SYNTHESIS AND REACTIONS OF NAPHTHYRIDINES (REVIEW)

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Methods for the preparation of 1,5-, 1,6-, 1,7-, and 1,8-naphthyridines and their chemical properties are examined.

The group consisting of six diazanaphthalenes that contain a nitrogen atom in each ring are called naphthyridines (or pyridoypridines); these six diazanaphthalenes consist of four types of 1,X-naphthyridines I-IV (X = 5, 6, 7, 8) and two types of 2,Y-naphthyridines (Y = 6 or 7).

I II III IV

Since 1927, when naphthyridines I [1] and IV [2] were first obtained, the interest in compounds of this class has been growing constantly, as reflected in earlier review papers [3-6]. Information of a review nature regarding the reactions of 1,5- and 1,6-naphthyridines [7, 8], the synthesis of quaternary salts of these compounds [9], and some aspects of nucleophilic substitution in the naphthyridine series [10] is available. Naphthyridines have found practical application as medicinals [5] (e.g., nalidixic acid and its derivatives) and as ligands of metal complexes [5].

The present review is devoted to the chemistry of 1,X-naphthyridines I-IV. In view of the specific characteristics of the synthesis of 2,6- and 2,7-naphthyridines, their chemistry requires a separate discussion.

Synthesis of Naphthyridines of the I-IV Type

The methods for the synthesis of naphthyridines are similar to the methods for the synthesis of quinolines. Thus compounds of the IV type are obtained from 2-aminopyridine or substituted 2-aminopyridines, compounds of the II type are obtained from 4-aminopyridine, and naphthyridines I or III are obtained from 3-aminopyridine. The most facile cyclization occurs with 3-aminopyridine, followed by 4-aminopyridine and 2-aminopyridine (the latter is the least reactive). Cyclization is facilitated when there is an electron donor group (OH, NH_2, CH_3) in the 6 position.

Unsubstituted naphthyridine I was obtained for the first time by the Skraup reaction from 3-aminopyridine [1]. The yield can be raised to 90% by using various oxidizing agents [11-14]; 1,2,3,4-tetrahydro-1,5-naphthyridine and 3-methyl- and 3-ethyl-1,5-naphthyridines are obtained along with 1,5-naphthyridine in this case, but ring closing takes place exclusively in the 2 position (isomer III was not detected) [13] as a result of the mesomeric effect, which is manifested more strongly in the 2 position than in the 4 position. However, if the 2 position is occupied by a hydroxy [15] or amino [16] group, ring closing takes place in the 4 position. 3-Aminopyridine N-oxide gives I [17]. This method was used to synthesize 2-hydroxy- [18], 4-hydroxy- [19], 2-amino- [20, 21], and 3-bromo-1,5-naphthyridines [22].

3-Amino-1,5-naphthyridine is initially formed from 3,5-diaminopyridine and is then converted to 3-hydroxy-1,5-naphthyridine of 1,5,9-triazaphenanthrene [22].

The first attempts to carry out the Skraup reaction with 4-aminopyridine were unsuccessful [23]. Compound II was obtained in 40% yield when the so-called "sulfo mix" (a mixture obtained by heating nitrobenzene with oleum) was used [24]. 1,6-Naphthyridine 6-oxide is formed from 4-aminopyridine N-oxide [25, 26] under the conditions of the Skraup reaction. The use of the sulfo mix in the Skraup reaction with 2-aminopyridine made it possible to ob-

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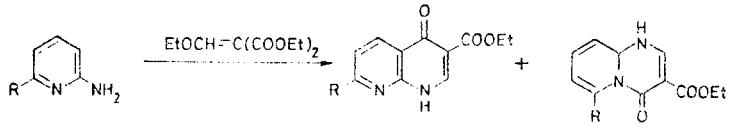
tain [27, 28] naphthyridine IV in 30% yield. Methylnaphthyridines of the IV type are obtained from the corresponding methyl-2-aminopyridines [14, 28].

3-Aminopyridine also undergoes condensation with α,β-unsaturated carbonyl compounds. Thus 2-methyl-, 3-methyl-, and 4-methyl-1,5-naphthyridines, respectively, were obtained with crotonaldehyde, methacrolein, and methyl vinyl ketone [29]. 2,4-Dimethyl-1,5-naphthyridine is formed in the reaction of 3-aminopyridine with acetaldehyde and acetone [20].

