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Synthesis and amination of naphthyridines

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ter verkrijging van de graad
van doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
dr. C.C.Oosterlee,
hoogleraar in de veeteeltwetenschappen,
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des namiddags te vier uur in de aula
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STELLINGEN

1 Op grond van de door Lammertsma gepubliceerde gegevens kan niet uitgesloten worden dat 1,2,3,6,7,8-hexahydropyreen protonering op C-4 en C-10 ondergaat, in plaats van op C-4 en C-9.
K. Lammertsma, J. Am. Chem. Soc., 1981, 103, 2062.

2 De vorming van pyrrolo[1,2-a] pyrazines uit alkylpyrazines en 1,2-dichloor-etheen is, in tegenstelling tot wat Houminer beweert, niet moeilijk te verklaren.
J. Houminer, J. Heterocyclic Chem., 1981, 18, 445.

3 Uit de samenstelling van de produkten, verkregen uit de cycloadditie van 2,3-dicarbomethoxynorbornadiënen met 1,3-dipolen, kunnen geen duidelijke conclusies getrokken worden omtrent de relatieve reactiviteit van de beide dubbele banden.
D. Christina, M. De Amici, C. De Micheli en R. Gandolfi, Tetrahedron, 1981, 37, 1349.

4 Op grond van infrarood gegevens kan worden aangenomen dat bij de reactie van 4-hydroxyisothiazolo [5,4-b] pyridine-5-carbonzuur met alkyljodide O-alkylering optreedt en niet, zoals wordt beweerd, N-alkylering.
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5 De door Tscheche en Streuff voorgestelde structuur voor het desmethylmarrubiaketon komt niet overeen met de resultaten van de röntgenanalyse.
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6 De in „Rodd's Chemistry of Carbon Compounds" gegeven structuurformule voor toxoflavine is onjuist.
G. Shaw in „Rodd's Chemistry of Carbon Compounds", Vol. IV, deel L (Ed. S. Caffey), Elsevier (1980).

7 De door Ouali et al. gesynthetiseerde 3-carbomethoxy-4-hydroxychinolines komen voornamelijk in de enolvorm voor.
M. Said Ouali, M. Vaultier en R. Carrié, Tetrahedron, 1980, 36, 1821.

8 Het voorbereiden van publicaties zou eenvoudiger zijn als alle tijdschriften dezelfde typografische eisen zouden stellen aan de in te zenden manuscripten.

9 De schaalverdeling in ppm op papier voor NMR spectra dient bij voorkeur decimaal te zijn.

10 De traagheid waarmee sommige automatische deuren opengaan doet het ergste vrezen over de snelheid waarmee de ontwerpers van deze deuren lopen.

H.J.W. van den Haak

Wageningen, 16 oktober 1981

Synthesis and amination of naphthyridines.

1 Introduction

1.1 General

Since the first naphthyridine synthesis by Reissert[1] in 1893 many publications on the chemistry of naphthyridines appeared and several reviews[2] on this subject have been published.
Because naphthyridines - like pyridines - are rather inert towards electrophilic reagents, but highly reactive towards nucleophilic attack, many of these publications deal with the subject of nucleophilic substitution. The behaviour of naphthyridines towards potassium amide in liquid ammonia (KNH_2/NH_3) is of special interest since this system can behave as very strong base as well as nucleophile. Therefore in this introduction we pay special attention to the different reaction types which can occur on treatment of naphthyridines and their halogeno derivatives with KNH_2/NH_3.

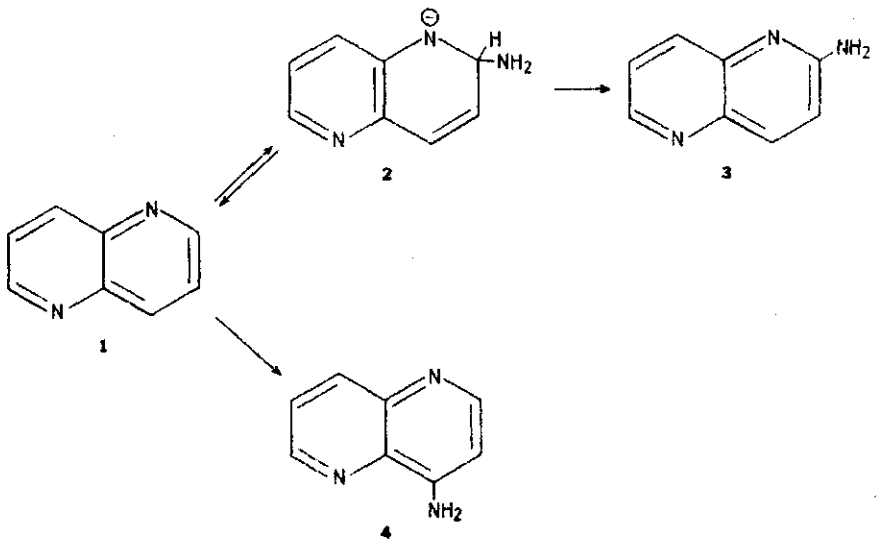
1.2 Chichibabin amination

At the start of our work in 1976 the Chichibabin amination (describing a reaction in which a ring hydrogen of an azaheteroaromatic system is replaced by an amino group) of the parent 1,X-naphthyridines[3] (X = 5,6,7,8) and of 2,7-naphthyridine[4] was known. However, little was understood of the factors which determine or influence the site of amination of these compounds, and sometimes contradictory results were obtained. In the following sections the Chichibabin amination of each of the parent naphthyridines is briefly reviewed.

1.2.1 1,5-Naphthyridine

The first report of a Chichibabin amination of a naphthyridine came from Hart[5], who converted 1,5-naphthyridine (1) into 2-amino-1,5-naphthyridine (3) with sodamide at -33°C.
Paudler and Kress showed[3] that potassium amide instead of sodamide and room temperature instead of -33°C were required to obtain the reported product 3.

Later Brown and Plasz[6] proved that the product obtained does not have structure 3, but its isomeric structure 4-amino-1,5-naphthyridine (4).

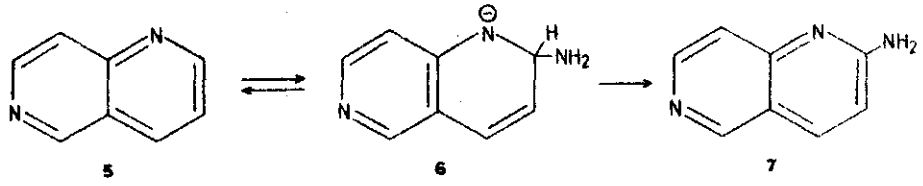


Scheme 1.1

Calculations of π electron densities[3,7,8] of 1 showed that the lowest electron density - and so the highest reactivity towards nucleophiles - is at position 2. Thus, the formation of 4 instead of 3 was not in accordance with the results of these calculations. Calculations which also took into account the nature of the acting nucleophile[8] confirmed that a charge-controlled attack of 1 by the amide anion preferably took place at position 2.
The actual formation of 4 instead of 3 is the more remarkable since it has been reported[9] that dissolving 1 in KNH_2/NH_3 at -40°C leads to the exclusive formation of σ adduct 2.

1.2.2 1,6-Naphthyridine

The amination of 1,6-naphthyridine (5) with potassium amide in liquid ammonia at room temperature yielded[3] 2-amino-1,6-naphthyridine (7) as the sole product (Scheme 1.2). In agreement with these results it was reported[9] that the NMR spectrum of a solution of 5 in liquid ammonia containing potassium amide showed only signals of the σ adduct 6 (Scheme 1.2)

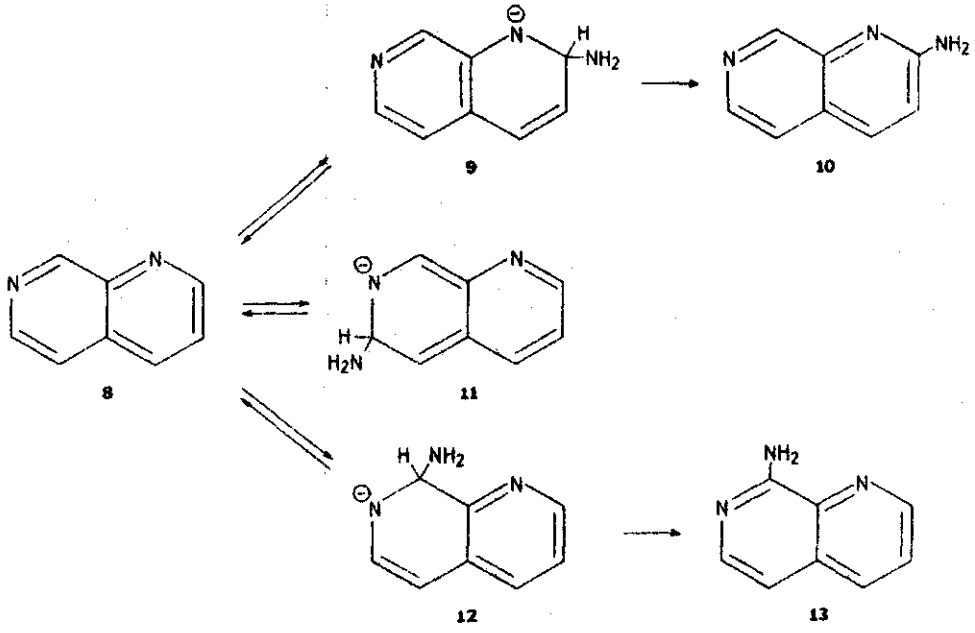


Scheme 1.2

It was not clear why, analogously to 1,5-naphthyridine, no 4-amino-1,6-naphthyridine was formed. Moreover, based on electron density calculations[3,7,8], it was predicted that both positions 2 and 5 should have about equal reactivity.

1.2.3 1,7-Naphthyridine

The behaviour of 1,7-naphthyridine (8) towards potassium amide has even more capricious features than its 1,5- and 1,6-isomers.
About the same electron density[3,7,8] was calculated for C-2 and C-8, but a mixture of three σ adducts i.e. 9, 11 and 12 was reported[9] to be formed when dissolving 8 in KNH_2/NH_3 (Scheme 1.3).

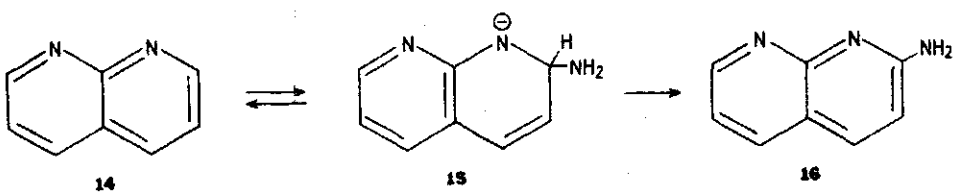


Scheme 1.3

However, as reaction products only the 2-amino compound 10 and the 8-amino compound 13 were obtained[10] when the amination of 8 was carried out at -33°C; 13 was the product of the amination of 8 when the reaction was carried out at room temperature[3].

1.2.4 1,8-Naphthyridine

The amination of 1,8-naphthyridine (14) with potassium amide at room temperature[3] has been reported to give 2-amino-1,8-naphthyridine (16), in agreement with electron density calculations[3,7,8] and the formation of σ adduct 15, when dissolving 14 in KNH_2/NH_3[9] (Scheme 1.4).



Scheme 1.4

It was not understood, however, why 14, just like its 1,5-analogue, did not form any 4-amino-1,8-naphthyridine.

1.2.5 2,6-Naphthyridine

No reports on amination or σ adduct formation of 2,6-naphthyridine were known at the start of our investigations. Electron density[3,7] calculations predicted a nucleophilic attack at position 1.

1.2.6 2,7-Naphthyridine

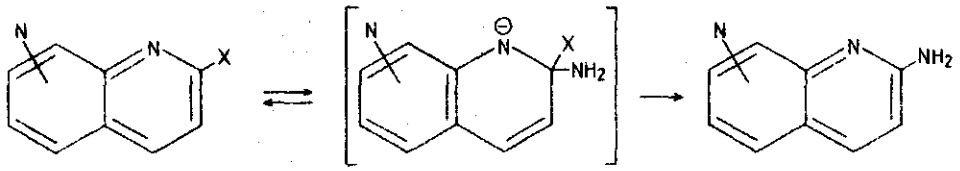
Amination of 2,7-naphthyridine (17) was reported[4] to yield 1-amino-2,7-naphthyridine (18). Electron density calculations showed[3,7] that position 1 is the most electron deficient. No indication for an intermediary σ-adduct had been reported when we started our research.

17 18

Scheme 1.5

1.3 Nucleophilic substitution according to an $S_N(AE)^{ipso}$ process

The $S_N(AE)^{ipso}$ substitution is the most classical substitution process which naphthyridines can undergo. In the first step the nucleophile adds to the same carbon atom (ipso position) to which the leaving group is attached. In the second step the leaving group is eliminated and the product is formed. (See for instance Scheme 1.6). This substitution pattern is generally observed in the reactions of nitrogen, oxygen or sulphur anions with the naphthyridines bearing a halogenosubstituent on a carbon atom activated by one of the nitrogen atoms. Substitutions of halogenonaphthyridines according to an $S_N(AE)^{ipso}$ mechanism with the strong base and nucleophile potassium amide are reported too.
The reactions of 2-halogeno-1,X-naphthyridines[11-14] into 2-amino-1,X-naphthyridines (X = 5,7,8, Scheme 1.6) and of 8-halogeno-1,7-naphthyridine into 8-amino-1,7-naphthyridine[12,13] are examples of $S_N(AE)^{ipso}$ substitutions.



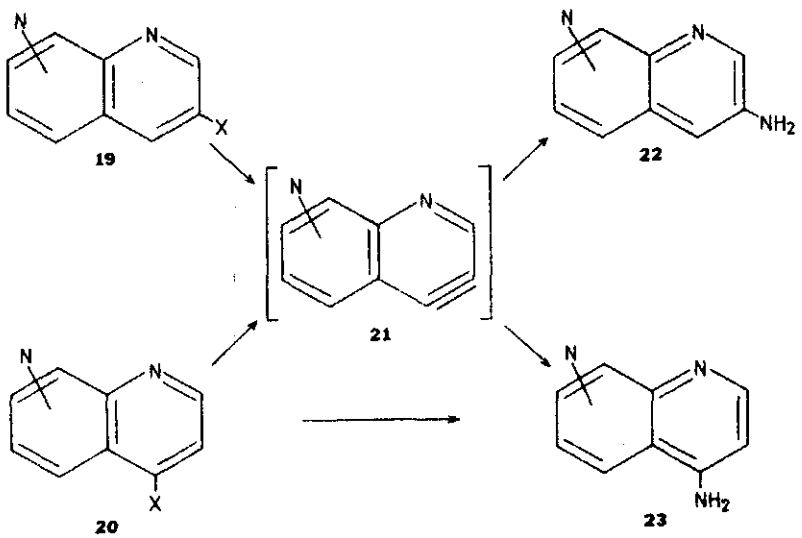
Scheme 1.6

However, due to the strongly basic character of the KNH_2/NH_3 system these direct substitutions are often accompanied by other reaction types (see sections 1.5 and 1.6).
Amino-dehalogenation by treatment of disubstituted naphthyridines with KNH_2/NH_3 are reported to occur in the aminations of 3-bromo-2-ethoxy-1,5-naphthyridine yielding 3-amino-2-ethoxy-1,5-naphthyridine[11], of 2,6-dibromo-1,5-naphthyridine

giving[17] 2-amino-6-bromo-1,5-naphthyridine and 2,6-diamino-1,5-naphthyridine, of 2,3-dibromo-1,5-naphthyridine affording[18] 2,4-diamino-1,5-naphthyridine and of 2,4-dibromo-1,6-naphthyridine yielding[19] 2,4-diamino-1,6-naphthyridine.

1.4 Nucleophilic substitution according to an $S_N(EA)$ process (hetaryne mechanism)

The elimination-addition (EA) reaction - first reported for halogenobenzenes[20] and later for several halogenopyridines[21] and -quinolines[21] - has also been found to occur in reactions of halogenonaphthyridines with strong basic reagents. The 3- and 4-halogeno-1,X-naphthyridines (19 and 20 respectively) can undergo dehydrohalogenations with potassium amide[11,14-16,22] (Scheme 1.7), leading to the hetaryne 21, to which ammonia (or amide ion) can add in two modes, yielding a mixture of 3- and 4-aminonaphthyridines (22 and 23). Besides this process 20 also undergoes an $S_N(AE)^{ipso}$ substitution leading to 23 (see section 1.3).

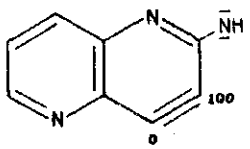


Scheme 1.7

Surprisingly 3-chloro-1,7- and 3-chloro-1,8-naphthyridine have been found to undergo σ adduct formation[14,22] at position 2 in KNH_2/NH_3 prior to hetaryne formation. It is not clear at the moment whether these σ adducts or the starting compounds undergo dehydrohalogenation.

There are only a few studies available concerning the influence of substituents on the addition of ammonia to the didehydro intermediate 21.

2-Amino-3-bromo-1,5-naphthyridine only yielded[18] 2,3-diamino-1,5-naphthyridine. This is due to the strong ortho-directing effect of the amino group in the didehydro intermediate 24 (Scheme 1.8).



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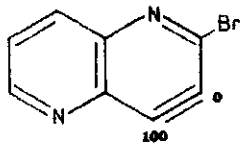

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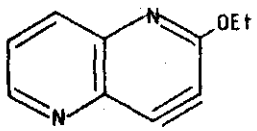

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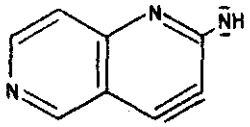


27

Scheme 1.8

An opposite effect is found[18] for a bromosubstituent : 2,3-dibromo-1,5-naphthyridine gave 4-amino-2-bromo-1,5-naphthyridine probably via 25. No 3-amino product was found. Anomalous behaviour is found[11] for the reaction of 3-bromo-2-ethoxy-1,5-naphthyridine with KNH_2/NH_3.
3-Amino-2-ethoxy-1,5-naphthyridine was reported as the only product. If this reaction should proceed via 26, 4-amino-2-ethoxy-1,5-naphthyridine is the expected product, analogously to the formation of 4-amino-2-ethoxyquinoline from 3-bromo-2-ethoxyquinoline[18].
2,4-Diamino-1,6-naphthyridine is obtained[19] on amination of 2,4-dibromo-1,6-naphthyridine. 27 is mentioned as a possible intermediate in this reaction, but its occurrence can be strongly questioned : the directing influence of the anionic amino group in 27 would give 2,3-diamino-1,6-naphthyridine as the main product and not 2,4-diamino-1,6-naphthyridine.

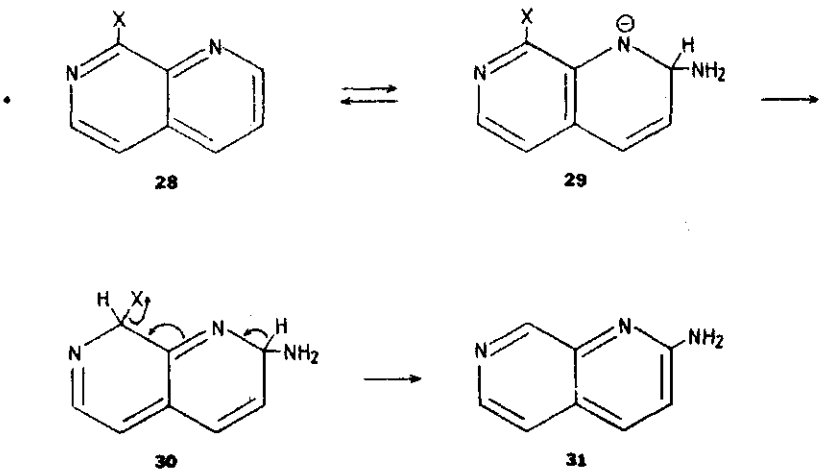
1.5 *Nucleophilic substitution according to an* $S_N(AE)^{tele}$ *process*

The process is called a telesubstitution when a nucleophile enters a molecule on a position more than one position removed from the position from which the leaving group departs. This reaction also involves as initial step an addition and as final step an elimination. So far two types of telesubstitutions are

distinguished in the naphthyridine field : the even- and the odd telesubstitution.

1.5.1 *Even telesubstitution*

We refer to a telesubstitution as even if the position of attack of the nucleophile and the position of departure of the leaving group are separated by an even number of atoms.
There are only a few examples of even telesubstitutions known in the naphthyridine system.
Amination of 8-halogeno-1,7-naphthyridine (28) with KNH_2/NH_3 yields[12,13] - among other products - 2-amino-1,7-naphthyridine (31). It was proved by NMR spectroscopy that in KNH_2/NH_3 28 first forms σ adduct 29 (Scheme 1.9).

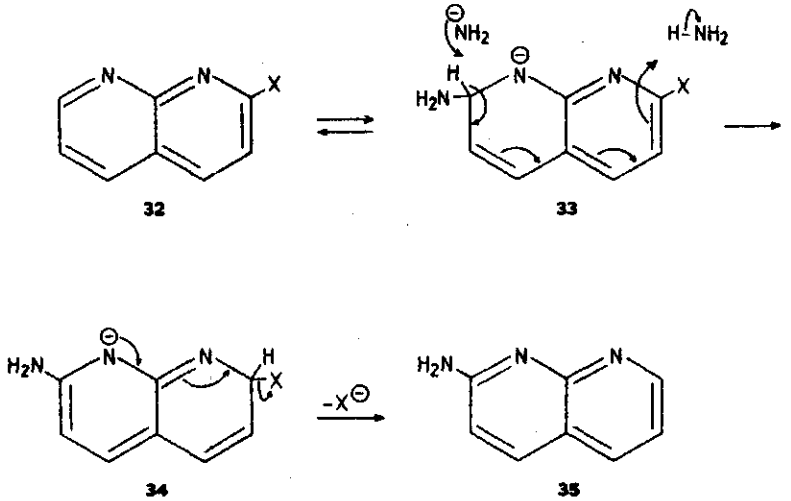


Scheme 1.9

The telesubstitution can be described as follows : after formation of 29 protonation occurs, leading to the dihydro intermediate 30, which undergoes a base-catalyzed 1,4-HX-elimination to yield 31. Similar intermediates occur in the conversion[12] of 2-halogeno-1,7-naphthyridine into 8-amino-1,7-naphthyridine, and in the formation[10] of 8-amino-1,7-naphthyridine from 5-halogeno-1,7-naphthyridine. The latter has strong similarities to the conversion[23] of 4-halogeno-isoquinoline into 1-aminoisoquinoline.

1.5.2 *Odd telesubstitution*

The process is referred to as an odd telesubstitution when an odd number of positions lies between the position of attack of the nucleophile and that from which the leaving group departs.
The amination of 2-halogeno-1,8-naphthyridine (32) into 7(=2)-amino-1,8-naphthyridine (35) was the first reported[13,14] odd telesubstitution in the naphthyridine system.
The formation of the intermediary 7-amino-7,X-dihydro-1,8-naphthyridinide (33) was proved by NMR spectroscopy. A 1,7-proton shift leads to the 7-amino-2,X-dihydro-1,8-naphthyridinide (34) which by loss of X^- is converted into 35 (Scheme 1.10).

