)pyridinophane (CXXXVI).



The enamines of β-diketones can be used for the production of (2,3)pyridinophanes with a keto group in the polymethylene chain. Thus, the reaction of 3-amino-2-cyclohepten-1-one with propynal gave 6,7,8,9-tetrahydro-5H-cyclohepta[*b*]pyridin-5-one (CXXXVIII) [54].



The pyridine (CXL) was synthesized in a similar way [55] by the cyclization of 3-(2-propynylamino)-2-cyclohexen-1-one (CXXXIX), which was in turn obtained by the reaction of propargylamine with dihydroresorcinol.

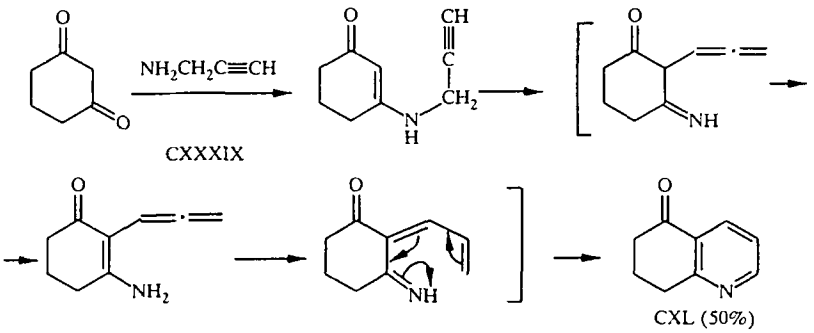
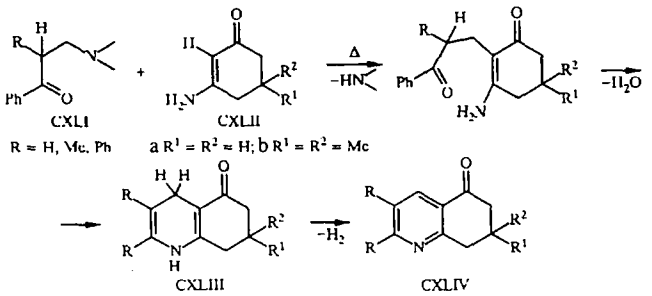


TABLE 1. Yields of 2,3-Pyridinophanes

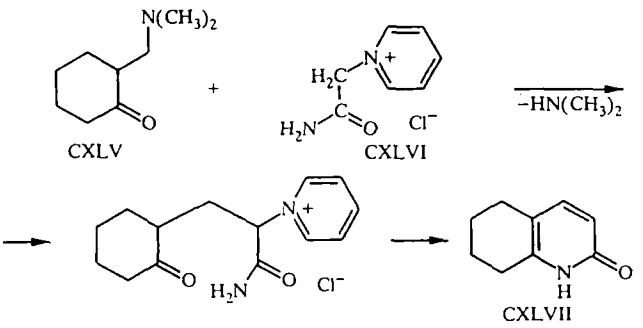
n	R	R^1	Yield, %	
			CL	CLI
3	$SiMe_3$	$SiMe_3$	77*2	—
3	CO_2Me	CO_2Me	68*2	—
3	Me	$SiMe_3$	70*2	0
4	$SiMe_3$	$SiMe_3$	77*3	—
4	CO_2Me	CO_2Me	83*4	—
4	CH_2OMe	CH_2OMe	33*2	—
4	Ph	Ph	4*5	—
4	Me	$SiMe_3$	70*2	0
4	H	n-Bu	40*2,*4	1
4	n-Bu	$SiMe_3$	56*2	0
4	Me	n-Bu	45*2	35*2
4	H	$SiMe_3$	29*2	0
4	Me	CO_2Et	43*2	11*2
5	$SiMe_3$	$SiMe_3$	25*2	—
5	CO_2Me	CO_2Me	95*6	—
3	Me	$SiMe_3$	66*2	0

*All the new compounds have the relevant spectral and analytical data.
*2A colorless oil.
*3mp 35°C.
*4mp 56-57°C.
*5mp 123°C.
*6mp 93-94°C.