2-Hydroxy-1,5-naphthyridines were obtained under the conditions of the Skraup and Doebner–Miller reactions from 5-amino-2-hydroxypyridines [30]. The corresponding 2-methyl- [31], 3-methyl- [27], and 4-methyl-1,6-naphthyridines are similarly obtained in the reaction of 4-aminopyridine with crotonaldehyde, methacrolein, or methyl vinyl ketone. Dimethyl-1,8-naphthyridines are formed in the condensation of the corresponding 2-amino-substituted methylpyridines with crotonaldehyde, methacrolein, or methyl vinyl ketone, while trimethyl-1,8-naphthyridines are obtained from 4,6-dimethyl-2-aminopyridine [6, 27, 32]. The yields of the products of the Skraup and Doebner–Miller reactions increase in the presence of sodium m-nitrobenzenesulfonate, ferric sulfate, and boric acid [14]. 2,4,5-Trimethyl-1,8-naphthyridine was also synthesized from 2-amino-4-methylpyridine by reaction with acetylacetone in the presence of phosphoric acid, i.e., under the conditions of the Combes reaction [33].

Another general method for the synthesis of naphthyridines of the I–IV type is condensation of aminopyridines with ethoxymethylenemalonic ester in Dowtherm, which leads to the formation of 4-hydroxy-3-carbethoxynaphthyridines. The reaction with 3- and 4-aminopyridines gives the corresponding compounds of the I [34–36] and II [11, 13, 37–39] type. When 3-aminopyridine N-oxide is used in this reaction, substitution takes place in the 4 position, and 3-carbethoxy-4-hydroxy-1,7-naphthyridine 7-oxide is formed [17, 40].

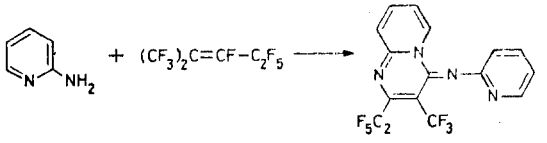
A similar condensation of 2-aminopyridine with subsequent cyclization leads to pyridopyrimidines [41–43], and cyclization in the 3 position to give the corresponding derivatives of naphthyridine IV occurs only when there is a methyl [34, 44], ethoxy [34], or amino group [34] in the 6 position.



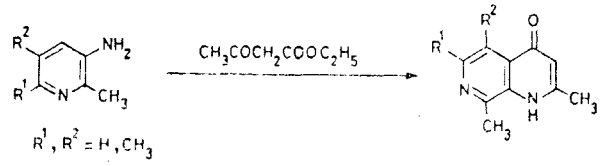
2,6-Diaminopyridine reacts with ethoxymethylenemalonic ester to give the isomeric 7-amino-2-hydroxy-1,8-naphthyridine (the Knorr reaction) rather than the 2-amino-5-hydroxy derivative of IV (the Conrad–Limpach reaction).

The possibilities of the synthesis of derivatives of naphthyridine IV from 2-aminopyridine when various methods are used are discussed in [46]. It has been reported that the condensation of 2,6-diaminopyridine with acetoacetic ester under the conditions of the Conrad–Limpach reaction gives 2-methyl-4-hydroxy-7-amino-1,8-naphthyridine [46]. Subsequent studies showed that 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine is actually formed [44, 47, 48]. A number of studies [47–55] have been devoted to the reactions of 2,6-diaminopyridine with dicarbonyl compounds — esters of oxalylpropionic [49], oxalylacetic [50], malonic, citric, acetonedicarboxylic [51], and other acids; 7-amino-2-hydroxy-1,8-naphthyridines are also formed in this case. In addition to dicarbonyl compounds, ethoxyacetophenone [56] and maleic acid [57] have been used for the condensation with 2,6-diaminopyridine.

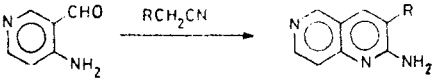
The reaction of 2-aminopyridine with α-methylacetoacetic ester in the presence of polyphosphoric acid (PPA) gives naphthyridine IV [58]. However, as we have already shown in the case of the reaction with ethoxymethylenemalonic ester, the condensation with 2-aminopyridines does not always lead to naphthyridines. For example, 2-amino-, 2-amino-4-methyl-, and 2-amino-6-methylpyridines react with perfluoro-2-methyl-2-pentene to give pyridopyrimidine derivatives instead of naphthyridine [59].



3-Benzyl-2,4-dihydroxy-1,5-naphthyridine was obtained from 3-aminopyridine and its derivatives with bis(2,4-dichlorophenyl) benzylmalonate [60]. The condensation of 3-aminopyridine with ethyl oxalylacetate gives 4-hydroxy-2-carboxy-1,5-naphthyridine [35]. 3-Aminopyridine reacts with acetoacetic ester under the conditions of the Conrad–Limpach reaction to give derivatives of naphthyridines I and III in a ratio of 4:1; however, it does not undergo the Knorr reaction [61]. The Conrad–Limpach reaction with 3-amino-2-methylpyridine leads to derivatives of III [62].