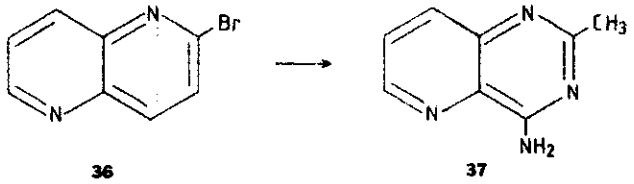


Scheme 1.10

Three more examples of odd telesubstitutions in the naphthyridine system are known: the small-yield conversion[10] of 5-halogeno-1,7-naphthyridines into 2-amino-1,7-naphthyridine, the formation[11] of 4-amino-1,5-naphthyridine from 2-bromo-1,5-naphthyridine and the formation[12] of 4-amino-1,7-naphthyridine from 2-halogeno-1,7-naphthyridines.

1.6 Ring Transformation

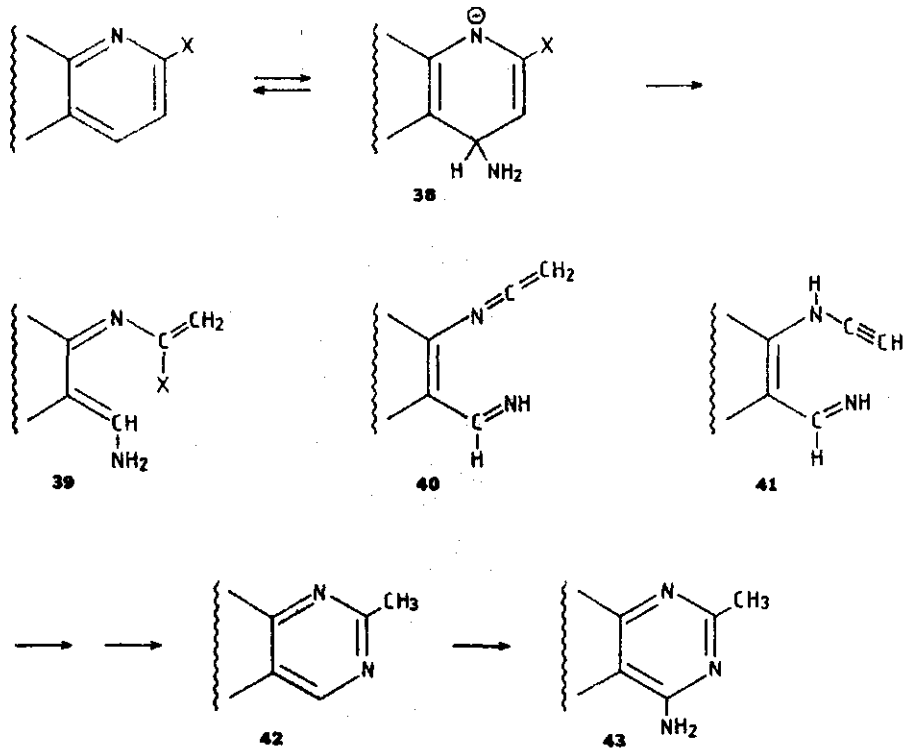
In many of the reactions of halogeno hetarenes ring transformations are reported to occur[24]. Also halogenonaphthyridines are able to undergo ring transformations. On reacting[11] 2-bromo-1,5-naphthyridine (36) with potassium amide in liquid ammonia, among other products 4-amino-2-methyl-1,3,5-triazanaphthalene (37) was obtained (Scheme 1.11).



36 37

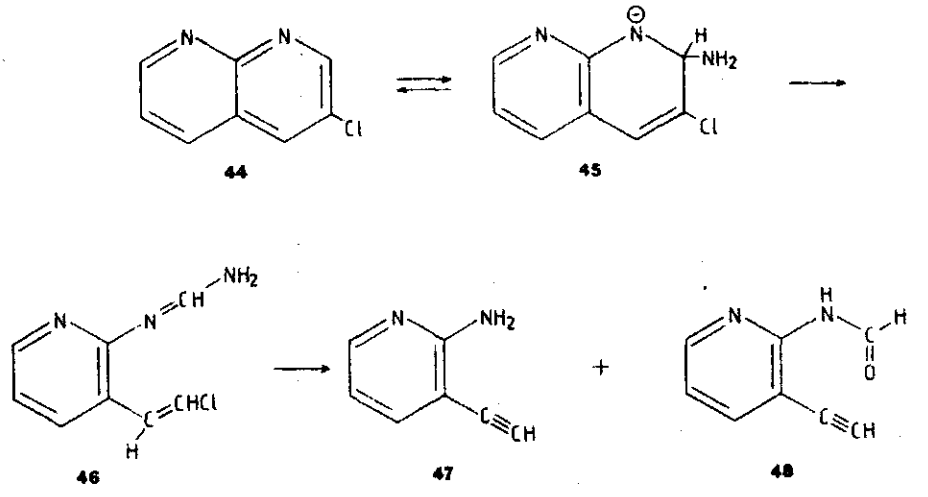
Scheme 1.11

A ring transformation, leading to compound 37 also occurs on amination[18] of 2,3-dibromo-1,5-naphthyridine with KNH_2/NH_3 and on amination of 2,6-dibromo-1,5-naphthyridine, giving 6-bromo-2-methyl-1,3,5-triazanaphthalene[17].
Similar ring transformations, involving the introduction of a nitrogen in the heterocyclic ring with simultaneous formation of a methyl group were reported for 2,6-dihalogenopyridines[25] leading to 4-amino-2-methylpyrimidine and for 2-bromoquinoline[26] yielding 2-methylquinazoline.
In the 1,6-naphthyridine series it has been reported that 2,4-dibromo-1,6-naphthyridine yielded[19] 4-bromo- and 4-amino-2-methyl-1,3,6-triazanaphthalene on treatment with KNH_2/NH_3. A similar conversion is reported when 2-halogeno-1,7-naphthyridine reacts with potassium amide, 4-amino-2-methyl-1,3,7-triazanaphthalene being obtained[12].
No ring transformation was found to occur when 2-halogeno-1,8-naphthyridine was reacted[13,14] with KNH_2/NH_3. The ring transformations mentioned above are supposed to proceed via a mechanism starting with the formation of a σ adduct at position 4 (38, Scheme 1.12). This σ adduct undergoes ring opening. No certainty exists about the structure of this open-chain intermediate due to its low stability, but structures 39, 40 or 41 have been proposed.



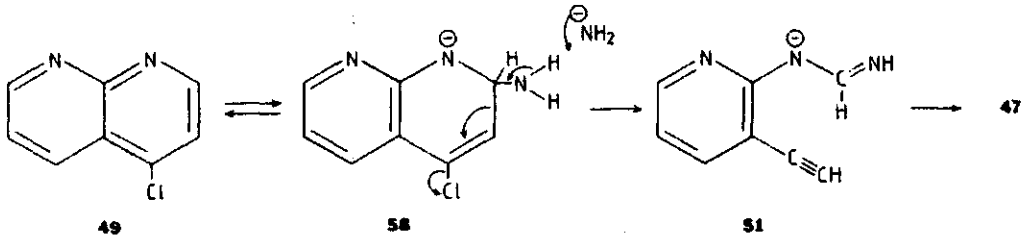
Scheme 1.12

Ring closure of one of these intermediates yielded 42, which depending on the substituents may undergo a subsequent Chichibabin amination yielding 43.
Ring opening products were found[14] on reaction of 3- or 4-chloro-1,8-naphthyridine with potassium amide. Thus 3-chloro-1,8-naphthyridine 44 yielded 2-amino-3-ethynylpyridine (47) and 2-(formylamino)-3-ethynylpyridine (48, Scheme 1.13). There is NMR spectroscopic evidence for the σ adduct 45, but not for 46. However its intermediary existence is plausible due to the formation of the products 47 and 48.
4-Chloro-1,8-naphthyridine 49 also gave[14] 47 as one of the amination products.



Scheme 1.13

Again σ adduct formation at C-2 (50) took place. Formation of 47 can be visualized as given in Scheme 1.14.



Scheme 1.14

1.7 Purpose and Scope

As mentioned in previous sections, some conflicting data in the amination of naphthyridines occur and no real knowledge of the factors which determine the course of the aminations exists.

Purpose of this investigation was to improve this knowledge of the reactivity of naphthyridines.

In chapters 2 and 3 of this thesis the formation of σ adducts between the six parent naphthyridines[27,28] and potassium amide is described.

Chapter 4 deals with the occurrence of even telesubstitutions in naphthyridines[29].

Chapter 5 describes the amination of 1-halogeno-2,7-naphthyridine, a system which was believed to be vulnerable to odd telesubstitution.
The structure of the open-chain intermediate occurring in the conversion of 8-bromo-1,7-phenanthroline into 4-amino-2-methyl-1,3,5-triazaphenanthrene is reported[31] in chapter 6.
In chapter 7 the occurrence of the $S_N(EA)$ mechanism in the amination of 3-bromo--2-ethoxy-1,5-naphthyridine and 3-bromo-1-ethyl-1,5-naphthyridin-2(1H)-one is discussed[30].

1.8 References

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2 The Chichibabin amination of 1,X-naphthyridines.

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2.1 Introduction

The Chichibabin amination of the 1,X-naphthyridines has been described by several investigators.[2-4] However, contradictory results were sometimes reported, and product formation did not always follow the predictions based on calculated electron densities.[3,5,6] Moreover 1:1 anionic σ adducts, formed on addition of the amide ion to the 1,X-naphthyridines,[7] were not always found to be the precursors of the products being obtained during the amination. We present here the results of investigations on this subject, giving an explanation of the contradictory results which have been reported thus far.

2.2 Amination of 1,5-naphthyridine (1)

The Chichibabin amination of 1 with sodamide at -33° was described first by Hart.[2] He claimed to have obtained 2-amino-1,5-naphthyridine (3). His results could not however be reproduced.[3,4] Paudler and Kress[3] reported that amination of 1 with potassium amide has to be carried out at room temperature in order to obtain the same compound (33%). It was shown later[4] that the amination product was not 3 but its isomer 4-amino-1,5-naphthyridine (5). When the reaction was carried out at 50°C the yield of 5 was considerably improved, but no further experimental details are available.[8] A few years ago it was shown by NMR spectroscopy that dissolving of 1 at -40°C in liquid ammonia containing a fourfold excess of potassium amide, gives very rapid[7] formation of the 2-amino-dihydro--1,5-naphthyridinide (2); no traces of 1 could be found, even if only a slight excess of potassium amide is used. On the basis of the Hammond postulate[9,10] one has to conclude that for reactions of this type, the transition state has a structure close to that of the starting material and thus that the attack of the amide ion is controlled by electron densities. This conclusion is in agreement with recent HMO-calculations on nucleophilic substitution reactions in 1,X-naphthyridines; in these calculations the nature of the nucleophilic rea-

Table 2.1 ^{1}H NMR Data of 1,5- and 1,7-Naphthyridine and their 1:1 σ Adducts with Amide Ions

Compound	Solvent	H-2	H-3	H-4	H-5	H-6	H-7	H-8
1	$CDCl_3$	8.96	7.55	8.37		8.96	7.55	8.37
2	NH_2^-/NH_3	4.97	5.38	a		6.80	a	a
	Δδ	3.99	2.17	-		2.16	-	-
4	NH_2^-/NH_3	a	4.18	4.59		7.31	a	a
	Δδ	-	3.37	3.78		1.65	-	-
11	$CDCl_3$	9.01	7.48	8.14	7.64	8.60		9.50
12	NH_2^-/NH_3	5.02	5.31	6.28	6.35	6.76		7.52
	Δδ	3.99	2.17	1.86	1.29	1.84		1.98
15	NH_2^-/NH_3	7.65[b]	6.77[b]	6.77[b]	4.52	7.01		5.13
	Δδ	1.46	0.71	1.37	3.12	1.59		4.37

a Coincidence of these signals made assignment impossible

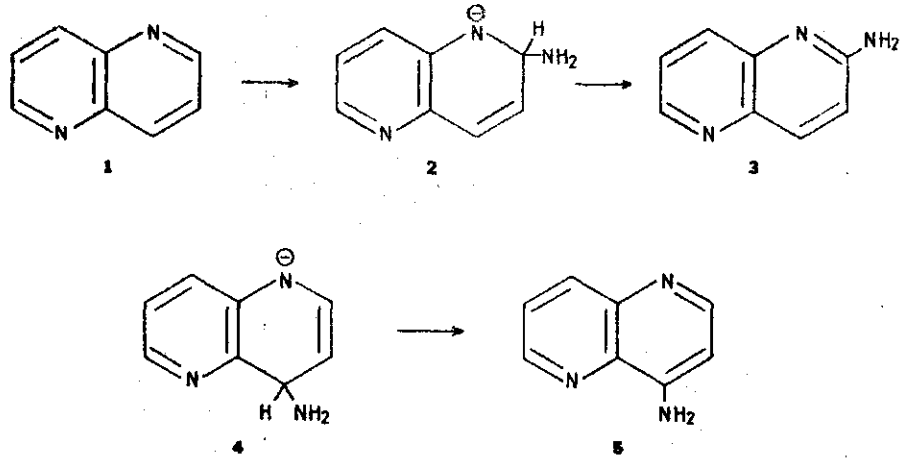
b These signals show deceptive simplicity

Table 2.2 ^{13}C NMR Data of 1,5- and 1,7-Naphthyridine and their 1:1 σ Adducts with Amide Ions

Compound	Solvent	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	$CDCl_3$	151.0	124.1	137.2		151.0	124.1	137.2	144.0	144.0
2	NH_2^-/NH_3	65.8	121.3	127.4[a]		125.1	122.7	121.6[a]	151.2	137.3
	Δδ	85.2	2.8	9.8		25.9	1.4	15.6	-7.2	6.7
4	NH_2^-/NH_3	141.8	92.2	50.9		134.6	121.2	125.1	145.8[a]	145.3[a]
	Δδ	9.2	31.9	86.3		16.4	2.9	12.1	-1,8	-1,3
11	$CDCl_3$	152.1	125.2	134.7	119.9	144.0		154.5	143.7	131.3
12	NH_2^-/NH_3	65.9	120.2	124.3	120.2	123.8		142.6		
	Δδ	86.2	5.0	10.4	-0.3	20.2		11.9		
15	NH_2^-/NH_3	138.2	121.9[a]	122.5[a]	80.2	151.8		71.0		
	Δδ	13.9	3.3	12.2	39.7	-7.8		83.5		

[a] The signals may be interchanged

gent[6] has also been taken into consideration.
Calculations[3,5,6] showed that position 2 in 1 has the lowest electron density and thus is most susceptible to a charge controlled attack of the amide ion. Therefore the formation of 5, which has as precursor the 4-amino-dihydro-1,5--naphthyridinide (4), can be considered as a surprising result.



Scheme 2.1

By studying the influence of the temperature on the NMR spectrum of a solution of the σ adduct 2 we found that when a solution of 2 in liquid ammonia containing potassium amide was heated from -40° to +10°C the NMR spectrum of the solution drastically changed. The doublet at 4.97 ppm (H-2 of 2) and the quartet at 5.38 ppm (H-3 of 2) disappeared and the spectrum featured a new doublet at 4.59 ppm and a new quartet at 4.18 ppm (see Table 2.1). We ascribed these peaks to H-4 and H-3, respectively, in adduct 4. The magnitude of the upfield shift of H-4 in 4 ($\Delta\delta$= 3.78 ppm) is in agreement with values reported[7] and is due to a change of the hybridization of the carbon atom ($sp^2 \rightarrow sp^3$). Our observations were fully supported by ^{13}C-NMR spectroscopy of both σ adducts 2 and 4 (Table 2.2). The dependency of the position of addition of the amide ion on the temperature has already been observed in quinoline.[9]
That σ adduct 2 is less stable than σ adduct 4 can be explained by a main contribution of the allylic resonance stabilization in 4, being absent in 2. That this stabilization is indeed important is clearly shown by the high ^{13}C $\Delta\delta$ value (= 31.9 ppm) of C-3 in 4 indicating that C-3 carries a considerable amount of negative charge.

Some intramolecular hydrogen bonding between the amino protons and the lone pair of the nitrogen at position 5 may also contribute to the higher stability of 4. This contribution will probably be weak as indicated by the fact that the C-4 adduct of quinoline in which intramolecular hydrogen bonding cannot operate is more stable than its C-2 isomer.[9]

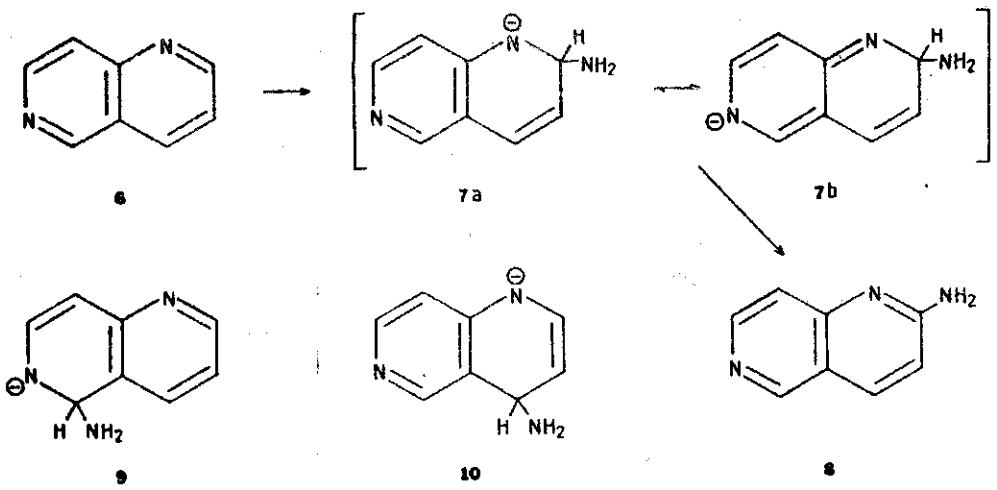
The above mentioned results and also those which will be discussed in the next sections strongly stress the point that in the Chichibabin amination of aza aromatics the temperature of the reaction plays a decisive role in the course of the reaction. Our results also provide us with a better understanding of the problem of why in the amination of 1 divergent results were obtained[2,3,4,8] and why at temperatures above $+10^{o}$ 5 instead of 3 is formed.

Recently the use of potassium permanganate in liquid ammonia as a useful reagent for the oxidation of 3-amino-dihydro-1,2,4,5-tetrazinides, the 1:1 σ adducts of ammonia to 1,2,4,5-tetrazines, into the corresponding 3-amino-1,2,4,5-tetrazines has been reported.[11] When applying this reagent for the preparation of 3 or 5 we found that addition of potassium permanganate to a solution of 2 in potassium amide/liquid ammonia gave 3 in 36% yield. However if 2 was allowed to isomerize into 4 and then potassium permanganate was added, only minor traces of both 3 and 5 were obtained.

2.3 Amination of 1,6-naphthyridine (6)

Amination of 6 with potassium amide in liquid ammonia has been reported to give 2-amino-1,6-naphthyridine (8) in a 33% yield at room temperature[3] and in a 83% yield when the amination was carried out at $50^{o}C$.[8] On the basis of calculations of the electron densities[3,5,6a] it can be predicted that positions 2 and 5 of 6 have about the same susceptibility for a charge-controlled attack by the amide ion. However, recent PPP MO calculations on naphthyridines show that C-2 of 6 has a lower electron density than C-5, indicating that kinetic σ adduct formation should preferably take place at C-2.[6b] By NMR spectroscopy it was shown[7] that when 6 was dissolved in liquid ammonia, containing potassium amide at -40^{o}, the solution contains only one σ adduct i.e. 2-amino-dihydro-1,6-naphthyridinide (7); no trace of the 5-amino-dihydro-1,6-naphthyridinide (9) could be detected.

We observed that when the temperature of the solution containing 7 was allowed to rise from $-40^{o}C$ to at least $+10^{o}C$ no change in the NMR spectrum was observed, indicating that σ adduct 7 was stable. That C-2 adduct 7 is thermodynamically the most stable one and not C-5 adduct 9 or the 4-amino-dihydro-

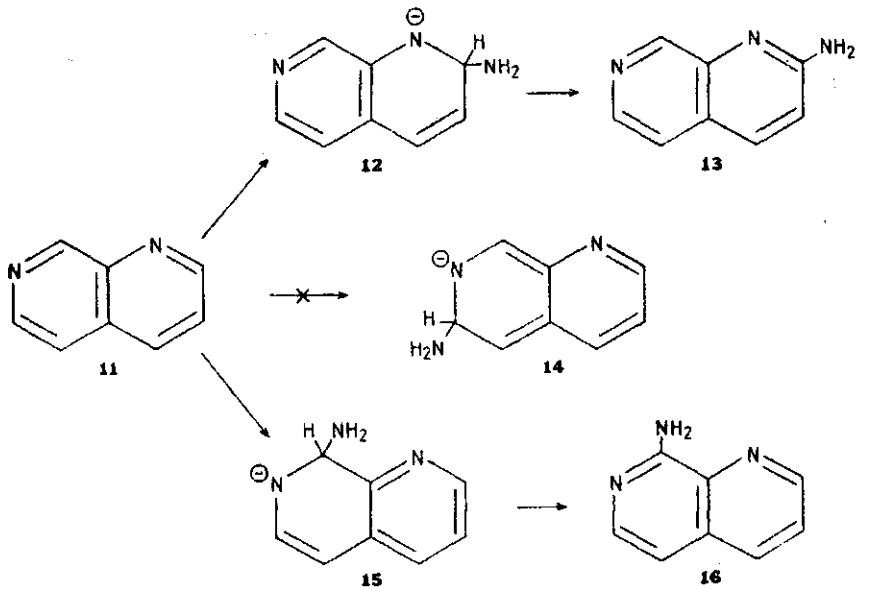


Scheme 2.2

1,6-naphthyridinide (10) can be explained by the fact that 7 can delocalize its negative charge over both nitrogen atoms by the para-para quinoid mesomeric contribution of 7b, while a similar delocalization for 9 or 10 would require the contribution of ortho-para or ortho-ortho quinoid resonance structures which are reported to be of less significance.[12]
That the contribution of a para-para quinoid resonance structure is important is clearly demonstrated by the high $\Delta\delta$ values of C-6 of 2 and 12 (Table 2.2), indicating that a considerable charge must be localized on position 6. From the results obtained with 6 we reach the conclusion that if nitrogen is present at position 6, the stabilization arising from the para-para quinoid structure 7b even exceeds the allylic stabilization in 9 or 10.
Oxidation of a solution of 7 in liquid ammonia containing potassium amide with potassium permanganate gave the 2-amino product 8 in a 40% yield; this method forms a useful extension of the methods described for the preparation of 8.