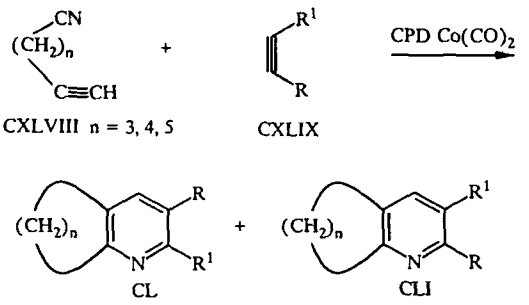
The condensation of Mannich bases (CXLI) and the enamines of dihydroresorcinol and dimedone (CXLII) leads to derivatives of dihydropyridine (CXLIII) [56], which is then aromatized to the corresponding pyridines (CXLIV).



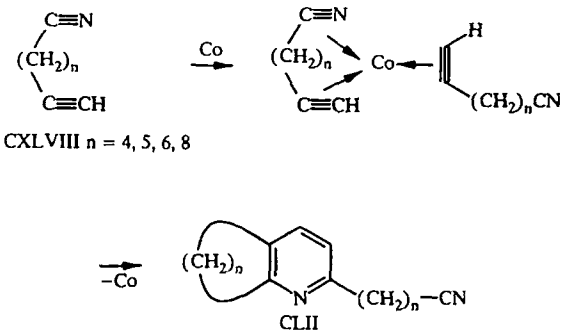
Alkylation of 2-dimethylaminomethylcyclohexanone (CXLV), i.e., the Mannich base from cyclohexanone, with the pyridinium salt (CXLVI) gave the pyridone (CXLVII) [57].



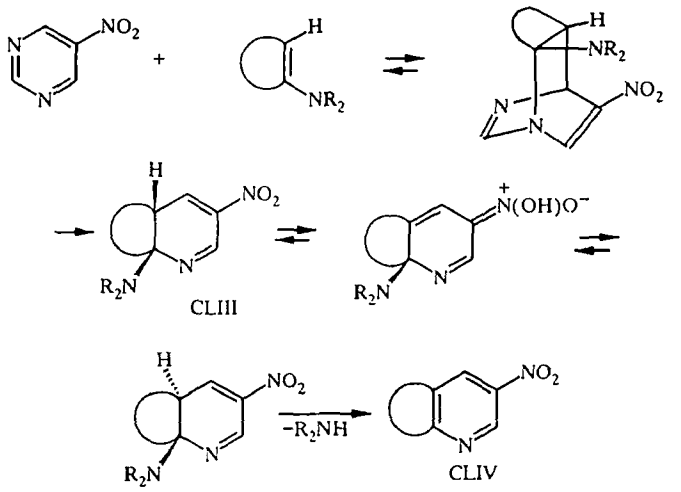
A series of substituted derivatives of (2,3)pyridinophane was obtained exclusively from acetylene derivatives in a single-stage synthesis. Thus, it was shown that α,ω-cyanoacetylenes (CXLVIII) in reaction with mono- and disubstituted acetylenes (CXLIX) in the presence of catalytic amounts of cyclopentadienylcarbonylcobalt [CPDCo(CO)$_2$] under the influence of UV radiation form a mixture of isomeric 2,3-pyridinophanes (CL) and (CLI) with a preference for (CL) [58].



More recently [59], the cyclodimerization of α,ω-cyanoacetylenes to the pyridinophane (CLII) was realized. The reaction is catalyzed by the 2-ethylhexanoatecobalt(II)−$AlEt_3$ system with Co−Al−(CXLV) molar ratios of 1:3:20.

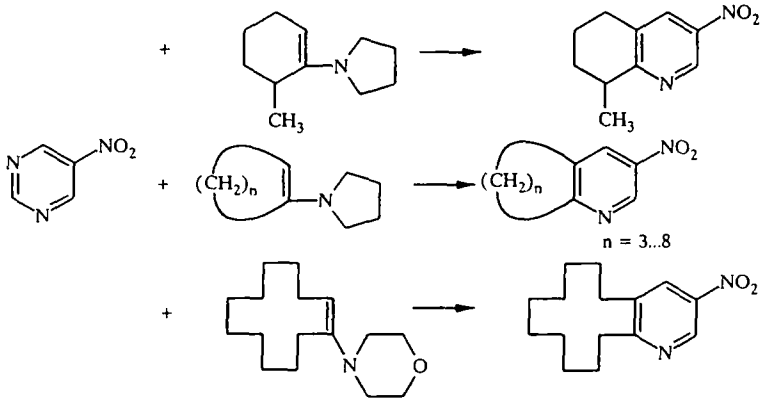


The Diels−Alder reaction of 5-nitropyrimidine with the enamines of cyclic ketones leads to the formation of 3-nitropyridines (CLIV) [60-62]. The cycloaddition is regioselective, and the enamine adds to the $N_{(1)}$ and $C_{(4)}$ atoms of the pyrimidine ring. In the bicyclic adduct (CLIII), produced after the elimination of hydrogen cyanide, the amino group and the hydrogen atom at the bridgehead are in the *cis* position, and *cis*−*trans* isomerization therefore occurs before elimination of the amine. The isomerization process is initiated by the presence of the nitro group, which is in the *aci* form.