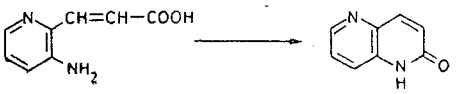


The application of the Friedländer method (i.e., the use of 2,3- and 3,4-amino aldehydes of the pyridine series) to the synthesis of naphthyridines I–IV gave very good results. 4-Aminonicotinaldehyde is converted to 2-amino-1,6-naphthyridines when it is condensed with substituted acetonitriles in the presence of an alkaline catalyst [63]. The condensation of 4-aminonicotinaldehyde was also carried out with esters and amides of malonic acid, ketones, aldehydes, and other bifunctional compounds [64-66]. A number of derivatives of naphthyridine IV were obtained in the reaction of 2-aminonicotinaldehyde and the corresponding ketones [67-69], and 3-aminonicotinaldehyde similarly gives derivatives of the I series [66].

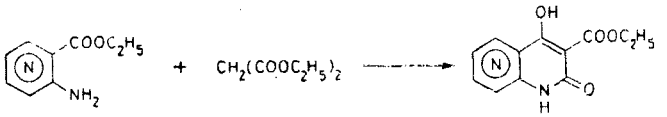


The principal product in the condensation of 2-amino-4,6-dimethylnicotinaldehyde with cyanoacetic ester is the corresponding 2-hydroxy-3-cyano-1,8-naphthyridine rather than 2-amino-3-carboxy-1,8-naphthyridine [69]. The condensation takes place even if the anil is used instead of the aldehyde [70]. For example, 1,7-naphthyridine derivatives were synthesized by this method.

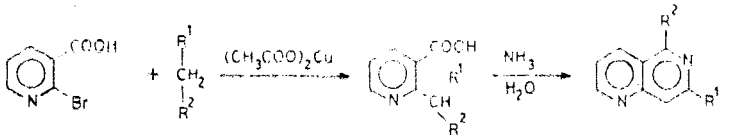
The intramolecular cyclization of β-(aminopyridinyl)acrylic acids can be considered to be the prototype of these reactions [71-73]:



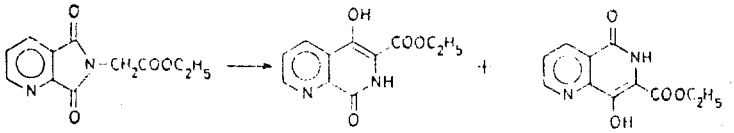
The condensation of aminopyridinecarboxylic acids or their esters with compounds with an active methylene group leads to naphthyridines of the I-IV type. Thus a number of compounds of the 2-methyl-4-hydroxy-3-carbethoxy-1,5-naphthyridine type were obtained from 3-aminopicolinic acid or its ester [73]. The reaction with nitroacetaldoxime gives 3-nitro-4-hydroxy-1,5-naphthyridine [19]. The reaction of o-aminopyridinecarboxylic acid esters with malonic ester makes it possible to synthesize all possible 2,4-dihydroxy-3-carboxynaphthyridines. The hydrolysis and decarboxylation of these compounds lead to the corresponding 2,4-dihydroxynaphthyridines [74-78]. 2,4-Dihydroxy-1,8-naphthyridine is also formed in the reaction with ethyl acetate [78].



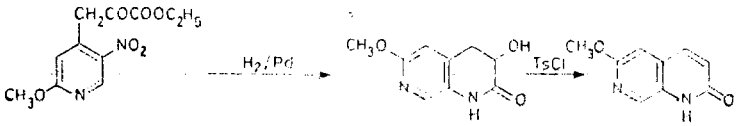
Chloro-, bromo-, and iodonicotinic acids react with compounds that contain an active methylene group [79] to give 5,7-disubstituted naphthyridines of the II type.



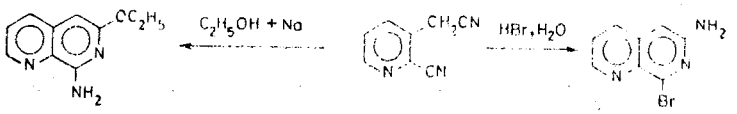
The rearrangement of quinolinic acid imides leads to 1,6- or 1,7-naphthyridines [15]:



Naphthyridines of the I and III series are formed in the reductive cyclization of some derivatives of nitropyridines [80]:

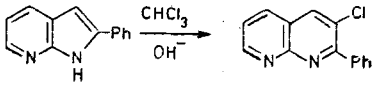


The acid hydrolysis of 2-cyano-3-pyridylacetonitrile [81] or its reduction with sodium in ethanol [82] gives derivatives of naphthyridine III.



A number of multistep syntheses of compounds of the I, II, and III type have also been described, but they all give the products in low yields [13, 77-87].

There is one example of expansion of the pyrrole ring of 7-azaindole under the influence of chloroform in the presence of alkalis to give 1,8-naphthyridines IV [88].



