ADVANCES IN THE CHEMISTRY OF 1,7-NAPHTHYRIDINE

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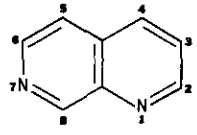
Abstract —— This review describes the physical properties of 1,7-naphthyridine and its derivatives, reports on the methods available to synthesize 1,7-naphthyridine derivatives, and discusses the reactivity of the 1,7-naphthyridine system to electrophilic and nucleophilic reagents, giving substitution and ring transformation, to N-alkylating agents, to reducing agents and to light. The review also includes a short paragraph on the pharmacogical use of 1,7-naphthyridines.

CONTENTS

1. INTRODUCTION

Of the four possible isomeric 1,X-naphthyridines (X=5,6,7 or 8) the chemistry of the parent system 1,7-naphthyridine (1) - also named 1,7-diazanaphthalene or pyrido [3,4-b] pyridine - has not well been developed, mainly due to long term difficulties in developing a good synthesis of this system. However, in the last decade this problem has been overcome and interest for 1,7-naphthyridine chemistry strongly increased, as evidence by the number of publications, dealing with physical and chemical properties and with new syntheses of this system.



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The chemistry of 1 has mostly been described in reviews concerning the chemistry of all naphthyridines: by Allen[1] (covering the literature up to 1947), by Weiss and Hauser[2] (up to 1958), by Paudler and Kress[3] (up to 1968), by Hamada and Takeuchi[4] (up to 1972), by Czuba[5,6] (up to 1979) and by Campbell.[7]

The aim of this article is to review especially the chemistry of 1 with a special attention to results obtained in the laboratories of both authors. Although the review is limited to 1,7-naphthyridine chemistry, occasionally - for reasons of comparison - reference to the chemistry of the isomeric naphthyridines is made.

In the present review, the literature has been covered till about 1981.

II. PHYSICAL PROPERTIES

II.1. Structure

1,7-Naphthyridine (1) is a crystalline compound. A variety of melting points are recorded: 65-66°;[8] 64°;[9] 61-62°;[10] 59-61°;[11] 58-60°;[12] 57-60° [13] (mp of picrate: 196.5-197.5°,[10] 205-206° [13]). The compound easily sublimes, is soluble in water and in common organic solvents, but only slightly

soluble in light petroleum ether. This solvent is found to be the most appropriate one for recrystallization of 1. The pentane/water coefficient is 0.02.[14]

It has been found that 1, like its 1,5- and 1,6-isomer, is planar.[15,16] Examination of the bond lengths in 1,5- and 2,7-naphthyridine showed that the degree of bond shortening and lengthening is nearly the same, when extending the ring system from pyridine to the naphthyridines, as from benzene to naphthalene. It can be predicted that the extent of bond fixation in 1 will be the same as in the isomeric naphthyridines.[3a]

II.2 Quantum Mechanical Calculations

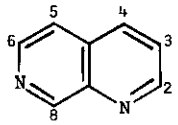
In recent years quantum mechanical calculations have been carried out to correlate the results with the various chemical and physical properties of the parent naphthyridines.

The total π-energy and the delocalization energy of 1 have been calculated[17,18] and comparison of the delocalization energy of 1 with those calculated for the other 1,X-naphthyridines showed that they are effectively the same. Calculations of the distribution of π-electron densities in ground-state 1,7-naphthyridine with the aid of a HMO nitrogen parameter, based on the polarographic half-wave reduction potentials of a large number of heterocyclic compounds,[19] showed the following order of positions: 1(1.41) > 7(1.38) > 5(0.99) > 3(0.98) > 6(0.89) > 4(0.86) > 8(0.81) > 2(0.78).[18]

A first-order perturbation method has been presented for calculation of the energy of π-electron levels and the electron densities at various positions of 1 and other azanaphthalenes.[20] The results were in good agreement with observed reactivity.

A simple additivity model was developed and used to predict total ($\sigma + \pi$) electron density (ΔQ_T) distributions in 1 and other azanaphthalenes.[21] The predicted ΔQ_T values were successfully applied for estimating ^1H nmr chemical shifts (δ_H). The δ_H values are in reasonable agreement with available experimental results (Table 1).

Table 1. Prediction of δ_H values for 1,7-naphthyridine, based on the additivity model

	Position	ΔQ_T	δ_H	
			predicted	experimental
	2	-0.405	-1.47	-1.73
	3	-0.009	-0.21	-0.34
	4	-0.151	-0.89	-0.90
	5	-0.008	-0.52	-0.33
	6	-0.290	-1.20	-1.32
	8	-0.381	-1.91	-2.25

Heteroatom integrals, determined from thermochemical data, were used in simple Hückel calculations to predict for 1 the π-binding energy, additive energy and resonance energy per π-electron.[22] Also energy levels, wave functions and charge distribution were reported.[23]

The spin density distribution in the radical anion of 1 was determined by the unrestricted Hartree-Fock method and the N splittings (α_N) were calculated by the relation of Karplus and Fraenkal.[24]

The electron spin resonance spectrum of the anion of 1 was interpreted by using MO theory.[25]

Results obtained with different theoretical procedures were compared and discussed.[25]

Semi-empirical calculations of the adiabatic electron affinities and the energies of two excited negative ion states of 1 were presented by Younkin et al.[26] The electron affinity values seem to be consistent with what is known about the stability of this negative ion.

Van der Weijer et al.[27] have studied the protonation of azanaphthalenes and azabenzenes, using CNDO/2 wave functions and perturbation theory in order to examine the correlation between pK_a values and quantum mechanical parameters. The calculations have shown that for 1 the correlation is rather poor and that the results are not consistent. The calculated Coulomb energy predicts that protonation will take place at position 7, whereas calculations of the gas phase protonation energy or the solvatation energy favour protonation at position 1. Also NDDO calculations prove that position 1 has the highest proton affinity.[28]

The Pariser-Parr-Pople (PPP) method[29] and its simplified version[30] have been used to calculated transition energies and intensities of the $\pi \rightarrow \pi^*$ bands in the electron spectra of 1 and 30 other azines. In general a good agreement between theoretical and experimental data was found. Polarizations of the first two electron transitions in 1 were calculated by configuration interaction in semi-emperical PPP approximation.[31]

PPP calculations taking into account limited configuration interaction were performed for 1 and other azaaromatic compounds.[32] Good correlations were found with experimentally observed ionization potentials, singlet-singlet transition energies, polarization and oscillator strengths as well as with ground state molecular geometries.

Correlations between experimental π and n ionization potentials in the photoelectron spectrum of 1 and those calculated by several semi-emperical quantum mechanical calculation methods have been made with varying success[33] (Tables 2 and 3).

A Modified Iterative Extended Hückel Method (MIEHM) was applied to the photoelectron spectrum of 1.[34] The thirteen highest molecular orbital energies were correlated with the experimentally obtained spectrum in the region 8-16 eV. This method gave more recognizable "lone pair" orbitals than the extended Hückel method.

Comparison of ^{13}C nmr chemical shifts of 1 with those calculated by applying simple LCAO and SCF - MO (PPP approximation) methods for π-electron systems showed a fairly good linear relationship.[35]

Table 2. Experimental and calculated π ionization potentials (IP) of 1,7-naphthyridine. All values in eV. The Hückel IP (π)'s are in units β

Orbital	IP (π) observed	IP (π) Hückel	IP (π) PPP-SCF	IP (π) Extended Hückel	IP (π) CNDO II
π_1	8.99	0.76	9.62	12.46	11.38
π_2	10.00	1.11	10.46	13.03	13.41
π_3	11.14	1.46	11.66	13.73	16.30

Table 3. Experimental and calculated n ionization potentials of 1,7-naphthyridine. All values in eV

$IP\ (n)_1$ observed	$IP\ (n)_2$ observed	Δ IP (n) observed	$IP\ (n)_1$ extended Hückel	$IP\ (n)_2$ extended Hückel	Δ IP (n) extended Hückel
9.30	10.00	0.70	12.45	12.00	0.45

II.3. Spectra

II.3.a. Infrared Spectra

The assignments of the bands in the infrared sprectrum of 1 (Fig. 1) in the region 1700-650 cm^{-1} has been determined[36] and correlated with those found for naphthalene and other azanaphthalenes.

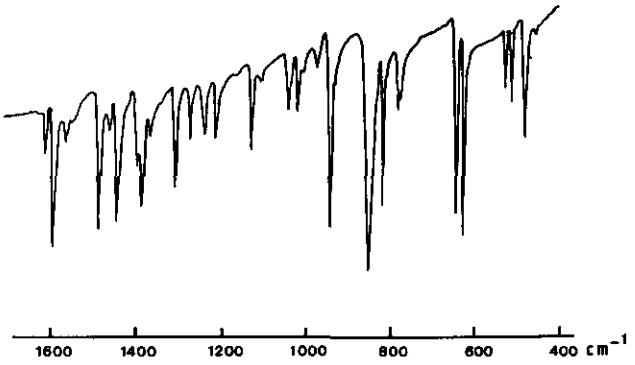


Fig.1 IR spectrum of 1,7-naphthyridine in the region 1600-400 cm^{-1}

A transferable valence force field has been developed for application to the out-of-plane vibrations of the parent substance 1.[37] The existing vibration frequency assignments have been reviewed, rationalized and revised. Moreover, the planar frequencies in the range 350-1000 cm^{-1} were reviewed.

Ikekawa[38] has reported the ir spectrum of 1 and its 4-chloro derivative in the range 700-920 cm^{-1} and has attempted to correlate the out-of-plane vibration frequencies with the patterns of substitution in naphthyridines. Similar attempts were made by Rapoport and Batcho.[14]

The ir spectra of 41 substituted 1,7-naphthyridines (with 10 different substitution patterns) have been examined for the presence of structural characteristic vibrations in the C-H out-of-plane bending frequencies.[39] With a few exceptions the compounds showed ring bending (skeletal) vibrations at 680-740 cm^{-1}; in case 3 adjacent hydrogens are present absorptions were found in the ranges 750-795 and 805-830 cm^{-1}; when 2 adjacent hydrogens are present the absorptions lie in the range of 780-855 cm^{-1} and an isolated hydrogen shows absorption at 855-920 cm^{-1}. For 8-hydroxy-1,7-naphthyridine[40] and 2-hydroxy-1,7-naphthyridine[41] the infrared stretching vibrations of the carbonyl 8-OH($CHCl_3$): 1665 cm^{-1}; 2-OH($CHCl_3$): 1662 cm^{-1} and the N-H group 8-OH(CCl_4): 3403 cm^{-1}; 2-OH($CHCl_3$): 3400 cm^{-1} were found, showing that these compounds mainly exist in the oxo form.

II.3.b. Electronic Spectra

The uv spectrum of 1 (in CH_3OH) showed the following characteristics [λ_{max}, mμ (log ε)] : 219(4.42), 262(3.58), 302(3.33), 313(3.28).[14] The spectrum strongly resembles that of 1,6-naphthyridine but differs from the spectra of 1,5- and 1,8-naphthyridine.[9] These differences have been succesfully used to distinguish 1,5-naphthyridine from 1,7-naphthyridine.[12,14] The uv spectra of 1, its 4-chloro and 4-oxo derivatives have been given by Ikekawa[13] (Fig. 2).

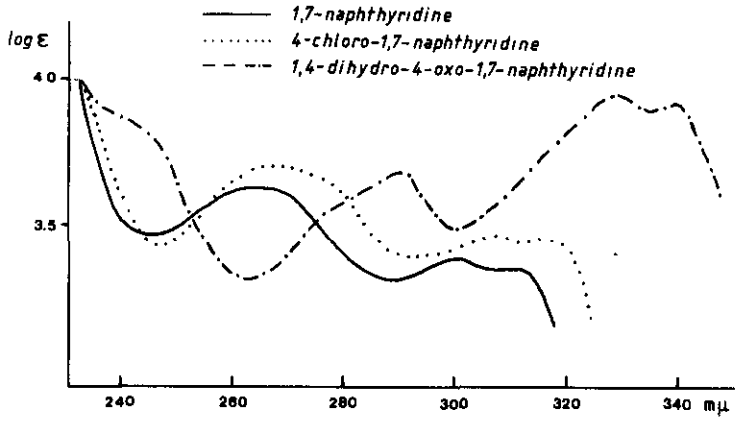


Fig.2 UV spectrum of 1,7-naphthyridine and its 4-chloro and 4-oxo derivatives (in MeOH)

Comparison of the uv spectrum of 8-hydroxy-1,7-naphthyridine (ethanol/water, isoelectric pH value= 7.32) with uv spectra of corresponding N-heteroaromatic compounds,[42] showed that in this solvent 8-hydroxy-1,7-naphthyridine is predominantly present in the oxo form.

The uv spectra of 7-methyl-1,7-naphthyridinium cation, its pseudo-base and methoxide adduct have

been reported.[43] Ross et al.[44] have studied the electronic low singlet-singlet transitions of eleven diazanaphthalenes, as dilute solid solutions in molt-grown, monocrystalline hosts at 4.2°K. The lowest observed transitions in 1 (in naphthalene) showed that $n \rightarrow \pi^*$ < $\pi \rightarrow \pi^*$ and that the separation between n and π^* was more than 0.25 eV. The computed lone pair splitting pattern, as well as the symmetry of the lowest unoccupied π^* levels were given.