As a rule, the cyclic adduct is insufficiently stable for isolation or even detection by NMR at low temperatures. Consequently, the suggestion that the reaction rate is determined by the cycloaddition stage is justified.

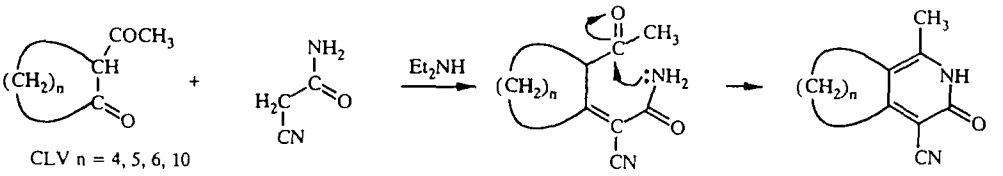
The following 3-nitropyridinophanes were obtained by using the enamines of various cyclic ketones:



7. (3,4)PYRIDINOPHANES

Only a few papers have been published on the synthesis of (3,4)pyridinophanes.

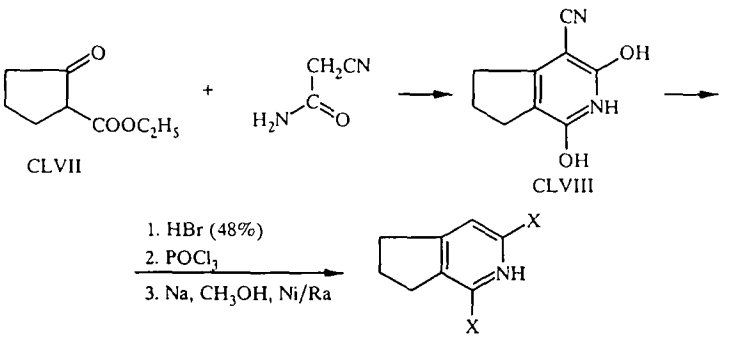
Thus, the condensation of cyclic β-diketones of the (CLV) type with cyanoacetamide gave the substituted (3,4)pyridinophanes (CLVI) [63, 64].



CLV n = 4, 5, 6, 10

CLVI n = 4, 5, 6, 10

The condensation of the β-keto ester (CLVII) with cyanoacetamide gives the dihydroxypyridine (CLVIII) [65]. If the cyanopyridine (CLVIII) is heated with hydrobromic acid, the cyano group is hydrolyzed with simultaneous decarboxylation and the formation of the pyridine (CLIX). Subsequent heating of the 2,6-dihydroxypyridine (CLIX) with phosphorus oxychloride at 180°C leads to the 2,6-dichloropyridine (CLX) with a yield of 65%. The pyridine (CLXI) was obtained with a yield of 84% by reduction with sodium in alcohol in the presence of Raney nickel.

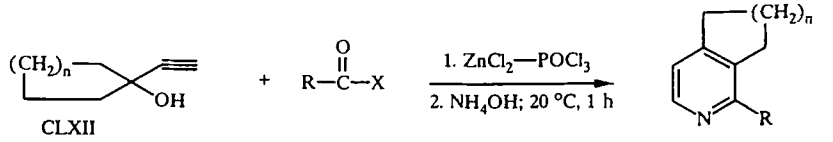


CLVII

CLVIII

CLIX X = OH; CLX X = Cl; CLXI X = H

The reaction of the cyclic ethynylcarbinols (CLXII) with carboxylic acid halides [66] in the presence of the two-component catalyst $ZnCl_2-POCl_3$ (1:1) under mild conditions (20°C, 1 h) followed by treatment of the reaction mixture with ammonia at 0°C gave 2-alkyl-(3,4)pyridinophanes (CLXIII-CLXXI) with high selectivity.