Electrophilic Substitution Reactions

Research on electrophilic substitution in the naphthyridine series provides evidence for retention of the typical "pyridine" β orientation in each of the rings. In fact, in addition to 3-bromonaphthyridines, dibromo derivatives with the second bromine atom in the 7 position for 1,5-, the 8 position for 1,6-, the 5 position for 1,7-, and the 6 position for 1,8-naphthyridines are obtained in the bromination of naphthyridines with bromine in oleum [89, 90], in CCl_4 in the presence of pyridine [16], or in nitrobenzene [91, 92]. 3-Bromo- and 3,6-dibromo derivatives are formed in the bromination of 1,5-naphthyridine N-oxide [93]. The side formation of 3,7-dibromo-1,5-naphthyridine in this case [93] is evidently due to bromination that takes place after removal of the N-oxide group.

The bromination of 2- or 4-hydroxynaphthyridines, which leads to 3-bromo derivatives, proceeds under milder conditions: with bromine in water for compounds of the I series [18] and with bromine in acetic acid or $KBrO_3$ in HBr for naphthyridines of the II [94], III [95], and IV [78, 96] series. The analogous chlorination (under the influence of $KClO_3$ in HCl) of 2-hydroxy-1,8-,4-hydroxy-1,6-, or 4-hydroxy-1,7-naphthyridines gives the 3-chloro derivatives [97].

Primarily 2,6-dibromo-1,5-naphthyridine containing the 2-monobromo derivatives is obtained in the bromination of naphthyridine in the gas phase (at 500°C), which probably proceeds via a radical mechanism.

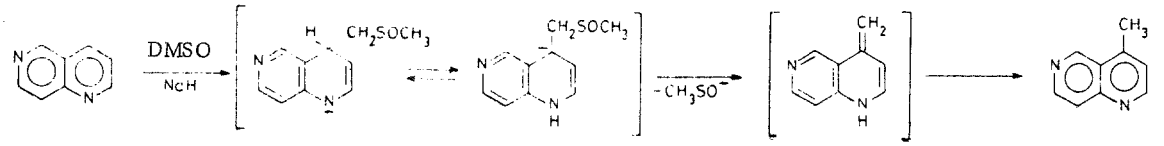
The nitration of naphthyridines is known [19, 37, 57, 90, 99-103] only for compounds that contain electron-donor groups (e.g., hydroxy groups) in the 2 or (and) 4 position.

Nucleophilic Substitution Reactions

The amination of naphthyridines I-IV with potassium amide in liquid ammonia [16] at room temperature leads to 2-amino derivatives in 30-56% yields. However, it has been proved [104] that the 4-amino derivative rather than the 2-amino derivatives is formed under these conditions from 1,5-naphthyridines [104]. An increase in the temperature to 50°C in the amination of 1,5-, 1,6-, and 1,8-naphthyridines improves the yields of amination products appreciably (up to 80%); the 4-amino compound is also formed from naphthyridine I in this case [6].

2-Phenylnaphthyridines are formed in ~25% yields under the influence of phenyllithium [105].

The methylation of naphthyridines I-IV was carried out with dimethyl sulfoxide (DMSO) in the presence of sodium hydride.



Only 4-methylnaphthyridine is formed from II, while I, III, and IV give, respectively, 4,8-dimethyl-1,5-, 4,8-dimethyl-1,7-, and 4,5-dimethyl-1,8-naphthyridines [106].

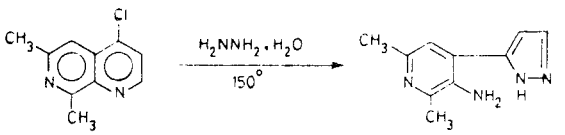
Hydroxy groups in the 2 or 4 position are replaced by bromine under the influence of $POBr_3$ or PBr_5 [22, 70, 78, 95-97, 107]. More detailed studies have shown that nucleophilic substitution of the hydroxy group in 4-hydroxy-1,6-naphthyridine under the influence of $POBr_3$ is accompanied by the formation of 4,8-dibromo and 4-hydroxy-8-bromo derivatives, whereas in the case of 2-hydroxy-1,8-naphthyridine a small amount of 2,6-dibromo-1,8-naphthyridine is formed along with the 2-bromo derivative [108]. The 3,8-dibromo derivative is obtained along with the 8-bromo derivative in the case of the reaction of $POBr_3$ [107] with 8-hydroxy-1,7-naphthyridine. 4-Hydroxy-1,6-naphthyridine undergoes reaction with PBr_5 to give two compounds — 4-hydroxy-3,8-dibromo- and 4-hydroxy-3,4,8-tribromo-1,6-naphthyridine [94]. A similar phenomenon was also observed in the case of replacement of the hydroxy group by chlorine under the influence of PCl_5—$POCl_3$ [109]. Chloronaphthyridines with chlorine atoms in the 2 or 4 positions were obtained by a classical method by the reaction of 2- or 4-hydroxynaphthyridines with phosphorus oxychloride [13, 78, 85, 92, 95, 110]. 2-Chloronaphthyridines are also formed in the reaction of N-methylnaphthyridinium salts with $POCl_3$ [111].