2.4 Amination of 1,7-naphthyridine (11)

Amination of 11 by potassium amide in liquid ammonia at -33°C gave a mixture of 2-amino- (13) and 8-amino-1,7-naphthyridines (16).[13]
The NMR spectrum of 11 in liquid ammonia containing potassium amide at -40° has been explained by suggesting the presence of three 1:1 σ adducts i.e. 2-, 6- and 8-amino-dihydro-1,7-naphthyridinides (12, 14 and 15), although not all the peaks in the NMR spectrum could be assigned.[7]



Scheme 2.3

More recent spectroscopic investigations on σ adduct formation between 2,6- and 2,7-naphthyridines and amide ions[14] induced us to reconsider whether some of the peaks of the spectrum of 11 in the potassium amide/liquid ammonia system were correctly assigned. This reinvestigation led us to the conclusion that the peaks originally ascribed to H-6 in 14 were in fact originated from H-5 in 15. That this assignment was correct was proved by the fact that in the NMR spectrum of a solution of 6,8-dideutero-1,7-naphthyridine in potassium amide/liquid ammonia the H-8 singlet - being observed in 15 at 5.13 ppm - disappeared and that the doublet of H-5 at 4.52 ppm changed into a singlet (Table 2.1). This considerable upfield shift for hydrogen being originally attached to an aromatic carbon atom and now present in an azaallylic position ($\Delta\delta$ = 3.12) is remarkably high, but not unusual. Similar upfield shifts are found for the corresponding hydrogen atoms in 1-aminodihydroisoquinolinide,[9] 1-aminodihydro-2,6-naphthyridinide[14] and 1-aminodihydro-2,7-naphthyridinide.[14] By this reassignment the NMR spectrum of 11 in liquid ammonia/potassium amide could now be completely resolved and led to the conclusion that on dissolving 11 in liquid ammonia/potassium amide, only 12 and 15 are formed and not 14, as originally suggested.[7] This fact is in good agreement with calculations showing that position 2 in 11 has the lowest electron density, closely followed by that on position 8.[3,5,6]

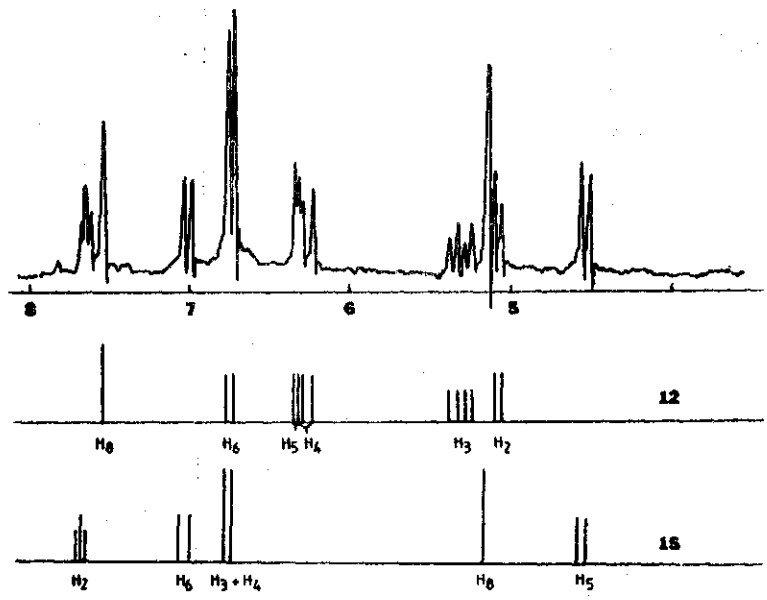
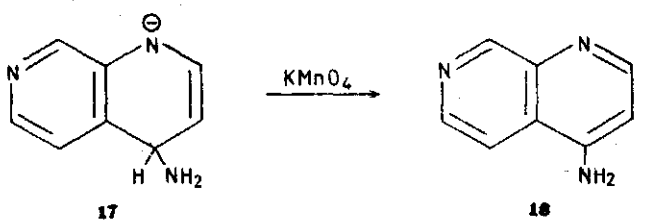


Figure. ^{1}H *NMR spectrum of 1,7-naphthyridine (11) in liquid ammonia, showing the assignment of the signals due to 12 and 15*

It was found that when the temperature of the solution containing this mixture of 12 and 15 was allowed to rise from -40°C to +10°C, the mixture irreversibly converts into 15. From this observation it is clear why 16 is the only product formed when the amination takes place at room temperature,[3] whereas a mixture of 13 and 16 is formed at -33°C.[13] The allylic resonance stabilizations, being possible in 15 but not in 12, account for the higher thermodynamic stability of 15. The high values for the ^{13}C- and ^{1}H upfield shifts being found for position 5 in 15, point in this direction (Tables 2.1 and 2.2).

When the solution of 12 and 15 in liquid ammonia-potassium amide at -40°C was treated with potassium permanganate a mixture of 2-amino- (13, 26%) and 8--amino-1,7-naphthyridine (16, 19%) was obtained, together with, unexpectedly, some 4-amino-1,7-naphthyridine (18, 10%). The formation of 18 suggests the intermediacy of the σ adduct 4-aminodihydro-1,7-naphthyridinide (17).

Its formation is kinetically less favorable than that of 12 and 15, as indicated by the higher electron density at C-4 in 11, but it is possible that on addition of the permanganate, 17 is formed as a short-lived intermediate which is immediately oxidized to 18.

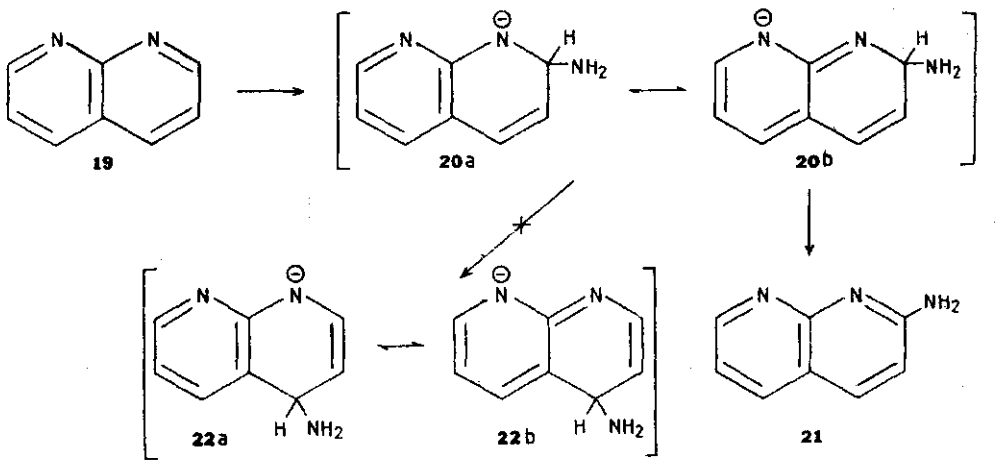


17 18

Scheme 2.4

2.5 Amination of 1,8-naphthyridine (19)

Amination of 19 with potassium amide in liquid ammonia has been reported to give at room temperature as well as at 50° the 2-amino-1,8-naphthyridine (21) in yields of 29% at room temperature[3] and 78% at 50°C.[8] It was already previously observed[7] that when 19 was dissolved in liquid ammonia-potassium amide at -40°C, only the σ adduct 2-aminodihydro-1,8-naphthyridinide (20) is formed. These results are in good accordance with calculations, predicting position 2 has the lowest electron density. We found however that when the temperature of the liquid-ammonia solution containing 20, was raised to +10°C, no change was observed and 20 was still the only adduct present. Apparently, adduct 20 is kinetically favored as well as being thermodynamically the most stable one. This seems surprising since the C-4 adduct of quinoline with amide i.e. 4--amino-1,4-dihydroquinolinide[9] and the C-4 adduct of 1,5-naphthyridine with amide i.e. 4 (see section 2.2) are more stable than their isomeric C-2 adducts. The reason why the C-2 adduct 20 is more stable than 4-aminodihydro-1,8-naphthy-



19 20a 20b 22a 22b 21

Scheme 2.5

ridinide (22) can be explained by a contribution of the ortho-para quinoid resonance structure 20b, which is of more importance than the ortho-ortho resonance contribution of 22b.
Treatment of the solution of 20 in liquid ammonia with potassium permanganate gave 21 in only a low yield (10%).

2.6 Experimental Section

All NMR spectra were obtained with a Varian XL-100-15 spectrometer. Spectra in liquid ammonia were recorded with sealed thick-walled NMR tubes. The procedure for measuring in liquid ammonia containing potassium amide has been described earlier.[15]
For ^{1}H spectra in liquid ammonia, ammonia (δ=0.95 ppm) was used as an internal standard.
^{13}C spectra were recorded with a Varian Fourier transform unit. The pulse separation was chosen as 0-1.25s, the spectral width was 5000 Hz (1.25 Hz/point) $(CH_3)_3N$ (δ=4.75 ppm) was used as an internal standard.
Starting materials: the following compounds were prepared according to known procedures: 1,5-naphthyridine,[16] 1,6-naphthyridine,[16] 1,7-naphthyridine,[17] 1,8-naphthyridine,[16] 2-amino-1,5-naphthyridine,[18] 4-amino-1,5-naphthyridine,[3,4] 2-amino-1,6-naphthyridine,[3] 2-amino-1,7-naphthyridine,[19] 4-amino-1,7-naphthyridine,[17] 8-amino-1,7-naphthyridine,[3] 2-amino-1,8-naphthyridine.[3]

Formation of the amino-1,X-naphthyridines

To 15 mL of liquid ammonia containing potassium amide, obtained by a reaction with 0.15 g of potassium was added all 0.20 g of the required 1,X-naphthyridine. After stirring for 10 minutes and addition of 0.80 g of $KMnO_4$ in small portions, the mixture was stirred for another 10 minutes. The potassium amide was then decomposed with $(NH_4)_2SO_4$ (1 g). After evaporation of the ammonia a concentrated aqueous solution of ammonia was added and the mixture was continuously extracted with chloroform during 48 hours. The residue obtained on evaporation of the chloroform was taken up in the minimum amount of methanol and brought by use of an autoliner Desaga Model 121000 on a plate (20 x 40 cm) covered by a 2 mm layer of silica gel PF_{254}.
The method of isolation of the amino compounds from the plates depends on the 1,X-naphthyridine used.

i) 1,5-Naphthyridine. Elution with chloroform-ethanol (10:1) gave one band which was extracted with methanol. Evaporation of the methanol gave 80 mg (36%) of 2-amino-1,5-naphthyridine (3), mp 203.5-205°C (lit.[18] 204-205°C).

ii) 1,6-Naphthyridine. The reaction was carried out as described above: Yield 90 mg (40%) of 2-amino-1,6-naphthyridine (8), mp 238-240°C (lit.[3] 238-240°C).

iii) 1,7-Naphthyridine. Elution with chloroform-ethanol (10:1) gave three bands. The lower band gave on extraction with methanol 22 mg (10%) of 4-amino--1,7-naphthyridine (18). mp 258-259°C (lit.[17] 259-260°C). Extraction of the middle band gave 57 mg (26%) of 2-amino-1,7-naphthyridine (13), mp 235-238°C (lit.[18] 236-238°C). The upper band was subjected to a second preparative TLC procedure, using chloroform as eluent. Two elutions gave two separate bands. Extraction with methanol of the lower band gave 42 mg (19%) of 8-amino-1,7--naphthyridine (16), mp 166-167°C (lit.[3] 165-166°C). Extraction of the upper band gave 7 mg of 1,7-naphthyridine, mp 63-65°C (lit.[17] 65-66°C).

iv) 1,8-Naphthyridine. The reaction was carried out as described for 1,5--naphthyridine. Yield 22 mg (10%) of 2-amino-1,8-naphthyridine (20), mp 135--138°C (lit.[3] 141-142°C).

2.7 References

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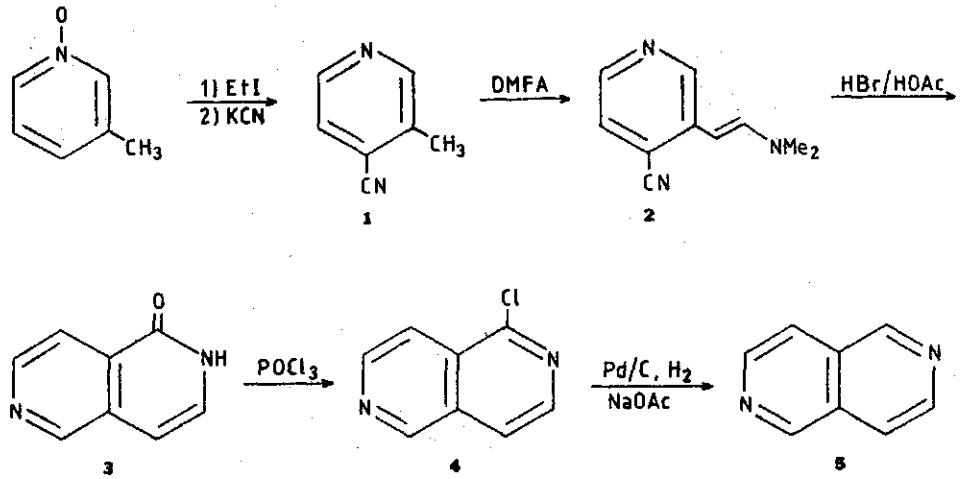
3 The Chichibabin amination of 2,6- and 2,7-naphthyridine.

Henk J. W. van den Haak, Henk C. van der Plas and Beb van Veldhuizen[1,2]

3.1 Introduction

In a recent publication[3] we reported on the occurrence of σ adduct formation between potassium amide and the four parent 1,X naphthyridines under kinetically and thermodynamically controlled conditions. The relative stabilities of these σ adducts proved to be a valuable tool for predicting the site of amination of the 1,X-naphthyridines. We now wish to report on adduct formation between potassium amide and 2,6- and 2,7-naphthyridine. Thusfar the chemistry of 2,6- and 2,7-naphthyridine is rather unexplored[4], partly due to the inaccessibility of these compounds. Paudler and Cornrich[5] published a convenient synthesis of 2,7-naphthyridine, but an easy method to synthesize the 2,6-isomer was not developed. We found however, that the procedure of Baldwin and others[6] for the synthesis of 2,7-naphthyridin-1(2H)-one from 3-cyano-4-picoline could easily be adapted to synthesize 2,6-naphthyridine-1(2H)-one from 4-cyano--picoline (1). The latter compound was reported to be obtained in a 15% yield as a by-product in the reaction of 3-picoline-N-oxide with methyl iodide and potassium cyanide at room temperature[7]. However we observed that when the reaction was carried out at 55°C and ethyl iodide was used instead of methyl iodide, 1 was obtained in a 60% yield. Reaction of 1 with dimethylformamide acetal (DMFA) into 1-N,N-dimethylamino-2-(4-cyano-3-pyridyl)ethene (2) and treatment of this product with hydrogen bromide in acetic acid gave 2,6-naphthyridin-1(2H)-one (3). This compound was converted with phosphorus oxychloride into 1-chloro-2,6-naphthyridine (4). Reduction with hydrogen and palladium on carbon yielded the parent 2,6-naphthyridine (5) (scheme 3.1). Since all these steps took place in reasonable yields (50-70%) 2,6-naphthyridine is now readily available.

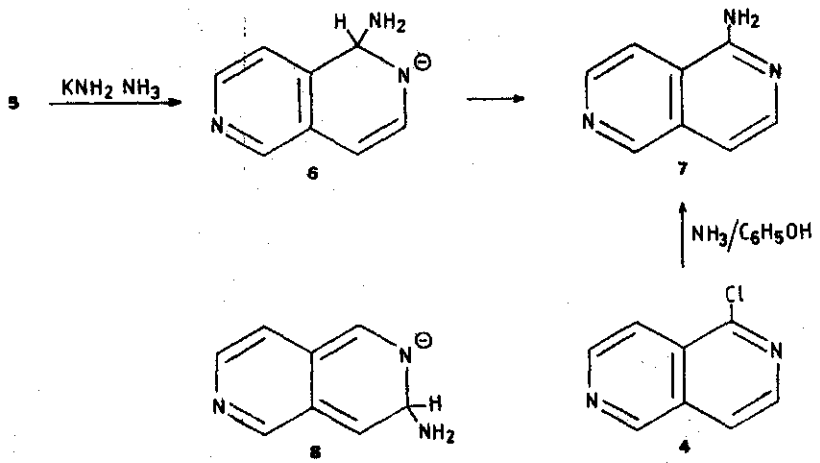


Scheme 3.1

3.2 Chichibabin amination

3.2.1 2,6-Naphthyridine

2,6-Naphthyridine (5) is reported[8] to have the lowest electron density on position 1. On the basis of earlier conclusions we may expect the kinetic attack of the amide anion to occur on this site, giving the 1-amino-1,2-dihydro--2,6-naphthyridinide (6) (scheme 3.2).

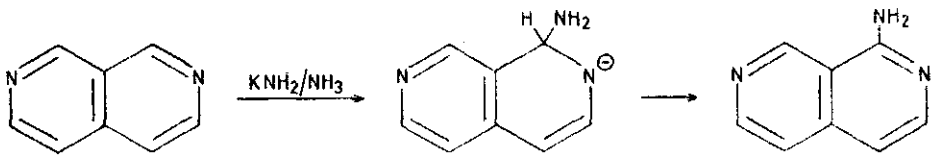


Scheme 3.2

When the NMR spectrum of a solution of 5 in liquid ammonia containing potassium amide was measured, it showed a singlet at 5.03 ppm (H-1) and an AB quartet at 4.70 and 7.09 ppm (H-4 and H-3 resp.). The upfield shifts of H-1 (4.24 ppm) and H-4 (2.99 ppm) are characteristic for σ adduct formation at position 1 in isoquinoline-like systems[3,9] (table 3.1).
^{13}C NMR spectroscopy confirms this observation (table 3.2).
The spectrum of 6 remained essentially unchanged when the temperature was raised to +20°C, so 6 is also the thermodynamically most stable σ-adduct. The great stability of 6 is due to the aza allylic stabilization, and in agreement with conclusions previously drawn with 1,X-naphthyridines[3]. The great upfield shift of C-4 ($\Delta\delta$ = 40.0 ppm), indicating the presence of considerable negative charge on C-4, supports this. Adduct formation on position 3 yielding 3-amino-2,3-dihydro-2,6-naphthyridinide (8) is less likely, since it disturbes the aromaticity of the other ring; thus 8 is thermodynamically less stable then 6.
Amination of 5 with potassium amide at room temperature (a procedure previously employed for 1,X-naphthyridines[8]) yielded 54% of 1-amino-2,6-naphthyridine (7). It was identical to the product obtained when treating 4 with phenol and ammonia.
Oxidation of anionic σ adducts with potassium permanganate is a very useful method for the preparation of amino compounds[3,10]. When this method was applied for the oxidation of 6 only 18% of 7 was yielded.

3.2.2 2,7-Naphthyridine

Paudler and Cornrich[5] reported the formation of 1-amino-2,7-naphthyridine (11) on amination of 2,7-naphthyridine (9) with potassium amide at room temperature. The low electron density of position 1 predicts the formation of the 1-amino--1,2-dihydro-2,7-naphthyridinide (10) on dissolving 9 in liquid ammonia containing potassium amide (scheme 3.3).



9 10 11

Scheme 3.3

Indeed, NMR spectroscopy of such a solution shows the formation of anion 10, as indicated by the upfield shift of 4.24 ppm for H-1 and of 3.10 ppm for H-4 (table 3.1).

Table 3.1 ^{1}H NMR data of 2,6- and 2,7-naphthyridine and their 1:1 σ adducts with amide anions

Compound	Solvent	H-1	H-3	H-4	H-5	H-6	H-7	H-8
5	$CDCl_3$	9.27	8.65	7.69	9.27	-	8.65	7.69
6	NH_2^-/NH_3	5.03	7.09	4.70	7.78	-	7.64	6.84
	Δδ	4.24	1.56	2.99	1.49	-	1.01	0.85
9	$CDCl_3$	9.37	8.68	7.59	7.59	8.68	-	9.37
10	NH_2^-/NH_3	5.03	7.16	4.59	6.28	7.63	-	7.67
	Δδ	4.34	1.52	3.00	1.31	1.05	-	1.70

Table 3.2 ^{13}C NMR spectra of 2,6- and 2,7-naphthyridine and their 1:1 σ adducts with amide anions

Compound	Solvent	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
5	$CDCl_3$	152.0	144.9	119.3	152.0	-	144.9	119.3	130.3	130.3
6	NH_2^-/NH_3	68.3	152.0	79.3	140.0	-	137.5	121.3	128.3	134.3
	Δδ	83.7	-7.1	40.0	12.0	-	7.4	-2.0	2.0	-2.0
9	$CDCl_3$	152.9	147.1	119.1	119.1	147.1	-	152.9	123.9	138.5
10	NH_2^-/NH_3	66.7	153.8	82.5	111.1	145.4	-	147.0	118.1	142.2
	Δδ	86.2	-6.7	36.6	8.0	1.7	-	5.9	5.8	-3.8

The large upfield shifts of H-4 and C-4 (table 3.2) show that a considerable amount of negative charge must be present on position 4 of 10. Due to this aza allylic stabilization, anion 10 is expected to be also the thermodynamically most favorable σ adduct of 9 with potassium amide. This was substantiated by the observation that on raising the temperature of the solution containing 10 from -40°C to +20°C the NMR spectrum did not alter.
Oxidation of 10 with potassium permanganate at -40°C gave 11 in a low yield (8%).

3.3 Experimental Part

All NMR spectra were obtained with a Varian XL-100-15 or a Varian EM 390 spectrometer. Spectra in liquid ammonia were recorded with sealed thick-walled NMR tubes. For ^{1}H NMR spectra in liquid ammonia, ammonia (δ = 0.95 ppm) was used as internal standard. ^{13}C spectra were recorded with a Varian Fourier transform unit. The pulse separation was chosen as 0-1.25 s, the spectral width was 5000 Hz (1.25 Hz/point); $(CH_3)_3N$ was used as internal standard (δ = 47.5 ppm).

Synthesis

2,7-Naphthyridine was prepared as described in the literature[5].

4-Cyano-3-picoline. 30 g (0.28 mol) of 3-picoline N-oxide were stirred during 16 hours with 50 ml of ethyl iodide (0.62 mol). Then 300 ml of water were added, and the water layer was separated and washed with ether. The water layer was heated to 50°C and a solution of 35 g of potassium cyanide in 90 ml of water was added during 1 hour. After stirring for 1 hour at 50°C the mixture was allowed to cool and after that extracted with ether. The ether layer was dried over $MgSO_4$ and the ether was evaporated in vacuo. Destillation of the residue (90-100°C/14 mm) gave 19.4 g (yield 60%) of a white solid which was not further purified but found sufficiently pure for use in the next step.

1-N,N-dimethylamino-2-(4-cyano-3-pyridyl)ethene (2). 19.4 g (0.16 mol) of 4--cyano-3-picoline were heated under nitrogen with 200 ml of dimethylformamide and 30 ml (0.25 mol) of dimethylformamide acetal (DMFA) during 5 days. Each day additional 5 ml of DMFA were added. The solution was then evaporated to dryness and the residue was crystallized from petroleum ether (b.r. 60-80°C) giving 13.1 g (yield 46%) of 2. An analytical sample was prepared by repeated crystal-

lization from cyclohexane, m.p. 85-86.5°C. ^1H NMR ($CDCl_3$) δ = 2.93 ppm (6H,s); δ = 5.24 ppm (1H,d,J = 13.5 Hz); δ = 7.12 ppm (1H,d, J = 13.5 Hz); δ = 7.18 ppm (1H,d, J = 5 Hz); δ = 8.06 ppm (1H,d, J = 5 Hz); δ = 8.63 ppm (1H,s). Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40. Found: C, 69.63; H, 6.64.

2,6-Naphthyridin-1(2H)-one (3). 13 g (75 mmol) of 2 were dissolved in 125 ml of glacial acetic acid and heated to 40°C. Under mechanical stirring 250 ml of 30% HBr in acetic acid were added dropwise in a 1½ hour period. The mixture was stirred at 55°C for an additional 2 hours and then evaporated to dryness. The residue was treated with ice, neutralized with Na_2CO_3 and continuously extracted with $CHCl_3$. (A previous extraction with ether did not yield any bromonaphthyridines). Evaporation of the $CHCl_3$ and sublimation of the residue at 180°C/0.1 mm gave 7.2 g (66%) of 3. m.p. 248-251°C. (from methanol, followed by recrystallization from water). ^1H NMR (DMSO): δ = 6.64 ppm (1H,d, J = 7.0 Hz); δ = 7.30 ppm (1H, d, J = 7.0 Hz); δ = 7.95 ppm (1H,d, J = 5.3 Hz); δ = 8.59 ppm (1H, d, J = 5.3 Hz); δ = 9.02 ppm (1H,s). Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.14. Found: C, 65.91; H,4.29.