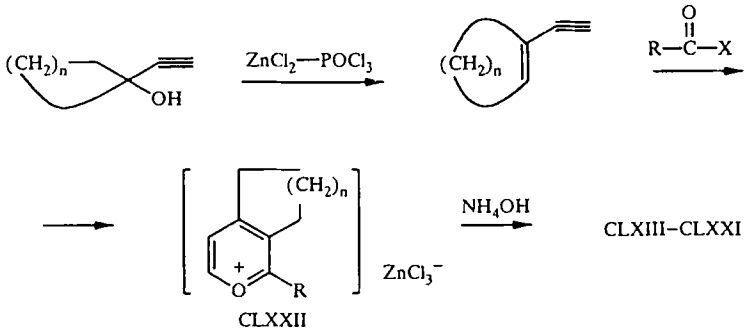


CLXIII X = Cl, Br, I; n = 1, R = Me;
CLXIV n = 1, R = Pr;
CLXV n = 1, R = Bu;

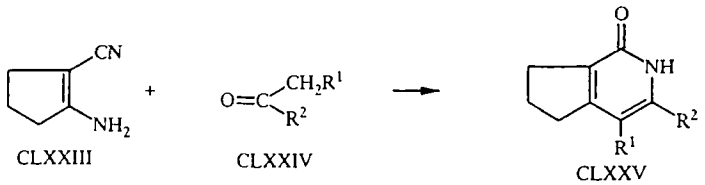
CLXVI n = 2, R = Bu;
CLXVII n = 3, R = Bu;
CLXVIII n = 2; R = Me;

CLXIX n = 2, R = *i*-Bu;
CLXX n = 3, R = Me;
CLXXI n = 3, R = *i*-Bu

Analysis of the experimental data made it possible to conclude that the molecules of the pyridines are formed from the ethynylcarbinols and carboxylic acid halides through the pyrylium salts (CLXXII), which are converted into compounds (CLXIII-CLXXI) when treated with aqueous ammonia according to the following scheme:

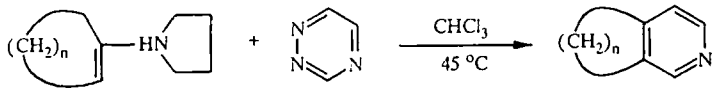


It was found [67] that 1-amino-2-cyano-1-cyclopentene (CLXXIII) reacts with the acyclic ketones (CLXXIV) in the presence of polyphosphoric acid at 120-140°C with the formation of the pyridones (CLXXV).



a $R^1 = H$, $R^2 = CH_3$; b $R^1 = R^2 = CH_3$

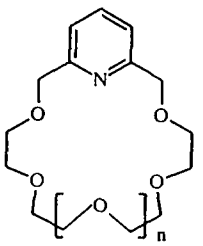
A method was described for the production of the 3,4-pyridinophanes (CLXXVII) by the cycloaddition of the enamines of cyclic ketones (CLXXVI) and 1,2,4-triazine, which takes place by a mechanism of the Diels–Alder type, where the 1,2,4-triazine serves as an azodiene [68].



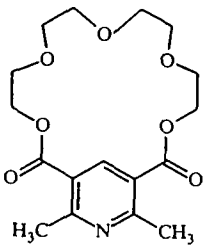
CLXXVI n = 3, 4, 5

CLXXVII

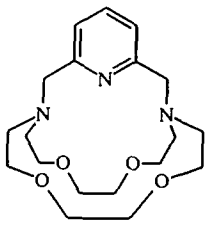
Analysis of the published data gives reason to conclude that all types of pyridinophanes are compounds fairly difficult to produce. On the basis of the data on the development of methods for the synthesis of natural muscopyridine [10], (3,5)pyridinophane with a natural musk odor was produced for use in perfumery [39]. Such a property of crown ethers as the ability to form complexes with the cations of alkali metals has prompted research [69, 70] into the synthesis of the azacrown ethers (CLXXVIII, CLXXIX), containing the nitrogen atom of the pyridine ring as donating heteroatom. Cryptands (CLXXX) of the pyridinophane series have also been obtained [71].



CLXXVIII
n = 0...6



CLXXIX



CLXXX

The material presented in the review demonstrates the prospects for further research into pyridinophanes, new approaches to their synthesis, and the possibilities of their practical utilization.

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