Nucleophilic substitution of halogen atoms was discussed in detail in an earlier review [10]. As a rule, exchange of bromine or chlorine in the 2 or 4 position of naphthyridine by an amino group takes place in solution in phenol and acetamide (180°C) when the mixture is treated with gaseous ammonia [21, 110].

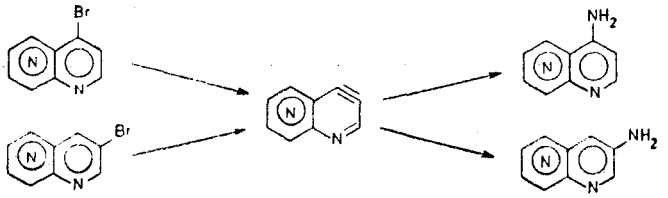
In the case of 2,4-dihalonaphthyridines the halogen atom in the 2 position undergoes nucleophilic substitution more readily than the halogen atom in the 4 position. Exchange by a hydroxy group under the influence of water [74] and aqueous solutions of HCl or HBr [29, 76, 78, 108] and by an amino or hydrazino group on reaction with ammonia or hydrazine [74], respectively, serve as examples of such reactions. The halogen atom in the 4 position is replaced in the reaction of 3,4-dibromo- or 3,4-dichloro-1,6-naphthyridines with tosylhydrazine [95]. However, the reaction is not selective in the case of 3,4-dihalo-1,7-naphthyridine [95]. This difference in the behavior of 3,4-dihalo derivatives of II and III is associated with the different positions of the nitrogen atom in the adjacent ring. In II the effects of both nitrogen atoms are concerted, whereas this is not true in the case of III.

4-Chloronaphthyridines are often used for the preparation of hydroxy, mercapto, and amino derivatives [34, 36, 109]. The chlorine atom in 4-chloro-1,7-naphthyridine was exchanged by a dialkylamino group during a search for physiologically active compounds [112], and the corresponding derivatives were obtained from 2-chloro-6-methoxy-1,5-naphthyridine and p-aminobenzenesulfonamide and thiourea [113].

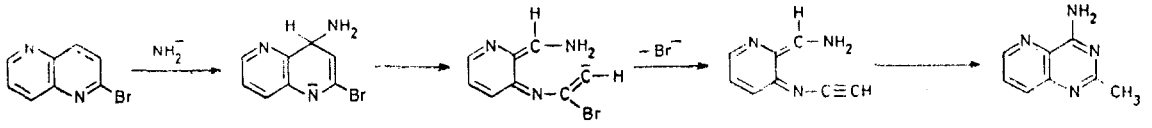
In the reaction of hydrazine with 4-chloro-1,7-naphthyridine one of the pyridine rings is cleaved with rearrangement to give pyrazolylpyridine derivatives [114, 115]. 4-chloro-1,8-naphthyridines also behave similarly in reactions with hydrazine, phenylhydrazine or β-hydrazinoethanol [116].



A mixture of 3- and 4-amino derivatives is obtained in the reaction of both 3-bromo- and 4-bromonaphthyridines of the I, II, and III series with potassium amide in liquid ammonia. In the case of 3-bromonaphthyridines these amines are formed in ratios of 86:14, 72:28, and 42:58, whereas in the case of 4-bromonaphthyridines they are formed in ratios of 72:28, 42:58, and 35:65 for compounds of the I, II, and III series, respectively [117-120]. It may be assumed that 3,4-dehydronaphthyridines are intermediates in the reaction. The nonidentical amounts of the 3- and 4-amino derivatives formed from 3- and 4-bromonaphthyridines make it possible to assume that the reaction also proceeds via an addition–cleavage mechanism. The different ratios of the amines obtained from the isomeric naphthyridines can be explained by the effect of the nitrogen atom in each ring.



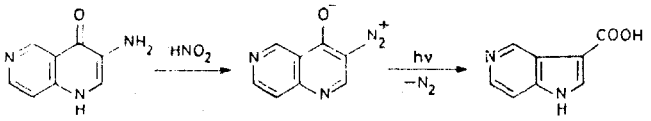
The reaction of 2-bromo-1,5-naphthyridine with potassium amide in liquid ammonia gives 2-amino-1,5-naphthyridine (as the principal product), 4-amino-1,5-naphthyridine, 1,5-naphthyridine [117], and 2-methyl-4-amino-1,3,5-triazanaphthalene, the structure of which was proved by alternative synthesis [121]. The mechanism of the converson of 2-bromo-1,5-naphthyridine to triazanaphthalene has been discussed frequently [6, 122-124]. A similar transformation to give 1,3,6-triazanaphthalene was observed in the reactions of 2,7-dibromo-1,5-naphthyridine [123], 2,3-dibromo-1,5-naphthyridine [124], and 2,4-dibromo-1,6-naphthyridine [125] with potassium amide in liquid ammonia.