1-Chloro-2,6-naphthyridine (4). 1 g (6.1 mmol) of 3 was refluxed with 40 ml of $POCl_3$ during 1½ hour. The excess of $POCl_3$ was evaporated in vacuo, the residu was treated with ice and the mixture was carefully neutralized with $NaHCO_3$. Extraction of the mixture with ether, drying of the ether layer with $MgSO_4$ and evaporation of the solvent gave 0.97 g of 1-chloro-2,6-naphthyridine, which is sufficiently pure for use in the next step (yield 77%). m.p. 92-93°C (from petroleum ether b.r. 60-80°C). ^1H NMR ($CDCl_3$ δ = 7.68 ppm (1H, d, J = 6.0 Hz); δ = 7.97 ppm (1H,d, J =6.0 Hz); δ = 8.40 ppm (1H,d,J = 6.0 Hz); δ = 8.75 ppm (1H,d,J = 6.0 Hz); δ = 9.28 ppm (1H,s). Anal. Calcd. for $C_8H_5N_2Cl$: C, 58.37; H, 3.06. Found: C, 58.65; H. 3.21.

2,6-Naphthyridine (5). 1,2 g (9.2 mmol) of 4 was hydrogenated at 40 p.s.i. in a Parr hydrogenation apparatus with 0.8 g of 3% Pd on carbon, 6 g of anhydrous sodium acetate and 200 ml of methanol. After uptake of the theoretical amount of hydrogen (requiring about 10 minutes) the mixture was filtered, the methanol was evaporated in vacuo and 50 ml of water and 10 ml of concentrated ammonia solution were added to the residue. This mixture was extracted with chloroform, the chloroform was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on a SiO_2 column using chloroform as eluent. 0.67 g of 5 was obtained (yield 71%), m.p. 117-119°C (lit.[11] 118-119°C).

1-Amino-2,6-naphthyridine (7). A solution of 0.97 g (5.9 mmol) of 4 in 6 g of phenol was heated at 175°C and NH_3 was bubbled through during 6 hours. 100 ml of H_2SO_4 (1N) were added to the cooled mixture, which was then steam destilled till no more phenol passed over. The residue was basified with an aqueous solution of sodium hydroxide (10%) and this solution was extracted continuously with chloroform. The solid residue which was obtained after evaporation of the chloroform in vacuo was sublimed at 180°C/0.05 mm, giving 0.50 g of 1-amino--2,6-naphthyridine (7) (yield 58%). m.p. 243-244°C (from water). ^1H NMR ($CDCl_3/CD_3OD$) δ = 7.01 ppm (1H,d,J = 5.7 Hz); δ = 7.84 ppm (1H,d,J = 5.7 Hz); δ = 7.88 ppm (1H,d,J = 5.7 Hz); δ = 8.43 ppm (1H,d,J = 5.7 Hz); δ = 8.96 ppm (1H, s). Anal. Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86. Found: C, 66.40; H, 4.67.

Amination of 5

This amination was carried out at room temperature as described in the literature for the amination of 9[5]. The solid residue obtained on evaporation of the organic layer was suspended in concentrated ammonia solution. The mixture was continuously extracted with chloroform. After evaporation of the chloroform the residue was dissolved in the minimum volume of methanol. This solution was brought on four plates (20x20 cm) covered with 0.5 mm of SiO_2. The chromatograms were developed with a chloroform-ethanol mixture (10:1). No starting material was found. Extraction of the band, containing the product with methanol gave 7 (yield 54%).

Oxidation of σ-adducts with $KMnO_4$

The procedure has been described previously[3]. The crude product obtained on continuous extraction of the reaction mixture was purified by thick-layer chromatography as described above. Yield of 7 from 6, 18%; yield of 11 from 10, 8%.

3.4 Acknowledgement

We are indebted to Mr. H. Jongejan for carrying out the microanalyses.

3.5 References

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4 The occurrence of even telesubstitutions in the amination of halogeno-1,5- and -2,6-naphthyridines.

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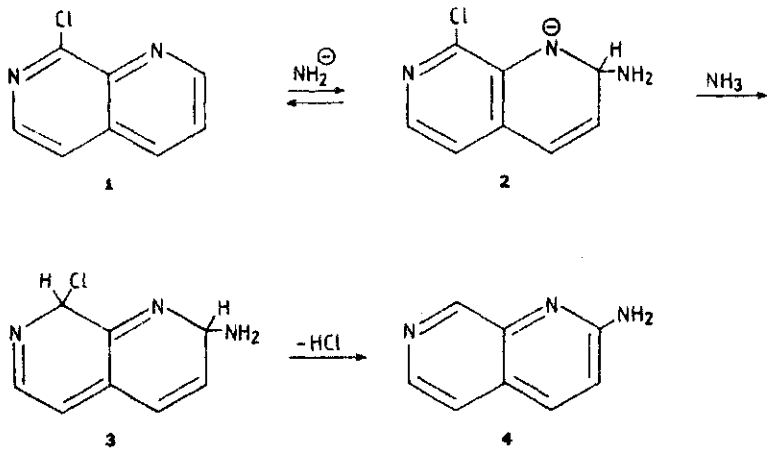
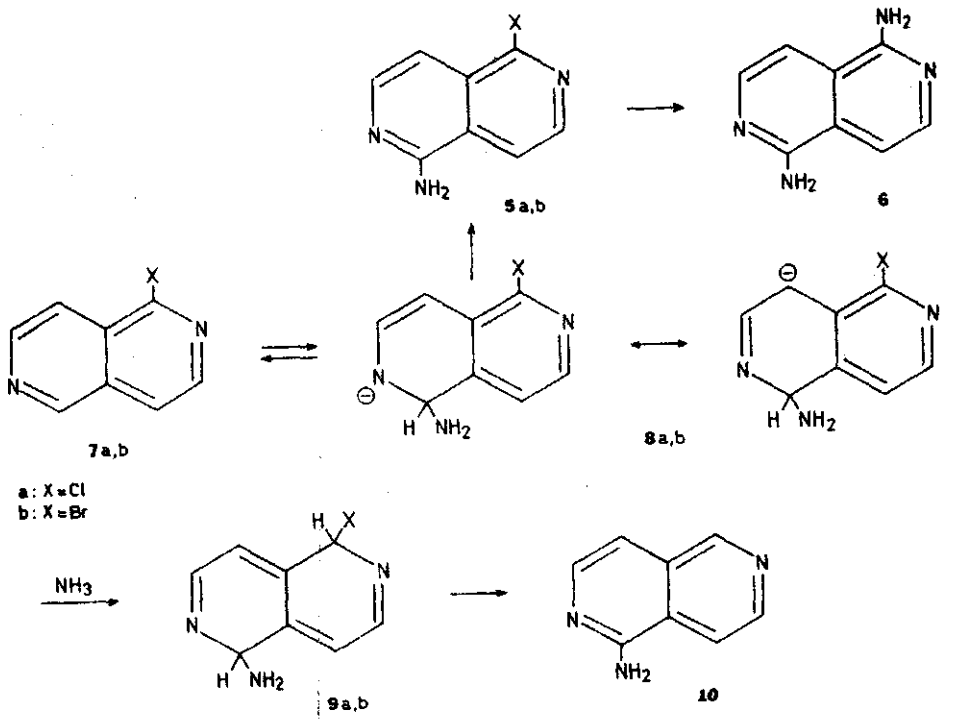
4.1 Introduction

It has been reported[4,5] that 8-chloro-1,7-naphthyridine (1) when reacted with potassium amide in liquid ammonia (KNH_2/NH_3) undergoes a teleamination, leading to 2-amino-1,7-naphthyridine (4). As an even number of positions lies between the position of attack of the nucleophile and the position of departure of the leaving group, this reaction can be classified as an even telesubstitution $\left[S_N(AE)^{tele}\right]$. Odd telesubstitutions are also described, as exemplified by the amination of 7-chloro-2-deutero-1,8-naphthyridine into 2-amino-1,8-naphthyridine.[4,5] The introductory step of the 1,4-teleamination of 8-chloro-1,7--naphthyridine (1) is the σ adduct formation at position 2, yielding 2-amino-8--chloro-2,X-dihydro-1,7-naphthyridinide (2); its formation has been proved by NMR spectroscopy. Adduct 2 undergoes protonation at C-8, into 3 which by a basecatalyzed dehydrohalogenation gives product 4 (Scheme 4.1).
This result induced us to study in more detail the generality of the phenomenon of even teleaminations in the naphthyridine series.



Scheme 4.1

Since recent investigations[3] have shown that 2,6-naphthyridine undergoes exclusively σ adduct formation at C-1 (C-5), when dissolved in KNH_2/NH_3, we became interested in the behaviour of the 1-chloro(bromo)-2,6-naphthyridine (7a,7b) towards potassium amide. It is possible that the 1-halogeno compounds 7a and 7b undergo addition at C-5, giving 8a and 8b respectively which after protonation and a 1,6-dehydrohalogenation give the teleamination product 5(1)-amino-2,6--naphthyridine (10) (Scheme 4.2).



Scheme 4.2

4.2 NMR spectroscopy of solutions of 1-halogeno-2,6-naphthyridines in KNH_2/NH_3

Compounds 7a en 7b, (being readily prepared from 2,6-naphthyridin-1(2H)-one[3]) when dissolved in liquid ammonia containing potassium amide form the σ adducts 8a and 8b, as is shown by NMR spectroscopy (Table 4.1). On comparing the chemical shifts observed in solutions of 7a and 7b in KNH_2/NH_3 with those in solutions of 7a and 7b in $CDCl_3$, all hydrogens have undergone upfield shifts, but especially the shift of H-5 is considerable (4.27 and 4.22 ppm respectively). This large upfield shift of H-5 can be explained by the fact that C-5

Table 4.1 ^{1}H NMR spectra of 1-chloro- (7a) and 1-bromo-2,6-naphthyridine (7b) and their σ adducts in KNH_2/NH_3

compound	solvent	H-3	H-4	H-5	H-7	H-8
7a	$CDCl_3$	8.40	7.57	9.28	8.75	7.93
8a	KNH_2/NH_3	7.42	6.84	5.01	7.21	4.74
Δδ	-	0.98	0.73	4.27	1.54	3.19
7b	$CDCl_3$	8.39	7.68	9.23	8.73	7.91
8b	KNH_2/NH_3	7.44	6.90	5.01	7.27	4.75
Δδ	-	0.95	0.78	4.22	1.46	3.16

Table 4.2 ^{13}C NMR-spectra of 1-chloro- (7a) and 1-bromo-2,6-naphthyridine (7b) and their σ adducts in KNH_2/NH_3

compound	solvent	C-1	C-3	C-4	C-5	C-7	C-8	C-9	C-10
7a	$CDCl_3$	151.0	143.6	119.5	152.1	146.3	117.8	129.5	132.0
8a	KNH_2/NH_3	-	134.8	121.4	68.1	153.2	78.1	138.5	131.8
Δδ	-	-	8.8	-1.9	84.0	-6.9	39.7	-9.0	0.2
7b	$CDCl_3$	144.5	144.1	120.0[a]	152.1	146.5	119.7[a]	131.7	131.7
8b	KNH_2/NH_3	-	135.3	121.8	68.5	153.2	80.1	-	-
Δδ	-	-	8.8	-1.8	83.6	-6.7	39.6	-	-

[a] These signals may be interchanged

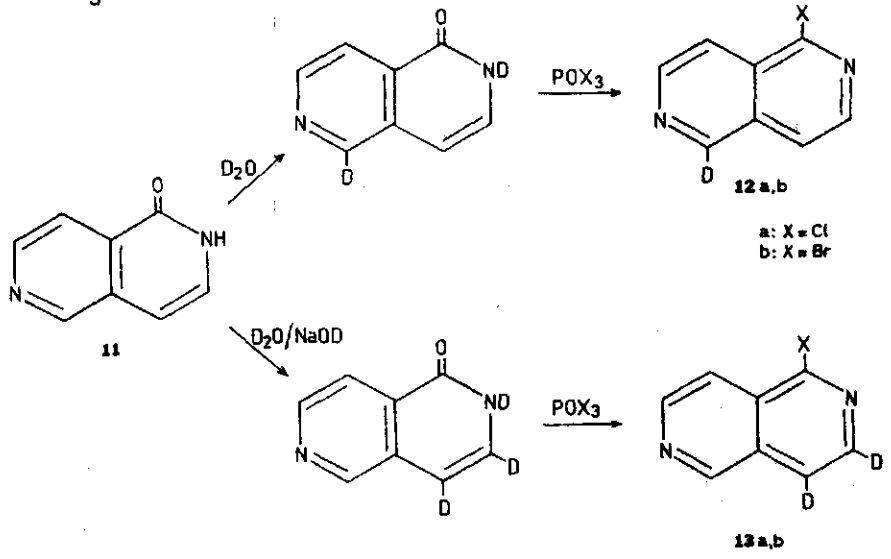
rehybridizes ($sp^2 \rightarrow sp^3$) due to σ adduct formation on this position, leading to the 5-amino-5,X-dihydro-1-halogeno-2,6-naphthyridinides (8a and 8b respectively).[6]

Supporting evidence for the formation of a covalent amino adduct at position 5 has been provided by ^{13}C NMR spectroscopy showing an upfield shift of about 84 ppm for C-5 (Table 4.2). C-8 in 8a and 8b has also undergone a great upfield shift (about 40 ppm) due to the aza allylic resonance contribution to stabilization which predicts a considerable negative charge at positions meta to the nitrogen atom (scheme 4.2). Aza allylic stabilization in dihydroazinides has been recognized before[3,7,8] as an important contribution to the stability of these anionic species.

4.3 Amination of 1-halogeno-2,6-naphthyridines

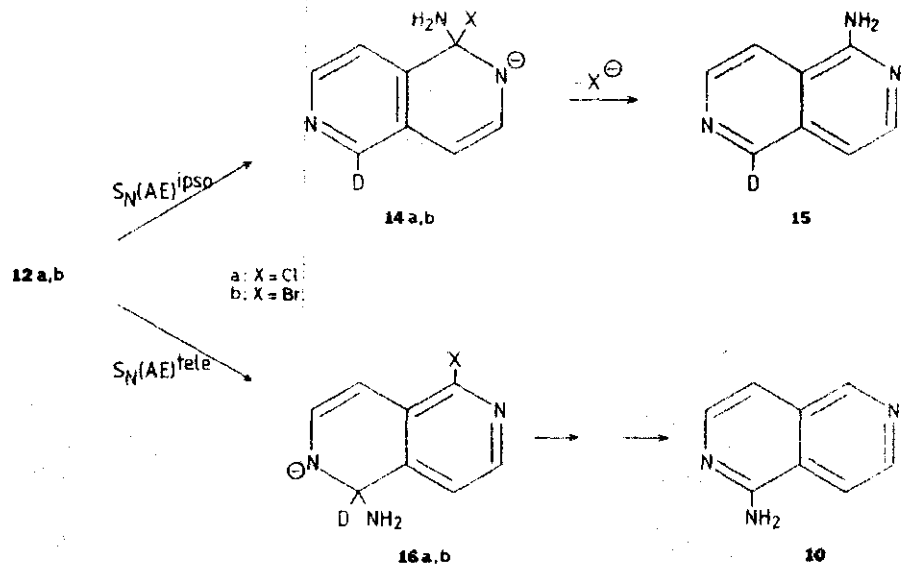
Treatment of 7a with KNH_2/NH_3 at -33^0C for 63 h yielded 5(1)-amino-2,6-naphthyridine (10, 20%), 1,5-diamino-2,6-naphthyridine (6, 17%) and 29% of the starting material 7a. Amination of 7b gave the products 10 and 6 in 28 and 14% yields respectively, together with 36% of the starting material 7b.

The formation of σ adducts 8a and 8b in KNH_2/NH_3 suggests that the conversion of 7 into 10 may occur via 8. To investigate this possible reaction pathway we prepared both 5-deutero-1-halogeno-2,6-naphthyridines 12a and 12b by heating of 2,6-naphthyridin-1(2H)-one (11) with D_2O and subsequent treatment of the product with POX_3 (Scheme 4.3).



Scheme 4.3

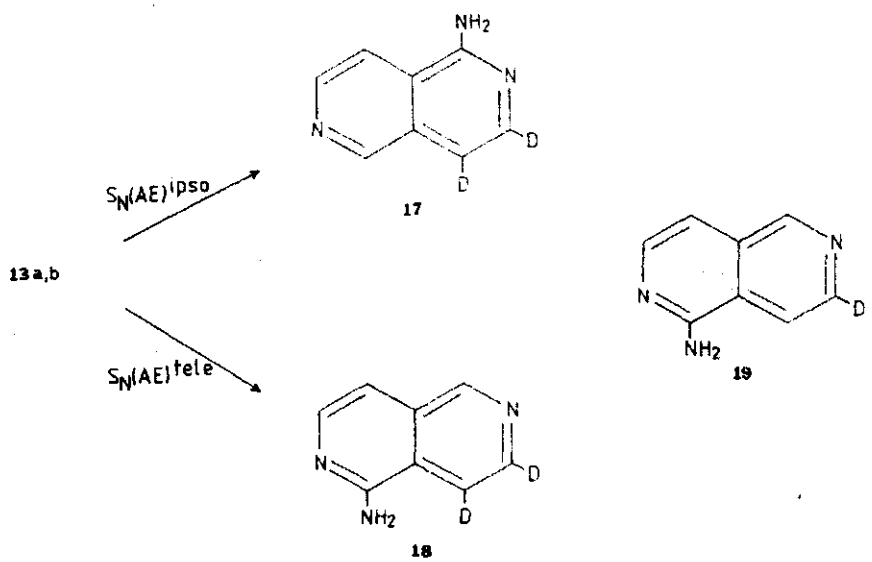
NMR spectroscopy showed that the major part of the deuterium label in 12a and 12b was present at position 5. From the two pathways for amination i.e. $S_N(AE)^{ipso}$, involving as intermediate 14a,b[9], and $S_N(AE)^{tele}$, involving 16a,b[9] (Scheme 4.4) it is evident that if the amination of 12a or 12b should occur via an $S_N(AE)^{ipso}$ process the 1-amino compound 15 still contains the same percentage of deuterium labelling at C-5 as present in the starting material 12a or 12b.



Scheme 4.4

In case the substitution occurs via the C-5 adduct 16a or 16b no deuterium should be present in the amino compound 10 any more. It was found that the amino product obtained on amination of 12a showed a percentage of deuterium label that was considerably lower than that of the starting material 12a. From mass spectroscopic data it was calculated that for the deuterated compound 12a the $S_N(AE)^{tele}$ process took place about 5 times faster than the $S_N(AE)^{ipso}$ process. Moreover it was found that the recovered starting material had a greater percentage of deuterium than present in the starting material before the reaction. From this deuterium enrichment it was calculated that the $S_N(AE)^{tele}$ process has a kinetic isotope effect of about 2.5. This means that for the undeuterated compound 7a the $S_N(AE)^{tele}$ substitution proceeds about 13 times faster than the $S_N(AE)^{ipso}$ process or in other words, on amination of 7a, about 93% of product 10 is formed in an $S_N(AE)^{tele}$ process.[9]

Carrying out the amination of 12b, similar results were obtained. It was found that 7b reacts for about 73% via an $S_N(AE)^{tele}$ pathway and that this tele-amination reaction was subjected to a kinetic isotope effect of about 1.3. Confirmation of these results was obtained by a study of the amination of the 3,4-dideutero-1-halogeno-2,6-naphthyridines 13a and 13b. These compounds were prepared by heating a basic solution of 11 in D_2O and treatment of the product obtained with POX_3 (Scheme 4.3). If 13a and 13b undergo amination according to an $S_N(AE)^{ipso}$ process, 3,4-dideutero-1-amino-2,6-naphthyridine (17) is the expected product, whereas in an $S_N(AE)^{tele}$ process, 3,4-dideutero-5-amino-2,6-naphthyridine (18) is yielded (Scheme 4.5).



Scheme 4.5

It was found that as the main product of the amination of both 13a and 13b neither 17 nor 18, but 3-deutero-5-amino-2,6-naphthyridine (19) was obtained. We assume that 19 is formed from 18, due to an exchange of H-4 in 18 by the potassium amide/liquid ammonia system.

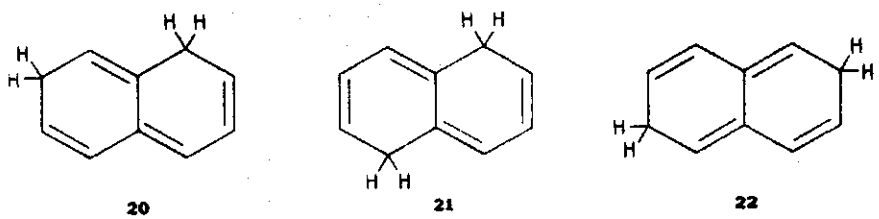
From the extent of deuteration at position 3 in 13a and in 19 it was calculated that the amination of 13a proceeded for 92% via the $S_N(AE)^{tele}$ pathway. This result is in excellent agreement with the results obtained from amination of 12a. Amination of 13b and investigation of the deuterium content of the product 19 confirmed the results obtained from amination of 12b.

Concerning the formation of the 1,5-diamino compound 6, it is certain that this

compound cannot be formed by subsequent amination of 1-amino-2,6-naphthyridine (10), since it has already been reported[3] that Chichibabin amination of 2,6-naphthyridine at room temperature gave 10 and no trace of 6. It seems more reasonable to explain the formation of 6 by a Chichibabin amination of 7a and 7b into 5-amino-1-halogeno-2,6-naphthyridine (5a and 5b) which reacts further to 6 (Scheme 4.2).

4.4 Discussion

The conversion of the halogeno compounds 1, 7a and 7b into their corresponding amino compounds 4 and 10 respectively are both examples of even telesubstitutions as we have seen. The amination of 7a proceeds for 93% via the tele-mechanism, the amination of 1 proceeds for 45% via a telepathway.[4,5]
To understand why 1 is less inclined to telesubstitution than 7a, the following suggestion can be made. There is a large energy difference between the non-aromatic dihydro intermediates 3 and 9 and the corresponding aromatic amino products 4 and 10 or the σ adducts 2 and 8a,b.
Since the activation energy of the dehydrohalogenations of the dihydro intermediates is probably relatively small, the assumption seems justified that the different abilities of naphthyridines to undergo even telesubstitutions has some relation with the stabilities of the dihydro intermediates.
The linearly conjugated 1,5-dihydro system 9a has probably somewhat more stability than the cross-conjugated 2,8-dihydro system 3 and therefore its formation is favoured. Some support for this statement can be taken from the fact that the estimated heat of formation of 1,7(=2,8)-dihydronaphthalene 20 is about 1,4 kJ/mol higher[10] than that of its 1,5-isomer 21 at 240 K (Scheme 4.6).

