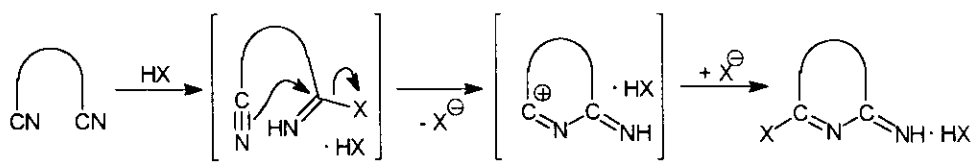
CYCLIZATION OF TAUTOMERIC 1,5-DINITRILE SYSTEMS WITH HYDROGEN HALIDES: A DEFINITIVE MECHANISTIC RATIONALIZATION?

Jordi Teixidó,* José I. Borrell, Blanca Serra, Josep Lluis Matallana, Carles Colominas, Francisco Carrión, Rosalia Pascual, Josep Lluis Falcó, and Xavier Batllori

Departament de Química Orgànica, Institut Químic de Sarrià, Universitat Ramon Llull, E-08017 Barcelona, Spain

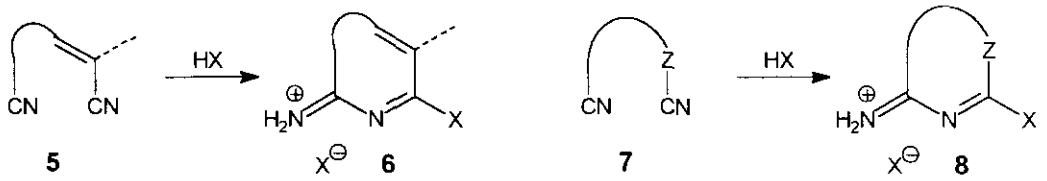
Abstract- A new mechanistic rationalization for the cyclization with hydrogen halides of tautomeric 1,5-dinitriles of general structures (**10**) (Z = N), (**14**) (Z = C-CN), (**16**) (Z = N), and (**18**) (Z = C-CN) is proposed (Scheme 5). In such rationalization, three factors play a major role on the direction of cyclization: Position of the equilibrium of the tautomeric 1,5-dintrile system, relative basicity of the cyano groups involved, and planarity of the reaction zone.

The cyclization of α,ϖ-dinitriles in the presence of hydrogen halides has attracted the interest of organic chemists due to the wide possibilities that offers for the synthesis of heterocyclic compounds.[1] In 1966 Johnson and Madroñero published[1a] a general revision on the synthesis of heterocycles by reaction of nitriles in acid medium which included a mechanistic rationalization for the cyclization of α,ϖ-dinitriles (Scheme 1). These authors proposed the addition of the hydrogen halide to one of the cyano groups of the α,ϖ-dinitrile system (**1**) followed by the cyclization of the other cyano group onto the intermediate imidoyl halide (**2**) causing the elimination of the halide. Finally, the halide should attack the carbon atom of the second cyano group in **3** to afford the cyclization product (**4**). Such proposal was mainly based on two experimental evidences: a) Grundmann *et al.*[2] detected the formation of halogenoimmonium halides during a study on the dimerization of nitriles with hydrogen halides at –5 to –50 °C. b) Johnson and Hunneman observed the formation of an imino thioester by treating 2-cyanobenzyl cyanide with hydrogen halides in the presence of a thiol.[3]



Scheme 1

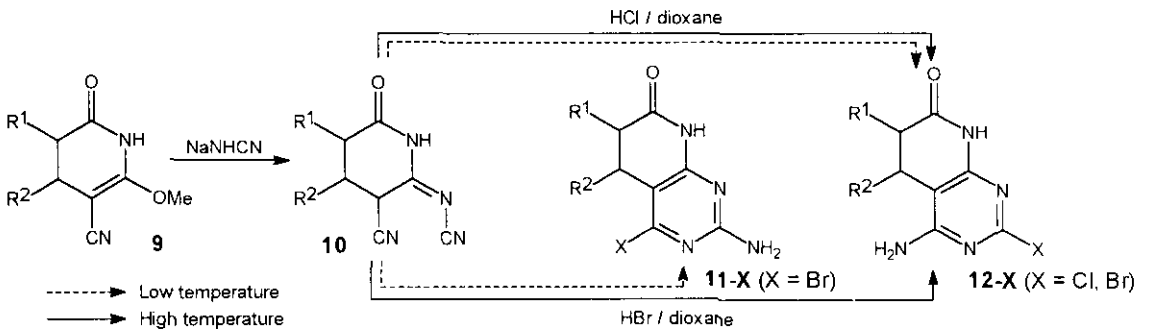
Based also on empirical evidences, Johnson and Madroñero gave a rule of thumb for the direction of cyclization in those systems which present a cyano group bonded to a sp^3 carbon and a second cyano group bonded to a sp^2 carbon (**5**) or to an heteroatom (**7**). Thus, the carbon atom of this later nitrile always bears the halogen atom in the cyclized products (**6**) and (**8**).



Scheme 2

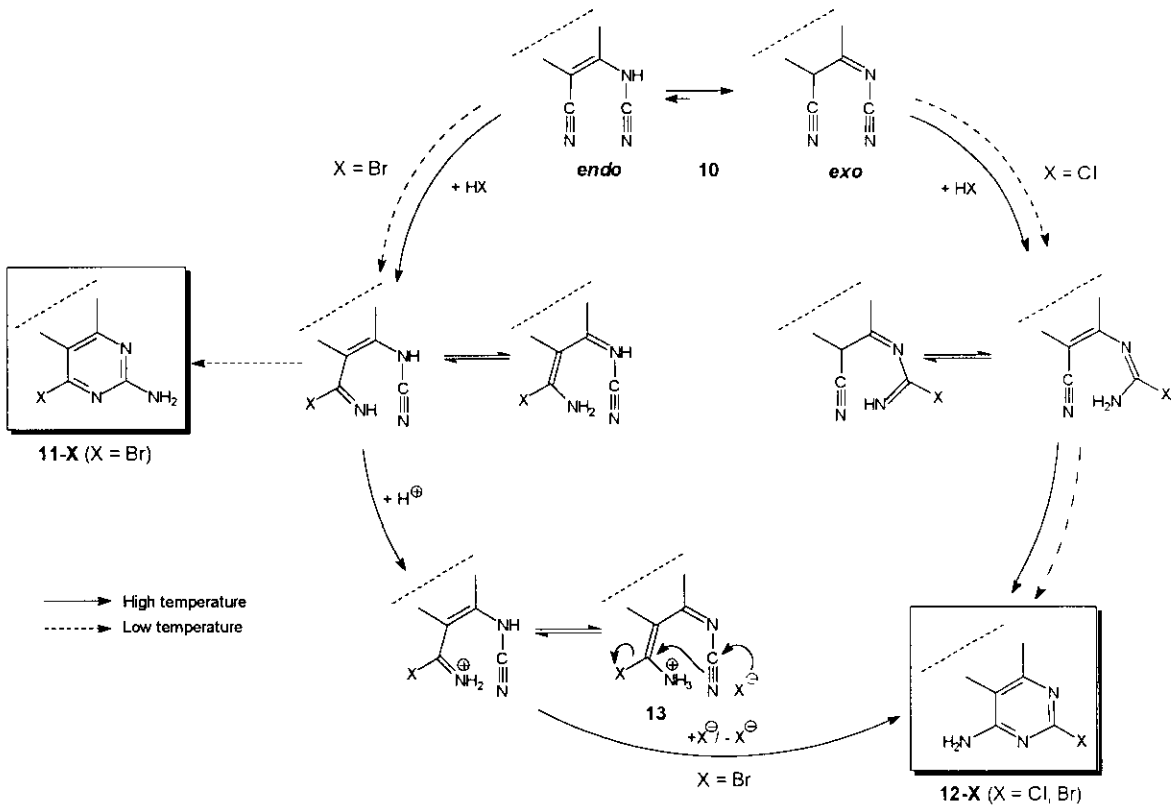
However, this empirical rule shows an apparent incongruity in relation to the proposed mechanism and the relative basicity expected for the cyano groups involved in the cyclization. In accordance with the idea that the cyano group bonded to the aliphatic carbon is less basic than both the cyano group bonded to the sp^2 carbon and the one bonded to the heteroatom, the HX should add to this later cyano group to give, following the mechanism depicted in Scheme 1, the regioisomer opposite to the one predicted by the aforementioned rule.

The interest of our group in the mechanism and regioselective character of this kind of cyclizations started in 1982 when the 1,5-dinitrile systems (**10**) (Scheme 3) were obtained by reaction of the corresponding 2-methoxy-1,4,5,6-tetrahydropyridine-3-carbonitrile (**9**) with sodium cyanamide.[4] When pyridones (**10**) were treated with hydrogen chloride using dioxane as solvent, the 4-amino-2-chloro-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (**12-Cl**) were obtained both at low (10-15°C) and high (95-100°C) temperature in an apparently regiospecific process.[5] However, the treatment of **10** with hydrogen bromide afforded both positional isomers (**11-Br**) and (**12-Br**) depending on the thermal level employed.[6] Thus, when the reaction was carried out at low temperature the 2-amino-4-bromo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones (**11-Br**) were selectively formed, but when it was done at high temperature the 4-amino-2-bromo-substituted compounds (**12-Br**) were predominantly obtained. This behavior was found to be independent of the nature and position of the substituents present on the pyridone ring.