Van der Ham and Van der Meer[33] presented the high-resolution He 584 Å photoelectron spectra of 1 (Fig. 3) and nine other diazanaphthalenes. The ordering of the π-orbitals and the nitrogen "lone pair" orbitals was discussed. From this study it was concluded that the first ionization in 1 takes place from a π-orbital (see Tables 2 and 3) and that there exists interaction of non-bonding electrons belonging to equivalently placed atoms.

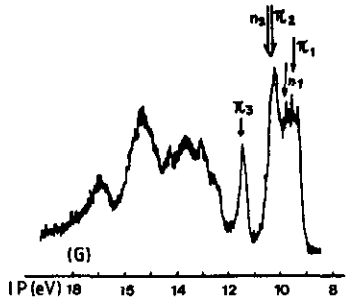


Fig. 3 Photoelectron spectrum of 1,7-naphthyridine

General outline of the photoelectron spectrum of 1 with indication of empirical corrected MIEHM energies was given by Spanget-Larsen.[34] The identification of π bands and nitrogen "lone pair" bands was in perfect agreement with the results of the Dutch chemists.[33]

II.3.c. Nuclear Magnetic Resonance Spectra

The ^1H nmr spectrum of 1 has been described in several papers.[8,10,19,45] The spectrum can be interpreted by first ordering splitting rules including meta, para and cross-ring spin-spin coupling. Fig. 4 presents the ^1H nmr spectrum of 1 (in $CDCl_3$), and in Table 4 the chemical shifts, as well as coupling constants are listed.[45]

Fig. 4 ^1H NMR spectrum of 1,7-naphthyridine

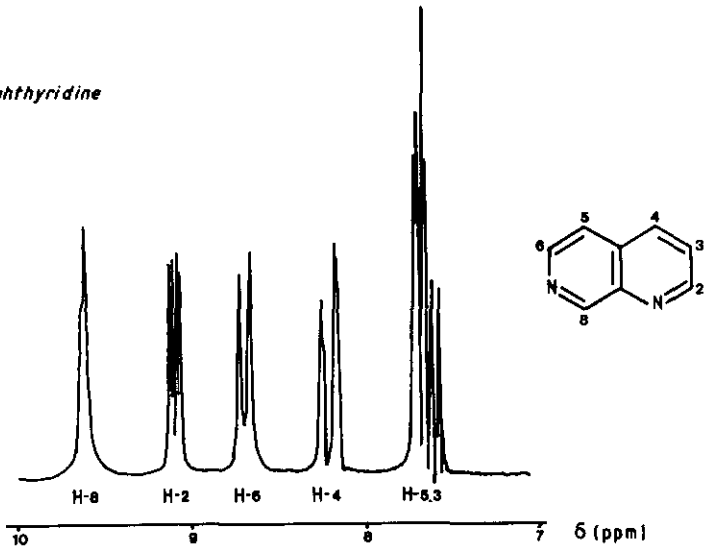


Table 4. Chemical shifts and coupling constants of 1,7-naphthyridine[45]

chemical shifts (δ)						coupling constants (Hz)					
H-2	H-3	H-4	H-5	H-6	H-8	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{5,6}$	$J_{5,8}$
9.14	7.67	8.26	7.72	8.73	9.66	4.2	1.6	8.4	0.9	5.6	0.9

In the expanded spectrum of 1 two long-range, spin-spin coupling can be observed: one cross-ring ($J_{4,8}$) and one para coupling ($J_{5,8}$).[45] ^{1}H nmr spectra of some 3- and 4-substituted 1,7-naphthyridines were analyzed and compared with the spectrum of the parent compound.[46]

^{1}H nmr spectroscopy has been found to be a useful tool in the determination of the structure of a number of 1,7-naphthyridines derivatives and facilitated investigation on substitution patterns. The site of oxidation of 1 (N-1 or N-7) has successfully been determined by application of ^{1}H nmr spectroscopy.[47] ^{1}H nmr spectroscopy was also succesfully used to establish that the site of monoprotonation and monomethylation of 1 is position 7.[48] These conclusions are based on the occurrence of a cross-nitrogen coupling between H-8 and H-6 indicating the absence of the lone-pair of nitrogen due to binding to the proton or alkyl group.

By ^{1}H nmr spectroscopy it was convincingly shown that the site of hydrogen bonding between 1 and water was at position 7, as determined by specific line broadening of H-6 and H-8.[49] The line broadening is caused by the spin-spin interaction between proton of the water molecule and the H-6 and H-8 protons.

Many papers describing the synthesis of new 1,7-naphthyridine derivatives usually report ^{1}H nmr data. They are however so numerous that they cannot be listed individually in this review. For references see the sections Preparation (III) and Reactions (IV).

Tris(dipivaloylmethanato)europium (Eu(DPM)$_3$) induced shifts of the proton resonances of 1 and a number of other azaaromatic compounds have been measured for solutions containing different equivalents of the shift reagent.[50] The differences observed in the various spectra of the complexed azaaromatics were discussed in terms of a steric relationship between the heterocycle and the complexing agent. In the case of 1, complex formation appears to occur almost specifically on the "isoquinoline type" nitrogen atom. The induced shifts are larger than those observed for protons in similar positions relative to the complexed nitrogen in isoquinoline.

Lanthanide Eu(fod)$_3$ induced shifts of the protons in 1 were estimated knowing the coordinating abilities of the nitrogen and their influence on the chemical shifts of the hydrogens in quinoline and isoquinoline.[51] The estimated relative induced proton shifts agreed almost quantitatively with observed values, however with the exception of H-8.

The ^{13}C nmr spectrum of 1 is given in Fig. 5.[35,52] The unambigous assignments of the chemical shifts were achieved by the selective heteronuclear decoupling. The observed chemical shifts were compared with those being calculated.[35]

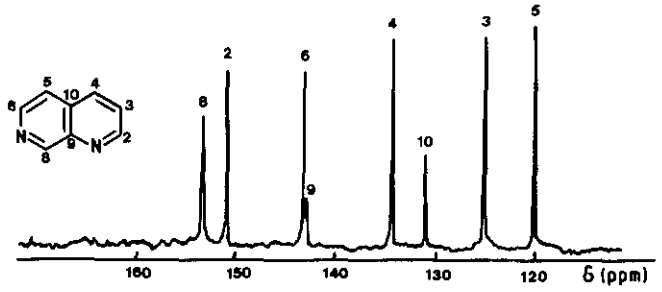


Fig. 5 ^{13}C NMR spectrum of 1,7-naphthyridine

The ^{13}C nmr spectrum of N-methyl-1,7-naphthyridinium fluorosulfonate has been reported.[53] It has been shown by comparison of a number of spectra of N-methylnaphthyridinium salts that N-methylation and N-protonation have a similar shift effect on ^{13}C chemical shifts. The ^{13}C chemical shifts of 1 have been recorded as function of the pH value. From these titration curves the pK_1(3.57) and pK_2(-1.12) values have been determined.[54,55] ^1H and ^{13}C nmr spectroscopy has been proved a useful technique for establishing that the sites of addition of amide ion to 1 are the positions 2 and 8.[56] The ^1H and ^{13}C nmr data of corresponding anionic σ-adducts have been reported.[56]

II.3.d. Mass Spectra

The mass spectrum of 1 was first reported by Paudler and Kress[57,3b] (Fig. 6). The spectrum is essentially identical with those of other 1,X-naphthyridines (X=5,6 or 8).

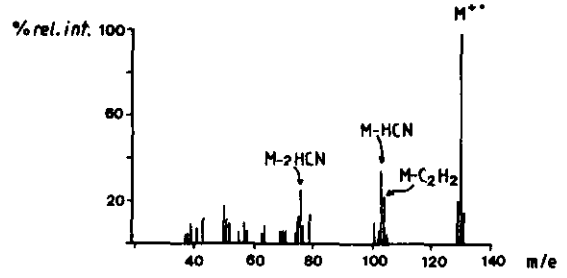


Fig.6 Mass spectrum of 1,7-naphthyridine

The three most abundant fragment ions in the spectrum of 1 were found at i) m/e = 103, the ion resulting from expulsion of HCN from the molecular ion; ii) m/e = 104, the fragment obtained by loss of C_2H_2 from the parent ion-radical and iii) m/e = 76, obtained from the m/e = 103 ion by loss of another molecule of HCN.

Mass spectra of 2- and 4-hydroxy-,[58] of 2,4-dihydroxy-,[58] of 2-, 3-, 4-, 5- and 8-monobromo-,[59] of 2,4- 3,4- and 3,5-dibromo-[59] and of 2-, 3-, 4- and 8-amino-1,7-naphthyridines[59] were reported and fragmentation mechanisms were proposed. 5-Amino-1,7-naphthyridine shows similar fragmentation patterns as 2- and 3-amino-1,7-naphthyridine.[60] Moreover, the mass spectral data of 4-hydroxy-3-nitro-, 8-hydroxy-5-nitro-, 8-amino-5-nitro- and 8-chloro-5-nitro-1,7-naphthyridines were recorded and fragmentation patterns of these nitroderivatives were suggested.[61]

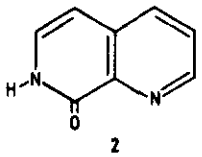
II.4. Ionization Properties

The pK_a value of 1 (=3.63,[9] 3.7,[14], 3.6-3.7[62]) (Table 5) has been reported as somewhat lower than the pK_a value of the 1,6-isomer (=3.78),[9] but higher than those of 1,5-isomer (pK=2.91)[9] and 1,8-isomer (pK_a=3.39).[9]

Table 5 pK_a's of some 1,7-naphthyridines

compound	pK_a's
1,7-naphthyridine	3.63,[9] 3.7,[14] 3.6-3.7[62]
1,2,3,4-tetrahydro-1,7-naphthyridine	7.08[122]
5,6,7,8-tetrahydro-1,7-naphthyridine	8.56[122]
trans-decahydro-1,7-naphthyridine	10.16[122]
8-oxo-7,8-dihydro-1,7-naphthyridine	2.64[63]

The greater basic strength of 1 seems to indicate that protonation occurs on N-7 rather than on N-1 (compare pK_a quinoline = 4.94, pK_a isoquinoline = 5.40) in agreement with data more recently obtained.[48,54]



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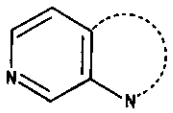
The pK_a of 8-hydroxy-1,7-naphthyridine (=2.64) is lower than that of the parent compound (Δ $pK_a \sim 1$); this is certainly due to the preference of the 8-hydroxy compound to exist in aqueous solution[63] in the oxo form 2. The preference for the oxo tautomer 2 is also supported by the results of uv spectroscopic measurements.[42]

II.5. Polarography

Polarography of 1 and its iodide salt showed that in acid media 1 gives 2 x 1F polarographic waves.[64] At certain pH's the first step produces a relatively stable radical cation that undergoes a H-shift from nitrogen to carbon, forming an unstable radical species at carbon which dimerizes. The process is an acid- or base-catalyzed first order reaction.

III. PREPARATION

Most routes to the synthesis of 1,X-naphthyridines are patterned on the synthesis of quinolines or isoquinolines. In all syntheses designed to prepare 1,7-naphthyridines, a pyridine derivative is used as starting material, having a substituent, in which a nitrogen is present, that is separated from the ring nitrogen by two carbon atoms. 3-Amino- or 3-nitropyridine derivatives (structural feature A) as well as 2-cyano-, 2-carboxamido- or 2-(aminomethyl)pyridine derivatives (structural feature B) have been found to be useful starting substances and are frequently applied for synthesizing 1,7-naphthyridines.



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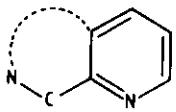

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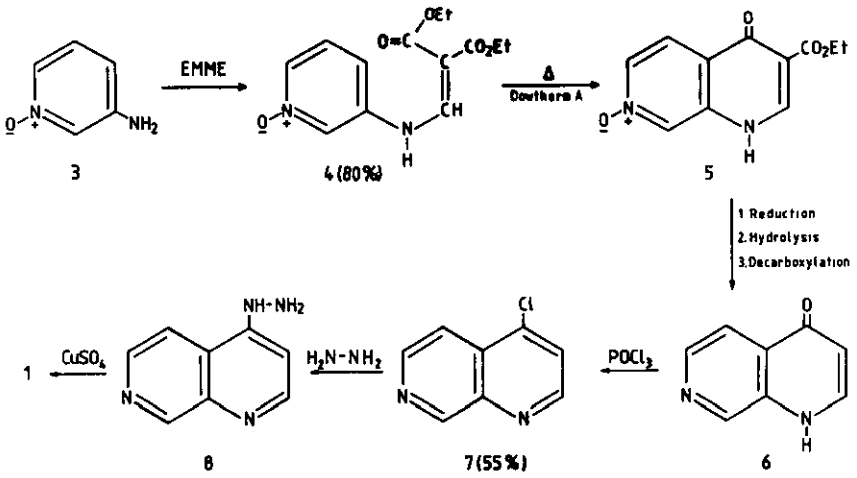
III.1. Syntheses of 1,7-naphthyridines from 3-substituted pyridine derivatives

When compounds with structural feature A are used as starting material for the synthesis of 1,7-naphthyridines, one has to be aware that the annellation can take place at C-4 of the pyridine ring (yielding 1,7-naphthyridines) or at C-2 (yielding 1,5-naphthyridines), sometimes leading to mixtures of both naphthyridines. A successful synthesis of 1,7-naphthyridines derivatives has been described from 3-aminopyridine N-oxide (3) and diethyl ethoxymethylenemalonate (EMME). It gave the condensation product 4 which undergoes cyclization in refluxing Dowtherm A to afford 3-carbethoxy-4-oxo-1,4-dihydro-1,7-naphthyridine 7-N-oxide (5).[65]

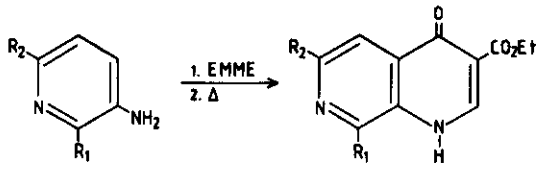


The presence of a N-oxide group is necessary to direct the annelation in the right position as was shown by the fact that the analogous reaction with 3-aminopyridine afforded only the 1,5-naphthyridine derivative.[66] Evidently the N-oxide function in 4 makes position 4 in the pyridine ring more nucleophilic and therefore promotes the addition of the electrophilic carbon of the ethoxycarbonyl group. When instead of EMME acrolein diacetal was used as cyclization agent only a small amount of a deoxygenated 1,5-naphthyridine was obtained.[12] This fact seems to indicate that cyclization at C-4 in 4 is not only determined by the structure of the pyridine derivative but also by the specificity of the reagent.[12]

Deoxygenation of compound 5 with iron in acetic acid[65] or with sodium dithionite[67] followed by hydrolysis and decarboxylation gave 4-oxo-1,4-dihydro-1,7-naphthyridine (6). Overall yield 4 → 6 about 22%.