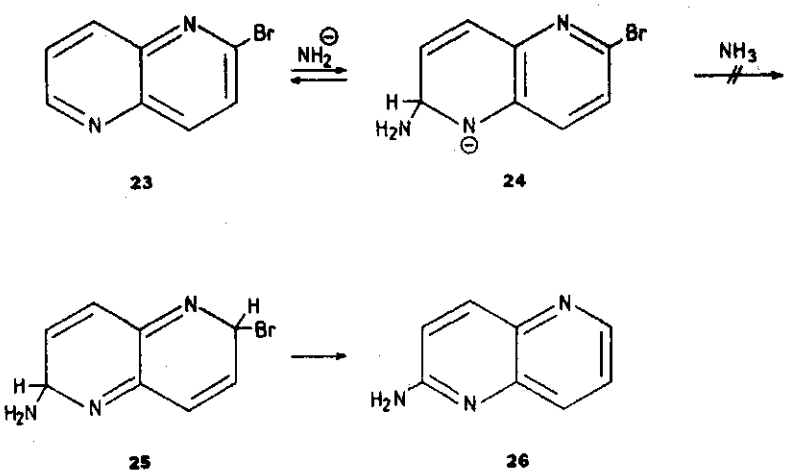


20 21 22

Scheme 4.6

The stability of 2,6-dihydronaphthalene (22) is estimated to be about 10 kJ/mol less than that of its 1,5 isomer (21).[10] Based on these data we may expect that an even telesubstitution in which a 2,6-dihydronaphthyridine derivative is an intermediate, is a very unfavourable process. In order to confirm this expec-

tation we investigated the occurrence of a teleamination with 2-bromo-1,5--naphthyridine (23). This compound should be able to give 2,6-dihydro intermediate 25 (Scheme 4.7), being considerably less stable than its isomers 3 and 9.

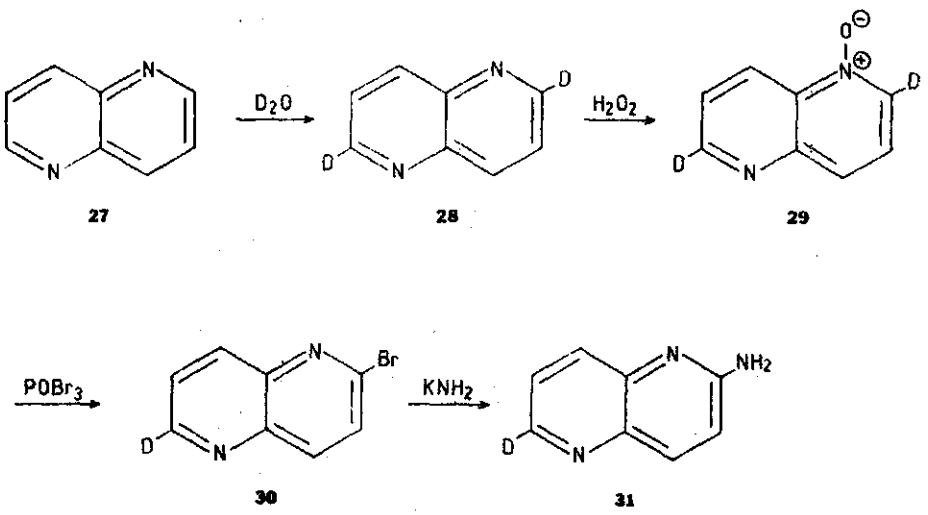


Scheme 4.7

There is convincing evidence for the formation of the 1:1 σ adduct 24 when dissolving 23 in KNH_2/NH_3. The NMR spectrum of this solution, although it could not be completely assigned, exhibits a double doublet at 5.34 ppm and a doublet at 4.94 ppm, being ascribed to the signals derived from H-7 and H-6 respectively of the 6-amino-2-bromo-6,X-dihydro-1,5-naphthyridinide (24). The upfield shift of H-6 ($\Delta\delta$ = 4.05 ppm) is in good agreement with the reported value for σ adduct formation in naphthyridines.[7,11]

Moreover, when the 2-bromo-6-deutero-1,5-naphthyridine (30) was used instead of 23 the peaks ascribed to H-6 disappeared and the signals due to H-7 changed from a double doublet into a doublet. On reacting 30 with potassium amide in liquid ammonia we found that the isolated amino product had the same extent of deuteration as the starting compound. This means that the amination of 23 must proceed via an $S_N(AE)^{ipso}$ substitution process, and not via an $S_N(AE)^{tele}$ substitution involving 24 and the unstable dihydro intermediate 25.

The preparation of 30 could not be accomplished by the procedure described for the preparation of 7a and 7b. Therefore we deuterated 1,5-naphthyridine (27) by heating it in D_2O. The 1,5-dideutero naphthyridine (28) was oxidized with H_2O_2 to the N-oxide (29) which on reaction with $POBr_3$ yielded 2-bromo-6-deutero-1,5-naphthyridine (30) (together with its 3-bromo isomer).



Scheme 4.8

4.5 Experimental Part

Melting points (uncorrected) were determined on a Kofler Plate. ^{1}H NMR spectra were recorded on a Varian XL-100-15 spectrometer, a Varian EM 390 spectrometer or a Hitachi Perkin-Elmer R-24B spectrometer. ^{13}C spectra were recorded on a Varian XL 100-15 spectrometer equipped with a Varian Fourier transform unit. The spectral width was 5000 Hz (1.25 Hz/point). Mass spectra were recorded on an AEI MS 902 instrument.

Starting Materials: The following compounds were prepared according to procedures described in the literature: 1-Chloro-2,6-naphthyridine (7a);[12] 2,6-naphthyridin-1(2H)-one (11);[3] 2,6-dideutero-1,5-naphthyridine[11] (28); 2,6-dideutero-1,5-naphthyridine-N-oxide (29) was prepared from 28, analogously to the procedure described for the undeuterated compound[13].

A. 1-Bromo-2,6-naphthyridine (7b)

0.49 g (3.4 mmol) 2,6-naphthyridin-2(1H)-one (11) and 1.8 g of $POBr_3$ (6,3 mmol) were heated at 130-140°C for 2 hours in a stoppered flask. The reaction mixture was then cooled, carefully treated with ice and sodium bicarbonate and extracted with ether. After drying of the ethereal layer on $MgSO_4$ the solvent was

evaporated off and the residue was purified by column chromatography on SiO_2, using $CHCl_3$ as eluent, yielding 0.50 g (71%) of 7b; mp 94.5-95.5°C. Anal. Calcd. for $C_8H_5N_2Br$: C, 45.96; H, 2.41. Found: C, 46.25; H, 2.54.

B. 1-Halogeno-5-deutero-2,6-naphthyridine (12a,b)

0.5 g (3.4 mmol) of 11 and 5 mL of D_2O were heated in a sealed tube at 155°C for 12 hours. After cooling the solvent was evaporated off in vacuo and the residue treated with $POCl_3$ on $POBr_3$ as described above.

C. 1-Halogeno-3,4-dideutero-2,6-naphthyridine (13a,b)

0.5 g (3.4 mmol) of 11, 0.1 g of NaOH and 5 mL of D_2O were heated in a sealed tube at 125°C for 16 hours. The mixture was neutralized with 1 N hydrochloric acid and continuously extracted with chloroform. Evaporation of the chloroform and treatment of the residue obtained with POX_3 (see above) gave 13a and 13b.

D. 2-Bromo-6-deutero-1,5-naphthyridine (30)

1.35 g (9.1 mmol) of 2,6-dideutero-1,5-naphthyridine-N-oxide (29) were suspended in 30 mL of chloroform. The mixture was cooled in ice and 3.67 g (12.7 mmol) of $POBr_3$ were added. After stirring in ice for 15 minutes and subsequent stirring at room temperature for additional 15 minutes, the mixture was poured onto ice, basified with concentrated ammonia solution and extracted with chloroform. The chloroform layer was dried on $MgSO_4$ and evaporated off in vacuo. The residue obtained was purified on a silicagel column using petroleum ether (br. 40-60°C)/acetone (14:1) as eluent. First 0.21 g (11%) of 3-bromo-2,6--dideutero-1,5-naphthyridine was eluted, then 1.15 g (60%) of 30, followed by traces of 2,6-dideutero-1,5-naphthyridine.

E. Amination of 1-chloro-2,6-naphthyridine (7a)

To a solution prepared by dissolving 0.20 g (5.1 mmol) of potassium in 30 mL of liquid ammonia containing a few crystals of ferric nitrate, 0.20 g (1.2 mmol) of 7a were added. After reacting at -33°C for 63 hours 0.50 g of ammonium sulfate were added and the ammonia was allowed to evaporate. 25 mL of concentrated ammonia solution were added and the mixture was continuously extracted with chloroform. The residue obtained on evaporation of the chloroform was dissolved in the minimum volume of methanol and brought on four plates (20x20

cm) covered with a 0.5 mm layer of silica GF 254. After developing the plates in chloroform-ethanol (9:1), three bands were detected. Extraction of the upper band with methanol gave 14.2 mg (7%) of starting material, extraction of the middle band gave 35.8 mg (20%) of the 1-amino compound 10, identical with an authentic specimen and by extraction of the lower band 32.6 mg (17%) of 1,5--diamino-2,6-naphthyridine (6) were isolated. It melted above 300°C; ^{1}H NMR (DMSO): δ=6.51 ppm (4H, NH_2, broad); δ=6.96 ppm (2H, H4, H8, d, J=5.0 Hz) δ=7.67 ppm (2H, H3, H7, d, J=5.0 Hz). It was analysed as its picrate (mp above 300°C). Anal. Calcd. for $C_8H_8N_4.C_6H_3N_3O_7$: C, 43.19; H, 2.85. Found: C, 43.42; H, 2.93.

F. 1-Bromo-2,6-naphthyridine (7b) was aminated in the same way as 7a. The amination of 6-deutero-2-bromo-1,5-naphthyridine (30) was carried out as described in the literature.[14]

4.6 Appendix

The kinetic isotope effect and the percentage of telesubstitution in the amination of halogeno naphthyridines were calculated in the following way:
If an unlabelled compound H reacts in a first order reaction the concentration $[H]$ is described by

$$\ln \frac{[H]}{[H_o]} = (k_H+k)t,$$

where $[H_o]$ = the concentration of H at t=o.

k_H = the reaction constant of the $S_N(AE)^{tele}$ reaction of the undeuterated compound.

k = the reaction constant of the $S_N(AE)^{ipso}$ reaction; k is assumed to be equal for the deuterated and the undeuterated compound.

For a deuterated compound D we find

$$\ln \frac{[D]}{[D_o]} = (k_D+k)t,$$

where $[D_o]$ = the concentration of D at t=o.

k_D = the reaction constant of the $S_N(AE)^{tele}$ reaction of the deuterated compound.

Combination of these equations gives

$$\frac{k_H}{k_D} = \frac{\ln [H] - \ln [H_o]}{\ln [D] - \ln [D_o]} \left(1 + \frac{k}{k_D}\right) - \frac{k}{k_D}$$

$\frac{k_H}{k_D}$ is the kinetic isotope effect of the $S_N(AE)^{tele}$ reaction.

The calculation of $\frac{k}{k_D}$, being the ratio of the reaction constants of the $S_N(AE)^{ipso}$ reaction and the $S_N(AE)^{tele}$ reaction of the deuterated compound, is shown by the following example:

	12a	⟶	10
0D	18.6%		73.9%
1D	66.1%		22.4%
2D	15.3%		3.6%

If 2D starting material reacts in an $S_N(AE)^{tele}$ reaction, 1D product is formed, whereas in an $S_N(AE)^{ipso}$ reaction of 2D starting material 2D product is formed (scheme 4.4). So if 15.3% of 2D starting material yields 3,6% of 2D product, 15.3-3.6=11.7% of 1D product is formed. This means that 11.7% of the 1D product is formed in an $S_N(AE)^{tele}$ reaction of the 2D starting material, the rest (22.4-11.7=10.7%) is formed in an $S_N(AE)^{ipso}$ reaction of 1D starting material. So from 66.1% of 1D product, 10.7% undergoes an $S_N(AE)^{ipso}$ reaction and the rest (66.1-10.7=55.4%) undergoes an $S_N(AE)^{tele}$ reaction, or in other words

$$\frac{k}{k_D} = \frac{10.7}{55.4} = 0.18$$

From $\frac{k_H}{k_D}$ and $\frac{k}{k_D}$, $\frac{k_H}{k}$ can be calculated.

$\frac{k_H}{k}$ is the ratio of the reaction rates of the $S_N(AE)^{tele}$ reaction in the undeuterated compound and the $S_N(AE)^{ipso}$ reaction.

4.7 Acknowledgement

We are indebted to Drs. C.A.Landheer for carrying out mass spectroscopy and to Mr. H.Jongejan for microanalyses.

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6) Formally the correct nomenclature for 8a and 8b is 1-amino-5-halogeno-1,X--dihydro-2,6-naphthyridinide. For the sake of clarity however, we prefered the nomenclature used here.
7) van den Haak, H.J.W.; van der Plas, H.C.; van Veldhuizen, A., J. Org. Chem., 1981, 46, 2134.
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9) The term $S_N(AE)^{ipso}$ denotes a nucleophilic substitution in which the nucleophile attacks the carbon atom bearing the leaving group.
The term $S_N(AE)^{tele}$ denotes a nucleophilic substitution in which the nucleophile enters the molecule more than one position removed from the position from which the leaving group departs.
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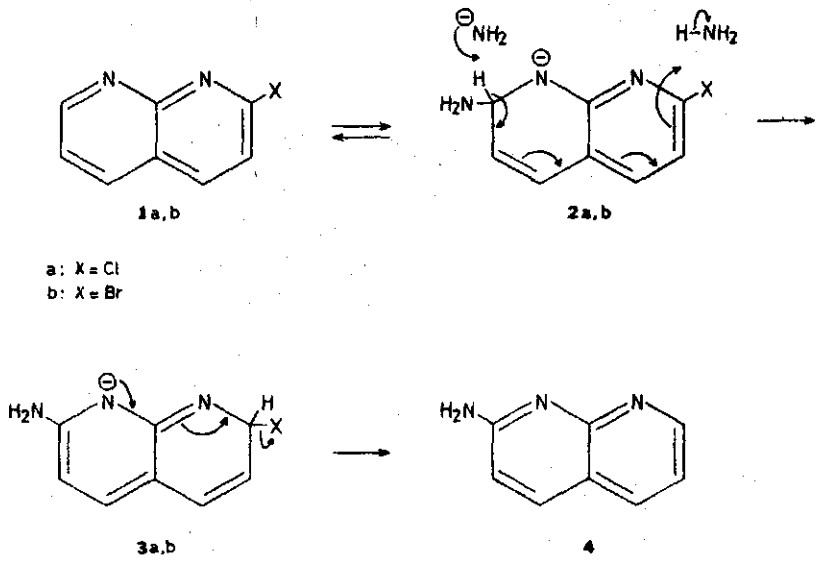
5 The amination of 1-halogeno-2,7-naphthyridines.

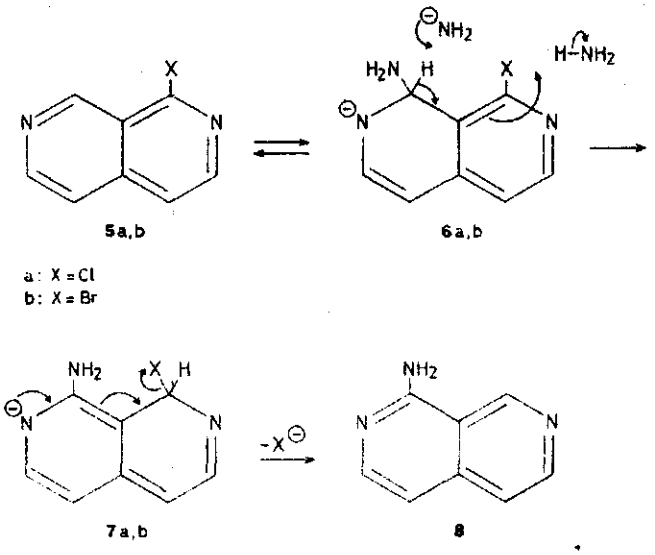
5.1 Introduction

In our studies on the amination of halogenated naphthyridines we encountered the phenomenon of the telesubstitution $\left[S_N(AE)^{tele}\right]$ several times. In telesubstitutions we can discern two types : the so-called even- and odd telesubstitutions. The occurrence of even telesubstitutions has been discussed before (see Chapter 4). Odd telesubstitutions comprise those reactions in which there is an odd number of positions lying between the carbon atom on which the nucleophile attacks and the one from which the leaving group departs. The conversion [1,2] of 2-halogeno-1,8-naphthyridine (1) into 2-amino-1,8-naphthyridine (4) is an example of a reaction that proceeds partly via an odd telesubstitution pathway. NMR spectroscopy showed that the initial step in this reaction is the formation of the σ adduct 2 (Scheme 5.1). A 1,7-proton shift in 2 leads to 3, which eliminates the halogen ion to yield 4.



Scheme 5.1

On aminating 2-bromo-7-deutero-1,8-naphthyridine and measuring the deuterium content in the 7(2)-amino product as well as in the recovered starting material it was calculated that the telesubstitution has a kinetic isotope effect of about 2 and that in the amination of 2-bromo-1,8-naphthyridine (1b) 45% of the product 4 was formed according to an $S_N(AE)^{tele}$ process.[3]
The occurrence of a kinetic isotope effect in the amination of the 2-bromo compound shows that in this reaction the proton shift is rate limiting.
The amination of 2-chloro(7-deutero)-1,8-naphthyridine proceeds for only 10% via the telemechanism and no isotope effect was measured.[1,2]
These results induced us to study the amide-induced amination of 1-halogeno-2,7-naphthyridines (5a,b). These compounds can in principle also undergo an odd telesubstitution (Scheme 5.2).
The parent system 2,7-naphthyridine has been found[4] to form very easily a σ adduct at C-1/C-8 and therefore it is possible that also 5a,b forms the σ adduct 6.



Scheme 5.2

A 1,3 proton shift in 6 might yield 7 which on elimination of the halogen ion should give the product 8. NMR spectroscopy showed that when 5 was dissolved in liquid ammonia containing potassium amide 8-amino-1-halogeno-8,X-dihydro-2,7-naphthyridinide (6) was actually formed : H-8 and C-8 of 5a,b had undergone up-field shifts of ∿ 4.3 ppm and ∿ 85 ppm respectively, indicating that C-8 had

Table 5.1 ^{1}H NMR spectra of 1-halogeno-2,7-naphthyridines and their σ adducts.

compound	solvent	H-3	H-4	H-5	H-6	H-8
5a	$CDCl_3$	8.38	7.54	7.62	8.73	9.61
6a	KNH_2/NH_3	7.37	6.24	4.68	7.23	5.36
Δδ		1.01	1.30	2.94	1.50	4.25
5b	$CDCl_3$	8.36	7.52	7.52	8.71	9.58
6b	KNH_2/NH_3	7.37	6.28	4.68	7.27	5.31
Δδ		0.99	1.24	2.84	1.43	4.27

Table 5.2 ^{13}C NMR spectra of 1-halogeno-2,7-naphthyridines and their σ adducts

compound	solvent	C-1	C-3	C-4	C-5	C-6	C-8	C-9	C-10
5a	$CDCl_3$	152.0	145.7	119.0[a]	119.4[a]	148.1	148.1	131.9	140.7
6a	KNH_2/NH_3	149.0	144.1	111.8	83.6	154.4	64.9	112.5	144.7
Δδ	-	3.0	1.6	7.2	35.8	- 6.3	83.2	19.4	- 4.0
5a	$CDCl_3$	145.1	146.2	119.7[a]	118.9[a]	148.1	153.6	123.8	140.5
6a	KNH_2/NH_3	143.2	144.6	112.2	83.7	154.1	67.2	114.5	143.2
Δδ		1.9	1.6	7.5	33.2	- 6.0	86.4	9.3	- 2.7

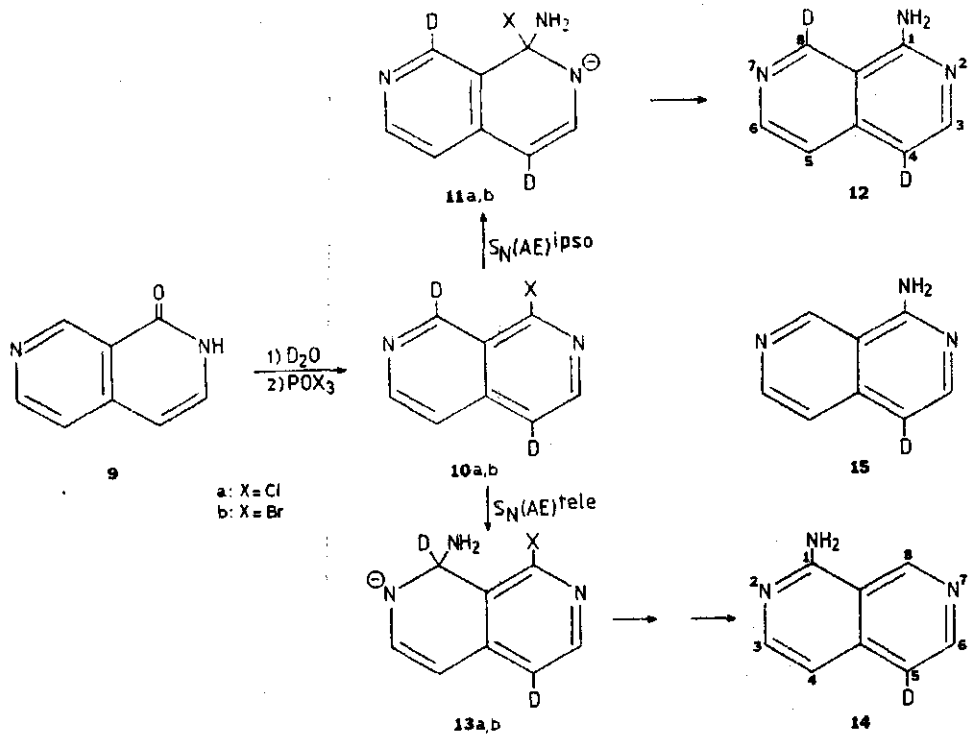
a : these signals may be interchanged

undergone rehybridization due to covalent amination ($sp^2 \rightarrow sp^3$, see Tables 5.1 and 5.2).

5.2 Amination

Amination of 5a and 5b during 63 hours gave, besides some 2,7-naphthyridine (4 and 10% respectively) in low yield 1-amino-2,7-naphthyridine (8) (8 and 24% respectively) and starting material (41 and 34% respectively). Much decomposition occurred.

In order to investigate whether the formation of 8 from 5a,b proceeds via the intermediates 6a,b and 7a,b we tried to prepare 1-halogeno-8-deutero-2,7-naphthyridine by heating of 2,7-naphthyridin-1(2H)-one (9) in D_2O in a sealed tube, and by subsequent treatment of the product obtained with POX_3. The deuteration however turned out to be rather unselective : besides deuteration at position 8 (± 50%) considerable deuteration (± 30%) at position 4 took place leading to the dideuterated products 10a,b (Scheme 5.3).



9 — 10a,b — 11a,b — 12 — 13a,b — 14 — 15

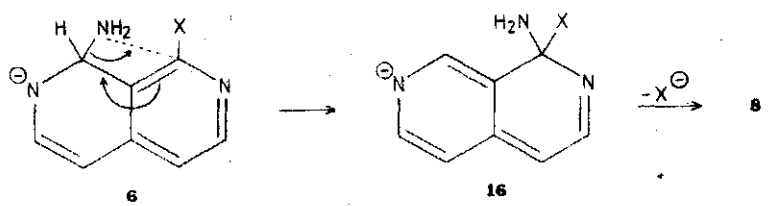
Scheme 5.3

It is evident that if the amination of 10a,b takes place via an $S_N(AE)^{ipso}$ substitution mechanism, i.e. via the intermediacy of 11a,b the amino product 12 should contain the same percentage of deuterium at C-8 as the starting material 10a,b, whereas a telesubstitution $\left[S_N(AE)^{tele}\right]$ via 13a,b, leads to an amino product containing no deuterium on position 8 (14, Scheme 5.3). Moreover, if the amination of 10a,b proceeds via 11a,b, product 12 should have a deuterium on position 4, whereas the pathway via 13a,b should yield product 14, having deuterium on position 5.