Scheme 3

In order to explain such results a mechanistic hypothesis (Scheme 4) was proposed for the cyclization of pyridones (**10**) which was based on three factors: kinetic control in the **10-*endo*** ⇌ **10-*exo*** tautomerism, initial protonation on the most basic cyano group involved in the cyclization (which is the C=N-CN group in **6-*exo*** and the C=C-CN group in the **6-*endo*** tautomer), and two possible reaction paths.[7] According to this hypothesis, the formation of **11-Br** would proceed through the protonation of the C=C-CN group in the **10-*endo*** tautomer. Even the formation of **12-Br** at high temperature could be rationalized through the **10-*endo*** tautomer if an addition-elimination mechanism through a protonated imidoyl halide (**13**), analogous to that proposed by Johnson and Madroñero, is accepted.

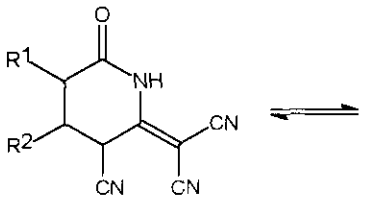


Scheme 4

Later we extended the study to other 1,5-dinitrile systems such as the dicyanomethylene-substituted pyridones (**14**) which underwent cyclization with hydrogen halides (HCl or HBr in dioxane/benzene) to afford regiospecifically the 7-amino-5-halo-8-cyano-1,2,3,4-tetrahydro-1,6-naphthyridin-2-ones (**15-X**, X = Cl, Br), the direction of the cyclization being independent of the temperature and the nature and position of the substituents R^1 and R^2.[8] To rationalize this result in agreement with the proposed mechanism it was necessary to postulate the key role of an endocyclic tautomer (**14-*endo***) which was not detected.

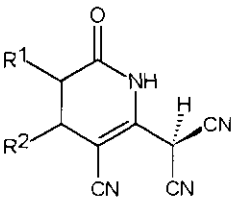
We also studied the cyclization of the 2-cyanoimino-1,2-dihydropyridine-3-carbonitriles (**16**)[9] and the 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles (**18**)[10] which afforded a sole halogenated

derivative in each case independently of the hydrogen halide and thermal level employed: the 4-amino-2-halopyrido[2,3-*d*]pyrimidines (**17**) and 5-amino-7-halo-1,6-naphthyridines (**19**), respectively.

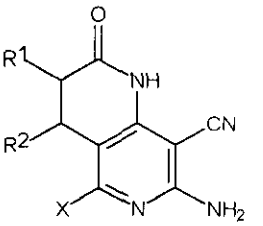


exo

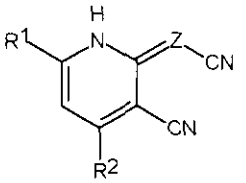
14



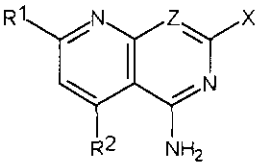
endo



15-X (X = Cl, Br)



16 (Z = N)
18 (Z = C-CN)



17-X (Z = N, X = Cl, Br)
19-X (Z = C-CN, X = Cl, Br)

All these results, some of them even seeming contradictory with our mechanistic proposal, led us to carefully reinvestigate the whole matter. This paper deals with the results obtained in such study.

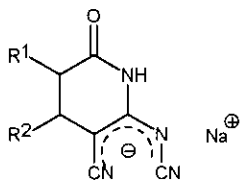
RESULTS AND DISCUSSION

First of all we have revised the cyclizations of the 5-cyano-6-cyanoimino-3,4-dihydropyridin-2(1*H*)-ones (**10**) to verify the observations previously reported by our group.[4-7] To carry out such revision we modified the isolation procedure of the halo-substituted pyridopyrimidines (**11-X**) and (**12-X**) to avoid any loss of material that could falsify the results. In particular, instead of filtering the solid obtained upon treatment with the corresponding HX, we decided to remove the solvent *in vacuo*, to suspend the resulting solid in methanol and to neutralize it with 2 *M* ammonia solution in methyl alcohol. After elimination *in vacuo* of the solvent and excess of base, the resulting solid was directly analyzed by reversed phase HPLC (RP-18 column, mixtures acetonitrile:water as the mobile phase, λ = 240 nm), avoiding the aqueous washing previously used, because the ammonium halides formed do not interfere the analysis.

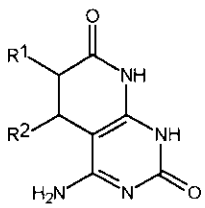
The cyclization study was carried out by using the sodium salts (**20a-d**) instead of the corresponding pyridones (**10a-d**) as starting materials because both have the same behavior in front of hydrogen halides. In fact, sodium salts (**20**) are precursors of the cyanoimino-substituted pyridones but they are more stable and manageable.

In order to cast light on the possible influence of tautomerism in the direction of the cyclization, the reactions have been carried out in five different solvents that cover a wide range of polarities: water, acetic acid (AcOH), 1,2-dichloroethane (DCE), 1,4-dioxane, and toluene. The treatment with the hydrogen halides was performed at different temperatures when possible.

The results obtained in the cyclizations of **20a-d** with hydrogen bromide are summarized in Table 1. As it can be seen the nature of the solvent greatly influences the direction of cyclization at the same reaction temperature. Thus, at room temperature, the reaction in water yielded almost exclusively the 2-bromo-substituted isomers (**12-Br**) but, on the contrary, when it was carried out in dioxane the 4-bromo derivatives (**11-Br**) were predominantly formed. The result obtained in water is surprising because this is the first case in which the cyclization with hydrogen bromide yields a sole regioisomer which, moreover, is the same one that is formed with HCl. In general, the behavior observed is in agreement with our previous findings: the greater polarity of the solvent and the higher thermal levels favour the formation of the more polar 2-bromo-susbtituted regioisomers (**12-Br**), although in some cases (i. e. AcOH and toluene) the behavior is not so clear. The use of 1,2-dichloroethane seems to be particularly interesting because there are no by-products at any temperature, the reactions being thus cleaner.



	R^1	R^2
a	Me	H
b	H	Me
c	Ph	H
d	H	Ph



20a-d **21a-d**

Table 1: Reactions of cyclization of sodium salts (20a-d) in the presence of hydrogen bromide: Influence of solvent and temperature

		20a		20b		20c		20d	
Solvent	Reaction Temp.	**12a-Br** : **11a-Br** [a]	(**11**+**12**) : **10a** [a]	**12b-Br** : **11b-Br** [a]	(**11**+**12**) : **10b** [a]	**12c-Br** : **11c-Br** [a]	(**11**+**12**) : **10c** [a]	**12d-Br** : **11d-Br** [a]	(**11**+**12**) : **10d** [a]
H_2O	rt	94 : 6	97 : 2	100 : 0	94 : 2 [b]	100 : 0	77 : 6 [b]	98 : 2	89 : 0 [b]
	reflux	—	—	—	—	98 : 2	12 : 10 [b]	—	1 . 0 [b]
AcOH	rt	64 : 36	91 : 0 [b]	41 : 59	80 . 19 [b]	47 : 53	85 : 4 [b]	39 : 61	95 : 0 [b]
	60°C	—	—	—	—	43 : 57	74 : 2 [b]	57 : 43	71 : 0 [b]
	reflux	—	—	—	—	55 : 45	74 : 2 [b]	60 : 40	66 : 2 [b]
DCE	- 78°C	80: 20	95 : 5	74 : 26	58 : 42	23 : 77	67 : 33	46 :54	39 : 60
	10°C	35 : 65	100 : 0	29 : 71	100 : 0	27 : 73	91 : 8	34 : 66	96 : 3
	rt	54 : 46	100 : 0	30 : 70	100 : 0	26 : 74	89 : 3 [b]	8 : 92	100 : 0
	60°C	59 : 41	100 : 0	30 : 70	93 : 3 [b]	58 : 42	91 : 7	28 : 72	96 : 3
	reflux	89 : 11	100 : 0	93 : 7	100 : 0	98 : 2	92 : 6	47 : 53	100 : 0
Dioxane	10°C	35 : 65	97 : 2	20 : 80	100 : 0	27 : 73	76 : 3 [b]	23 : 77	79 : 21
	rt	35 : 65	87 : 2 [b]	18 : 82	97 . 3	39 : 61	88 : 4 [b]	31 : 69	98 : 2
	60°C	55 : 45	52 : 2 [b]	21 : 79	44 : 0 [b]	47 : 53	67 : 0 [b]	31 : 69	98 : 2
	reflux	65 : 35	46 : 2 [b]	54 : 46	52 : 0 [b]	70 : 30	82 : 4 [b]	37 : 63	92 : 6
Toluene	10°C	52 : 48	100 : 0	40 : 60	73 : 27	25 : 75	75 : 24	11 : 89	96 · 3
	rt	31 : 69	96 : 2	48 : 52	100 : 0	23 : 77	90 : 4 [b]	20 : 80	91 · 5 [b]
	60°C	52 : 48	97 : 2	28 : 72	62 : 21 [b]	21 : 79	84 . 3 [b]	16 : 84	79 0 [b]
	reflux	—	—	—	—	23 : 77	90 : 2 [b]	45 : 55	80 . 0 [b]

a: Determined by HPLC as a ratio of concentrations. b: Presence of by-products.