Heating of compound 6 with phosphorus oxychloride gave 4-chloro-1,7-naphthyridine (7).[65]. Ikekawa[13] and independently Albert[9] converted compound 7 into 4-hydrazino-1,7-naphthyridine (8) from which by oxidation with cupric sulphate 1 was obtained. This route constituted the first preparation of 1 (yield 7 → 1: 40-60%).

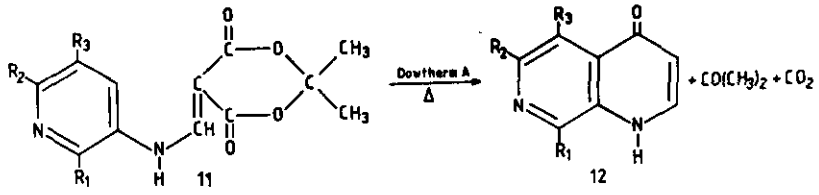
EMME has found wide applicability as reagent in the synthesis of 3-carbethoxy-4-oxo-1,4-dihydro-1,7-naphthyridine derivatives (10).[68-71] As substrates were used either the N-oxides of various 3-aminopyridines, or 3-aminopyridines containing a blocking substituent in the 2(6)-position i.e. 9 (R_1, R_2 = lower alkyl, alkanoyl, alkenyl, alkanoylamino, hydroxy, amino, hydroxymethyl, alkanoyloxymethyl).



9 10

By a sequence of reactions, involving hydrolysis and alkylation (or reversed, first alkylation and then hydrolysis) a great number of 1-alkyl-3-carboxy-4-oxo-1,4-dihydro-1,7-naphthyridines was prepared from 10. However, these reactions are somewhat complicated by the fact that alkylation of 10 (or the corresponding acid) not only occurs at N-1 but also at N-7 and at C-4 oxygen; product distributions were found to be strongly influenced by steric factors.[69,71]

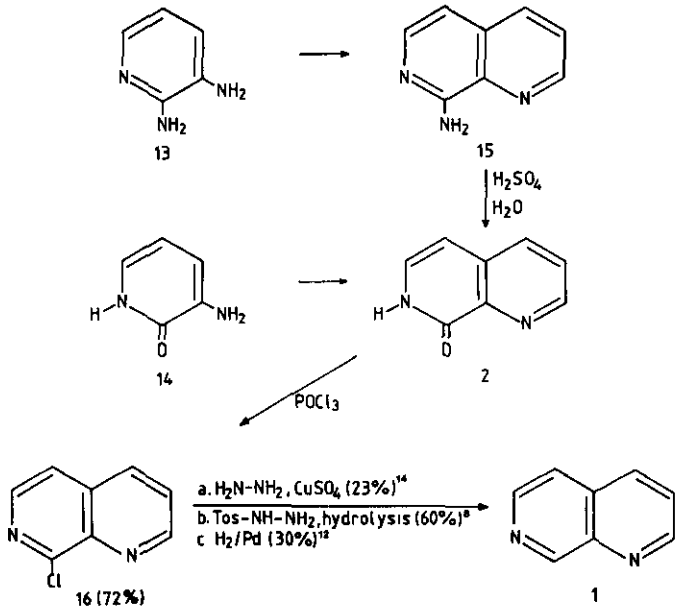
A modification of the method described above has been reported in the patent literature;[72] heating of the isopropylidene-3-pyridylaminomethylenemalonates (11) in Dowtherm A gave the corresponding 4-oxo-1,4-dihydro-1,7-naphthyridines (12). With 11 (R_1=H) besides cyclization at C-4 yielding 12, cyclization occurs at C-2, giving the isomeric 4-oxo-1,4-dihydro-1,5-naphthyridines.



11 12

R_1 = H, Me, Et, n-Bu , $NHCOCH_3$; R_2 = H, Me, $N(CH_3)_2$, OC_2H_5; R_3 = H, Me

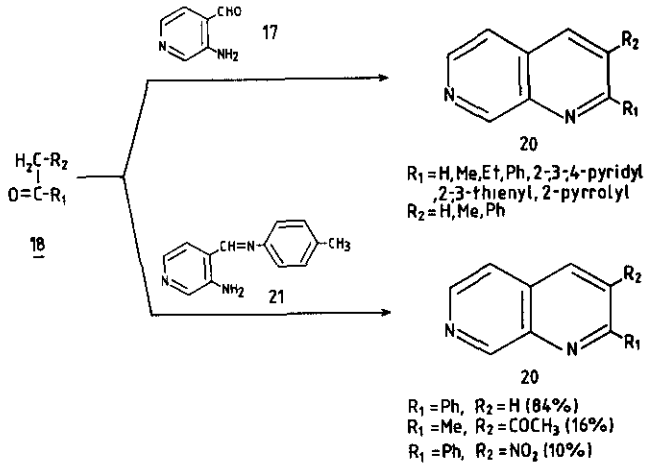
The Skraup method, being successfully applied for preparing 1,X-naphthyridines (X=5,6 or 8),[3c,73] has only a very limited applicability for synthesing 1,7-naphthyridines, since the Skraup cyclization of 3-aminopyridines rather proceeds at position 2 of the pyridine ring yielding 1,5-naphthyridines,[14] than at position 4. Only 3-aminopyridines with a strongly electron-donating group at position 2 i.e. 13 or 14 are found to be succesfully "Skrauped" into 8-amino- (15)[18,74] *and 8-oxo-*7,8-dihydro-1,7-naphthyridine (2)[8,75] respectively (yields 20-25%). There is one report mentioning a yield of 90% in the conversion 14 → 2.[14] In our hands this yield could never be obtained; we always found yields between 20-25%.

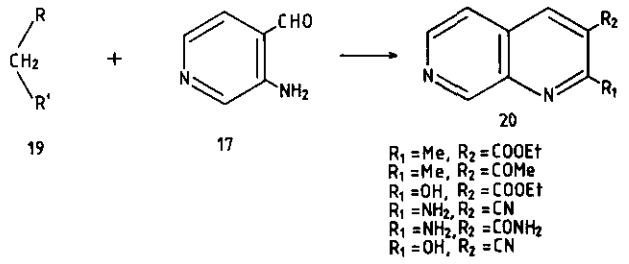


Compound 2 could also be obtained by acid hydrolysis of 15 in high yield (81%).[76] The oxo group in 2 can easily be replaced by a chloro atom yielding 16[8,14] *from which one may obtain* 1 *by means of* several methods (see Scheme). On the basis of our own experience, the authors prefer the sequence

13 → 15 → 2 → 16 → 1 (16 → 1 according to method b) as the most convenient way of preparing 1, since the starting material 13 is commercially available and all the required steps are simple and proceed with fair yield. It is noteworthy that in the patent literature[77] the synthesis of 1 from 3-aminopyridine N-oxide is reported (yield 2-3%). This result, however, was not confirmed.[12] The patent also mentioned the synthesis of 2-, 3- and 4-methyl-1,7-naphthyridine and their 7-N-oxides.[77]

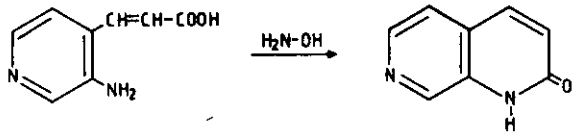
The Friedländer method of preparing quinoline by reaction of an o-aminoarylaldehyde with a reagent capable to react with both amino and aldehyde substituents, has been widely applied to the synthesis of a number of 2- and 3-mono- and 2,3-di-substituted 1,7-naphthyridines. When 3-aminoisonicotinaldehyde (17) is reacted with aldehydes or ketones i.e. 18 or with active methylene compounds, carrying ester, keto or nitrile functions, i.e. 19 the 1,7-naphthyridines 20 are formed.[78,79] Compound 17 was obtained by reduction of methyl 3-aminoisonicotinate in about 80% yield.[79] However no experimental details were given.





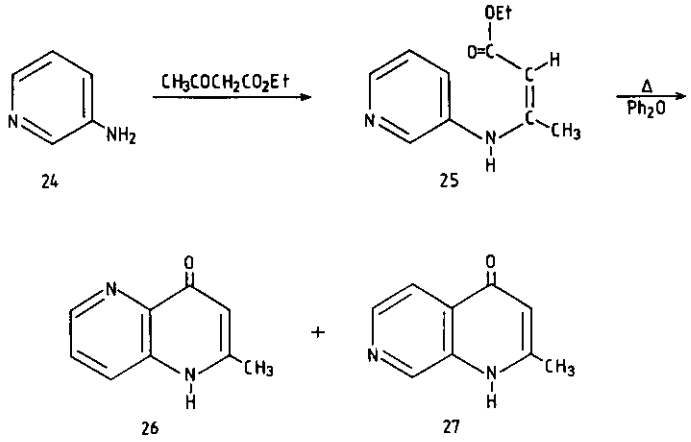
The Borsche modification of the Friedländer quinoline synthesis, involving condensation of the keto compound 18 with the Schiff base 21 has been shown to be also useful in the preparation of some 2-mono- and 2,3-di-substituted 1,7-naphthyridines (20).[80,81] However a disadvantage of this method is that the preparation of 21 is troublesome and that the yields obtained strongly vary, depending

on the substituents R_1 and R_2 present in 18. Another interesting modification of the methods discussed above is the use of β-(3-amino-4-pyridyl)acrylic acid (22) as starting substance; reaction with hydroxylamine gave the 2-oxo-1,2-dihydro-1,7-naphthyridine (23).[81] Unfortunately, compound 22 is not readily accesible.



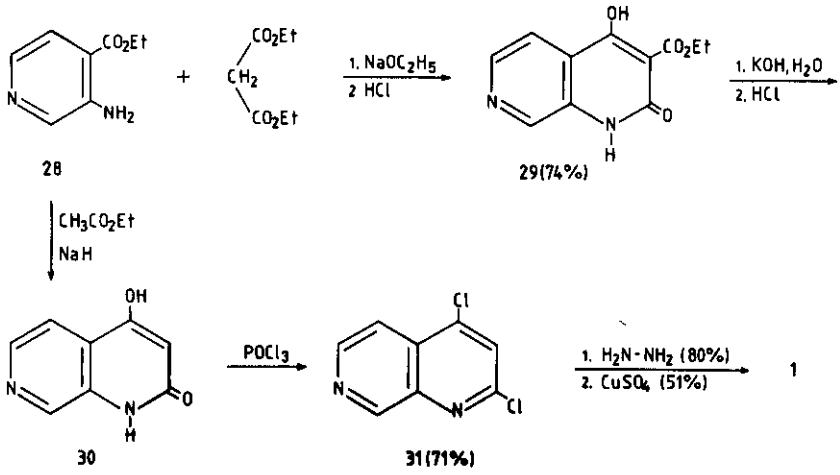
22 23(30%)

Previous attempts to apply the Conrad-Limpach reaction to the preparation of naphthyridines, utilizing 3-aminopyridine (24) as starting substance has been reported to be unsuccesful[82] or to proceed with a very poor yield to a product of undetermined structure.[83] Recently it was found[84] however, that ethyl β-(3-pyridylamino)crotonate (25), obtained from 24 and ethyl acetoacetate, undergoes cyclization in refluxing diphenyl ether to give in 75% yield a mixture of 2-methyl-4-oxo-1,4-dihydro-1,5-naphthyridine (26) and 2-methyl-4-oxo-1,4-dihydro-1,7-naphthyridine (27) (ratio 4 : 1).