It was found that in the product obtained on amination of 10a,b the percentage of deuterium on position 8 had decreased (from 95% to 58% in the case of 10a and from 50% to 17% in the case of 10b). However, not the telesubstitution product 14 was obtained but 1-amino-4-deutero-2,7-naphthyridine (15). No indication for the presence of any deuterium on C-5 - indicated by the signal of H-6 partly appearing as a doublet in the ^1H NMR spectrum - was obtained. Since the percentage of deuterium on position 4 is not decreased and no deuterium is found at position 5, it shows that 15 must be formed in an $S_N(AE)^{ipso}$ substitution process via 11a,b, even though 5 was completely converted into the tele-adduct 6 when dissolved in KNH_2/NH_3. That 15 and not 12 was obtained during this $S_N(AE)^{ipso}$ process must be due to a D/H exchange at C-8.

The non-occurrence of an $S_N(AE)^{tele}$ substitution is surprising in the light of the fact that the conversion of 1b into 4 proceeds for 45% via a telesubstitution mechanism.

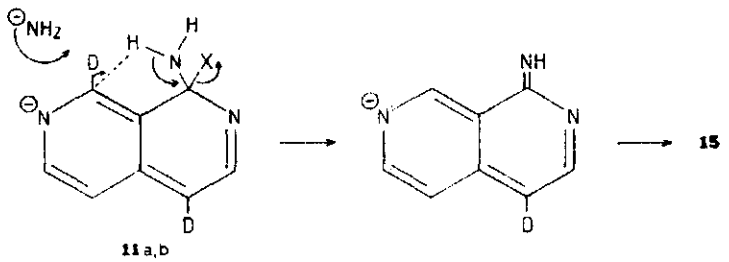
The suggestion can be made that 6 instead of undergoing a proton shift into 7 undergoes a 1,3-amino shift yielding 16 (Scheme 5.4) which looses fast a halide ion to yield 8.



Scheme 5.4

It is peculiar that neither the recovered starting material 10a,b nor 12 on treatment with KNH_2/NH_3 showed any decrease in the percentage of deuterium on C-8. It seems to suggest that the D/H exchange has to occur in an intermediary stage. We propose - cautiously - that the D/H exchange occurs in 11a,b

(Scheme 5.5) through internal assistance of the amino group.



Scheme 5.5

These results show clearly that if amination of a deuterated halogenonaphthyridine yields an undeuterated amino product, it does not always have to mean that the amination takes place via an $S_N(AE)^{tele}$ process, even though neither the starting compound nor the product undergoes D/H exchange in KNH_2/NH_3, since D/H exchange in one of the intermediary stages may occur.
This throws a new light on the occurrence of the $S_N(AE)^{tele}$ pathway in the amination of 1a,b. New investigations are required to find out whether the amination of 1a,b occurs via an odd telesubstitution process or not.

5.3 Experimental Part

Melting points (uncorrected) were determined on a Kofler Plate. ^1H NMR spectra were recorded on a Varian XL-100-15 spectrometer, a Varian EM 390 spectrometer or an Hitachi Perkin-Elmer R-24B spectrometer. ^{13}C spectra were recorded on a Varian XL-100-15 spectrometer equipped with a Varian Fourier transform unit. The spectral width was 5000 Hz (1.25 Hz/point). Mass spectra were recorded on an AEI MS 902 instrument.
Starting materials : The following compounds were prepared as described in the literature: 1-Chloro-2,7-naphthyridine (5a)[5], 2.7-naphthyridin-1(2H)-one (9)[6].

A. 1-bromo-2,7-naphthyridine (5b)

0.60 g (4.1 mmol) of 2,7-naphthyridin-1(2H)-one and 1.20 g (4.2 mmol) of $POBr_3$ were heated for 3 hours at 140°C in a stoppered flask. After cooling, the reaction mixture was treated carefully with ice and sodium bicarbonate. The mixture was extracted with chloroform and the extract dried over $MgSO_4$. The chloroform was evaporated off and the residue obtained was purified by chromatography on a SiO_2 column, using $CHCl_3$ as eluent. Yield: 0.52 g (60%) of 5b;

m.p. 128-129°C (from petroleum ether b.r. 60-80°C). Anal. Calcd. for $C_8H_5N_2Br$: C, 45.96; H, 2.41. Found: C, 45.71; H, 2.51.

B. Deutero-1-halogeno-2,7-naphthyridine (10a,b)

0.6 g (4,1 mmol) of 9 and 3 ml of D_2O were heated in a sealed tube at 145°C for 18 hours. The D_2O was then evaporated and the product obtained was treated with POX_3 as described above.

E. Amination procedure

The aminations of 5a,b and 10a,b were carried out as described previously for 1-halogeno-2,6-naphthyridines (chapter 4).

5.4 Acknowledgement

We are indebted to Drs.C.A.Landheer for carrying out mass spectroscopy, to Mr.H.Jongejan for elemental analyses and to Mr.A.van Veldhuizen for NMR spectroscopic assistance.

5.5 References

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2) Van der Plas, H.C.; Woźniak, M. and Van Veldhuizen A. Recl.Trav.Chim. (Pays-Bas) 1978, 97, 130.
3) In the original paper[2] 27% of $S_N(AE)^{tele}$ substitution was reported for amination of 1-bromo-7-deutero-1,8-naphthyridine. However, when a more accurate method of calculation was used and the isotope effect was taken into account, we calculated that amination of 1-bromo-1,8-naphthyridine proceeded for 45% via the $S_N(AE)^{tele}$ pathway.
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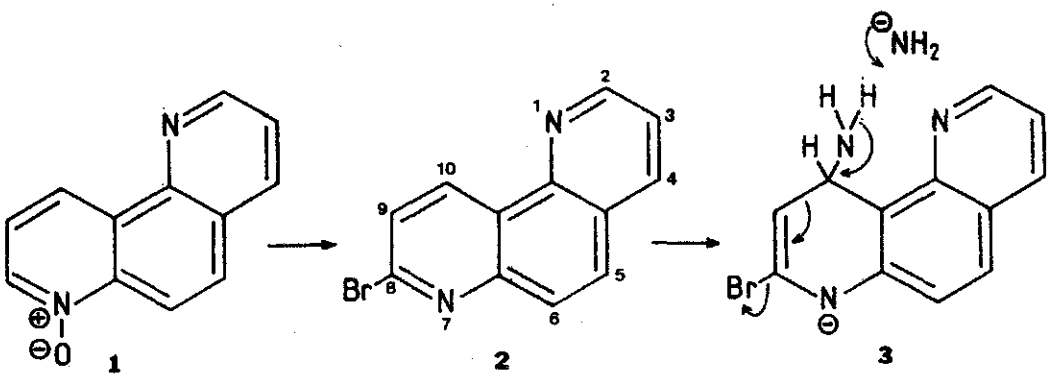
6 The amination of 8-bromo-1,7-phenanthroline.

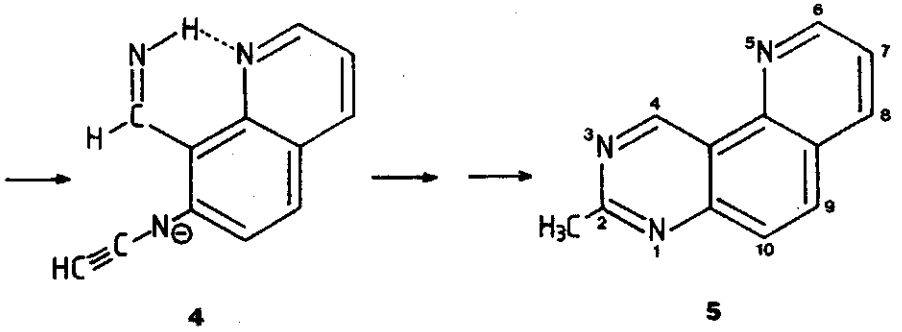
Henk. J.W. van den Haak, Jan P. Bouw and Henk C. van der Plas

6.1 Synthesis and Amination

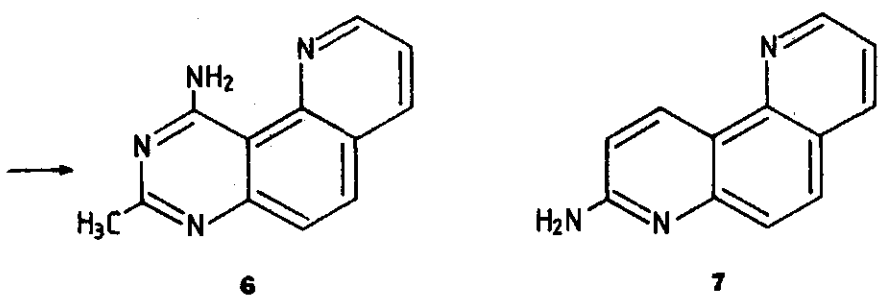
Our ongoing interest in the occurrence of telesubstitutions[1] in heterocyclic arylhalides induced us to study the behaviour of 8-bromo-1,7-phenanthroline (2) towards potassium amide in liquid ammonia. Compound 2 was easily prepared by reaction of 1,7-phenanthroline-7-oxide (1) with acetic anhydride and subsequent treatment of the product obtained with phosphoroxybromide. Reaction of 2 with KNH_2/NH_3 for 4 hours, gave no trace of a teleamination product, i.e. 2- or 10--amino-1,7-phenanthroline but nearly exclusively ring transformation products, i.e. 2-mehtyl-1,3,5-triazaphenanthrene (5) and a trace of its 4-aminoderivative 6, together with some 8-amino-1,7-phenanthroline (7).
The structure of 5 could unequivocally be assigned from its NMR spectrum. Alongside the expected chemical shifts and splitting patterns of H-6, H-7, H-8, H-9 and H-10 (see the experimental part) a singlet at a very low field (δ=10.44 ppm, 1-H, H-4) and a singlet at high field (δ=2.96 ppm, 3-H, CH_3) were detected. They are characteristic for the presence of the 2-methylpyrimido ring in 5. Compound 5 crystallizes with 1 mol of water. The NMR spectrum shows that this molecule of water has not been added to the 3,4-C=N band, forming a covalent hydrate. The NMR spectrum of a solution of 5 in D_2O/D_2SO_4, showed that 5 can easily undergo covalent hydratation, analogous to the covalent hydratation reported for quinazoline. As a consequence of the rehybridization of C-4 ($sp^2 \rightarrow sp^3$) H-4 had undergone an upfield shift of 3.32 ppm (see the experimental part). When dissolving 5 in KNH_2/NH_3 σ adduct formation took place at position 4, as indicated by the large upfield shift ($\Delta\delta$=4.23 ppm, see the experimental part) of H-4. When considering the mechanism of the ring transformation of 2 into 5 it starts by an attack of the amide anion at C-10 of 2, leading to the 10-amino-8-bromo-dihydrophenanthrolinide (3). Ring opening as indicated gives via 4 product 5. In an attempt to obtain experimental evidence for the formation of this C-10 adduct by NMR spectroscopy we measured the ^1H NMR spectrum of a solution of 2 in KNH_2/NH_3. However the spectrum did not exhibit signals of 3,



1 2 3



4 5



6 7

but signals which could only be assigned to the presence of the anion of 7--ethynylaminoquinoline-8-aldimine (4). Alongside the proton signals which are characteristic for a 7,8-disubstituted quinoline (see table), we found the CH in the aldimino side chain as a doublet at 9.56 ppm and the NH as a doublet at 11.54 ppm (J=22.8 Hz). That the doublet is found at a very low field, compared with the NH in other imines[2] is certainly due to the influence of the lone pair of the nitrogen atom in the quinoline ring (see 4)[3].

Table. ^{1}H NMR spectrum of 7-ethynylaminoquinoline-8-aldimine (4) in KNH_2/NH_3

H-2	H-3	H-4	H-5	H-6	H-10	NH
8.24	6.68	7.57	7.83	7.07	9.56	11.54

$J_{2,3}$=4.6 Hz; $J_{2,4}$=1.6 Hz; $J_{3,4}$=8.0 Hz; $J_{5,6}$=10.0 Hz; $J_{NH,H-10}$=22.8 Hz

No signal of the ethynyl proton is detected in the ^{1}H NMR spectrum, since in the KNH_2/NH_3 system this proton is abstracted. The presence of the ethynyl group is indicated by signals at 110.4 ppm and 118.3 ppm in the ^{13}C spectrum of 4. These values are in good agreement with those reported[4] for the ethynyl part of the ring opening product of pyrimidines with potassium amide.
The quinoline-8-aldimine (4) was found to be stable in liquid ammonia. During work-up cyclization into 5 takes place.
Although the conversion of a pyridine ring into a pyrimidine ring is not unprecedented[5,6], the formation of the ethynylamino compound 4, provides the first experimental evidence for the structure of the open chain intermediate formed when the pyridine ring is opened by potassium amide. Previously the structure of the open chain intermediates formed during the ring transformations of pyrimidines into s-triazines was also established[4] by ^{13}C NMR spectroscopy.

6.2 Experimental Section

Melting points (uncorrected) were determined on a Kofler plate. NMR spectra were recorded on a Varian X1-100-15, a Hitachi Perkin Elmer R24 B or a Bruker CXP-300 spectrometer.

A. 8-bromo-1,7-phenanthroline (2)

2.1 g. (10.7 mmol) of 1,7-phenanthroline-7-oxide (1)[7,8] and 15 ml. of acetic anhydride were refluxed during 2 hours. The mixture was then poured onto 150 g of ice and stirred for 3 hours. Solid Na_2CO_3 was added to neutralize the mixture. The precipitate was filtered off and dried in vacuo over P_2O_5. A mixture of this material and 7.9 g. (27.5 mmol) of $POBr_3$ was heated at 140°C in a stoppered flask for 4 hours. The reaction mixture was then poured onto ice and neutralized with concentrated ammonia, the solution was continuously extracted with $CHCl_3$. Evaporation of the solvent and purification of the residue by column chromatography on SiO_2 with $CHCl_3$ as eluent gave 640 mg of 2 (23%) m.p. 146-147°C.
^1H NMR ($CDCl_3$): δ=9.14 ppm (H-10, d, J=8.5 Hz); δ=8.86 ppm (H-2, dd, J=5.5 Hz and 2 Hz); δ=8.17 ppm (H-4, dd, J=8 Hz and 2 Hz); δ=7.81 ppm (H-5 and H-6, s); δ=7.63 ppm (H-9, d, J=8.5 Hz); δ=7.53 ppm (H-3, dd, J=5.5 Hz and 8 Hz).

B. Amination of 8-bromo-1,7-phenanthroline (1)

The amination of 1 with 4 equivalents of potassium amide was carried out as described before[9]. The reaction time was 4 hours. The reaction mixture was separated by column chromatography on SiO_2 with $CHCl_3$/EtOH as eluent, yielding the following compounds:

2-Methyl-1,3,5-triazaphenanthrene (5, 23%) m.p. 129-130°C.
Anal. Calcd. for $C_{12}H_9N_3.H_2O$: C, 67.59; H, 5.20. Found: C, 67.38; H, 5.37.
^1H NMR ($CDCl_3$): δ=10.44 ppm (H-4, s); δ=9.98 ppm (H-6, dd, J=4 Hz and 2 Hz); δ=8.17 ppm (H-8, dd, J=8 Hz and 2 Hz); δ=8.04 ppm (H-9 or H-10, d, J=9 Hz); δ=7.81 ppm (H-10 or H-9, d, J=9 Hz); δ=7.52 ppm (H-7, dd, J=8 Hz and 4 Hz); δ=2.96 ppm (CH_3, s).
D_2O/D_2SO_4: δ=9.20 ppm (H-8, dd, J=1.5 Hz and 8.5 Hz); δ=9.15 ppm (H-6, dd, J=1.5 Hz and 5.5 Hz); δ=8.45 ppm (H-10, d, J=9 Hz); δ=8.16 ppm (H-7, dd, J=5.5 and 8.5 Hz); δ=7.79 ppm (H-9, d, J=9Hz); δ=7.12 ppm (H-4, s); δ=2.68 ppm (CH_3, s).

KNH_2/NH_3: δ=8.55 ppm (H-6, dd, J=2 Hz and 4.5 Hz); δ=7.92 ppm (H-8, dd, J=2 Hz and 7.5 Hz); δ=7.41 ppm (H-10, d, J=9 Hz); δ=7.01 ppm (H-9, d, J= 9Hz); δ=6.98 ppm (H-7, dd, J=4.5 Hz and 7.5 Hz); δ=6.21 ppm (H-4, t, J=6.5 Hz).

8-Amino-1,7-phenanthroline (7, trace) m.p. 206-208°C.
^{1}H NMR: δ=9.18 ppm (H-10, d, J=9 Hz); δ=8.97 ppm (H-2, dd, J=2 Hz and 4.5 Hz); δ=8.06 ppm (H-4, dd, J=2 Hz and 9 Hz); δ=7.73 ppm (H-5 and H-6, s); δ=7.36 ppm (H-3, dd, J=9 Hz and 4.5 Hz); δ=6.83 ppm (H-9, d, J=9 Hz); δ=5.40 ppm (NH_2, b).

4-Amino-3-methyl-1,3,5-triazanaphthalene (6, trace) m.p. 218-220°C.
^{1}H-NMR: δ=8.82 ppm (H-6, dd, J=2 Hz and 5 Hz); δ=8.14 ppm (H-8, dd, J=2 Hz and 7 Hz); δ=7.90 ppm (H-9 or H-10, d, J=8 Hz); δ=7.65 ppm (H-10 or H-9, d, J=8 Hz); δ=7.41 ppm (H-7, dd, J=5 Hz and 8 Hz); δ=3.20 ppm (NH_2, b); δ=2.64 ppm (CH_3, s).

6.3 Acknowledgement

We are indebted to Mr. A. van Veldhuizen for measuring some NMR spectra, and to Mr. H. Jongejan for carrying out the microanalysis.

6.4 References and Notes

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2) Dephenylketimine for instance absorbs at 9.4 ppm.
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7 The amination of 3-bromo-2-ethoxy-1,5-naphthyridine. A reinvestigation.

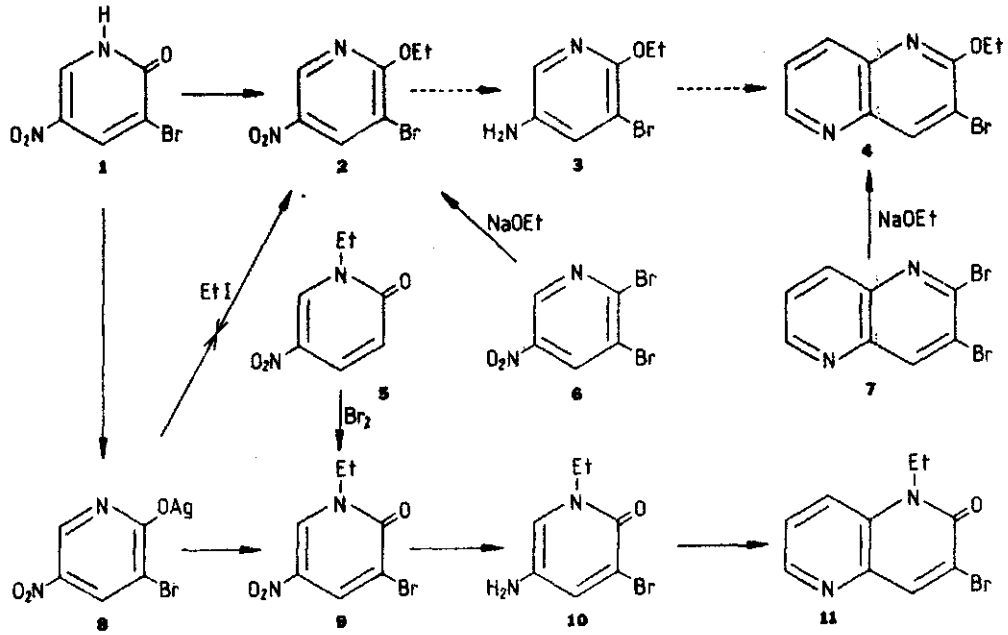
H. J. W. van den Haak and H. C. van der Plas[ψ]

7.1 Introduction

The reactions of 1,X-naphthyridines and their halogeno derivatives with potassium amide in liquid ammonia have been studied in this laboratory and in others. Many interesting and unexpected reaction-patterns have been found, such as Chichibabin reactions[1], telesubstitutions[2-4], cine substitutions[4-6], ring-opening[4] and ring-transformation reactions[2]. Very often these reactions were initiated by the formation of anionic 1:1 σ adducts between the naphthyridines and the amide anion[2,3,6-8]. If a halogen atom was present in the 3-position of the 1,X-naphthyridines, the reaction always proceeded via the 3,4-didehydro compounds. Addition of ammonia to these didehydro compounds yielded mixtures of 3- and 4-amino 1,X-naphthyridines[4-6,9].
It has been reported however that 3-bromo-2-ethoxy-1,5-naphthyridine (4), on treatment with potassium amide in liquid ammonia, yielded exclusively 3-amino-2-ethoxy-1,5-naphthyridine[9]. This is a remarkable result, especially in the light of the fact that 3-bromo-2-ethoxypyridine[10] and 3-bromo-2-ethoxyquinoline[11] gave the respective 4-amino-2-ethoxy compounds as the main products. In order to find out whether the formation of an 1:1 σ adduct between the 3-bromo-2-ethoxy-1,5-naphthyridine and the amide anion might possibly cause this anomalous behaviour[12], we reinvestigated the reaction of this compound with potassium amide in liquid ammonia.

On the preparation of 3-bromo-2-ethoxy-1,5-naphtyridine (4)

3-Bromo-2-ethoxy-1,5-naphtyridine (4) was supposed to be obtained[9] in a series of reactions, using 3-bromo-5-nitro-2(1H)-pyridinone (1) as starting substance, and involving the formation of the silver salt (8), ethylation of 8 with ethyl iodide to 3-bromo-2-ethoxy-5-nitropyridine (2), reduction of 2 to the corresponding 5-amino-3-bromo-2-ethoxypyridine (3) and a Skraup reaction converting 3 into 4 (Scheme 7.1).



Scheme 7.1

Preparation of 2 by treatment of 1 with triethyloxoniumfluoroborate (TOF)[13] gave a compound (m.p. 62-64°C) with molecular formula $C_7H_7N_2O_3Br$, indicating that an ethyl group had been introduced. The melting point was very different from that reported by Czuba[9] for the compound obtained by reacting the silver-salt 8 with ethyl iodide. Furthermore it was found that the product obtained from 1 and TOF is fully identical with the product obtained from 2,3-dibromo-5--nitropyridine (6) with sodium ethoxide. These results led us to the conclusion that in the ethylation of 1 with TOF, compound 2 is obtained, and that in the reaction of 8 with ethyl iodide not 2 but the isomeric 3-bromo-1-ethyl-5-nitro--2(1H)-pyridinone (9) is formed.

This structure assignment has been confirmed by showing that 9 is identical with the product obtained on bromination of 1-ethyl-5-nitro-2(1H)-pyridinone (5).

An important consequence is that the compounds mentioned in the literature[9] as being derived from 2 have incorrect structures, and are in fact derivatives of 9: 5-amino-3-bromo-2-ethoxypyridine (3) has the structure of 5-amino-3-bromo-1-ethyl-2(1H)-pyridinone (10) and 3-bromo-2-ethoxy-1,5-naphthyridine (4) that of 3-bromo-1-ethyl-1,5-naphthyridin-2(1H)-one (11).