The reactions carried out in water yielded compounds (**21a-d**) as by-products. In order to clarify the way of formation of these 4-amino-2-oxopyrido[2,3-*d*]pyrimidines, compounds (**12-Br**) were treated with 45% HBr at reflux for 4 h to yield **21a-d** in 60-85% yield. We also proved that **21a** is also directly formed in 85% yield by treatment of the sodium salt (**20a**) with 45% HBr at reflux. Consequently, it seemed reasonable to consider that compounds (**21**) are formed by hydrolysis of the 2-bromo-substituted pyridopyrimidines, so we extended the method to the 4-bromo derivatives to afford the corresponding 2-amino-4-oxopyrido[2,3-*d*]pyrimidines. This methodology was separately published as a part of an unequivocal synthesis of 4-amino-2-oxo- and 2-amino-4-oxopyrido[2,3-*d*]pyrimidines.[11]

On the other hand, a careful revision of the cyclization of compounds (**20a-b**) with hydrogen chloride (Table 2) clearly showed the non-regiospecific character of the reaction because, in all the conditions assayed, the second chromatographic peak detected was assigned to the 4-chloro-substituted derivative (**11-Cl**). As it was in no case possible to separate the minor isomer, the assignment was done by comparison of the UV spectrum of the chromatographic peak (by using a diode array detector) and the UV spectra of the 2-amino-4-bromopyrido[2,3-*d*]pyrimidines (**11-Br**). This assignment can be considered reliable due to the characteristic shape of the UV spectra of the 4-halo-substituted derivatives, being also supported by the ^{13}C NMR spectra and elemental analyses of the mixtures of **11-Cl** and **12-Cl**.

The amount of **11-Cl** formed in each case could not easily be determined due to the practical impossibility of isolating them. Consequently, the percentages included in Table 2 were calculated as a ratio of the areas under the curve, an approximation which probably overestimates the amount of the 2-chloro regioisomers (**12-Cl**) due to the higher absorption coefficient expected for them.

Table 2: Reactions of cyclization of sodium salts (20a-b) in the presence of hydrogen chloride: Influence of solvent and temperature

		20a		**20b**	
Solvent	Reaction Temp.	**12a-Cl** : **11a-Cl** [a]	(11+12) : **10a** [a]	**12b-Cl** : **11b-Cl** [a]	(11+12) : **10b** [a]
H_2O	rt	97 : 3	70 : 1 [b]	98 : 2	47 : 2 [b]
AcOH	rt	99 : 1	95 : 1	99 : 1	98 : 1
DCE	rt	96 : 4	100 : 0	98 : 2	97 : 2
	60°C	98 : 2	100 : 0	99 : 1	98 : 1
Dioxane	rt	90 : 10	95 : 2	94 : 6	100 : 0
Toluene	rt	80 : 20	100 : 0	93 : 7	100 : 0

a: Determined by HPLC as a ratio of areas under the curve.
b: Presence of by-products.

The second part of our study was the revision of the cyclizations with HBr and HCl of the 5-cyano-6-dicyanomethylene-3,4-dihydropyridin-2(1*H*)-ones (**14a-d**) by using the methodology described above.

The results obtained (Table 3 and Table 4) clearly showed that, contrary to our previous findings, the reaction of **14a-d** with hydrogen halides is no regiospecific, both regioisomers (**15-X**) and (**22-X**) being always formed. In fact, this is the first time that we have detected and isolated, by reaction of **14a-d**

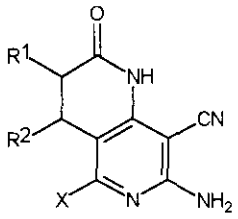
with HBr or HCl in acetic acid followed by recrystallization from AcOEt:MeOH and chromatographic separation, the two positional isomers (**15-X**) (X = Cl, Br) and (**22-X**) (X = Cl, Br).

Table 3: Reactions of cyclization of 14a-d in the presence of hydrogen bromide: Influence of solvent and temperature

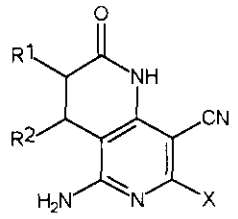
		14a		**14b**		**14c**		**14d**	
Solvent	Reaction Temp.	**15a-Br** : **22a-Br** [a]	(**15+22**) : **14a** [a]	**15b-Br** : **22b-Br** [a]	(**15+22**) : **14b** [a]	**15c-Br** : **22c-Br** [a]	(**15+22**) : **14c** [a]	**15d-Br** : **22d-Br** [a]	(**15+22**) : **14d** [a]
H_2O	rt	84 : 16	35 : 64	75 : 25	82 : 17	71 : 29	16 : 82	43 : 57	8 : 90
	60°C	53 : 47	68 : 25 [b]	78 : 22	92 : 5 [b]	78 : 22	30 : 66 [b]	25 : 75	6 : 93
	reflux	11 : 89	15 : 35 [b]	73 : 27	65 : 12 [b]	36 : 64	40 : 20 [b]	11 : 89	17 : 39 [b]
AcOH	rt	85 : 15	98 : 1	90 : 10	99 : 0	92 : 8	98 : 1	83 : 17	99 : 1
	60°C	86 : 14	98 : 1	88 : 12	98 : 0	90 : 10	98 : 1	79 : 21	98 : 1
	reflux	72 : 28	86 : 8 [b]	73 : 27	66 : 13 [b]	84 : 16	84 : 1 [b]	81 : 19	92 : 3 [b]
Dioxane	rt	92 : 8	97 : 0	93 : 7	97 : 0 [b]	100 : 0	83 : 5 [b]	95 : 5	99 : 1
	60°C	94 : 6	98 : 0	90 : 10	98 : 0 [b]	98 : 2	68 : 1 [b]	88 : 12	97 : 1
	reflux	—	0 : 99	—	0 : 99	74 : 26	58 : 28 [b]	69 : 31	3 : 96
Toluene	rt	85 : 15	100 : 0	90 : 10	95 : 0 [b]	92 : 8	94 : 1 [b]	90 : 10	99 : 1
	60°C	74 : 26	92 : 8	78 : 22	83 : 0 [b]	80 : 20	96 : 2 [b]	79 : 21	99 : 1
	reflux	54 : 46	41 : 57	69 : 31	8 : 90	87 : 13	78 : 8 [b]	55 : 45	7 : 62 [b]

a: Determined by HPLC as a ratio of concentrations. b: Presence of by-products.

Cyclizations in dioxane always afforded higher yields than those previously described.[8] In addition, the use of this solvent produces the lowest proportion of **22-X**, reinforcing the idea that the 7-halo-substituted compounds (**22-X**) were inadvertently removed during recrystallization, being thus not detected.



15-X (X = Cl, Br)



22-X (X = Cl, Br)

The behavior of both hydrogen halides can be considered as similar. However, the HCl is less reactive giving lower yields but a higher amount of the 7-halo-substituted isomer (**22-X**). It is interesting to note that cyclizations carried out with HCl at high temperature gave very low yields, independently of the solvent used. On the other hand, reactions carried out with HBr proceed with high yields in general but not in water where the amount of by-products formed rapidly increases.

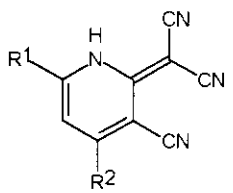
Once more, formation of the more polar 5-amino-7-bromo-1,6-naphthyridine (**22-Br**) is favored by increasing the polarity of the solvent and the temperature of reaction. However, the use of high thermal levels also causes an increase in the amount of by-products formed.