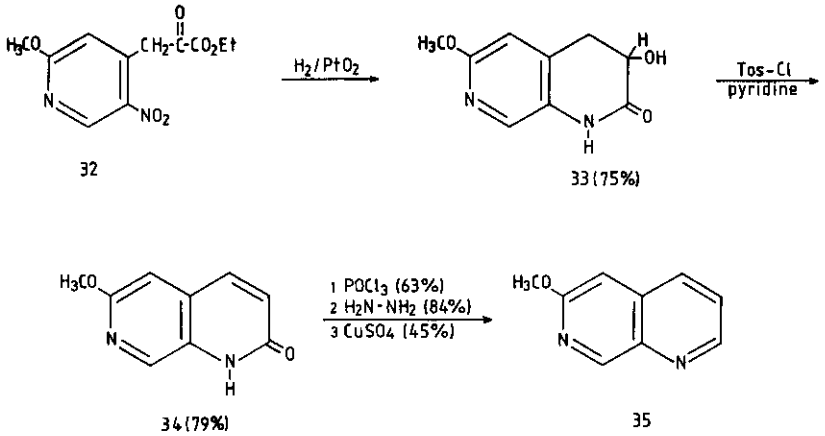
24 25 26 27

Niementowski's method using ethyl 3-aminoisonicotinate (28) and ethyl malonate was found to give a convenient procedure for preparing ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,7-naphthyridine-3-carboxylate (29).[11] After hydrolysis and decarboxylation 4-hydroxy-2-oxo-1,2-dihydro-1,7-naphthyridine (30, 97%) was obtained.[11]

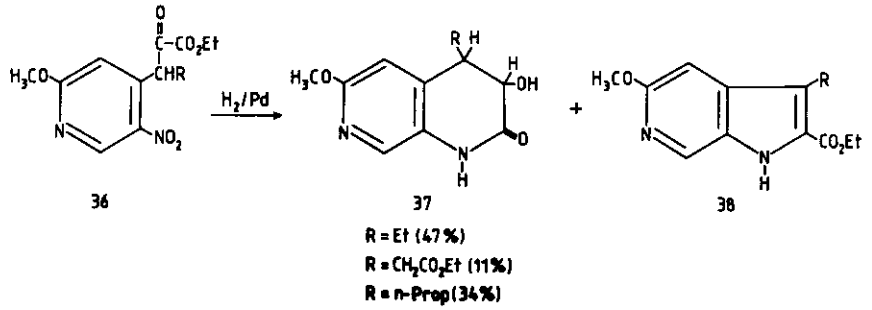


Compound 30 was also prepared directly by treatment of 28 with ethyl acetate in the presence of sodium hydride.[85,86] From 30 2,4-dichloro-1,7-naphtyridine (31) can be prepared, which easily undergoes hydrazinolysis into 2,4-hydrazino-1,7-naphthyridine.[11] Oxidation with cupric sulphate gave 1.

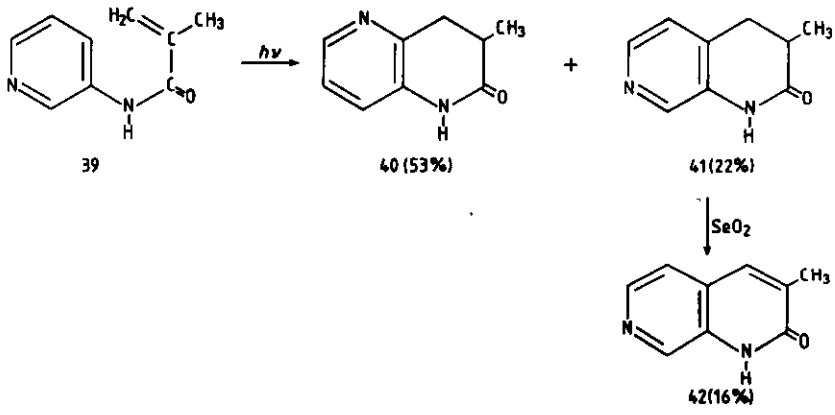
3-Nitropyridine derivatives as starting material for the preparations of some 1,7-naphthyridines have been reported. An example is the reductive cyclization of ethyl (2-methoxy-5-nitro-4-pyridyl)-pyruvate (32) under influence of H_2/PtO_2 affording 3-hydroxy-6-methoxy-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine (33).[87,88] Treatment of 33 with p-toluenesulphonylchloride leads to dehydration yielding 6-methoxy-2-oxo-1,2-dihydro-1,7-naphthyridine (34). This compound was converted by the conventional sequence of reactions into 6-methoxy-1,6-naphthyridine (35).[88]



Analogously, reductive cyclization of 36 (R=Et, CH_2CO_2Et) by H_2/Pd gave the tetrahydro-1,7-naphtyridine 37 and the 6-azaindole derivative 38.[89] In case of 36 (R=Prop) only 37 was obtained.

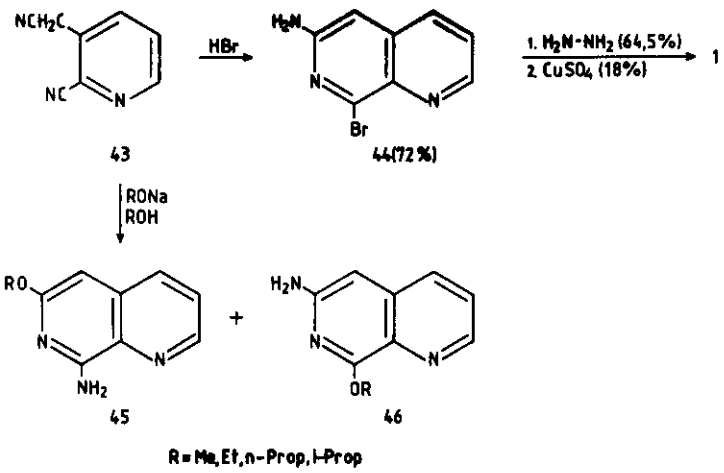


Upon irradiation of 3-methacryloylaminopyridine (39) with a 450 W high pressure mercury arc lamp through pyrex filter a mixture of the tetrahydro derivatives of 1,5- (40) and 1,7-naphthyridine (41) was obtained.[90] Oxidation of 41 with selenium dioxide gave 3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridine (42).

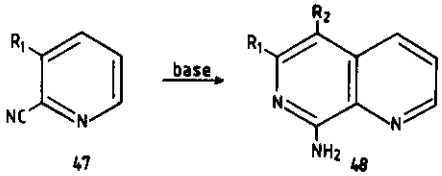


III.2. Syntheses of 1,7-naphthyridines from 2-substituted pyridine derivatives

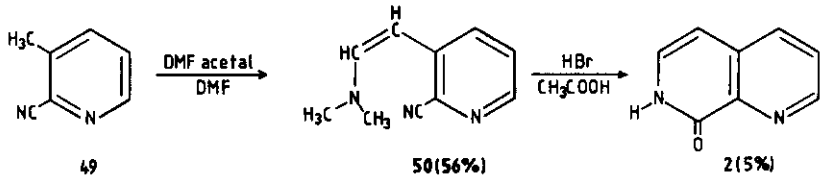
A number of interesting syntheses of 1,7-naphthyridines has been described using 2-cyanopyridine derivatives as starting substances. Subjecting (2-cyano-3-pyridyl)acetonitrile (43) to treatment with hydrobromic acid in ether 6-amino-8-bromo-1,7-naphthyridine (44) has been obtained.[10] By a conventional series of reactions 1 could be obtained.[10] Treatment of compound 43 with sodium alkoxides gave 6-alkoxy-8-amino-1,7-naphthyridines (45) as main product together with some 8-alkoxy-6-amino-1,7-naphthyridines (46).[91,92]



A great number of 6-R_1-8-amino- and 5,6-R_1,R_2-8-amino-1,7-naphthyridines (48) was prepared by a base-catalyzed condensation of 2-cyano-3-R_1-pyridines (47). In this conversion 2-cyano-3-R_1-pyridines (47) may react either with themselves or with other nitriles.[93-95]



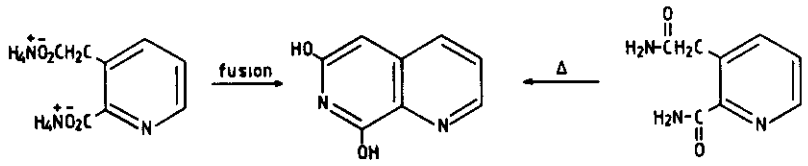
An interesting modification in the preparation of 1,7-naphthyridines from 2-cyanopyridines derivatives is developed by Baldwin and co-workers.[96] They prepared 8-oxo-7,8-dihydro-1,7-naphthyridine (2) -in low yield- by an acid-catalyzed cyclization of enamine 50. The enamine 50 was obtained by the reaction of 2-cyano-3-methylpyridine (49) and dimethylformamide dimethyl acetal in DMF.



Some syntheses of 1,7-naphthyridine derivatives have been reported using 2-carboxamidopyridine derivatives as starting material. 6,8-Dihydroxy-1,7-naphthyridine (52)* was synthesized by cycliza-

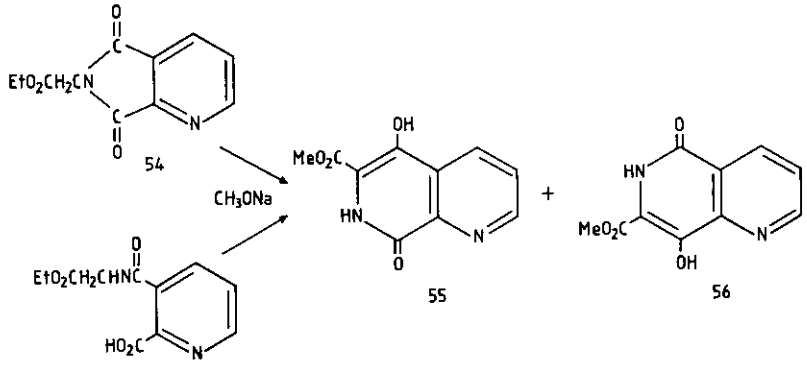
* Since the tautomeric structure is not known we refer to compound 52 as the 6,8-dihydroxy compound.

tion of the ammonium salt of β-homoquinolinic acid (51) on fusion[81] or from the diamide of β-homoquinolinic acid (53) by heating in boiling n-amyl alcohol.[97]



51 52 53

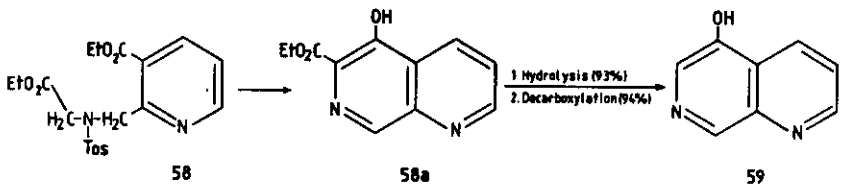
A modification of this method is the sodium methoxide catalyzed ring transformation of the cyclic imide (54) affording a mixture of methyl-5-hydroxy-8-oxo-7,8-dihydro-1,7-naphthyridine-6-carboxylate (55, 20%) and the 8-hydroxy-5-oxo-5,6-dihydro-1,6-naphthyridine-7-carboxylate (56, 50%).[75] It is of



54 55 56 57

interest to mention that this reaction has been described earlier[98,99,100] as a method for preparing 1,6-naphthyridines. However the 1,7-naphthyridine 55 escaped detection due to its large solubility in water. The same compounds 55 and 56 were also obtained from the quinolinic acid derivative 57 upon reaction with a methanolic solution of CH_3ONa.[101]

One reaction has been reported in which a 1,7-naphthyridine is obtained from a 2-(aminomethyl)pyridine derivative: heating of the tosyl derivative 56 gave product 58a, from which after hydrolysis and decarboxylation 5-hydroxy-1,7-naphthyridine (59) could be obtained in good yield.[102]



58 58a 59

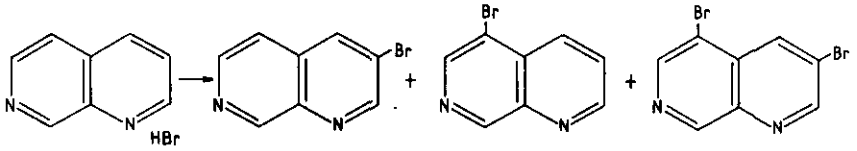
IV. REACTIONS

IV.1. Substitution Reactions

IV.1.a. Electrophilic Substitution

In 1,7-naphthyridine with its ten delocalized π-electrons located in five molecular orbitals the positions α and γ to the nitrogen have a lower π-electron density than the β-positions. As can be expected, electrophiles react primarily with the ring nitrogen to give a cationic species being deactivated for a further electrophilic attack on the ring carbon atom. If substitution on carbon takes place, position 3 is more favourite than position 5. Bromination of hydrobromide (60) of 1,7-naphthyridine in nitrobenzene with 1.1 equivalent of bromine afforded 3-bromo-1,7-naphthyridine (61), 5-bromo-1,7-naphthyridine (62) and 3,5-dibromo-1,7-naphthyridine (63).[103]

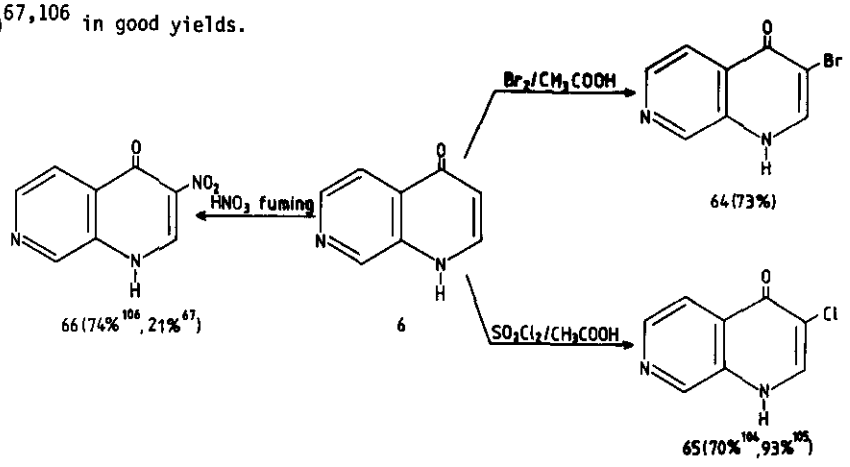
With an excess of bromine (2.5 equiv.) 60 gave almost exclusively the dibromo compound 63 in the yield of 75%.