These assignment were strongly supported by the presence of strong carbonyl

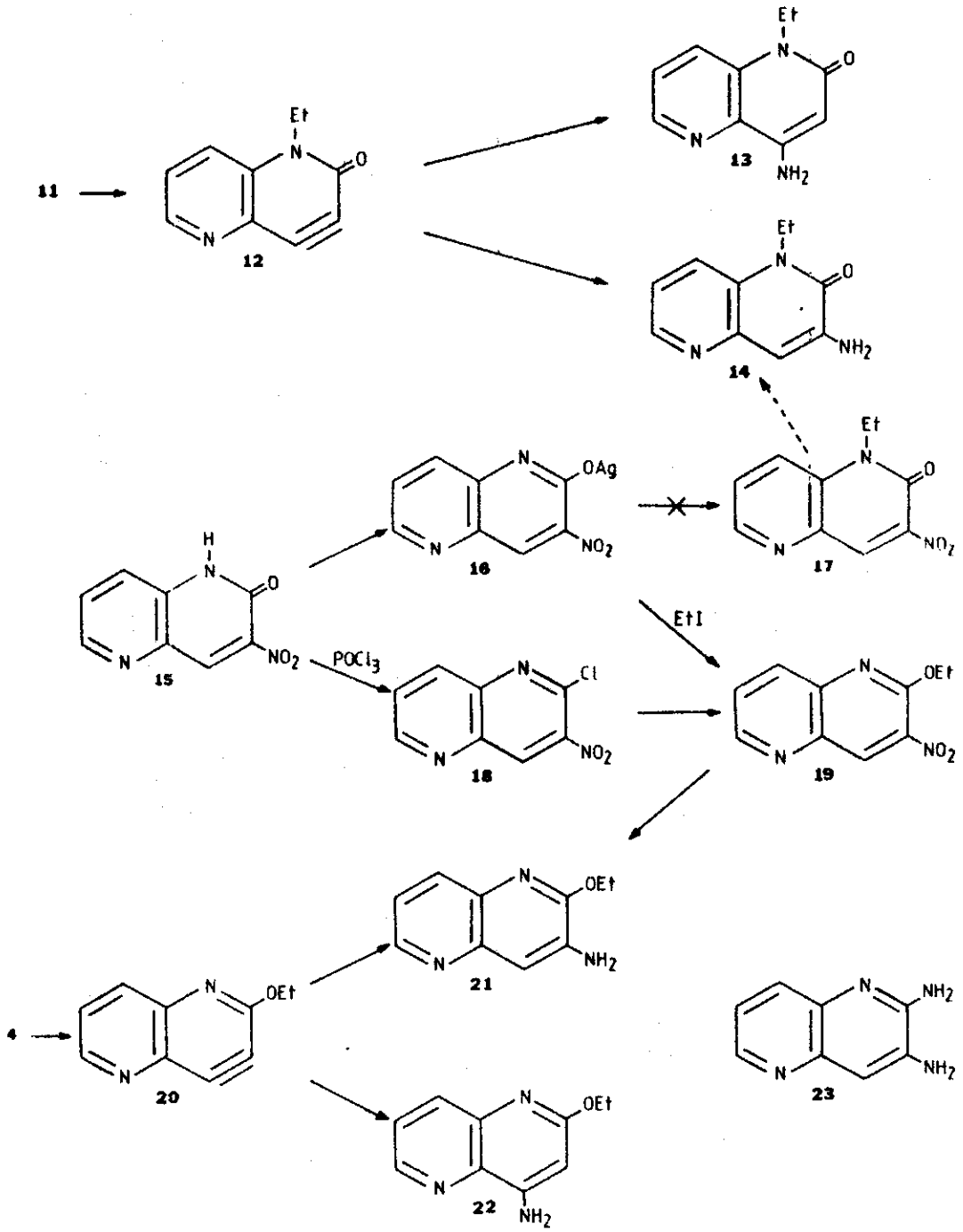
absorptions in the region 1650-1660 cm^{-1} in the IR spectra of all these compounds.

The isomeric 3-bromo-2-ethoxy-1,5-naphthyridine (4) was synthesized from 2,3-dibromo-1,5-naphthyridine (7) and sodium ethoxide. Its IR spectrum showed no carbonyl absorption, but absorptions at 1040 and 1260 cm^{-1} due to the presence of the ether function. That the ethoxy group was introduced into position 2 was proved by reduction of 4 to 2-ethoxy-1,5-naphthyridine, which was identical to the reaction product of 2-bromo-1,5-naphthyridine and sodium ethoxide.

7.2 Amination

A. 3-Bromo-1-ethyl-1,5-naphthyridin-2(1H)-one (11).

The reaction of 11 with potassium amide in liquid ammonia gave besides 3-amino-1-ethyl-1,5-naphthyridin-2(1H)-one (14, 13%) the 4-isomer 13 (58%). The structures of 13 and 14 follow from their ^{1}H- and ^{13}C-NMR spectra (see Tables 7.2 and 7.3 in the experimental part). Especially the broadening of the peak present at 7.06 ppm in the ^{1}H-NMR spectrum of 14 (Table 7.2) indicates the presence of a hydrogen at position 4 (J 4,8)[14]. The ^{1}H-NMR spectrum of 13 shows a singlet at 6.14 ppm. A peak at such a high field can be due only to the presence of a proton in position 3. An attempt to prove the structure of 14 by an independent synthesis involving i treatment of the silversalt of 3-nitro-1,5-naphthyridin-2(1H)-one (16) with ethyl iodide and ii subsequent reduction of the product obtained, failed. In the IR spectrum of the compound obtained on treatment of 16 with ethyl iodide no carbonyl absorption was present, but absorptions at 1070 and 1260 cm^{-1} due to the presence of an ether function.
It is evident that by treatment of the silversalt 16 with ethyl iodide we have not obtained 17, but 2-ethoxy-3-nitro-1,5-naphthyridine (19). This was unequivocally proved by showing its identity with the product obtained by i conversion of 15 with phophorylchloride to 2-chloro-3-nitro-1,5-naphthyridine (18) and ii subsequent treatment of 18 with sodium ethoxide.
From these series of reactions it can be concluded that treatment of the silversalt 16 gives O-ethylation yielding the 2-ethoxy compound 19, a surprising result, especially in the light of the previously mentioned result that treatment of the silversalt 8 with ethyl iodide gives N-ethylation.
We propose that in the amination of 11 the 3,4-didehydro-1-ethylnaphthyridin-2(1H)-one (12) is an intermediate. Since it has been proved that the attack of a nucleophile on a didehydroarene is governed by the inductive effect of the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17
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23
4
Et
N
O
NH2
OAg
NO2
H
POCl3
Cl
EtI
OEt

Scheme 7.3

substituent adjacent to the C-C bond[15], it is evident that the electron-attracting inductive effect (-I effect) of the carbonyl group favours position 4 for nucleophilic attack.

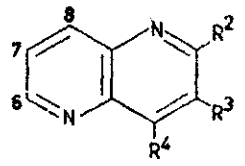
B. 3-Bromo-2-ethoxy-1,5-naphthyridine (4)

Reaction of 4 with potassium amide in liquid ammonia gives in good yield (∿ 80%) a mixture of 3-amino-2-ethoxy-1,5-naphthyridine (21) and 4-amino-2-ethoxy-1,5-naphthyridine (22) (ratio 1:4,5); furthermore a trace of 2,3-diamino-1,5-naphthyridine (23) is formed. The last mentioned compound cannot be obtained from traces of 2,3-dibromo-1,5-naphthyridine (7) possibly present as contamination in the starting material (4) since it has been reported[11] that amination of 7 yields 2,4-diamino-1,5-naphthyridine as the main product.
The structure of 21 was proved by its identity with the reduction product of 19. In the ^{1}H-NMR spectrum the J 4,8 coupling is clearly visible by the doublet signal of H-4. The structure of 22 follows from its ^{1}H- and ^{13}C-NMR data (see Tables 7.1 and 7.3 in the experimental part). Again the presence of a singlet in the ^{1}H-NMR spectrum at high field (6.11 ppm) indicates that position 3 is unsubstituted. The formation of both 3- and 4-amino-2-ethoxy-1,5-naphthyridine points to the intermediacy of the 3,4-didehydro-2-ethoxy-1,5-naphthyridine 20. Due to the - I effect of the ethoxy group the addition preferably takes place at position 4[10,11,16,17]. The ratio observed with 2-ethoxy-3,4-didehydroquinoline for addition to position 3 and position 4 is about 1:75[11]. The relatively less favoured addition to position 4 in 20 when compared with the addition of the amide ion to 2-ethoxy-3,4-didehydroquinoline, can be explained by the presence of the nitrogen lone pair at position 5 in 2-ethoxy-1,5-naphthyridine hindering attack of the nucleophilic amide ion at position 4 due to Coulomb repulsion.

7.3 NMR spectroscopy

Attempts to detect σ adducts between the amide ion and both substrates 11 and 4 proved to be unsuccesful. When dissolving 11 and 4 in liquid ammonia containing potassium amide, spectra were obtained which were nearly identical which those of the 4-amino compounds 13 and 22 in KNH_2/NH_3. This is in contrast to 3-chloro-1,7-naphthyridine[6] and 3-chloro-1,8-naphthyridine[4], which showed the formation of anionic σ adducts prior to didehydro formation.

Table 7.1 Proton chemical shifts[a] and coupling constants[b] of some 1,5-naphthyridines in $CDCl_3$.[c]



	R_2	R_3	R_4	H_3	H_4	H_6	H_7	H_8
4	OEt	Br	H	-	8.43 (d)	8.69 (dd)	7.45 (dd)	8.05 (m)
18	Cl	NO_2	H	-	8.76 (d)	9.03 (dd)	7.73 (dd)	8.33 (m)
19	OEt	NO_2	H	-	8.65 (d)	8.82 (dd)	7.58 (dd)	8.10 (m)
21	OEt	NH_2	H	-	7.33 (d)	8.61 (dd)	7.25 (dd)	8.00 (m)
22	OEt	H	NH_2	6.11 (s)	-	8.45 (dd)	7.36 (dd)	7.92 (dd)
	OEt	H	H	7.05 (d)	8.14(dd)	8.70 (dd)	7.43 (dd)	8.04 (m)

	NH_2	CH_2	CH_3	J3,4	J6,7	J7,8	J6,8	J4,8
4	-	4.57 (q)	1.49 (t)	-	4.3	8.4	1.5	0.8
18	-	-	-	-	4.0	8.6	1.4	0.7
19	-	4.65 (q)	1.50 (t)	-	4.1	8.3	1.7	0.8
21	4.50 (b)	4.57 (q)	1.46 (t)	-	4.3	8.3	1.7	d
22	5.35 (b)	4.42 (q)	1.34 (t)	-	4.0	8.3	1.8	-
	-	4.51 (q)	1.43 (t)	8.9	4.1	8.8	1.7	0.7

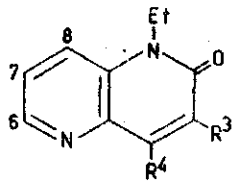
[a] Shifts in ppm downfield from TMS

[b] Coupling constants in Hz

[c] All spectra were supposed to be first order

[d] These couplings could only be detected as a broadening of the concerned peaks

Table 7.2 Proton chemical shifts[a] and coupling constants[b] of the 1-ethyl-1,5--naphthyridin-2(1H)-ones 11, 13 and 14 in $CDCl_3$.[c]



	R_3	R_4	H_3	H_4	H_6	H_7	H_8
11	Br	H	-	8.33 (d)	8.54 (dd)	7.49 (dd)	7.75 (dd)
13	H	NH_2	6.14 (s)	-	8.31 (dd)	7.34 (dd)	7.59 (dd)
14	NH_2	H		7.06 (d)	8.46 (dd(	7.16 (dd)	7.68 (m)

	NH_2	CH_2	CH_3	J6,7	J7,8	J6,8	J4,8
11	-	4.39 (q)	1.37 (t)	4.2	8.5	1.5	d
13	5.80 (b)	4.22 (q)	1.28 (t)	3.8	8.9	1.7	-
14	6.05 (b)	4.59 (q)	1.39 (t)	4.4	8.2	1.6	d

[a] Shifts in ppm downfield from TMS

[b] Coupling constants in Hz

[c] All spectra were supposed to be first order

[d] These couplings could only be detected as a broadening of the concerned peaks

Table 7.3 ^{13}C chemical shifts of the compounds 13 and 22 in $CDCl_3/CD_3OD$

	C_2	C_3	C_4	$C_4{}^a$	C_6	C_7	C_8	$C_8{}^a$	CH_2	CH_3
13	163.7	95.7	152.1	133.4[a]	142.7	122.2	125.5	135.9[a]	36.5	13.1
22	164.1	93.0	152.2	134.6[a]	144.9	124.7	135.0	142.4[a]	61.7	14.7

[a] These signals may be interchanged

7.4 Experimental section

Melting points (uncorrected) were determined on Kofler Plate. The ^{1}H-NMR spectra were recorded in $CDCl_3$ solutions on a Hitachi Perkin Elmer R-24B apparatus; TMS (δ = 0.0) was used as internal standard. The ^{13}C-NMR spectra were recorded on a Varian XL 100-15 spectrometer, operating at 25.2 MHz and were measured from internal TMS.
All NMR data are collected in tables 7.1, 7.2 and 7.3.
Infrared spectra were recorded on a Perkin Elmer 237 spectrophotometer in KBr.

A. The following compounds were prepared as described in the literature:

3-Bromo-5-nitro-2(1H)-pyridinone[18] (1); 1-ethyl-5-nitro-2(1H)-pyridinone[19] (5); 2,3-dibromo-5-nitropyridine[18] (6); 2,3-dibromo-1,5-naphthyridine[11] (7); 3-nitro-1,5-naphthyridin-2(1H)-one[20] (15); 2-chloro-3-nitro-1,5-naphthyridine[21] (18); 2-bromo-1,5-naphthyridine[22].

B. 3-Bromo-1-ethyl-1,5-naphthyridin-2(1H)-one (11)

We prepared 11 from 1 according to the same procedures as described by Czuba[9]. The melting points of the compounds obtained as intermediates were nearly the same as described. Compound 1 was treated with silvernitrate and ethyl iodide, yielding 81% of 3-bromo-1-ethyl-5-nitro-2(1H)-pyridinone (9) IR: 1660 cm^{-1} (C=O). This compound was reduced with $SnCl_2$ yielding 90% of 5-amino-3-bromo-1-ethyl-2(1H)-pyridinone (10). Skraup reaction of 10 gave 11 in a 65% yield, m.p. 134.5-135^{o}C, IR: 1650 cm^{-1} (C=O).

C. 3-Bromo-2-ethoxy-1,5-naphthyridine (4)

This compound was prepared by reacting a solution of 1.73 g of 7 in 200 ml of absolute ethanol with a solution prepared by adding 2.56 g of sodium to 300 ml of absolute ethanol. This solution was refluxed for 2½ h, acidified with diluted hydrochloric acid and evaporated. 100 ml of water were added and the mixture basified with ammonia solution. The water layer was extracted with ether. After drying over $MgSO_4$ and evaporation of the solvent, the product was further purified by column chromatography on a silica column. Elution with chloroform and recrystallization of the product in petroleum ether (b.r. 60-80^{o}C) yielded 1,2 g of 4 m.p. 96.5-97.5^{o}C. Anal.: calc. for $C_{10}H_9N_2OBr$: C, 47.45; H, 3.58. Found C, 47.17; H, 3.67.

D. Amination of 3-bromo-1-ethyl-1,5-naphthyridin-2(1H)-one (11)

Amination of 0.3 g of 11 was carried out as described previously[9]. The reaction time in our experiments was 1½ h.
After evaporation of the ammonia, water was added and the mixture was continuously extracted with ether. The gummy solid which was left after evaporation of the ether was separated on a silica column. Elution with chloroform gave:

4-Amino-1-ethyl-1,5-naphtyridin-2(1H)-one (13) 0.13 g (58%) m.p. 196-198°C. Anal: calc. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; Found: C, 63.35; H, 5.61. IR: 1640 cm^{-1} (C=O).

3-Amino-1-ethyl-1,5-naphthyridin-2(1H)-one (14) 0.03 g (13%) m.p. 205-207°C. Anal: calc. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86. Found C, 63.10; H, 6.22. IR: 1680 cm^{-1} (C=O).

E. Amination of 3-bromo-2-ethoxy-1,5-naphthyridine (4)

Amination of 0.83 g of 4 was carried out as described in Section D. Column chromatography on silica with chloroform as eluent yielded the following compounds:

4-Amino-2-ethoxy-1,5-naphthyridine (22) 0.46 g (74%) m.p. 137-138°C. Anal: calc. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86. Found: C, 63.34; H, 5.56. IR: 1030 and 1200 cm^{-1} (ether group).

3-Amino-2-ethoxy-1,5-naphthyridine (21) 0.04 g (6.5%) m.p. 114-117°C. Anal: calc. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; Found C, 63.15; H, 5.81. IR: 1040 and 1260 cm^{-1} (ether function). It gave no depression of melting points when mixed with an authentic specimen (see J).

2,3-Diamino-1,5-naphthyridine (23) trace. m.p. 260-265°C (dec) (lit.[11]: 260-265°C).

F. 3-Bromo-2-ethoxy-5-nitropyridine (2)

1) From *3-bromo-5-nitro-2(1H)-pyridinone (1)* 0.5 g of 1 was heated with 1 g of TOF at 90°C during 75 min. After cooling 50 ml of a 10% Na_2CO_3 solution was added. The mixture was extracted with chloroform. After drying ($MgSO_4$) and evaporation of the solvent 0.3 g of 2 was obtained, m.p. 62-64°C. IR: 1045 and 1225 cm^{-1} (ether group).

2) From *2,3-dibromo-5-nitropyridine (6)*. A solution of sodium ethoxide (prepared from 0.07 g of sodium and 5 ml of absolute ethanol) was added to a solution of 0.2 g of 6 in 5 ml of absolute ethanol. After standing at room temperature for 30 min the reaction mixture was worked up as described above for the preparation of 3-bromo-2-ethoxy-1,5-naphthyridine (4) (see C). Yield 0.15 g, m.p. 64.5-65.5°C (ethanol/water). Anal: calc. for $C_7H_7N_2O_3Br$: C, 34.03; H, 2.86; Found: C, 34.30; H, 2.89.

G. Bromination of 1-ethyl-5-nitropyridone-2 (5)

To a solution of 0.28 g of 5 in 5 ml of acetic acid an excess of bromine was added. After stirring for 2 h at 90°C the mixture was poured into an aqueous Na_2SO_3 solution and neutralized with solid Na_2CO_3. The mixture was extracted with ether and the ethereal extracts were dried with $MgSO_4$ and then evaporated. 0.29 g of 9 was yielded m.p. 124-126°C (lit.[9] 122-123°C).

H. 2-Ethoxy-3-nitro-1,5-naphthyridine (19)

0.74 g of 18 was stirred overnight in 50 ml of absolute ethanol containing 250 mg of KOH. The reaction mixture was then acidified with 10% hydrochloric acid. The ethanol was evaporated and to the residue 100 ml of water were added. The mixture was basified with concentrated ammonia solution and the resulting solution was extracted with chloroform. After drying ($MgSO_4$) and evaporation of the solvent 0.7 g of 19 was obtained, m.p. 134.5-136°C (lit.[9] 135.5-136°C). IR: 1070 and 1260 cm^{-1} (ether group).

I. 3-Amino-2-ethoxy-1,5-naphthyridine (21)

A solution of 0.2 g of 19 in 20 ml of ethanol containing 0.5 g of KOH, was shaken in a hydrogen atmosphere at 250 kPa, with 0.12 g of Pd on carbon (3%). The mixture was filtered, acidified with 10% hydrochloric acid and the solvent was evaporated. 50 ml of water were added and the resulting solution was basified with concentrated ammonia solution. The solution was extracted with chloroform. The chloroform layer was dried ($MgSO_4$) and evaporated, yielding 80 mg of 21. The product was further purified by recrystallization from petroleum ether (b.r. 60-80°C), m.p. 115-117°C.

J. 2-Ethoxy-1,5-naphthyridine

1) From *3-bromo-2-ethoxy-1,5-naphthyridine (4)*. 4 Was reduced in a hydrogen atmosphere as described in I; yield 63% m.p. 44.5-45.5°C. Monopicrate, m.p. 169-173°C (from ethanol). Anal.: calc. for $C_{16}H_{13}N_5O_8$: C, 47.65; H, 3.25; Found: C, 47.92, H, 3.14.

2) From 2-bromo-1,5-naphthyridine

2-Ethoxy-1,5-naphthyridine was prepared from 2-bromo-1,5-naphthyridine according to the procedures described in C. Yield: 95% m.p. 44-45.5°C.

7.5 Acknowledgement

We are indebted to Mr H. Jongejan for carrying out microanalyses and to Mr. A. van Veldhuizen for measuring the ^1H- and ^{13}C-NMR spectra.

7.6 References

Ψ Part XL on Hetarynes. See for part XXXIX, H. C. van der Plas, M. Wozniak and A. van Veldhuizen, Recl. Trav. Chim. Pays-Bas 97, 130 (1978).

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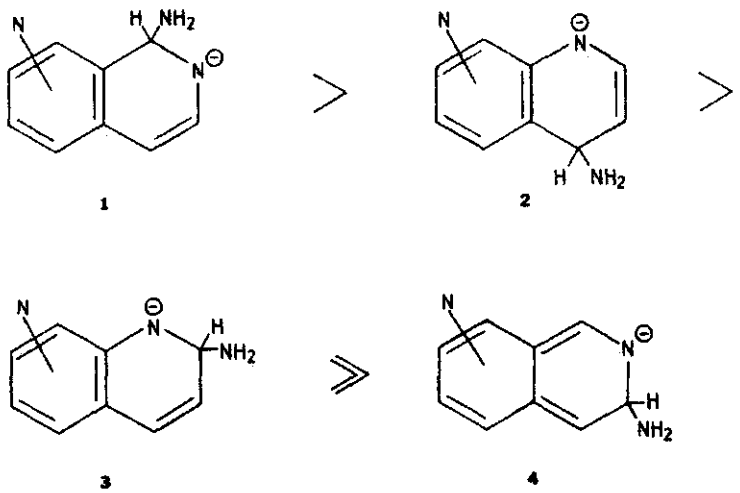
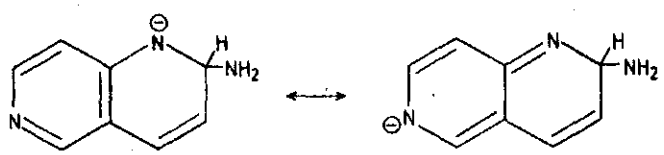
8 General discussion.

In this thesis the results of a study on the behaviour of naphthyridines towards potassium amide in liquid ammonia are described. It was found that in these reactions σ adduct formation of naphthyridines plays an important role. Therefore we started our work with an extensive study on this phenomenon.
It was found that the σ adduct formation is governed by either kinetical factors or by thermodynamically favoured conditions.
The kinetically favoured σ adduct formation takes place on the position with the lowest electron density. In some cases however this does not lead to the most stable σ adduct and rearrangement into a thermodynamically more favoured adduct occurs.
The factors which determine the thermodynamic stabilities of the σ adducts formed between naphthyridines and potassium amide are well understood now.
From our observations it can be concluded that the 1-amino-1,X-dihydroisoquinolinide-like structure element 1 in a σ adduct is more stable than the 4-amino-4,X-dihydroquinolinide-like structure element 2 (Scheme 8.1).