Table 4: Reactions of cyclization of 14a-d in the presence of hydrogen chloride: Influence of solvent and temperature

		14a		14b		14c		14d	
Solvent	Reaction Temp.	**15a-Cl** : **22a-Cl** [a]	(**15**+**22**) : **14a** [a]	**15b-Cl** : **22b-Cl** [a]	(**15**+**22**) : **14b** [a]	**15c-Cl** : **22c-Cl** [a]	(**15**+**22**) : **14c** [a]	**15d-Cl** : **22d-Cl** [a]	(**15**+**22**) : **14d** [a]
H_2O	rt	75 : 25	63 : 16 [b]	50 : 50	41 : 40 [b]	13 : 87	72 : 12 [b]	38 : 62	59 : 39
	60°C	40 : 60	45 : 36 [b]	50 : 50	46 : 1 [b]	43 : 57	71 : 2 [b]	42 : 58	84 : 8 [b]
	reflux	44 : 56	31 : 32 [b]	43 : 57	18 : 44 [b]	45 : 55	52 : 10 [b]	30 : 70	22 : 40 [b]
AcOH	rt	91 : 9	97 : 2	92 : 8	80 : 18	95 : 5	88 : 10	87 : 13	72 : 28
	60°C	87 : 13	75 : 24	76 : 24	18 : 81	84 : 16	66 : 32	68 : 32	22 : 75 [b]
	reflux	52 : 48	2 : 96	91 : 9	1 : 93 [b]	53 : 47	21 : 59 [b]	41 : 59	3 : 94 [b]
Dioxane	rt	93 : 7	69 : 31	—	0 : 99	85 : 15	99 : 1	98 : 2	98 : 1
	60°C	68 : 32	17 : 83	—	0 : 99	61 : 39	7 : 92	59 : 41	3 : 96
	reflux	—	0 : 99	—	0 : 99	—	0 : 99	—	0 : 99
Toluene	rt	—	0 : 98	—	0 : 99	75 : 25	17 : 81	—	0 : 98
	60°C	—	0 : 99	—	0 : 99	—	0 : 98	—	0 : 99
	reflux	—	0 : 99	—	0 : 99	—	0 : 98	—	0 : 99

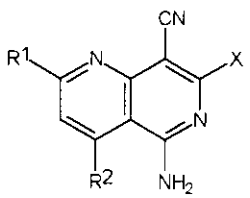
a: Determined by HPLC as a ratio of concentrations. b: Presence of by-products.

The third part of the study was devoted to the cyclization of 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles (**18e-i**) in the presence of HBr. The same approach described above was used to evaluate the ratio of the two isomers formed: 5-amino-7-bromo- and 7-amino-5-bromo-8-cyano-1,6-naphthyridines (**19-Br**) and (**23-Br**) (Table 5).

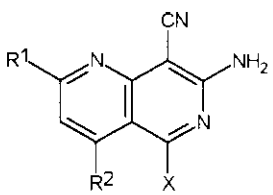


18e-i

	R^1	R^2
e	Me	H
f	Ph	H
g	Me	Me
h	Ph	Ph
i	Ph	Me



19-X (X = Cl, Br)



23-X (X = Cl, Br)

A first look at the results obtained clearly pointed out that, in contrast to our previous findings,[10] the cyclization of compounds (**18**) is far from being regiospecific, the two isomers being obtained in almost all cases. The selective removal of **23-X** during the recrystallization from methanol, due to the big difference in solubility of **19-X** and **23-X,** was again the cause for such misconception.

The 5-amino-7-bromo- substituted isomer (**19-Br**) predominates in general, however its proportion depends on the presence or absence of the substituent R^2. Thus, the yields of **19-Br** obtained for **18g**, **18h,** and **18i** were higher than tose obtained in the case of **18e** and **18f**. This fact seems to introduce the steric constraint as a factor which influences on the direction of cyclization of compounds **18**.

On the other hand, the ratio between **19-Br** and **23-Br** clearly depends on the nature of the solvent and temperature of reaction. Thus, a decrease in the polarity of the solvent and the use of low temperatures

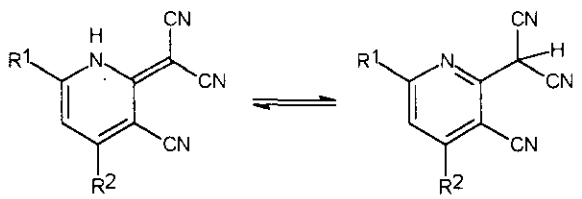
favors the formation of the 7-amino-5-bromo- substituted isomer (**23-Br**), this later being predominant in the case of **18e** and **18f**.

Table 5: Reactions of cyclization of 18e-i in the presence of hydrogen bromide: Influence of solvent and temperature

		18e		**18f**		**18g**		**18h**		**18i**	
Solvent	Reaction Temp.	**19e-Br : 23e-Br** [a]	**(19+23) : 18e** [a]	**19f-Br : 23f-Br** [a]	**(19+23) : 18f** [a]	**19g-Br : 23g-Br** [a]	**(19+23) : 18g** [a]	**19h-Br : 23h-Br** [a]	**(19+23) : 18h** [a]	**19i-Br : 23i-Br** [a]	**(19+23) : 18i** [a]
H_2O	rt	87 : 13	92 : 2	90 : 10	93 : 5	94 : 6	72 : 21	—	—[b]	96 : 4	23 : 70
	reflux	—	—[b]	—	—[b]	10 : 90	5 : 43[b]	—	0 : 48[b]	100 : 0	100 : 0
AcOH	rt	29 : 71	100 : 0	41 : 59	100 : 0	97 : 3	85 : 1	65 : 35	84 : 0	90 : 10	82 : 1
	reflux	70 : 30	87 : 0[b]	60 : 40	100 : 0	92 : 8	43 : 2[b]	77 : 23	68 : 4[b]	92 : 8	65 : 3[b]
Dioxane	rt	18 : 82	45 : 7[b]	97 : 3	92 : 0[b]	99 : 1	97 : 1	82 : 18	91 : 2[b]	97 : 3	80 : 2[b]
	reflux	—	—[b]	90 : 10	87 : 1[b]	82 : 18	45 : 30[b]	65 : 35	25 : 13[b]	99 : 1	45 : 30[b]
DCE	rt	38 : 62	100 : 0	73 : 27	100 : 0	90 : 10	1 : 95	99 : 1	24 : 52	86 : 14	40 : 54
	reflux	89 : 11	100 : 0	95 : 5	71 : 20[b]	99 : 1	5 : 70[b]	100 : 0	3 : 90[b]	97 : 3	3 : 95
Toluene	rt	20 : 80	83 : 10	42 : 58	86 : 5	89 : 11	78 : 5	52 : 48	60 : 36	48 : 52	36 : 40
	reflux	40 : 60	20 : 77	97 : 3	62 : 30	100 : 0	2 : 75[b]	100 : 0	5 : 90[b]	100 : 0	20 : 79

a: Determined by HPLC as a ratio of concentrations. b: Presence of by-products.

Such dependence of the isomer ratio on the polarity of the solvent is in agreement with the existence of the tautomeric equilibrium **18-*exo*** ⇌ **18-*endo*** and is similar to the dependence found in isoelectronic systems such as in the 2-pyridone ⇌ 2-hydroxypyridine equilibrium.[12] Thus, the use of polar solvents shifts the equilibrium to the more polar ***exo*** form favoring the formation of **19-Br**. However, a higher proportion of **23-Br** is obtained if the temperature is increased. Contrary, the use of nonpolar solvents shifts the equilibrium to the ***endo*** form increasing the amount of **23-Br** formed. As it can be seen, this behavior is clearly modulated by the presence or absence of the substituent R^2.



exo **18** ***endo***

NEW MECHANISTIC PROPOSSAL

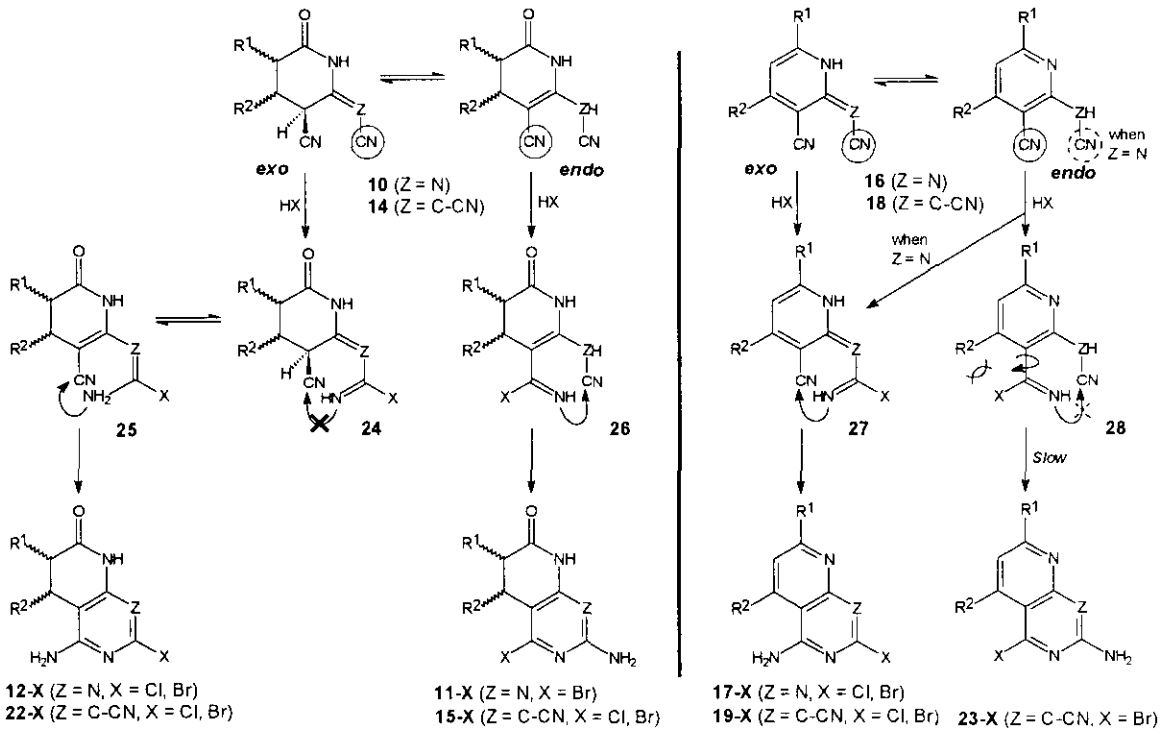
Our previous mechanistic hypothesis (Scheme 4) was based on the assumption that the reaction started by the initial protonation on the most basic cyano group involved in the cyclization, leading to the corresponding imidoyl halide which then attacks the other cyano group. According to this idea, the direction of cyclization of tautomeric 1,5-dinitrile systems should only depend on the relative basicity of the cyano groups involved and on the position of the tautomeric equilibrium. However, we have to consider the possibility that the initial imidoyl halide reverts to the starting product if the cyclization is blocked by any extra factor. In those cases, the cyclization could even proceed by a less favorable