60 61 (14%) 62 (8%) 63 (46%)

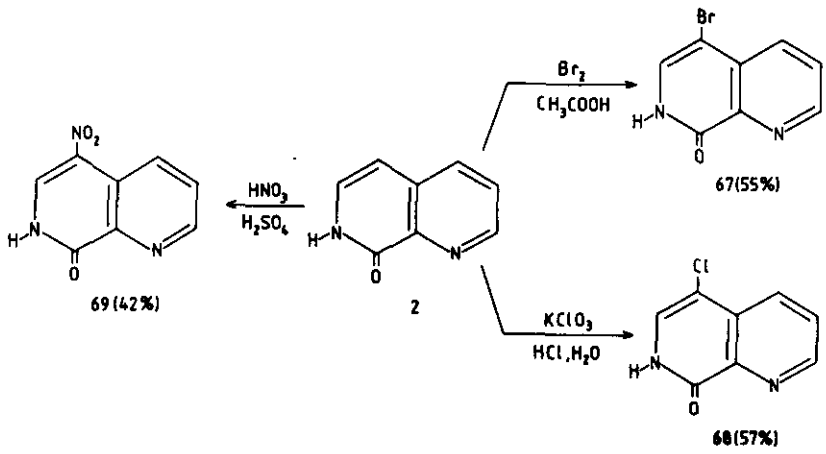
Similarly, bromination of the hydrochloride salt of 1,7-naphthyridine gave besides bromo compounds 61, 62 and 63, also small amounts of chloro and bromochloro derivatives of 1,7-naphthyridine.[103] Surprisingly, treatment of unsubstituted 1,7-naphthyridine with bromine in CCl_4 gave no 61, but only in low yield 62 (25%) and 63 (2%).[18]

The presence of powerful electron-donating substituents facilitates electrophilic substitution. Thus, with the appropriate reagents, 4-oxo-1,4-dihydro-1,7-naphthyridine (6) could be easily converted into the 3-bromo- (64),[104] 3-chloro- (65)[104,105] and 3-nitro-4-oxo-1,4-dihydro-1,7-naphthyridine (66)[67,106] in good yields.

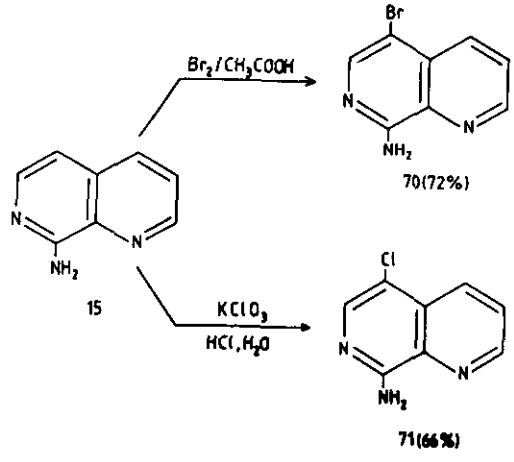


66 (74%[106], 21%[67]) 6 64 (73%) 65 (70%[104], 93%[105])

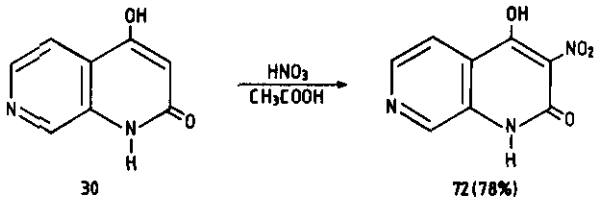
Halogenation and nitration of 7,8-dihydro-8-oxo-1,7-naphthyridine (2) also takes place readily. The entering electrophile is directed to the 5 position affording 5-bromo-(67)-,5-chloro- (68) and 5-nitro-8-oxo-7,8-dihydro-1,7-naphthyridine (69) in reasonable yields.[76]



Bromination and chlorination of 8-amino-1,7-naphthyridine (15) proceeds similarly; the entering electrophile attacks the position para to the amino group giving 5-bromo- (70) and 5-chloro-8-amino-1,7-naphthyridine (71).[76]



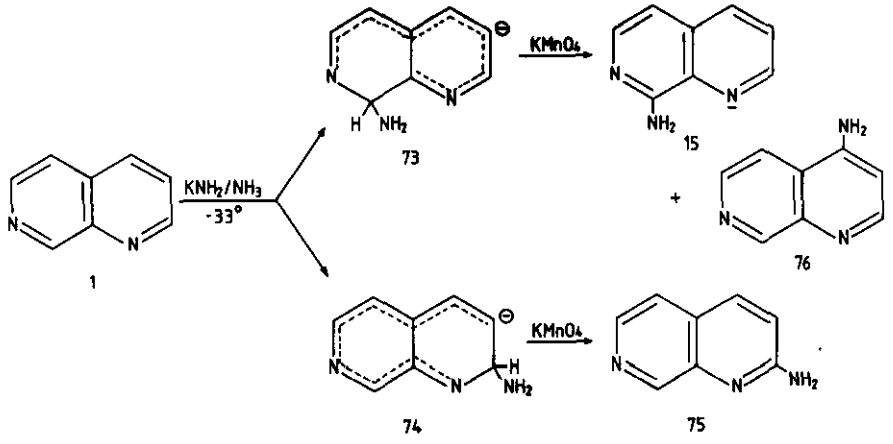
The presence of two electron donating groups makes nitration to proceed very easily. For example, 4-hydroxy-2-oxo-1,2-dihydro-1,7-naphthyridine (30) afforded the corresponding 3-nitro-1,7-naphthyridine derivative 72 in high yield.[85]



IV.1.b. Nucleophilic Substitution

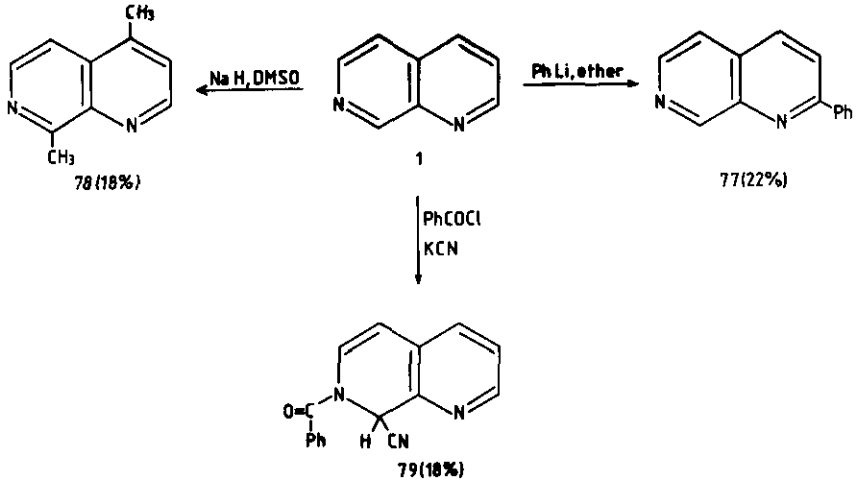
The π-deficient character of the 1,7-naphthyridine ring makes this system highly vulnerable to nucleophilic attack; it is therefore not surprising that quite a number of papers has appeared dealing with the various aspects of nucleophilic substitution of 1 and its derivatives. The reactivity of the parent system towards amide ion, leading to amino-1,7-naphthyridines, towards phenyllithium, yielding phenyl 1,7-naphthyridines and towards methylsulfinylcarbanion in DMSO, affording methyl 1,7-naphthyridines has extensively been investigated. The experimental results have been screened against the predictions, based on semi-empirical quantum mechanical calculations of nucleophilic substitutions.[107,108]

Paudler and Kress aminated 1,7-naphthyridine (1) with potassium aminde in liquid ammonia at room temperature for 8 days and obtained as sole product 8-amino-1,7-naphthyridine (15, 56%).[18] However it was found that when 1 is treated by potassium amide in liquid ammonia at -33° for 4 h a mixture of 2-amino-(75, 8%) and 8-amino-1,7-naphthyridine (15, 8%) was obtained.[76] By nmr spectroscopy it was shown that dissolving 1 in liquid ammonia containing potassium amide gave very rapidly two 1:1 σ-adducts i.e. 2-amino- (74) and 8-amino-dihydro-1,7-naphthyridinides (73).[56]



It has been suggested,[56,109] that the rapid formation of the σ-adducts indicates that the transition state has a structure closely related to that of the starting material and thus the attack of the amide ion is controlled by the electron densities on the several positions in the 1,7-naphthyridine ring.[56,107,108] *Recent HMO calculations on nucleophilic substitutions reactions in* 1,7-naphthyridine (in which calculations the nature of the nucleophilic reagent has also been taken into consideration), indicate that position 2 in 1 has the lowest electron density, followed by that on position 8.[18,23,107,108] These calculations are in good accordance with the experimental results, in contrast to *calculations on reactivity indices such as the super delocalizability* (Sr^-) and frontier orbital density toward nucleophiles (fr^-), which predict reactivities on positions being sometimes inconsistent with experimental results.[107] Interestingly it was found[56] that changing the temperature of the solution containing 73 and 74 from -40°C to +10°C, the mixture irreversibly converts into 73. *From this observation it is clear why 15 is the only product formed* when the amination takes place at room temperature,[18] and why a mixture of 15 and 75 is formed at --33°C.[76] The higher thermodynamic stability of 73 has been ascribed to the aza-allylic resonance stabilization, being possible in 73 but not in 74. High ^{13}C- and ^{1}H-upfield shift values being found for position 5 in 73 confirm this hypothesis. It was also observed that when potassium permanganate was added to the solution of 73 and 74 in liquid ammonia-potassium amide at -40°C a mixture of 75, (26%) and 15 (19%) was obtained, together with, unexpectedly, some 4-amino-1,7-naphthyridine (76, 10%).[56]

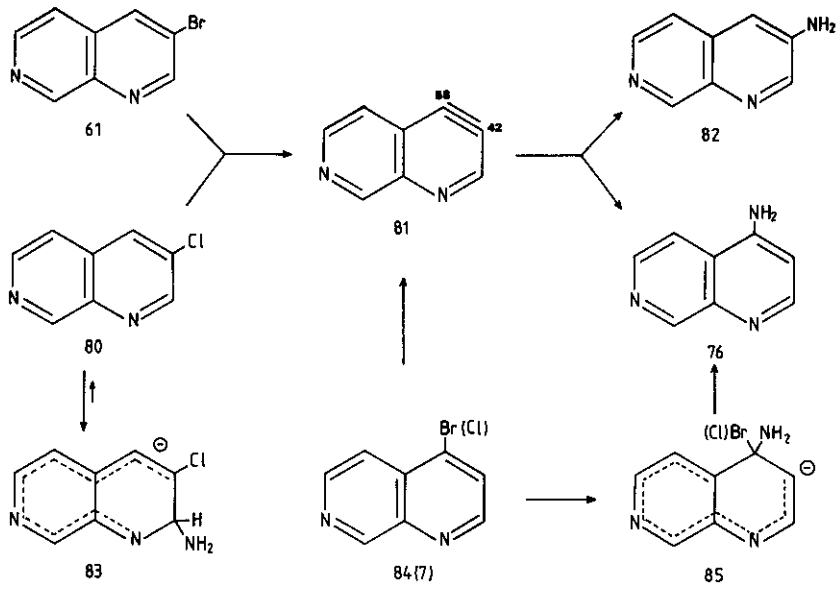
Phenylation of 1 with phenyllithium at 15-20° gave 2-phenyl-1,7-naphthyridine (77).[12] The orientation in the phenylation to C-2 is not in accordance with that found in the amination at room temperature.



78 (18%) 1 77 (22%) 79 (18%)

Methylation of 1 with methylsulfinylcarbanion at 70° afforded 4,8-dimethyl-1,7-naphthyridine (78). The frontier orbital density (fr^-) has been found to be the most suitable index for predicting the site of attack for this anion (C-4 > C-8).[107] Reaction of benzoyl chloride and potassium cyanide with 1,7-naphthyridine furnished the Reissert compound 79.[12]

Halogen displacement reactions in 1,7-naphthyridines have extensively been investigated. In recent years much attention has been paid to the reactions of halogeno-1,7-naphthyridines with potassium amide in liquid ammonia. Amination of 3-bromo- (61) and 3-chloro-1,7-naphthyridine (80) by potassium amide in liquid ammonia gave a mixture of 3-amino- (82) and 4-amino-1,7-naphthyridines (76) (total yield of 96% from 61 and total yield of 25% from 80) formed in the ratio 42:58.[110] This ratio is independent of the nature of halogen and is nearly the same as the ratio of 3- and 4-amino derivatives formed in analogous reactions from 3-bromo-1,8-naphthyridine, 3-bromo-1,6-naphthyridine[111] and 3-bromoquinoline.[112] These facts present good evidence for the intermediacy of 3,4-didehydro-1,7-naphthyridine (81) in the amination reactions of 61 and 80.