The only product of amination of 3-bromo-2-ethoxy-1,5-naphthyridine was 3-amino-2-ethoxy-1,5-naphthyridine instead of the expected 4-amino derivative [117, 124]. Replacement of the bromine atom in 2-bromo-3-amino-1,5-naphthyridine to give the 2,3-diamino derivative occurs in the same way [120].

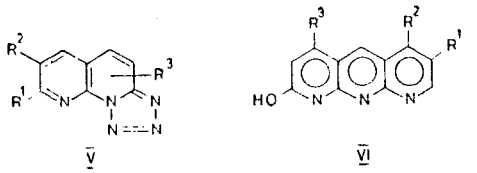
Reactions of Aminonaphthyridines

The diazotization of 3-amino-1,6-naphthyrid-4-one with subsequent photochemical rearrangement [43] accompanied by nitrogen evolution and ring contraction leads to 3-carboxy-5-azaindole [37, 103]. Similar reactions are also known for other isomeric naphthyridines [102, 103].



2-Hydroxy-1,8-naphthyridine is obtained instead of 1,8,9-triazaanthracene in the Skraup reaction with 2-amino-1,8-naphthyridine; 2-amino-1,6-naphthyridine behaves similarly [126].

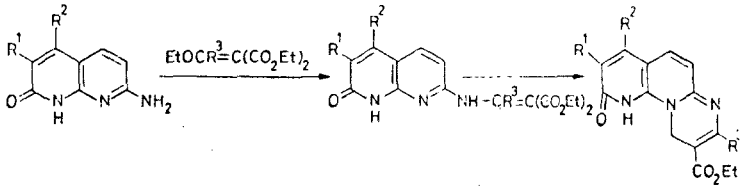
A number of studies [56, 57, 63, 127-129] have been devoted to the conversion of 2-amino-1,8-naphthyridine and its derivatives to tetrazoles of the V type.



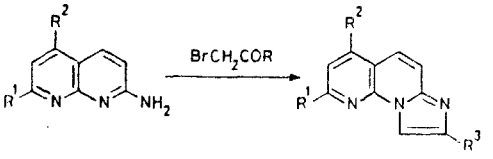
V VI

1,8,9-Triazaanthracene derivatives (VI) are obtained along with products involving substitution at the amino group in the condensation of 2-amino-7-hydroxy-1,8-naphthyridine and its derivatives with ethoxymethylenemalonic ester, acetylacetone, and β-ketoglutaric acid ester [130-136].

However, the products of cyclization of 2-amino-7-hydroxy-1,8-naphthyridine with compounds such as acetoacetic, ethoxymethylenemalonic, ethoxymethyleneacetoacetic, and ethoxymethylenecyanoacetic esters have angular structures [137]. The condensation of 2-amino-1,8-



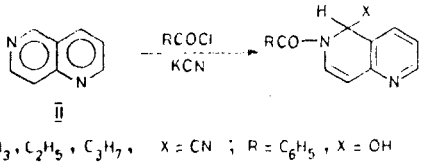
naphthyridines with α-bromo carbonyl compounds also leads to angular imidazo[1,2-a]-1,8-naphthyridines [137]:



The 1,5,10-triazaphenanthrene system is formed when the Skraup reaction is carried out with 4-amino-1,5-naphthyridine [138] and in the condensation with ethoxymethylenemalonic ester [104].

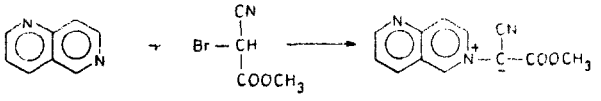
Other Reactions of Naphthyridines

The Reissert reaction has been carried out only with naphthyridine II [139, 140]. When N,N-diphenylcarbamoyl chloride is used, this reaction gives the product in good yield [139], whereas the yields are low in the remaining cases.

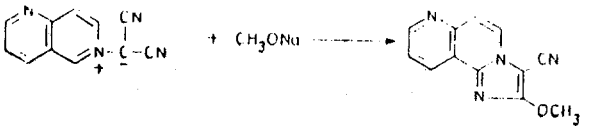


The reaction of compounds of the I type with methyl iodide gives the N-monomethiodide [141], which undergoes oxidation by potassium ferricyanide in alkaline media to give 1-methyl-1,5-naphthyrid-2-one [29]. 1,5-Dimethyl-1,5-naphthyridine-2,6-dione is formed by repeated methylation and oxidation. 1,5-Dimethyl-1,5-naphthyridine sulfate is obtained by methylation of I with dimethyl sulfate [142].