path.

In this context, we consider that the planarity of the reaction zone plays a major role on the regioselectivity of this kind of cyclizations. That is to say, for the cyclization to take place, the imidoyl halide and the cyano group involved should be capable of adopting a coplanar or almost coplanar arrangement. Consequently, any factor that could prevent the achievement of such planarity would have a dramatic effect on the results of the cyclization.

Taking these ideas into consideration, we have developed a new mechanistic rationalization (Scheme 5) for the cyclization of tautomeric 1,5-dinitriles in the presence of hydrogen halides which is based on three factors:

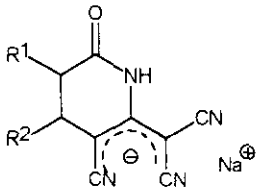
a) Position of the equilibrium of the tautomeric 1,5-dinitrile system: In the case of the 1,5-dinitriles (**10**, **14**, **16** and **18**), the equilibrium lies well to the ***exo*** form both in solution and solid state. However, a higher population of one of the tautomers does not imply that the major final product necessarily comes from such tautomer. This assumption underlies in the explanation given by Victory and Garriga in 1985 to explain their results.[4-6]



Scheme 5

In any case, an increase in the population of one of the tautomers will certainly cause an increase in the amount of the corresponding final product. It is clear that the polarity of the solvent and temperature could greatly influence such equilibrium as we have inferred from the results of cyclization of compounds (**18**).

In this context, we recently claimed, as a direct evidence of the tautomeric equilibrium, the detection of the ***endo*** tautomer in the ^{13}C NMR spectra of pyridones (**18**) when they were recorded in DMSO-d_6.[13] However, in the course of this reinvestigation we were able to obtain the sodium salts (**29a-d**), proving that the extra signals in the ^{13}C NMR of compounds (**18**) correspond in fact to its conjugate base (**29**).[14]



29a-d

b) Planarity of the reaction zone: This seems to be a factor that sometimes could determine the reaction rate. In the case of pyridones (**10**) and (**14**), the exo tautomer leads to the imidoyl halide (**24**) which presents a cyano group that is out of the plane of the reaction zone (in Scheme 5 this cyano group has been represented coming out of the plane of the paper, but the situation is the same for the opposite configuration). It is then necessary an additional tautomerization to **25** in order the cyclization to proceed, causing the slowing down of the reaction.

On the other hand, the addition of HX to the ***exo*** tautomer of compounds (**16**) and (**18**) leads to the imidoyl halide (**27**). This later presents a coplanar reaction zone that favors the cylization process. On the contrary, the addtion of HX to the cyano group bonded to the ring of the ***endo*** tautomer of **18** leads to the imidoyl halide (**28**). The presence of a substituent R^2 causes a steric strain, forcing the imidoyl halide to adopt a conformation that rends the cyclization difficult as it was observed in the case of **18g-i**. The absence of R^2 makes easier the formation of the corresponding cyclization product (**23-X**), that is the case of **18e** and **18f** (Table 5).

c) Relative basicity of the cyano groups involved: *The relative basicity of the cyano groups present in* each tautomer plays a major role in the direction of the cyclization because the most basic cyano group will add the hydrogen halide to form the corresponding imidoyl halide, deciding in absence of other factors the structure of the final product.

It is difficult to predict the relative basicity of the cyano groups present in such kind of tautomeric systems. Consequently, we have used semiempirical AM1 calculations to predict them. The results obtained[15] pointed out to the encircled cyano groups (Scheme 5) as the most basic ones of each tautomer. Nevertheless, the aforementioned predictions have been carried out *in vacuo* not taking into account the influence of the solvent. In order to improve the goodness of the prediction, *ab initio* and solvent calculations of a series of non tautomeric nitriles have been carried out[16] as a first step to predict the relative basicities of our tautomeric 1,5-dinitriles.

In the case of the ***exo*** tautomer of dinitriles (**16**) and (**18**), the Z-CN group is the most basic one, causing the isomers (**17-X**) and (**19-X**) to be normally predominant. In compounds (**18**) the

displacement of the tautomeric equilibrium to the ***endo*** form by the change of the solvent and temperature consequently favors the formation of the regioisomer (**23-X**), the ring-bonded cyano group being now the most basic one. However, in the case of compounds (**16**), the calculations pointed to the ZH-CN group as the most basic one. This result implies that the treatment of **16-*endo*** with HX would form the imidoyl halide (**27**), reverting again to the isomer (**17-X**). This could be the explanation of the apparent regiospecificity observed in the cyclization of compounds **16**.[9]

The case of compounds (**10**) and (**14**) require special attention. For compounds (**14**) (Z = C-CN) both HCl and HBr preferentially react with the minor ***endo*** tautomer leading to the corresponding **15-X** isomer, kinetically favored as explained by the precedent factor. For compounds (**10**) (Z = N), HBr shows a similar behavior leading to **11-Br**. On the contrary, HCl seems to react primarily and slowly with the predominant **10-*exo*** tautomer giving always an unusually high proportion of **12-Cl**. This fact suggests that, in the presence of HCl, the initial tautomeric equilibrium may be shifted towards the ***exo*** form. Only when the tautomeric equilibrium can be shifted to the ***endo*** form by effect of the solvent or the temperature, it is possible to obtain a higher proportion of the corresponding regioisomer **11-Cl** (see the results with toluene in Table 2).

In conclusion, we have developed a mechanistic hypothesis which clarifies the results obtained during the study of the cyclization of the tautomeric 1,5-dinitriles (**10**, **14**, **16** and **18**). Moreover, we consider that such hypothesis and the methodology employed could be of general use to study the behavior of similar 1,5-dinitrile systems.

ACKNOWLEDGMENTS

Support of this work by a grant from the Comissió Interdepartamental de Recerca i Innovació Tecnològica (CIRIT) within the Programa de Química Fina (QFN93-4420) is gratefully acknowledged. One of us (J. L. M.) would like to thank the CIRIT for a grant within the Formació de Personal Investigador en Àrees Prioritàries del Pla de Recerca. Two of us (B. S. and C. C.) are grateful to the Fundació Joan Salañer and IBM España, respectively, for a grant.

EXPERIMENTAL

Compounds (**9a-d**) were prepared according to reported procedures.[4-7] The same applies for compounds (**11a-d**,[4-7,11] **14a-d**,[8] **15a-d**,[8] **18f-h**,[10] **19f-h**,[10] and **20a-d**[4]). IR spectra were recorded on a Perkin-Elmer 683 and a Nicolet Magna 560 FTIR spectrophotometers. UV spectra were registered on a Hewlett-Packard 8450 spectrophotometer. NMR spectra were recorded on a Varian Gemini 300 spectrometer (300 and 75.5 MHz for ^{1}H and ^{13}C, respectively) using TSPNa as internal standard. MS spectra were obtained on a Hewlett-Packard 5995 A spectrometer. Elemental analyses were obtained on a Carlo-Erba CHNS-O/EA 1108 analyzer. Column chromatography was carried out on silica gel (70-230 mesh). HPLC analyses were performed with a Merck-Hitachi L-6200 with a D-2500 data module and a L-4000 UV detector with a fixed wavelength of 230 or 240 nm. All separations were carried out at room temperature at a flow rate of 1.0 mL/min.