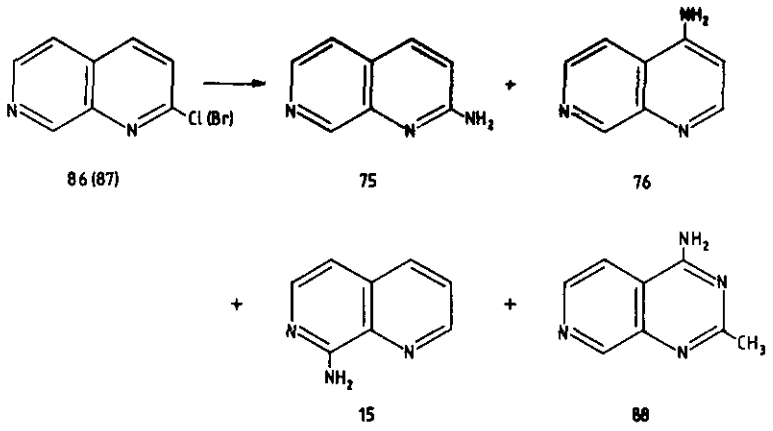


^1H nmr spectroscopy showed that 3-chloro-1,7-naphthyridine (80) forms with the amide ion the σ-adduct 2-amino-3-chloro-dihydro-1,7-naphthyridinide (83) in a very fast reaction.[110] It is an interesting question whether the adduct formation precedes the formation of the didehydro compound (81) or whether 81 is directly formed from 80 still being present in a small equilibrium concentration.

Amination of 4-bromo- (84) and 4-chloro-1,7-naphthyridine (7) by KNH_2/liquid NH_3 afforded also the

mixture of 3- and 4-amino compounds 82 and 76 (83% from 84 and 58% from 7).[113] However, the ratio of 82:76 is different; 35:65 from 84 and 22:78 from 7. This result suggests that the 4-halogeno-1,7-naphthyridines 84 and 7 are aminated not only through 81 but also according to an addition-elimination mechanism, involving intermediate 85 [S_N(AE) process].

2-Chloro- (86) and 2-bromo-1,7-naphthyridine (87) gave on treatment with potassium amide in liquid ammonia a series of products: 2-amino-1,7-naphthyridine (75) formed by the S_N(AE) mechanism, 4-amino- (76) and 8-amino-1,7-naphthyridine (15), formed by a tele-amination process and 4-amino-2-methyl-1,3,7-triazanaphthalene (88).[74]



86 (87) 75 76 15 88

^1H *nmr spectroscopy of a solution of* 86 *in liquid ammonia containing potassium amide* (see figure 7 on the next page) showed that 86 is converted into a mixture of two σ-adducts i.e. the 8-amino- (89) and the 4-amino-2-chloro-dihydro-1,7-naphthyridinides (90).[56,114] A former interpretation of the ^1H nmr spectrum leading to the conclusion that besides these two adducts a third adduct i.e. 6-amino-2-chloro-dihydro-1,7-naphthyridinide was formed,[74] was found to be incorrect.[56,114]

Adduct 90 is the precursor of both 76 and 88 (see section IV.4.) and 89 is the precursor of 15. The tele-amination 89 → 15 can be described to involve as intermediate the 8-amino-2-chloro-1,8-dihydro-1,7-naphthyridinide (91) which undergoes a base-catalyzed dehydrochlorination into 15.

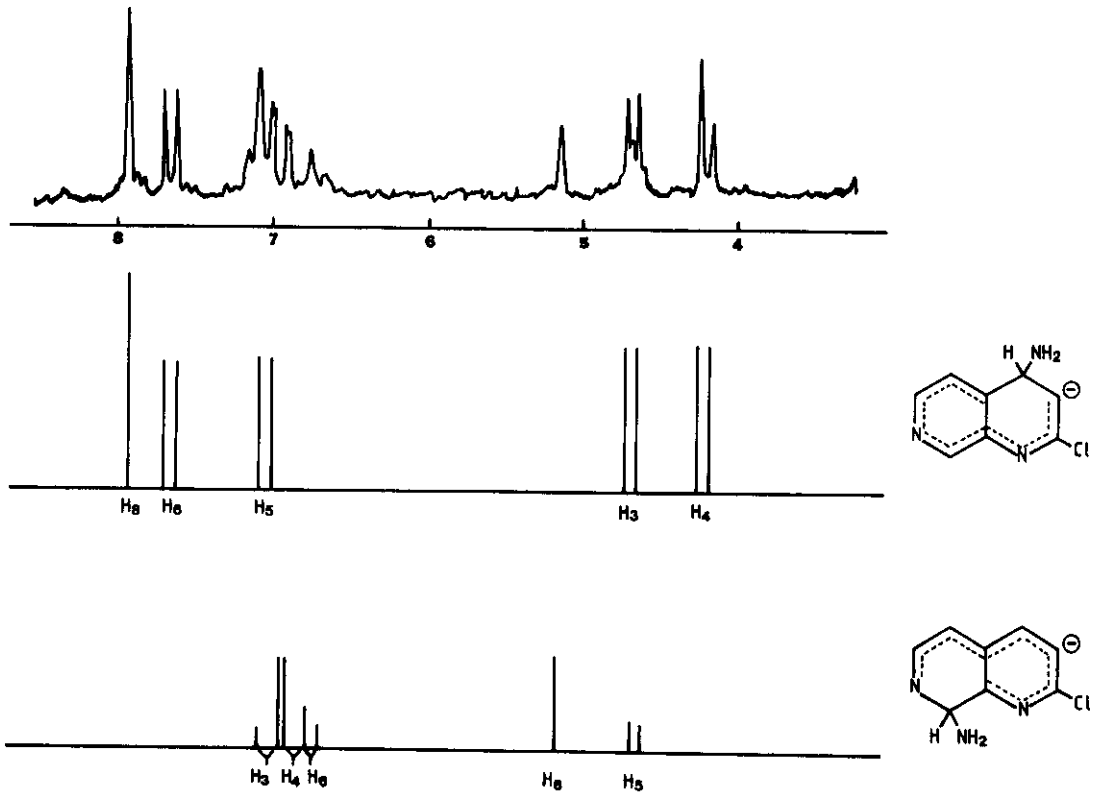
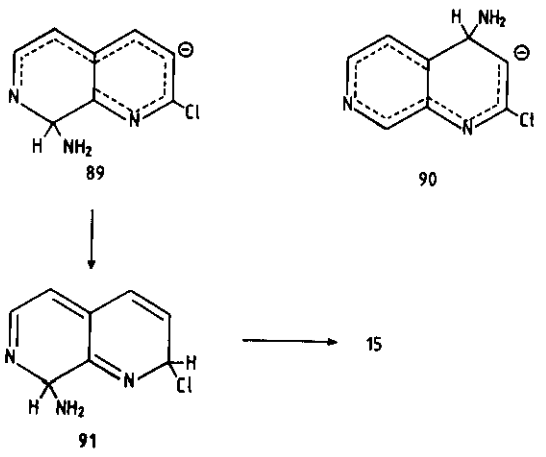
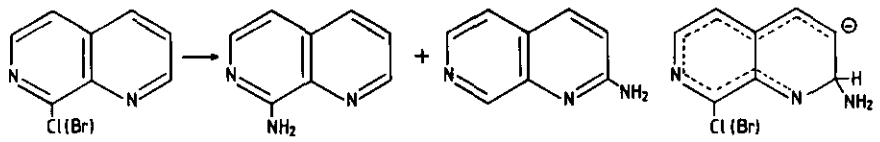


Fig. 7 ^{1}H *NMR spectrum of a solution of 2-chloro-1,7-naphthyridine in* KNH_2/NH_3

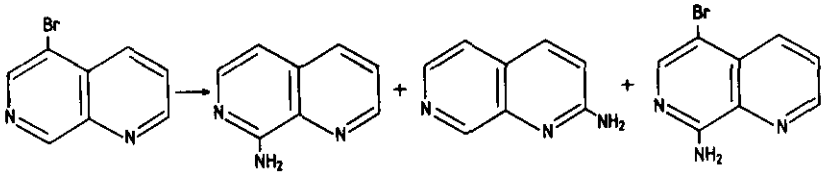


Another example of a tele-amination has been found with 8-chloro(bromo)-1,7-naphthyridine (16, 92); in this reaction besides 8-amino-1,7-naphthyridine (15) [S_N(AE) process] 2-amino-1,7-naphthyridine (75) was found. The formation of 75 involves the intermediacy of σ-adduct 93 and 2-amino-8-chloro-2,8-dihydro-1,7-naphthyridine (the isomer of 91). There is some nmr evidence for the occurrence of σ-intermediate (93).[74,115]



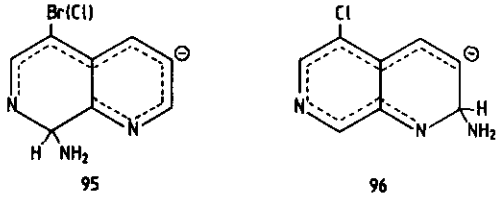
16 (92) 15 75 93

On amination with potassium amide in liquid ammonia 5-bromo-1,7-naphthyridine (62) underwent a tele-amination into 8-amino- (15) and 2-amino-1,7-naphthyridine (75) and a Chichibabin reaction yielding 8-amino-5-bromo-1,7-naphthyridine (94).[76]



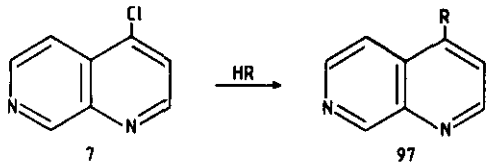
62 15(42%) 75(3%) 94(5%)

The analogous reaction with 5-chloro-1,7-naphthyridine was found to occur at a much lower rate than with 62 and gave only 8-amino-5-chloro-1,7-naphthyridine (in a small yield) and traces of 15. ^{1}H nmr evidence has been presented which convincingly shows that both the 5-bromo- and 5-chloro-1,7-naphthyridine undergo addition of the amide ion at position 8 i.e. 95 and that the 5-chloro compound also gives some addition at position 2 i.e. 96.[76]



95 96

Halogen in position α or γ to the ring nitrogen atoms in 1,7-naphthyridine can readily be replaced by amino, hydrazino and methoxy groups. Thus, the replacement of the chloro atom in 2-chloro- (86)[11] and 4-chloro-1,7-naphthyridine (7)[113] on treatment with ammonia in phenol leading to 2-amino- (75, 51%) and 4-amino-1,7-naphthyridine (76, 52%) can be easily achieved. 4-Chloro-1,7-naphthyridine (7) reacts with substituted amines at elevated temperature to yield 4-alkyl(aryl) amino derivatives (97).[116]



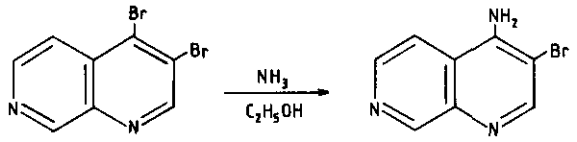
7 97

R = a. $-N(CH_3)-CH_2-CH_2-CH_2-N(C_2H_5)_2$ (73%)

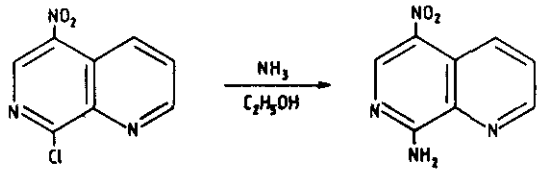
b $-NH-CH_2-CH_2-CH_2-N(C_2H_5)_2$ (70%)

c. $-NH-C_6H_3(OH)-CH_2N(C_2H_5)_2$ (59%)

With ethanolic ammonia 3,4-dibromo-1,7-naphthyridine (98) (130°, 4 h) and 8-chloro-5-nitro-1,7-naphtyridine (100) (110°, 4 h) give 4-amino-3-bromo- (99)[60] and 8-amino-5-nitro-1,7-naphtyridine (101)[61] respectively.