Scheme 8.1

The latter is more favourable than the 2-amino-2,X-dihydroquinolinide-like structure element 3.
The formation of the 3-amino-3,X-dihydroisoquinolinide-like structure element 4 would affect the aromatic character of the second ring and is therefore the most unfavourable of all four.
So far no σ adducts containing this structure element are known. This stability order is essentially the one given by Shepherd and Fredrick[1].
However, if charge delocalization can occur to the second nitrogen atom considerable enhancement of the stability of a σ adduct is observed; especially the para-paraquinoid resonance structure contributes more to stability than the ortho-paraquinoid resonance structure. These contributions can even surpass those of the structure elements 1-4. So σ adduct 5 is more stable than its isomers 6 and 7, even though it contains the less stable structure element 3, since it can delocalize its negative charge in a para-paraquinoid resonance structure, whereas charge delocalizations in 6 and 7 require ortho-para- and ortho-orthoquinoid resonance structures respectively (Scheme 8.2).



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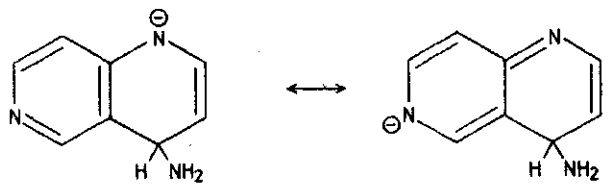

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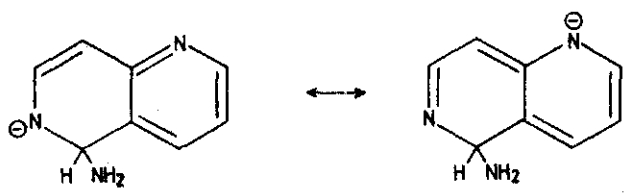
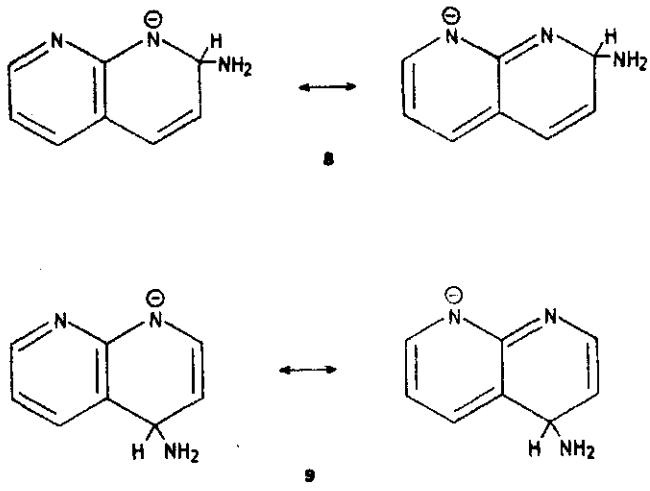


7

Scheme 8.2

The same argument can be used to explain why 1,8-naphthyridine yields the σ adduct 8 and not 9, although the latter contains structure element 2, being more stable than structure element 3, present in 8. However, 9 requires a relatively unfavourable ortho-orthoquinoid resonance structure for charge delocalization to the second nitrogen atom (Scheme 8.3).



Scheme 8.3

With these rules, the sites of amination of the naphthyridines at room temperature - under these conditions the formation of the σ adduct is thermodynamically controlled - are easily understood now.

1,5-Naphthyridine - no charge delocalization to the second nitrogen atom being possible - is aminated[2,3] at position 4 and not at position 2, due to the higher stability of structure element 2 with respect to 3. Based on this consideration it is evident that the σ adduct formed at -33°C between 1,5-naphthyridine and the amide anion at position 2 - a kinetically controlled reaction - is found to rearrange to an adduct at position 4 at higher temperatures.

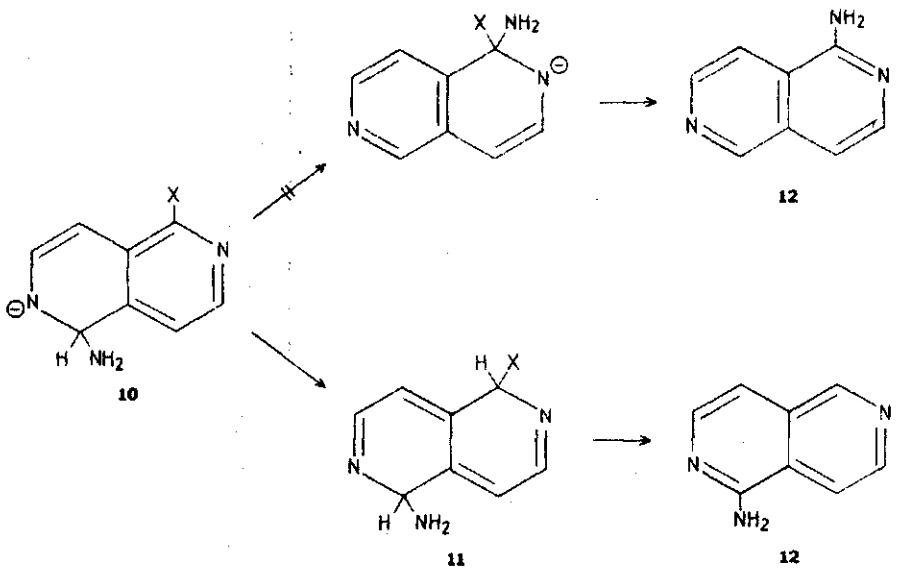
Amination of 1,6-naphthyridine[3] with potassium amide takes place on position 2 and is in agreement with all the rules mentioned above.

Amination of 1,7-naphthyridine at room temperature yields[3] 8-amino-1,7-naphthyridine instead of 4-amino-1,7-naphthyridine due to the higher stability of structure element 1. Amination of 1,7-naphthyridine at -33°C yields[4] a mixture of 2- and 8-amino-1,7-naphthyridine, in agreement with the calculated charge distribution in the starting compound.

All considerations given above do explain why amination of 1,8-naphthyridine yields[3] exclusively 2-amino-1,8-naphthyridine. Amination of 2,6-naphthyridine only affords 1-amino-2,6-naphthyridine, and amination of 2,7-naphthyridine gives[5] 1-amino-2,7-naphthyridine.

Concerning the amination of halogenonaphthyridines we observed that the formation of σ adducts is of particular importance for the further course of the reaction. Depending on the position, to which σ adduct formation takes place and on the position and the nature of the leaving group $S_N(AE)^{ipso}$, $S_N(AE)^{tele}$ (even or odd) substitutions or ring transformations can occur.

Particular examples showing this behaviour are the amination of 1-halogeno-2,6-naphthyridine and 2-bromo-1,5-naphthyridine. It was found that 1-halogeno-2,6-naphthyridine undergoes σ adduct formation at position 5, yielding 10 (Scheme 8.4).

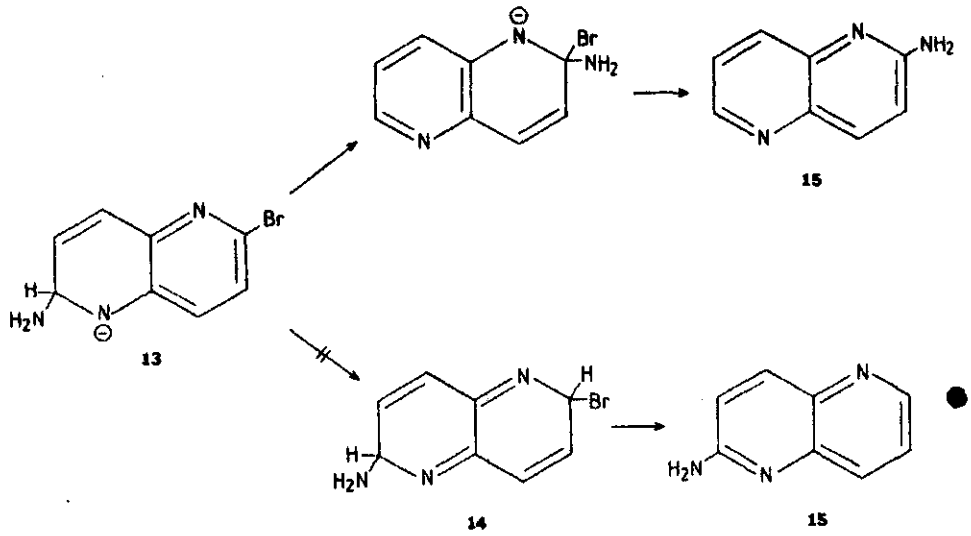


Scheme 8.4

This system proved to be very sensitive for protonation, due to the relative stability of the linearly conjugated dihydro intermediate 11 formed.

A base-catalyzed dehydrohalogenation yields the telesubstitution product 5(=1)amino-2,6-naphthyridine (12). Proof for the nearly exclusive occurrence of an $S_N(AE)^{tele}$ mechanism instead of an $S_N(AE)^{ipso}$ mechanism, leading to the same product 12, is based on experiments with deuterated compounds. The telesubstitution of 2-bromo-1,5-naphthyridine was found to take place to only a

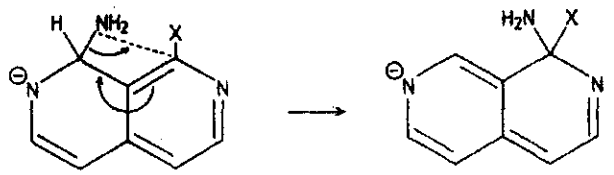
minor extent, if any, and a direct (ipso) substitution [$S_N(AE)^{ipso}$] is preferred.



Scheme 8.5

Thus, although σ adduct 13 is formed - as proved by NMR-spectroscopy - it does not convert into the dihydro-1,5-naphthyridine 14. The reason is probably that this double cross conjugated system is less easily formed than the linearly conjugated dihydro intermediate 11.

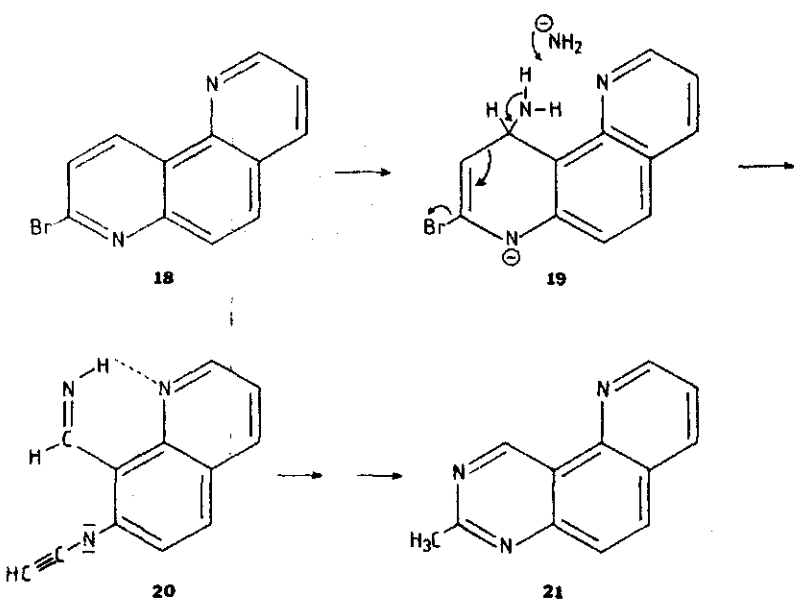
The formation of 4-amino-1,5- or -1,7-naphthyridine[6,7] from 2-halogeno-1,5- or -1,7-naphthyridine is an example of an odd telesubstitution, starting with σ adduct formation on position 4[8]. The formation of a 4-amino compound does not occur when 2-halogeno-1,8-naphthyridine is reacted[9] with potassium amide. The σ adduct at position 2 or 7 in that system has much more stability than the σ adduct at position 4. This prevents the formation of a σ adduct on position 4, which is required for the formation of 4-amino-1,8-naphthyridine from 2-halogeno-1,8-naphthyridine. It is interesting that the formation of a σ adduct on position 7 does indeed occur (as proved by NMR spectroscopy and the formation of the odd telesubstitution product 7(=2)-amino-1,8-naphthyridine). The formation of the last-mentioned compound is established by using 7-deutero-2-halogeno-1,8-naphthyridine. Remarkably 1-halogeno-2,7-naphthyridine did not undergo an odd telesubstitution, even though σ adduct formation at position 8 takes place quantitatively. We have postulated that presumably σ adduct 16 undergoes an internal substitution via 17 (Scheme 8.6), which ultimately leads to $S_N(AE)^{ipso}$ substitution.



16 17

Scheme 8.6

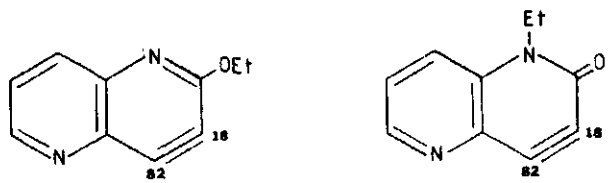
Ring transformation reactions are found when reacting 2-halogeno-1,5- or -1,7-naphthyridine[6,7] with potassium amide, giving (4-amino)-2-methyl-1,3,5- or -1,3,7-triazanaphthalene respectively. Such reactions were not found[9] when aminating 2-halogeno-1,8-naphthyridine, probably again due to its inability to undergo σ adduct formation on C-4. The structure of the open-chain intermediates occurring in the ring transformations of 2-halogeno-1,5- or - 1,7-naphthyridine was thus far only postulated. The low stability of these open-chain intermediates prevented isolation or further characterization by NMR spectroscopy.



18 19 20 21

Scheme 8.7

We were however successful to establish by NMR spectroscopy the structure of the open-chain intermediate occurring in the conversion of 8-bromo-1,7-phenanthroline (18) into 2-methyl-1,3,5-triazaphenanthrene (21). This intermediate has enough stability to be measured and based on its ^{1}H- and ^{13}C-NMR spectra it was unequivocally assigned structure 20 (Scheme 8.7).
Adduct formation - the favourite process of naphthyridines - has not been found in the amination of 3-bromo-2-ethoxy-1,5-naphthyridine. A mixture of 4-amino- and 3-amino-2-ethoxy-1,5-naphthyridine was found and its formation can be explained by a hetaryne as intermediate.
The directing effect of the ethoxy group on addition of ammonia to the hetaryne 22 was the same as already reported for the analogous quinoline compound[10] (Scheme 8.8).



22 23

Scheme 8.8.

The same selectivity is found for addition of ammonia to the hetaryne 23, which is an intermediate in the amination of 3-bromo-1-ethyl-1,5-naphthyridin-2(1H)-one.

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8) The formation of 4-amino-1,5-naphthyridine from 2-bromo-1,5-naphthyridine might also be explained by an even telesubstitution, involving a σ-adduct on position 8, analogously to the formation of 8-amino-1,7-naphthyridine from 2-halogeno-1,7-naphthyridine. This does not explain however the formation of 4-amino-1,7-naphthyridine from 2-halogeno-1,7-naphthyridine.

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10) Pomorski, J.; Den Hertog, H.J.; Buurman, D.J. and Bakker, N.H. Recl.Trav. Chim.(Pays-Bas) 1973, 92, 970.

Summary

In the introduction of this thesis (chapter 1) the reactions of naphthyridines with potassium amide which were known at the start of our research are reviewed.
It is shown in chapter 2, that in the amination of 1,X-naphthyridines with potassium amide in liquid ammonia at about -35° to -45°C the initial adduct formation is charge controlled. Thus, at these temperatures the site with the lowest electron density is most susceptible for amide attack (C-2 in 1,5-naphthyridine, C-2 in 1,6-naphthyridine, C-2 and C-8 in 1,7-naphthyridine, C-2 in 1,8-naphthyridine), as proved by NMR spectroscopy. On raising the temperature to about 10°C the site of addition has been found to change for 1,5- and 1,7-naphthyridine (NMR spectroscopy): from C-2 to C-4 in 1,5-naphthyridine and from C-2 and C-8 to C-8 only in 1,7-naphthyridine. Thus, at about 10°C the amination is thermodynamically controlled. The several factors which contribute to the stability of these addition products have been discussed.
It has been found that the anionic σ adducts (2(4,8)-aminodihydro-1,X-naphthyridinides) can easily be oxidized with potassium permanganate into their corresponding 2(4,8)-amino-1,X-naphthyridines.
In chapter 3 a facile synthesis of 2,6-naphthyridine is described. Both 2,6- and 2,7-naphthyridine undergo with potassium amide under kinetically and thermodynamically controlled conditions σ adduct formation at position 1. Chichibabin amination of 2,6-naphthyridine yields 1-amino-2,6-naphthyridine in 54% yield.
The conversion of 1-halogeno-2,6-naphthyridines into 1-amino-2,6-naphthyridine is shown in chapter 4 to proceed via an even telesubstitution process [$S_N(AE)^{tele}$ process]. The amination of 2-bromo-1,5-naphthyridine into 2-amino-1,5-naphthyridine is shown to proceed via an $S_N(AE)^{ipso}$ substitution mechanism.
Chapter 5 deals with the reaction of 1-halogeno-2,7-naphthyridines with KNH_2/NH_3 yielding 1-amino-2,7-naphthyridine. Experiments with deuterated compounds show tnat these reactions proceed via an $S_N(AE)^{ipso}$ process and not via an $S_N(AE)^{tele}$ process, even though σ adduct formation at C-8 takes place, as is shown by NMR spectroscopy.
In chapter 6 the occurrence of an open-chain intermediate in the amination of 8-bromo-1,7-phenanthroline is shown by NMR spectroscopy. The reaction of 3-bromo-2-ethoxy-1,5-naphthyridine with KNH_2/NH_3 is described in chapter 7. The procedure

in the literature for its preparation does not lead to this compound but to the isomeric 3-bromo-1-ethyl-1,5-naphthyridin-2(1H)-one. Reaction of this compound with KNH_2/NH_3 yields 3- and 4-amino-1-ethyl-1,5-naphthyridin-2(1H)-one, the latter being the main product. 3-Bromo-2-ethoxy-1,5-naphthyridine was prepared on reacting 2,3-dibromo-1,5-naphthyridine with sodium ethoxide. A mixture of 3- and 4-amino-2-ethoxy-1,5-naphthyridine was obtained on amination of 3-bromo-2-ethoxy-1,5-naphthyridine. In both cases the intermediacy of the respective 3,4-dihydro compounds was proposed.

Samenvatting

In de inleiding van dit proefschrift (hoofdstuk 1) is een overzicht gegeven van de reakties tussen naftyridines en kaliumamide, welke bekend waren aan het begin van het onderzoek.

In hoofdstuk 2 wordt aangetoond dat bij de aminering van 1,X-naftyridines met kaliumamide in vloeibare ammoniak bij ongeveer -35 tot -45°C de adductvorming door de ladingsverdeling bepaald wordt. Dus bij deze temperatuur is de plaats met de laagste elektronendichtheid het gevoeligst voor aanval door het amide anion (C-2 in 1,5-naftyridine, C-2 in 1,6-naftyridine, C-2 en C-8 in 1,7-naftyridine en C-2 in 1,8-naftyridine), zoals werd aangetoond met NMR spectroscopie. Toen de temperatuur verhoogd werd tot ongeveer 10°C veranderde de plaats van adductvorming bij 1,5- en 1,7-naftyridine van C-2 naar C-4 bij 1,5-naftyridine en van C-2 en C-8 naar alleen C-8 bij 1,7-naftyridine. Bij 1,6- en 1,8-naftyridine werd geen verandering waargenomen.

De adductvorming bij 10°C is dus een thermodynamisch bepaald proces. De verschillende faktoren die bijdragen aan de stabiliteit van deze σ adducten worden besproken.

De σ adducten bleken gemakkelijk geoxideerd te kunnen worden met kaliumpermanganaat tot de overeenkomstige aminonaftyridines.

Hoofdstuk 3 geeft een eenvoudige synthese van 2,6-naftyridine. Zowel 2,6- als 2,7-naftyridine ondergaan met kaliumamide σ adductvorming op positie 1, onder kinetische en thermodynamische omstandigheden. Chichibabin aminering van 2,6-naftyridine geeft 1-amino-2,6-naftyridine in een opbrengst van 54%.

Dat de omzetting van 1-halogeen-2,6-naftyridine in 1-amino-2,6-naftyridine met kaliumamide verloopt via een even telesubstitutie proces [$S_N(AE)^{tele}$ proces] is aangetoond in hoofdstuk 4. Het mechanisme van deze reaktie werd gegeven.

De aminering van 2-broom-1,5-naftyridine met kaliumamide geeft 2-amino-1,5-naftyridine via een $S_N(AE)^{ipso}$ mechanisme.

Hoofdstuk 5 behandelt de reaktie van 1-halogeen-2,7-naftyridines met kaliumamide tot 1-amino-2,7-naftyridine. Experimenten met gedeutereerde verbindingen toonden aan dat deze reaktie verloopt via een $S_N(AE)^{ipso}$ proces, en niet via een $S_N(AE)^{tele}$ proces, hoewel een σ adduct op positie 8 gevormd wordt.

In hoofdstuk 6 is het voorkomen van een openketen intermediair in de aminering

van 8-broom-1,7-fenantroline met NMR spectroscopie aangetoond.
De reaktie van 3-broom-2-ethoxy-1,5-naftyridine met kaliumamide is beschreven in hoofdstuk 7. De procedure uit de literatuur voor de bereiding hiervan geeft niet deze stof maar de isomeer 3-broom-1-ethyl-1,5-naftyridin-2(1H)-on. Reaktie hiervan met kaliumamide geeft 3- en 4-amino-1-ethyl-1,5-naftyridin-2(1H)-on, waarvan de laatste het hoofdprodukt is. 3-Broom-2-ethoxy-1,5-naftyridine werd bereid door reaktie van 2,3-dibroom-1,5-naftyridine met natrium ethoxide. Aminering gaf een mengsel van 3- en 4-amino-2-ethoxy-1,5-naftyridine.
In beide gevallen werd een 3,4-didehydroverbinding als intermediair verondersteld.

Nawoord

Aan het einde van mijn proefschrift wil ik iedereen bedanken die aan de totstandkoming ervan heeft bijgedragen.
Zonder jouw steun en liefderijke zorgen, Tilly, zou het me zeker niet gelukt zijn dit proefschrift te schrijven.
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Curriculum vitae

Na het afleggen van het eindexamen HBS-B aan het Christelijk Lyceum Dr. W.A. Visser-'t Hooft te Leiden in 1968 begon ik in september van dat jaar aan mijn scheikunde studie aan de Rijksuniversiteit te Leiden. Het kandidaatsexamen (letter S 2) werd in oktober 1971 afgelegd.
Onder leiding van Prof.Dr.H. Kloosterziel (organische chemie), Dr.J.C. Verstelle (electronica) en Prof.Dr.H.W. Joustra (fysische chemie) bereidde ik mij voor op het doctoraalexamen, dat in februari 1976 cum laude werd afgelegd.
Van 1972 tot 1976 ben ik als student assistent verbonden geweest aan de Rijksuniversiteit te Leiden.
Van 1971 tot 1979 ben ik als docent scheikunde verbonden geweest aan achtereenvolgens de avondscholengemeenschap „Noctua" te Den Haag, de rooms-katholieke scholengemeenschap „St.Agnes" te Leiden, de avondscholengemeenschap „Boerhaave" te Leiden en de scholengemeenschap „Christien Broekema-Bakker" te Wageningen.
Vanaf juni 1976 ben ik als wetenschappelijk medewerker in dienst van de Landbouwhogeschool te Wageningen, waar ik onder leiding van Prof.Dr.H.C.van der Plas het in dit proefschrift beschreven onderzoek verrichtte.