2-Dicyanomethylene-1,2-dihydro-6-methylpyridine-3-carbonitrile (18e). 2.65 g (37.9 mmol) of methyl vinyl ketone and 5 g (37.9 mmol) of 2-amino-1,1,3-tricyanopropene were added to a solution of 0.1 g of sodium (4.34 mmol) in 30 mL of ethanol and the mixture was refluxed for 1.5 h. The solution was neutralized with a 6 M HCl solution and the solid obtained was filtered off and recrystallized from ethanol to give 2.41 g (35%) of **18e**, mp 223-224°C (decomp). IR ν: 3240, 3150 and 3080 (N-H), 2210, 2180 and 2160 (C≡N), 1610 and 1530 (C=C). ^{1}H NMR (DMSO-d_6) δ: 2.47 ppm (3H, d, *J*= 0.3 Hz, Me), 6.73 (1H, m, *J*= 7.8 Hz, *J*= 0.3 Hz, H-5), 8.09 (1H, d, *J*= 7.8 Hz, H-4), 5.84 (1H, s, exchangeable with D_2O, N-H). ^{13}C NMR (DMSO-d_6) δ: 156.5 (C2), 153.6 (C6), 149.5 (C4), 117.5 and 114. 8 (CN), 113.6 (C5), 97.5 (C3), 40.4 (=C-(CN)$_2$), 20.1 (Me). MS, m/z (%): 183 (16), 182 (76) [M$^+$], 181 (100), 117 (12). *Anal.* Calcd for $C_{10}H_6N_4$: C, 65.93; H, 3.29; N, 30.77. Found: C, 65.78; H, 3.33; N, 30.89.

2-Dicyanomethylene-1,2-dihydro-4-methyl-6-phenylpyridine-3-carbonitrile (18i). 3 g (19 mmol) of benzoylacetone and 5 g (37.9 mmol) of 2-amino-1,1,3-tricyanopropene were added to a solution of 0.6 g of sodium (26.1 mmol) in 40 mL of ethanol and the mixture was refluxed for 5 min. The solution was neutralized with 6 M HCl solution, the solid obtained was filtered off and recrystallized from ethanol to give 2.80g (58%) of **18i**, mp 227-228°C (decomp). IR ν: 3421 and 3242 (N-H), 2221, 2211 and 2188 (C≡N), 1632, 1598 and 1575 (C=C). ^{1}H NMR (DMSO-d_6) δ: 2.45 (3H, s, Me), 7.22 (1H, s, H-5), 7.57 and 7.95 (5H, m, Ph), 7.21 (1H, br s, exchangeable with D_2O, N-H). ^{13}C NMR (DMSO-d_6): δ: 157.7 (C2), 156.3 (C6), 154.4 (C4), 135.4, 130.6, 128.7 and 127.4 (Ph), 120.5 and 115.4 (CN), 111.9 (C5), 96.3 (C3), 20.8 (Me). MS, m/z (%): 258 (100)[M$^+$], 243 (12), 218 (15), 179 (9). *Anal.* Calcd for $C_{16}H_{10}N_4$: C, 74.42; H, 3.88; N, 21.70. Found: C, 74.54; H, 3.91; N, 21.54.

General Procedure for the Study of the Cyclization of 1,5-Dinitrile Systems in Different Solvents:

A stream of anhydrous hydrogen chloride or hydrogen bromide was bubbled through a suspension of the corresponding 1,5-dinitrile system in the desired solvent and at the desired temperature until saturation (1-2 h). The mixture was then stirred at rt in a closed vessel. The solvent was removed *in vacuo*, the resulting solid was suspended in methanol, neutralized with 2 M ammonia solution in methyl alcohol and concentrated under reduced pressure. The solid obtained was directly analyzed by reversed phase HPLC (RP-18 column, acetonitrile:water mixtures as the mobile phase). Results are summarized in Tables 1 to 5.

5-Amino-7-bromo-8-cyano-2-methyl-1,6-naphthyridine and 7-Amino-5-bromo-8-cyano-2-methyl-1,6-naphthyridine (19e-Br and 23e-Br). A mixture of 1.95 g (10.7 mmol) of **18e** and 40 mL of 33% HBr in AcOH was stirred for 24 h at rt. The resulting mixture was concentrated *in vacuo*, the residue was suspended in methanol and the pH adjusted to 9 with a 2 M ammonia solution in methanol. The solution was concentrated under reduced pressure, and the two isomers contained in the residue were separated by column chromatography (AcOEt:hexane, 1:1). **19e-Br**: mp > 300°C (AcOEt:hexane, 1:1).

IR ν: 3359, 3323 and 3135 (N-H), 2231 (C≡N), 1667 (N-H), 1599, 1578 and 1544 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 8.63 (1H, d, *J*= 8.7 Hz, H-4), 7.58 (1H, d, *J*= 8.7 Hz, H-3), 8.62 (2H, s, exchangeable with D_2O, NH_2), 2.71 (3H, s, Me). ^{13}C NMR (DMSO-d_6) δ: 165 (C5), 159 (C2), 152 (C8a), 145 (C7), 134 (C4), 123 (C3), 117 (CN), 109 (C4a), 96 (C8), 25 (Me). *Anal.* Calcd for $C_{10}H_7N_4Br$: C, 45.80; H, 2.67; N, 21.37. Found: C, 46.01; H, 2.79; N, 21.12. **23e-Br:** mp > 300ºC (AcOEt:hexane, 1:1). IR ν (cm^{-1}): 3408, 3339 and 3221 (N-H), 2216 (C≡N), 1683 (N-H), 1664 and 1605 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 8.13 (1H, d, *J*= 8.1 Hz, H-4), 7.07 (1H, d, *J*= 8.1 Hz, H-3), 7.06 (2H, s, exchangeable with D_2O, NH_2), 2.53 (3H, s, Me). ^{13}C NMR (DMSO-d_6) δ: 164 (C7), 161 (C2), 155 (C8a), 154 (C5), 135 (C4), 118 (C3), 117 (CN), 112 (C4a), 67 (C8), 25 (Me). MS, m/z (%): 265 (40), 264 (99), 263 (44), 262 (100) [M^+], 183 (85), 157 (14). *Anal.* Calcd for $C_{10}H_7N_4Br$: C, 45.80; H, 2.67; N, 21.37. Found: C, 45.93; H, 2.75; N, 21.29.

7-Amino-5-bromo-8-cyano-2-phenyl-1,6-naphthyridine (23f-Br). As stated above but using 3 g (12.3 mmol) of **18f** in 60 mL of 33% HBr/AcOH. The two isomers contained in the residue were separated by column chromatography (AcOEt:hexane, 2:1). **23f-Br**: mp > 300ºC (AcOEt:hexane, 2:1). IR ν: 3447, 3326 and 3212 (N-H), 2211 (C≡N), 1673 (N-H), 1644, 1608, 1593 and 1569 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 7.55-7.61 and 8.23-8.26 (5H, m, Ph), 7.80 (1H, d, *J*= 8.4 Hz, H-3), 8.32 (d, *J*= 8.4 Hz, 1H, H-4), 7.15 (2H, br s, NH_2). ^{13}C NMR (DMSO-d_6) δ: 162 (C7), 160 (C2), 156 (C8a), 155 (C5), 136 (C4), 115 (C3), 113 (C4), 68 (C8), 117 (CN), 138, 131 and 127 (Ph). *Anal.* Calcd for $C_{15}H_9N_4Br$: C, 55.56; H, 2.78; N, 17.28. Found: C, 55.75; H, 2.98; N, 17.10.

7-Amino-5-bromo-8-cyano-2,4-dimethyl-1,6-naphthyridine (23g-Br). As stated above but using 1 g (3.62 mmol) of **18g** in 20 mL of 33% HBr/AcOH. The residue obtained was column chromatographed (AcOEt:hexane, 3:1) to afford a mixture of the two isomers (**19g-Br**) and (**23g-Br**) in a 4.8:1 ratio. The assignment of the ^{1}H and ^{13}C NMR signals corresponding to **23g-Br** was carried out by comparison with a pure sample of **19g-Br**.[10] ^{1}H NMR (DMSO-d_6) δ: 6.85 (1H,s, H-3), 2.64 (3H, s, Me), 2.45 (3H, s, Me). ^{13}C NMR (DMSO-d_6) δ: 163 (C2), 162 (C7), 156 (C8a), 155 (C5), 150 (C4), 121 (C3), 111 (C4a), 68.0 (C8), 117 (CN), 24.4 (Me-C2), 21.8 (Me-C4).

7-Amino-5-bromo-8-cyano-2,4-diphenyl-1,6-naphthyridine (23h-Br). As stated above but using 2 g (6.3 mmol) of **18h** in 40 mL of 33% HBr/AcOH. The residue obtained was column chromatographed (AcOEt:hexane, 2:1) to afford a mixture of the two isomers (**19h-Br**) and (**23h-Br**) in a 1.4:1 ratio. The assignment of the ^{1}H and ^{13}C NMR signals corresponding to **23h-Br** was carried out by comparison with a pure sample of **19h-Br**.[10] ^{1}H NMR (DMSO-d_6) δ: 7.44 (1H, s, H-3), 7.38-7.42, 7.53-7.59 and 8.26-8.29 (10 H, m, Ph). ^{13}C NMR (DMSO-d_6) δ: 158 (C2), 156 (C7), 156 (C8a), 153 (C5), 141 (C4), 127-137 (Ph), 117 (C3), 110 (C4a), 68.3 (C8), 117 (CN).