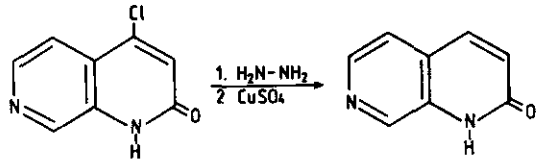
98 99 (80%)



100 101 (61%)

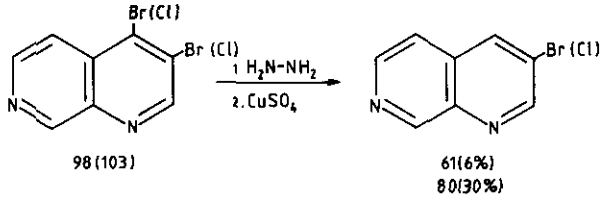
2,4-Dichloro-1,7-naphthyridine (35) heated at 150° for 15 h in ethanolic ammonia solution gave a mixture of 2-amino-4-chloro- and 4-amino-2-chloro-1,7-naphthyridines in nearly equal amounts.[60] The hydrazino compounds were often used as intermediate to replace a halogen atom at the α- or

4-position by a hydrogen atom. This replacement can take place by oxidation of the hydrazino compound, usually cupric sulphate being used as oxidator. See for examples, Chapter III. (7 → 1;[9,13] 16 → 1;[14] 31 → 1;[11,117] 44 → 1;[10] 34 → 35[88]) and 4-chloro-2-oxo-1,2-dihydro-1,7-naphthyridine (102) into 2-oxo-1,2-dihydro-1,7-naphthyridine (23).[11,118]

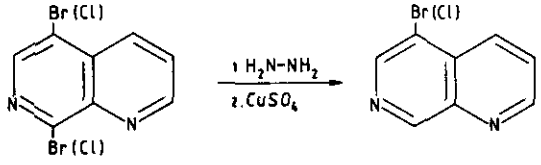


102 23(58%)

3,4-Dibromo- (98)[103] and 3,4-dichloro-1,7-naphthyridine (103)[105,110] react with hydrazine under mild conditions (20°) predominantly at the 4 position. After oxidation of the hydrazino derivatives 3-bromo- (61)[103] and 3-chloro-1,7-naphthyridine (80)[105,110] were obtained. In both reactions 1,7-naphthyridine (1) was isolated as well indicating that hydrazino-dehalogenation, besides at position 4, also occurs at position 3. Similarly, from 5,8-dibromo- (104) and 5,8-dichloro-1,7-naphthyridine (105), 5-bromo- (62) and 5-chloro-1,7-naphthyridine (106) were obtained.[76] Tosylhydrazine reacts with 8-chloro-1,7-naphthyridine[8] but was found to be unreactive with 3,4-dihalogeno-1,7-naphthyridines.[104]



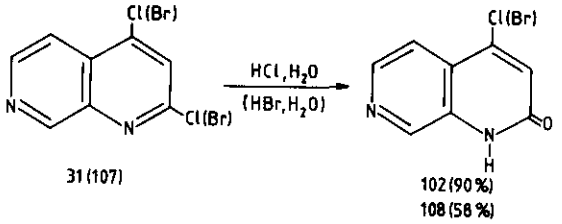
98(103) 61(6%) 80(30%)



104(105) 62(18%) 106(28%)

2- and 4-Chloro-1,7-naphthyridines react with methoxide yielding the corresponding 2- and 4-methoxy-1,7-naphthyridine (25%).[105] 2,4-Dichloro- (31) or 2,4-dibromo-1,7-naphthyridine (107) on treatment with boiling aqueous hydrochloric or hydrobromic acid afforded 4-chloro- (102)[11] and 4-bromo-2-oxo-1,2-dihydro-1,7-naphthyridine (108)[39] respectively. In contrast to the reaction with ammonia

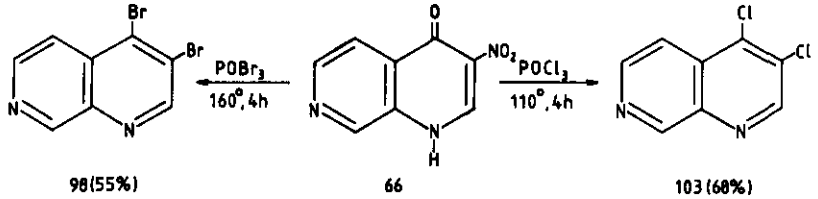
it is evident that under these conditions the halogeno atom at position 2 in 31 in and 107 is preferentially displaced. Position 4 is also vulnerable for nucleophilic exchange as appears from the fact that upon heating of the 2,4-dibromo-1,7-naphthyridine (107) with aqueous hydrochloric acid, besides the 4-bromo compound 108, 4-chloro-2-oxo-1,2-dihydro-1,7-naphthyridine (102) was formed as well.[60]



31 (107) 102 (90 %) 108 (58 %)

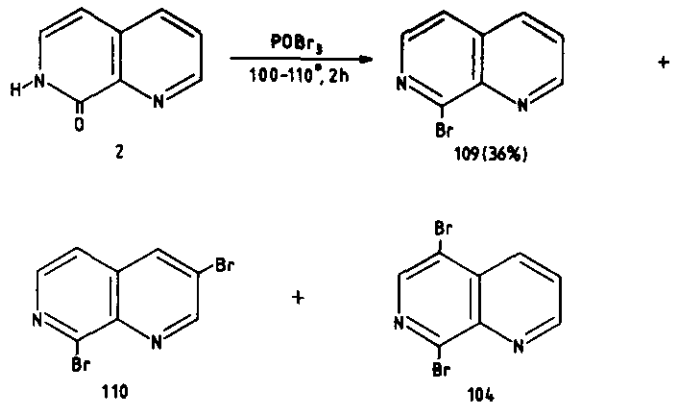
Numerous examples are described in which oxo groups in positions α or γ to the ring nitrogen atoms are converted into chloro or bromo groups by the action of $POCl_3$ or $POBr_3$. Thus, from 2-oxo-,[11,88] 4-oxo-[65,113] and 8-oxo-dihydro-1,7-naphthyridines[8,14,74] the corresponding chloro and bromo derivatives were obtained. Similarly, from 4-hydroxy-2-oxo-1,2-dihydro-, 3-bromo-(or chloro)-4-oxo-1,4-dihydro- and 5-bromo-(or chloro)-8-oxo-7,8-dihydro-1,7-naphthyridines the corresponding 2,4-,[11] 3,4-[104] and 5,8-[76] dibromo and -dichloro compounds were synthesized.

While 8-oxo-5-nitro-7,8-dihydro-1,7-naphthyridine on treatment with $POCl_3$ only gave the 8-chloro-5-nitro derivative,[76] with 3-nitro-4-oxo-1,4-dihydro-1,7-naphthyridine (66) both oxo and nitro group were replaced, giving 3,4-dichloro-1,7-naphthyridine (103).[104] Replacement of a nitro group was also observed when 66 was heated with $POBr_3$ 3,4-dibromo-1,7-naphthyridine (98) being obtained.[60] It is interesting to note that 3-nitro-4-oxo-1,4-dihydro-1,5,[119] -1.6-[119] and -1,8-naphthyridines[120] with $POCl_3$ gave only the 4-chloro-3-nitro derivatives.



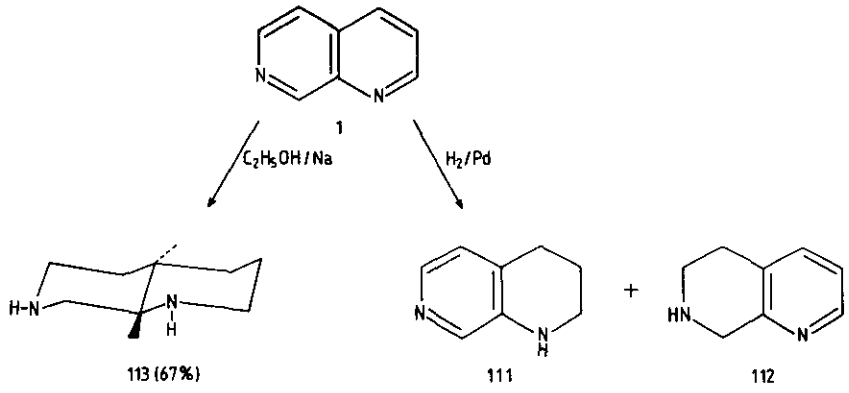
98 (55%) 66 103 (68%)

It has been found[74] that reaction of 8-oxo-7,8-dihydro-1,7-naphthyridine (2) with $POBr_3$ gave as main product the 8-bromo-1,7-naphthyridine (109) and in addition small yields (ca 2%) of 3,8-dibromo- (110) and 5,8-dibromo-1,7-naphthyridines (104).[121]

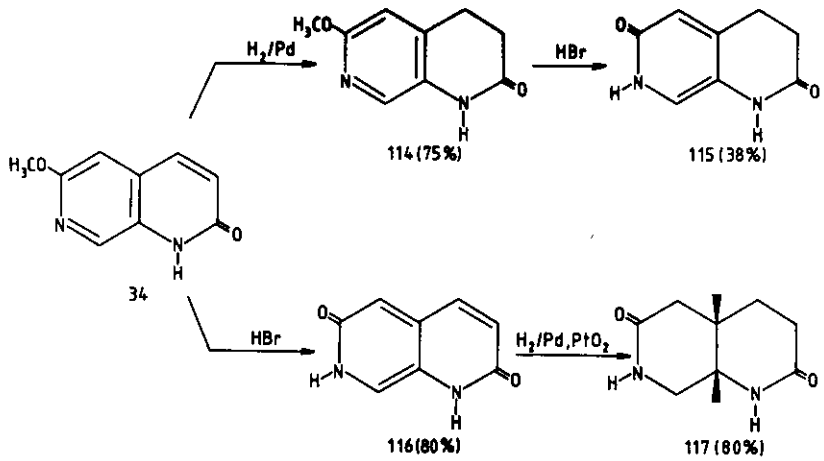


IV.2. Reduction

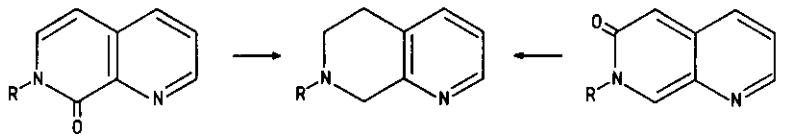
Catalytic hydrogenation of 1,7-naphthyridine (1) over Pd-$CaCO_3$ (Pd 15%) afforded 98% of 1,2,3,4-tetrahydro- (111) and 2% of 5,6,7,8-tetrahydro-1,7-naphthyridine (112).[62] *Reinvestigation of this* reduction showed that hydrogenation of 1 over palladium on charcoal (5% Pd) gave a mixture of different composition i.e. 111 (57%) and 112 (43%).[122] Reduction of 1 with sodium in ethanol gave trans decahydro-1,7-naphthyridine (113).[122]



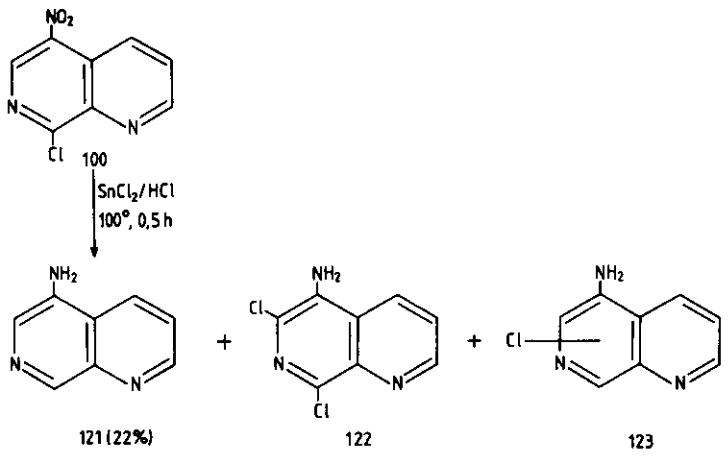
Hydrogenation of 6-methoxy-2-oxo-1,2-dihydro-1,7-naphthyridine (34) *over Pd/charcoal afforded* 6-methoxy-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine (114).[88] Treatment of 34 with hydrogen bromide gave 2,6-dioxo-1,2,6,7-tetrahydro-1,7-naphthyridine (116) which on further reduction with hydrogen over platinum oxide and palladium yielded cis-2,6-dioxo-decahydro-1,7-naphthyridine (117). 2,6-Dioxo-1,2,3,4,6,7-hexahydro-1,7-naphthyridine (115) was obtained by fission of methoxy group in 114 by HBr.



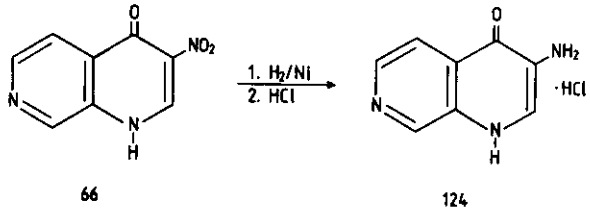
Lithium aluminium hydride has been used as reagent to prepare 5,6,7,8-tetrahydro-1,7-naphthyridine (119) from either compound 118 or 120.[123]



Reduction of 8-chloro-1,7-naphthyridine with hydrogen over Pd/C gave 1,7-naphthyridine in 30% yield.[12] Hydrogenation of 6-amino-8-bromo-1,7-naphthyridine (44) in alcoholic KOH solution over 10% Pd/C leads to debromination producing 6-amino-1,7-naphthyridine (81% yield).[10] Attempts to obtain 5-amino-1,7-naphthyridine (121) by reduction of 8-chloro-5-nitro-1,7-naphthyridine (100) failed when H_2/Pd or Zn/H_2SO_4 were used as reagent,[76] but were succesful when $SnCl_2$/HCl was used.[60] Besides 121 also small amounts of 5-amino-6,8-dichloro- (122) and 5-amino-8(or 6)-chloro-1,7-naphthyridines (123) were formed.

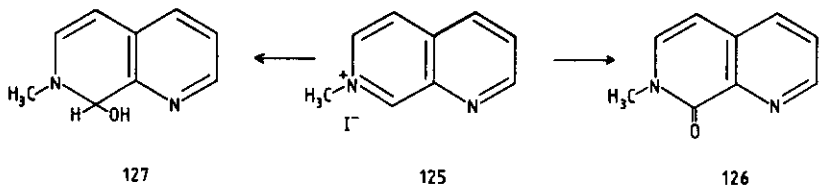


Reduction of 3-nitro-4-oxo-1,4-dihydro-1,7-naphthyridine (66) with Raney nickel gave the 3-amino compound 124.[67,106]

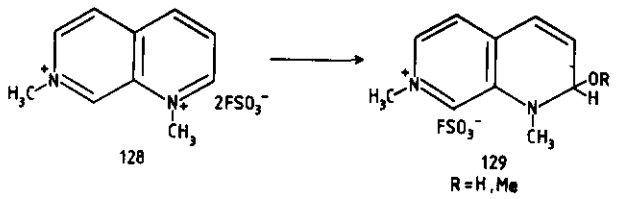


IV.3. Reactions on Nitrogen

Quaternization of 1,7-naphthyridine with methyl iodide takes place at N-7, yielding 7-methyl-1,7-naphthyridinium iodide (125).[48] The position of methylation was proven by the structure of the oxidation product i.e. 126 obtained from the salt 125 by treatment with potassium ferricyanide in alkaline medium. In alkaline medium 125 undergoes covalent hydration at C-8, yielding the 1:1 σ-adduct 127.[43]



Methylation of 1,7-naphthyridine by means of methyl fluorosulfonate ("magic methyl") afforded 1,7-dimethyl-1,7-naphthyridinium difluorosulfonate (128).[124] This salt has been found to be highly reactive to nucleophilic addition at position 2 giving 129.