The quaternization of II with methyl iodide takes place at the nitrogen atom in the 6 position; this was proved by oxidation to 6-methyl-1,6-naphthyrid-5-one [111]. The structure of 1,7-naphthyridine methiodide was confirmed [111] by the PMR spectra and by oxidation to 7-methyl-1,7-naphthyrid-8-one. Like the three preceding naphthyridines, IV forms only a monomethiodide with methyl iodide [111]. The methylation of 2,4-dimethoxy-1,8-naphthyridine proceeds only at the 8-N atom [143]. The kinetics of quaternization of naphthyridines [144] and the structures of the pseudo bases [142, 145-151] have been recently investigated.

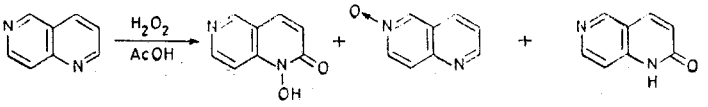


The reaction of methyl bromocyanoacetate with naphthyridine II gives an ylid [152]. Compound III reacts with tetracyanoethylene oxide to give an ylid, which is converted to an imidazo[1,2-f]-1,6-naphthyridine derivative by the action of sodium methoxide.

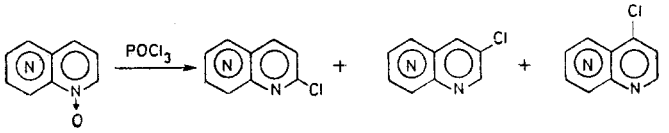


Naphthyridine N-Oxides

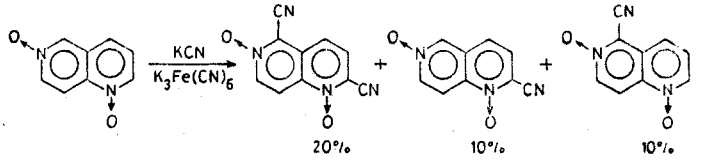
All naphthyridines of the I-IV type and a number of their derivatives form N-monoxides and N,N'-dioxides on oxidation with peracids or hydrogen peroxide in acetic acid [12, 21, 30, 153, 154]. The N-oxide group can sometimes also be retained during construction of the naphthyridine ring; thus, depending on the reaction temperature, naphthyridine I or its N-oxide is formed in preponderant amounts in the Skraup reaction with 3-aminopyridine N-oxide. The chief reaction product at 110-140°C is the N-oxide, whereas naphthyridine I is the principal product at 150°C [109]. 2-Hydroxy-1,6-naphthyridine is formed along with 1,6-naphthyridine 6-oxide in the oxidation of naphthyridine II with hydrogen peroxide in acetic acid, whereas the 1,6-dioxide is isolated in good yield in the presence of sodium tungstate [155]. In the course of subsequent studies it was shown that a mixture of three compounds is formed as a result of oxidation [156]:



3-Chloronaphthyridines are obtained along with the 2- and 4-chloro derivatives in the reaction of phosphorus oxychloride with 1-oxides of isomeric naphthyridines I-IV (the Meisenheimer reaction [155, 157-160]; the ratios of the 2-, 3-, and 4-chloro derivatives formed in the reaction are 34:2, 5:43, 15:2:9, 56:3:35, and 36:7:57 for naphthyridines I, II, III, and IV, respectively. The analogous reaction of 1,6-naphthyridine 6-oxide leads to 5-chloro-1,6-naphthyridine [155], whereas 2,5-, 3,4-, 4,5-dichloro-, and 5-chloro-1,6-naphthyridines are obtained from 1,6-naphthyridine 1,6-dioxide [161].

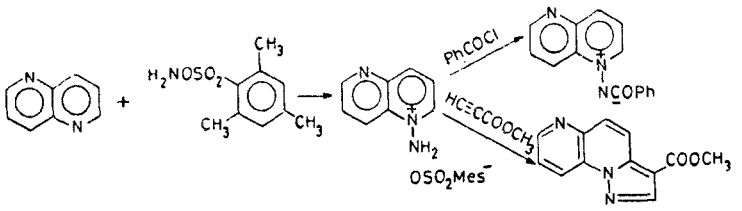


The Reissert reaction with 1,6-naphthyridine 1-oxide gives 2-cyano-1,6-naphthyridine, which is also obtained by the action of HCN on this N-oxide in methanol. Under the conditions of the Reissert reaction 1,6-naphthyridine 6-oxide and 1,6-dioxide form, respectively, 5-cyano- and 2,5-dicyano-1,6-naphthyridines; 5-hydroxy-1,6-naphthyridine is a side product in the case of the 6-oxide [140]. A mixture of 1,6-naphthyridine-5-carboxamide and 5-cyano-1,6-naphthyridine, as well as 2-methoxy-1,6-naphthyridine, was obtained by the action of KCN in methanol on the 1,6-dioxide of II [140, 162]. This reaction gives a number of compounds in the presence of $K_3Fe(CN)_6$ [163] via the scheme



N-Amino Derivatives of Naphthyridines

Compounds I and IV react with O-mesitylenylsulfonylhydroxylamine to give salts of N-amino derivatives [164], which are readily benzoylated [165]. N-Amino-1,5-naphthyridine salts undergo cycloaddition with acetylene derivatives. The reaction of the N-amino derivative of IV with acetylenedicarboxylic acid ester has also been carried out [166] (see scheme on following page).