5-Amino-7-bromo-8-cyano-2-phenyl-4-methyl-1,6-naphthyridine and 7-Amino-5-bromo-8-cyano-2-

phenyl-4-methyl-1,6-naphthyridine (19i-Br and 23i-Br). As stated above but using 1 g (3.88 mmol) of **18i** in 40 mL of 33% HBr/AcOH. The residue obtained was column chromatographed (AcOEt:Cl_2CH_2, 1:3) to afford a mixture of the two isomers (**19i-Br**) and (**23i-Br**) in a 1.7:1 ratio. The assignment of the ^1H and ^{13}C NMR signals corresponding to **23i-Br** was carried out by comparison with a pure sample of **19i-Br**, obtained by a second column chromatography (AcOEt:hexane, 3:1) of the aforementioned mixture. **19i-Br**: mp > 300ºC (AcOEt:hexane, 3:1). IR ν : 3366, 3274 and 3158 (N-H), 2233 (C≡N), 1635 (N-H), 1616,1599 and 1538 (C=C and C=N). ^1H NMR (DMSO-d_6) δ: 8.09 (1H, s, H-3), 8.34-8.31 and 7.62-7.60 (5H, m, Ph), 2.93 (3 H, s, Me). ^{13}C NMR (DMSO-d_6) δ: 159 (C5), 159 (C2), 154 (C8a), 148 (C4), 144 (C7), 137-127 (Ph), 121 (C3), 111 (C4a), 97(C8), 117 (CN), 23 (Me). **23i-Br** (mixture with **19i-Br**): ^1H NMR (DMSO-d_6) δ: 7.57 (1H, s, H-3), 7.55-7.56 and 8.23-8.25 (5H, m, Ph), 2.785 (3 H, s, Me). ^{13}C NMR (DMSO-d_6) δ: 158 (C2), 158 (C7), 156 (C8a), 151 (C5), 143 (C4), 138-127(Ph), 117 (C3), 106 (C4a), 68 (C8), 117 (CN), 23 (Me).

5-Amino-7-bromo-8-cyano-3-methyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22a-Br). A mixture of 3.2 g (0.016 mol) of **14a** and 450 mL of 33% HBr in AcOH was stirred for 1.5 h at 50ºC. The resulting mixture was concentrated *in vacuo*, the residue was suspended in 50 mL of methanol and the pH adjusted to 9 with a 2 M ammonia solution in methanol. The solution was concentrated under reduced pressure and the solid obtained was washed with water and dried over P_2O_5. Recrystallization from methanol afforded after filtration the corresponding 7-amino-5-bromo isomer (**15a-Br**), mp 290-291ºC.[8] The filtrate was concentrated and column chromatographed using AcOEt:hexane (2:3) as the eluent to yield 450 mg (10%) of **22a-Br**, mp 284-285ºC (AcOEt:hexane, 2:3). IR ν: 3500, 3295, 3240 and 3150 (N-H), 2220 (C≡N), 1715 (C=O), 1595 and 1560 (C=C and C=N). ^1H NMR (DMSO-d_6) δ: 1.16 (3H, d, *J*=7 Hz, Me-3), 2.31 (1H, dd, *J*=15 Hz, *J*=12 Hz, H-4), 2.66 (1H, m, H-3), 2.83 (1H, dd, *J*=15 Hz, *J*=6 Hz, H-4), 7.23 (2H, s, NH_2, exchangeable with D_2O), 10.20 (1H, br s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 15.0 (Me-3), 26.2 (C4), 33.3 (C3), 87.7 (C8), 98.6 (C4a), 115.7 (CN), 141.7 (C7), 148.5 (C8a), 158.1 (C5), 173.1 (C2). MS, m/z (%): 282 (88), 280 (M^+, 86), 267 (100), 265 (91). UV (CH_3CN/H_2O): λ_{max}(log ε): 201 (4.07), 248 (4.54), 273 (4.05), 302 (3.74).

5-Amino-7-bromo-8-cyano-4-methyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22b-Br). As stated above but using 3.2 g (0.016 mol) of **14b** in 450 mL of 33% HBr/AcOH. Stirring was maintained for 1.5 h at 50ºC. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (2:3) as the eluent to yield 177 mg (11%) of **22b-Br**, mp 275-276ºC (AcOEt:hexane, 2:3). IR ν: 3420, 3380, 3320 and 3210 (N-H), 2210 (C≡N), 1705 (C=O), 1605 and 1560 (C=C and C=N). ^1H NMR (DMSO-d_6) δ: 1.00 (3H, d, *J*=7 Hz, Me-4), 2.33 (1H, dd, *J*=15 Hz, *J*=1 Hz, H-3), 2.80 (1H, dd, *J*=15 Hz, *J*=6 Hz, H-3), 3.09 (1H, m, H-4), 7.31 (2H, s, NH_2, exchangeable with D_2O), 10.22 (1H, br s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 16.9 (Me-4), 24.4 (C4), 37.0 (C3), 87.9 (C8), 103.4 (C4a), 115.6 (CN), 141.8 (C7), 147.3 (C8a), 157.7 (C5),

169.7 (C2). MS, m/z (%): 282 (35), 280 (M^+, 33), 267 (100), 265 (95). UV (CH_3CN/H_2O): λ_{max} (log ε): 202 (4.10), 246 (4.55), 249 (4.56), 275 (4.10). *Anal.* Calcd for $C_{10}H_9N_4OBr$: C, 42.73; H, 3.23; N, 19.93. Found: C, 43.07; H, 3.50; N, 19.72.

5-Amino-7-bromo-8-cyano-3-phenyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22c-Br). As stated above but using 4 g (0.015 mol) of **14c** in 200 mL of 33% HBr/AcOH. Stirring was maintained for 24 h at rt. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (1:1) as the eluent to yield 308 mg (6%) of **22c-Br**, mp >300°C (AcOEt:hexane, 1:1). IR ν: 3520, 3315, 3270, 3180 and 2950 (N-H), 2240 (C≡N), 1740 (C=O), 1610 and 1580 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 2.90 (2H, m, H-4), 4.00 (1H, d×d, *J*=7 Hz, *J*=10 Hz, H-3), 7.30 (7H, m, Ph and NH_2, exchangeable with D_2O), 10.5 (1H, br s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 26.2 (C4), 44.8 (C3), 87.6 (C8), 98.7 (C4a), 115.6 (CN), 141.9 (C7), 148.0 (C8a), 158.1 (C5), 170.9 (C2), 127.1, 128.3 and 138.3 (Ph). MS, m/z (%): 344 (100), 342 (M^+, 92), 267 (49), 265 (46), 118 (55). UV (CH_3CN/H_2O): λ_{max}(log ε): 248 (4.56). *Anal.* Calcd for $C_{15}H_{11}N_4OBr$: C, 52.50; H, 3.23; N, 16.33. Found: C, 52.73; H, 3.43; N, 16.31.

5-Amino-7-bromo-8-cyano-4-phenyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22d-Br). As stated above but using 4 g (0.015 mol) of **14d** in 200 mL of 33% HBr/AcOH. Stirring was maintained for 24 h at rt. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (1:1) as the eluent to yield 720 mg (14%) of **22d-Br**, mp 249-252°C (AcOEt:hexane, 1:1). IR ν: 3460, 3340, 3200, and 2920 (N-H), 2215 (C≡N), 1690 (C=O), 1595 and 1550 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 2.66 (1H, dd, *J*=16 Hz, *J*=1 Hz, H-3), 3.14 (1H, dd, *J*=16 Hz, *J*=7 Hz, H-3), 4.32 (1H, d, *J*=6 Hz, H-4), 7.2 (7H, m, Ph and NH_2, exchangeable with D_2O), 10.2 (1H, s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 34.1 (C4), 38.0 (C3), 88.0 (C8), 101.0 (C4a), 115.5 (CN), 142.7 (C7), 148.5 (C8a), 158.3 (C5), 169.1 (C2), 126.8, 127.1, 128.6 and 139.6 (Ph). MS, m/z (%): 344 (100), 342 (M^+, 90), 267 (42), 265 (40). UV ($MeCN/H_2O$): λ_{max}(log ε): 248 (4.38). *Anal.* Calcd for $C_{15}H_{11}N_4OBr$: C, 52.50; H, 3.24; N, 16.33. Found: C, 52.56; H, 3.54; N, 16.19.