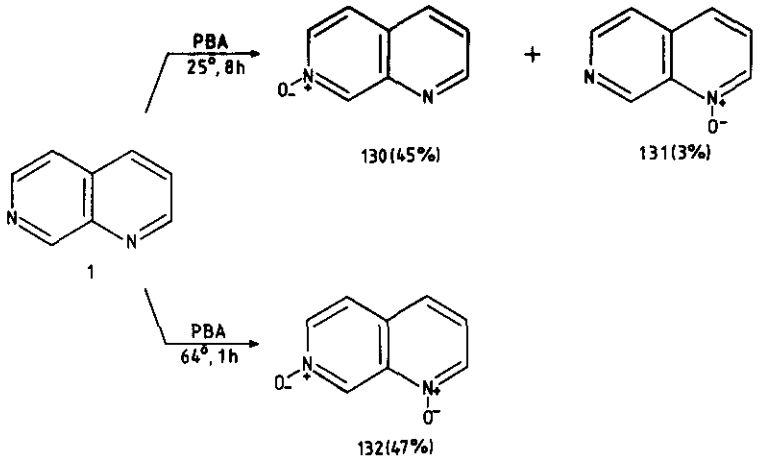


128 129 R=H,Me

Protonation of 1,7-naphthyridine also occurs at N-7, as was proven by nmr spectroscopy[48,54] (see Chapter II.3c.).

Since the discovery that 3-carboxy-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine (nalidixic acid) was a antibacterial agent, many analogous 1,7-naphthyridine derivatives were synthesized and screened on activity. The patent literature covers much information about the preparation of a great number of N-1 and N-7 derivatives of various 3-carboxy-4-oxo-1,4-dihydro-1,7-naphthyridine and their esters.[68-71,125]

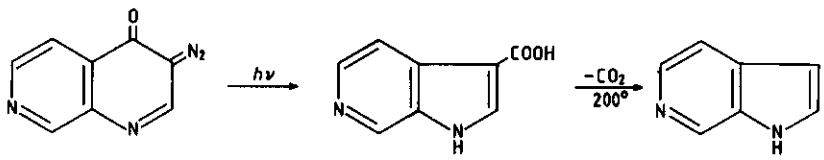
1,7-Naphthyridine on treatment with perbenzoic acid (PBA) in $CHCl_3$ at room temperature afforded a mixture of the 7-N oxide 130 and 1-N oxide 131 in the ratio 15:1.[47] This ratio seems to reflect the relative basicity of the two nitrogen atoms, since the isoquinoline-like nitrogen i.e. N-7 is more basic than the quinoline-like atom i.e. N-1. If the oxidation of 1 with perbenzoic acid was carried out in boiling chloroform 1,7-naphthyridine 1,7-di-N-oxide (132) was obtained.[47] The yield of the 1,7-di-N-oxide 132 was considerable improved when the oxidation of 1 was carried out with $NAWO_4/H_2O_2$.[105] By reduction of 132 with H_2/Raney nickel 1,7-naphthyridine 1-N-oxide (131) was obtained in 26% yield.[105]



130(45%) 131(3%) 1 132(47%)

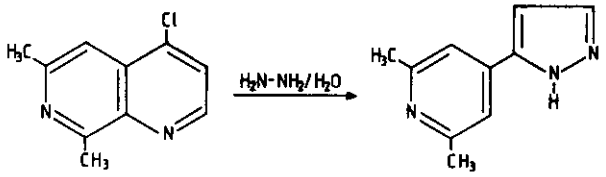
IV.4. Ring Transformations

A photo-induced ring transformation in the 1,7-naphthyridine series is found when 1,7-naphthyridine-3,4-chinon-3-diazide (133) is irradiated with uv light; nitrogen is lost and 3-carboxy-6-azaindole (134) is obtained; on decarboxylation 6-azaindole (135) (harmyrine) is yielded.[67,106]



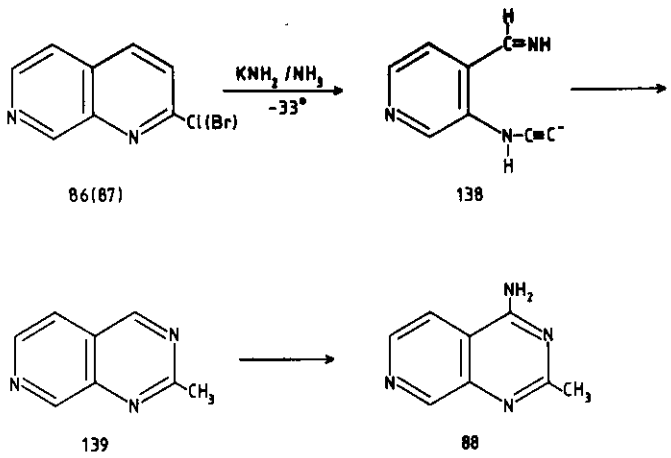
133 134(90%[106],57%[67]) 135

4-Chloro-6,8-dimethyl-1,7-naphthyridine (136) has been found to rearrange on treatment with hydrazine hydrate in a sealed tube at 150°, into 2,6-dimethyl-4-(pyrazol-5-yl)pyridine (137).[126] A similar ring transformation has been observed with 4-bromo-1,7-naphthyridine.[127]



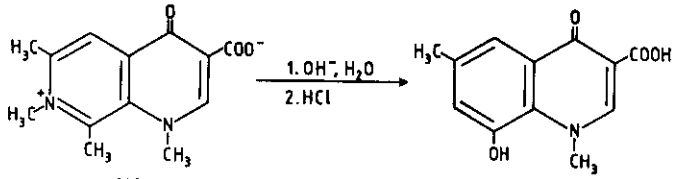
136 137

As already mentioned in section IV.1.b. 2-chloro- (86) and 2-bromo-1,7-naphthyridine (87) form, when reacted with potassium amide in liquid ammonia, besides other products, 4-amino-2-methyl-1,3,7-triazanaphthalene (88).[74] The ring transformation reaction is suggested to start with the addition of the amide ion to C-4 yielding adduct 90, which rearranges via the open-chain intermediate 138 into 2-methyl-1,3,7-triazanaphthalene (139). Since the pyrimidine ring is vulnerable for a nucleophilic attack at position 4, 139 undergoes a subsequent Chichibabin amination at C-4, yielding 88.



86(87) 138 139 88

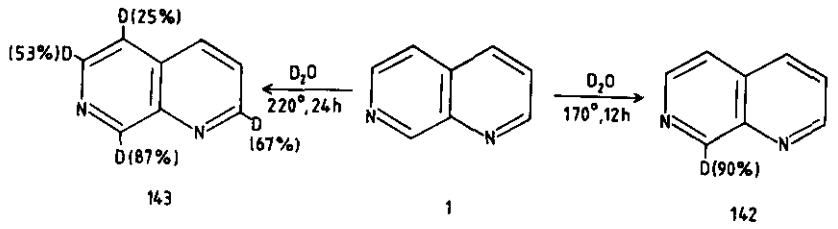
1,7-Naphthyridinium inner salts are converted into 8-hydroxyquinoline derivatives in good yields when subject to treatment with an aqueous base; we give as example the conversion of 140 → 141.[69-71] The ring transformation reaction occurs by an initial nucleophilic attack of the base on C-8 in 140. This adduct undergoes ring opening and ring closure into the quinoline derivative 141.



140 141

IV.5. Hydrogen-Deuterium Exchange

It has been demonstrated that the H/D exchange rate is different for several positions in 1,7-naphthyridine and is depending on the reaction conditions and on the nature of substituents. This makes it possible to obtain 1,7-naphthyridines deuterated in different positions. 1,7-Naphthyridine (1) when heated with deuterated water at 170° underwent H/D exchange nearly selective in position 8, i.e. 142.[52] However, the same reaction when carried out under more severe conditions gave mainly the tetradeuterated product 143.[52] The conditions to be applied and the position where H/D exchange in several derivatives of 1 occurs are given in Table 5.



143 1 142

Table 6. Results of H/D exchange of some 1,7-naphthyridines

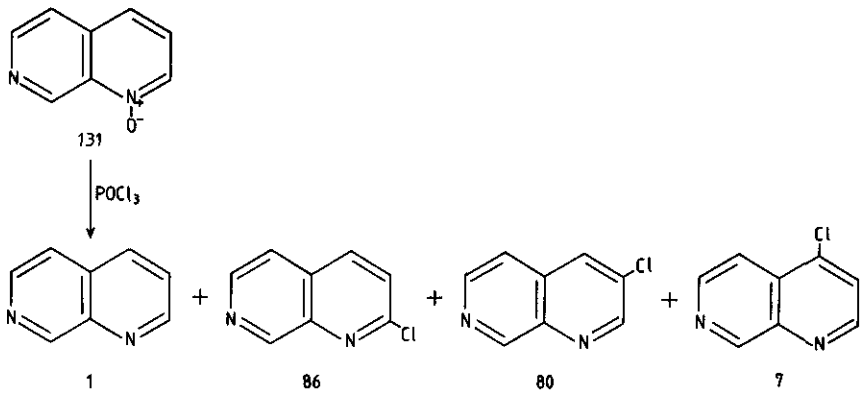
Substrate	Temperature	Time of heating	% Deuterium (position)
2-oxo-1,2-dihydro-1,7-naphthyridine[74]	230°	25 h	95-100(8), 92-95(6)
2-oxo-1,2-dihydro-1,7-naphthyridine[74]	200°	12 h	95(8), 20(6)
2-oxo-1,2-dihydro-1,7-naphthyridine[74]	170°	12 h	95(8)
3-chloro-1,7-naphthyridine[110]	170°	12 h	75(8), 60(5), 25(2)
5-chloro-1,7-naphthyridine[76]	170°	12 h	55(8), 22(6), 9(2)

The base-catalyzed hydrogen-deuterium exchange rates of the 1,X-naphthyridines were determined. An explanation as to their relative exchange rates and positional reactivity was offered.[128]

IV.6. Miscellaneous

The Meisenheimer reaction of 1,7-naphthyridine N-1 oxide (131) involving treatment with phosphoryl chloride afforded a mixture of 1,7-naphthyridine (1) and its 2-, 3- and 4-chloro derivatives 86, 80 and 7 in the ratio 4:56:3:35.[105] The mechanisms of this reaction was suggested to involve an intramolecular process.

Metal complexes of 8-oxo-7,8-dihydro-1,7-naphthyridine (2) with Cu^{+2}, Ni^{+2}, Fe^{+2} and Fe^{+3} have been prepared.[63] Compound 2 chelates less readily than 8-hydroxyquinoline. The charge-transfer complex of 4-amino-1,7-naphthyridine (76) with 7,7,8,8-tetracyanoquinodimethane was prepared and it showed to posses resistivity 10^{-1} ohm/cm and an activation energy of conduction of 0.07 eV.[129]



V. APPLICATION

Since the discovery that 3-carboxy-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine (nalidixic acid)[3e] is a powerful antibacterial agent, many analogous 1,7-naphthyridines have been synthesized. The 1-(lower alkyl)-4-oxo-1,4-dihydro-1,7-naphthyridine-3-carboxylic acid and their derivatives were found to posses antibacterial activity in vitro as well as in vivo against gram-positive bacteries.[69] Also 4-oxo-1,4-dihydro-1,7-naphthyridine-3-carboxylic acids and their esters were found to have in vivo antimalarial activity against Plasmodium berghei infection.[69] Some of these compounds also showed antiviral activity, for example against influenza.[69] Analogously, 1,7-naphthyridines containing a 2-(5-nitro-2-furyl)vinyl substituent in position 8 posses, besides antibacterial properties, anthelminthic activity.[125]

Some of the substituted 8-amino-1,7-naphthyridines were useful as antifungal, antibacterial and anti-obesity agents.[93-95] Ureidopenicillins containing the 1,7-naphthyridine moiety are highly active against grampositive and gramnegative bacteries.[130] 4-Hydroxy-3-nitro-2-oxo-1,2-dihydro-1,7-naphthyridine appeared to have a good anti-allergic activity by its ability to inhibit the release of spasmogens.[85,86]

4-Oxo-1,4-dihydro-1,7-naphthyridine and 1,7-naphthyridine analogs of chloroquine and amodiaquine were found to have antimalarial activity against Plasmodium berghei.[116] 1,7-Naphthyridine-4-carbamates proved to be useful as insecticides without adverse affects on useful insects and fish at concentration normally used.[131]

Alkylene-bis-1,7-naphthyridines were found to be useful in treatment of thrombosis.[132] Some of the 7-alkylamino-5,6,7,8-tetrahydro-1,7-naphthyridines showed marked hypotensive activity.[133] The possibility of using 6,8-dihydroxy-1,7-naphthyridine as a chelating agent like riboflavine was considered.[97] The complex forming ability of 8-oxo-7,8-dihydro-1,7-naphthyridine was correlated with its antibacterial action.[134]

1,7-Naphthyridine derivatives were detected in tobacco smoke.[135]

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Received, 17th August, 1981