Oxidation of Methylnaphthyridines

When 2-methyl-1,5-naphthyridine was heated with SeO_2, the methyl group was oxidized to a carboxy group [167], whereas the analogous oxidation of the N,N'-dioxide of this naphthyridine led to the aldehyde. An aldehyde was also formed in the oxidation of 4-methyl-1,8-naphthyridine [6].

Reduction of Naphthyridine Derivatives

The hydrogenation of naphthyridine over PtO_2 or Pd leads primarily to tetrahydro compounds [20, 37, 168, 169]. Both rings can be reduced by the action of sodium in ethanol or amyl alcohol [20, 37, 83, 168, 170-172]; all of the naphthyridines form only trans isomers [170]. However, if the hydrogenation is carried out over PtO_2 in acetic acid, a mixture of cis- and trans-decahydronaphthyridines is obtained [170].

Lithium aluminum hydride was used in the reduction of 7,8-dihydro-7-alkyl-1,7-naphthyrid-8-one and 5,6,7,8-tetrahydro-7-alkyl-1,7-naphthyrid-6-one to the corresponding 5,6,7,8-tetrahydronaphthyridine [173].

A number of other syntheses that make it possible to obtain hydrogenated derivatives of naphthyridine of the I [174-176], II [33, 175-180], III [176, 181-186], and IV [175, 176, 181, 185-195] type have been described.

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ARYL- AND ARYLOXYFURANS AS COMPONENTS OF THE DIENE SYNTHESIS WITH DIMETHYL ACETYLENEDICARBOXYLATE

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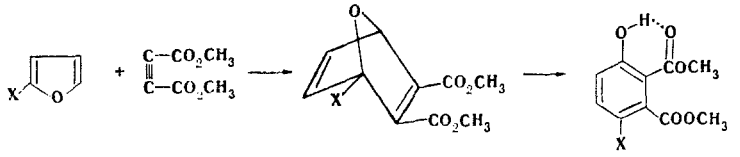
The diene synthesis of 2-aryl- and 2-aryloxyfurans with dimethyl acetylenedicarboxylate gives adducts, the aromatizatio of which under the influence of acetic acid leads to esters of 3-aryl- and 3-aryloxy-6-hydroxyphthalic acids.

The high reactivity of furan and its homologs as diene components in the Diels—Alder reaction is widely known. The behavior of arylfurans in this reaction has been studied in individual cases [1], whereas the behavior of aryloxyfurans in this reaction has not been studied at all.

We have shown that the reaction of aryl- and aryloxyfurans with dimethyl acetylenedicarboxylate give dimethyl 3,6-endoxo-3,6-dihydrophthalates (I), which are converted to methyl 6-hydroxyphthalates (II) as a result of aromatization under the influence of acetic



Ia-g IIa-g

I, II a $X=C_6H_4NHCOCH_3$; b $X=C_6H_4CH_3$-*p*; c $X=C_6H_4OH$-*p*; d $X=C_6H_4OC_4H_9$-*p*; e $X=C_6H_4Cl$-*p*; f $X=OC_6H_4CH_3$-*p*; g $X=OC_6H_5$

acid. Adduct Ia was isolated in quantitative yield; adducts Ib,c were obtained in the form of oils, which we were able to crystallize only partially. In this connection, adducts Ib-g were subjected to aromatization without prior purification.

The presence of the signal of a hydroxy group at 10.77-10.92 ppm and two singlets of ester groups at 3.59-3.92 ppm is characteristic of the PMR spectra of substituted hydroxydiphenyls II. As a rule, the signals of the protons in the 4 and 5 positions and the protons of the substituent in the 3 position are overlapped and form a complex multiplet (Table 1).

Two bands of stretching vibrations of the CO group of the carbomethoxy substituents (high-frequency band at 1733-1744 cm^{-1} and low-frequency band at 1679-1685 cm^{-1} in CCl_4) and ν_{OH} bands of a phenolic hydroxy group (3430-3440 and 3125-3165 cm^{-1} in CCl_4, Table 2) are observed in the IR spectra of crystalline II and solutions of II.

It is apparent from the results (Table 2) that the yields of the adducts of arylfurans with dimethyl acetylenedicarboxylate, which subsequently undergo conversion to hydroxyphthalic acids, depend on the character of the substituent in the benzene ring of the arylfurans;

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