5-Amino-7-chloro-8-cyano-3-methyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22a-Cl). As stated above but using 3.2 g (0.016 mol) of **14a** in 450 mL of HCl/AcOH (prepared by bubbling hydrogen chloride in acetic acid until saturation). Stirring was maintained for 21 h at rt. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (2:3) as the eluent to yield 302 mg (8%) of **22a-Cl**, mp 268°C (AcOEt:hexane, 2:3).IR ν: 3500, 3300, 3250 and 3160 (N-H), 2220 (C≡N), 1710 (C=O), 1595 and 1565 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 1.16 (3H, d, *J*=7 Hz, Me-3), 2.32 (1H, dd, *J*=15 Hz, *J*=12 Hz, H-4), 2.66 (1H, m, H-3), 2.85 (1H, dd, *J*=15 Hz, *J*=6 Hz, H-4), 7.24 (2H, s, NH_2, exchangeable with D_2O), 10.05 (1H, br s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 14.9 (Me-3), 26.1 (C4), 33.3 (C3), 84.3 (C8), 98.4

(C4a), 114.5 (CN), 150.2 (C7), 148.3 (C8a), 158.2 (C5), 173.0 (C2). MS, m/z (%): 238 (25), 236 (M^+, 69), 223 (32), 221 (100). UV (MeCN/H_2O): λ_{max} (log ε): 246 (4.13), 275 (3.63), 310 (3.32).

5-Amino-7-chloro-8-cyano-4-methyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22b-Cl). As stated above but using 3.2 g (0.016 mol) of **14b** in 450 mL of HCl/AcOH. Stirring was maintained for 96 h at rt. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (1:1) as the eluent to yield 265 mg (7%) of **22b-Cl**, mp 274-275°C (AcOEt:hexane, 1:1). IR ν: 3450, 3310, and 3190 (N-H), 2210 (C≡N), 1715 (C=O), 1595 and 1565 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 1.01 (3H, d, *J*=7 Hz, Me-4), 2.34 (1H, dd, *J*=16 Hz, *J*=2 Hz, H-3), 2.81 (1H, dd, *J*=16 Hz, *J*=7 Hz, H-3), 3.10 (1H, m, H-4), 7.33 (2H, s, NH_2, exchangeable with D_2O), 9.98 (1H, br s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 17.0 (Me-4), 24.3 (C4), 37.0 (C3), 84.5 (C8), 103.2 (C4a), 114.4 (CN), 150.4 (C7), 147.2 (C8a), 157.7 (C5), 169.6 (C2). MS, m/z (%): 238 (10), 236 (M^+, 28), 223 (33), 221 (100). UV (MeCN/H_2O): λ_{max} (log ε): 245 (4.51), 247 (4.52), 273 (4.06). *Anal.* Calcd for $C_{10}H_9N_4OCl$: C, 50.75; H, 3.83; N, 23.67. Found: C, 50.46; H, 4.10; N, 23.67.

5-Amino-7-chloro-8-cyano-3-phenyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22c-Cl). As stated above but using 4 g (0.015 mol) of **14c** in 200 mL of HCl/AcOH. Stirring was maintained for 24 h at rt. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (1:1) as the eluent to yield 143 mg (3%) of **22c-Cl**, mp 268-272°C (AcOEt:hexane, 1:1). IR ν: 3480, 3340, 3150, 2920 and 2340 (N-H), 2215 (C≡N), 1715 (C=O), 1595 and 1565 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 2.90 and 4.00 (2H, m and 1H, m, H-3 and H-4), 7.30 (7H, m, Ph and NH_2, exchangeable with D_2O), 10.50 (1H, br s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 26.2 (C4), 44.8 (C3), 84.2 (C8), 98.5 (C4a), 114.3 (CN), 150.4 (C7), 147.9 (C8a), 158.1 (C5), 170.8 (C2), 127.1, 128.3 and 138.2 (Ph). MS, m/z (%): 300 (30), 298 (M^+, 100), 223 (12), 221 (36), 118 (71). UV (MeCN/H_2O): λ_{max} (log ε): 247 (4.47). *Anal.* Calcd for $C_{15}H_{11}N_4OBr$: C, 60.31; H, 3.71; N, 18.76. Found: C, 60.31; H, 4.26; N, 18.67.

5-Amino-7-chloro-8-cyano-4-phenyl-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one (22d-Cl). As stated above but using 4 g (0.015 mol) of **14d** in 200 mL of HCl/AcOH. Stirring was maintained for 24 h at rt. The crude material was recrystallized from methanol, the filtrate was concentrated and column chromatographed using AcOEt:hexane (1:1) as the eluent to yield 447 mg (10%) of **22d-Cl**, mp 233-235°C (AcOEt:hexane, 1:1). IR ν: 3440, 3340 and 3230 (N-H), 2220 (C≡N), 1700 (C=O), 1610 and 1560 (C=C and C=N). ^{1}H NMR (DMSO-d_6) δ: 2.76 (1H, d, *J*=16 Hz, H-3), 3.14 (1H, dd, *J*=16 Hz, *J*=6 Hz, H-3), 4.34 (1H, d, *J*=6 Hz, H-4), 7.25 (7H, m, Ph and NH_2, exchangeable with D_2O), 10.41 (1H, s, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6) δ: 34.2 (C4), 38.1 (C3), 84.7 (C8), 100.8 (C4a), 114.4 (CN), 151.2 (C7), 148.7 (C8a), 158.3 (C5), 169.2 (C2), 126.9, 127.2, 128.7 and 139.7 (Ph). MS,

m/z (%): 300 (31), 298 (M^+, 100), 223 (18), 221 (55). UV (MeCN/H_2O): λ_{max} (log ε): 248 (4.54), 306 (3.70), 352 (3.49). *Anal.* Calcd for $C_{15}H_{11}N_4OCl$: C, 60.31; H, 3.71; N, 18.76. Found: C, 60.10; H, 3.98; N, 18.58.

REFERENCES

1. (a) F. Johnson and R. Madroñero, 'Advances in Heterocyclic Chemistry', Vol. 6, ed. by A. R. Katritzky, Academic Press Inc, New York, 1966, pp. 95-146. (b) A. I. Meyers and J. C. Sircar, 'The Chemistry of the Cyano Group', ed. by Z. Rappoport, Interscience Publishers, London-New York, 1970, pp. 341-421. (c) S. Yangida, M. Okahara, and S. Komori, 'Advances in Organic Chemistry', Vol. 9, part 2, ed. by H. Böhme and H. G. Viehe, John Wiley and Sons, New York, 1979, pp. 527-571.
2. C. Grundmann, G. Wiesse, and S. Seide, *Ann.*, **1952**, *577*, 77.
3. Heating in acetic acid of the intermediate imino thioester caused the formation of a 3-amino-2-alkylthioisoquinoline in which the alkylthio group is beard by the carbon atom of the arylic nitrile present in 2-cyanobenzyl cyanide.
4. P. Victory, R. Nomen, O. Colomina, M. Garriga, and A. Crespo, *Heterocycles*, **1985**, *23*, 1135.
5. P. Victory and M. Garriga, *Heterocycles*, **1985**, *23*, 1947.
6. P. Victory and M. Garriga, *Heterocycles*, **1985**, *23*, 2853.
7. P. Victory and M. Garriga, *Heterocycles*, **1986**, *24*, 3053.
8. (a) P. Victory, J. Teixidó, and J. I. Borrell, *Heterocycles*, **1992**, *34*, 1905. (b) P. Victory, J. Teixidó, J. I. Borrell, and N. Busquets, *Heterocycles*, **1993**, *36*, 1.
9. P. Victory, J. Cirujeda, and A. Vidal-Ferran, *Tetrahedron*, **1995**, *51*, 10253.
10. P. Victory, N. Busquets, J. I. Borrell, J. Teixidó, B. Serra, J. L. Matallana, H. Junek, and H. Sterk, *Heterocycles*, **1995**, *41*, 1013.
11. J. I. Borrell, J. Teixidó, B. Martínez-Teipel, B. Serra, J. L. Matallana, M. Costa, and X. Batllori, *Coll. Czech. Chem. Commun.*, **1996**, *61*, 901.
12. (a) A. Gordon and A. R. Katritzky, *Tetrahedron Lett.*, **1968**, 2767. (b) P. Cieplak, P. Bash, U. C. Singh, and A. P. Kollman, *J. Am. Chem. Soc.*, **1987**, *109*, 6283. (c) P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **1976**, *98*, 171.
13. J. Teixidó, J. I. Borrell, B. Serra, C. Colominas, X. Batllori, J. F. Piniella, and A. Alvarez-Larena, *Tetrahedron*, **1997**, *53*, 4487.
14. R. Pascual, Master Thesis, Institut Químic de Sarrià, Universitat Ramon Llull, Barcelona, 1998.
15. B. Serra, *Estudi del mecanisme de ciclació de sistemes 1,5-dinitrilics amb possibilitat de tautomeria.* PhD Disertation, Universitat Ramon Llull, Barcelona, 1996.
16. C. Colominas, M. Orozco, F. J. Luque, J. I. Borrell, and J. Teixidó, *J. Org. Chem.*, **1998**, *63*, 4947.

Received, 13th July, 1998