

CYCLIZATION OF DINITRILES BY HYDROGEN HALIDES. 3.¹
 THE INFLUENCE OF THE TAUTOMERISM²

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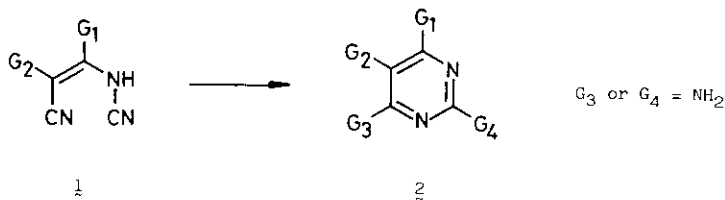
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Abstract - In order to study the possible influence of the tautomerism in the direction of cyclization by hydrogen halides of the 6-cyanamino-5-cyano-3,4-dihydro-2-pyridones (3), the non-tautomeric N-methylcyanamino substituted derivatives 10 have been synthesized. The reaction of 10 with hydrogen halides leads regiospecifically to the 4-halogeno-2-imino-1-methyl-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones 12, 13 and 14, showing the insufficient reactivity of the N-cyano group in front of the conjugated one. On the basis of the results of the cyclization of 10, an interpretation of the more complex cyclization of 3 is proposed.

The cyclization reaction of α,ω -dinitriles by addition of hydrogen halides is a useful method for the synthesis of heterocycles,³ and is known to be regiospecific when one of the cyano groups is bonded to a heteroatom or conjugated with a double bond or an aromatic ring, while the other one is attached to a saturated carbon. In these cases the former will always bear the halogen atom in the cyclized product.⁴

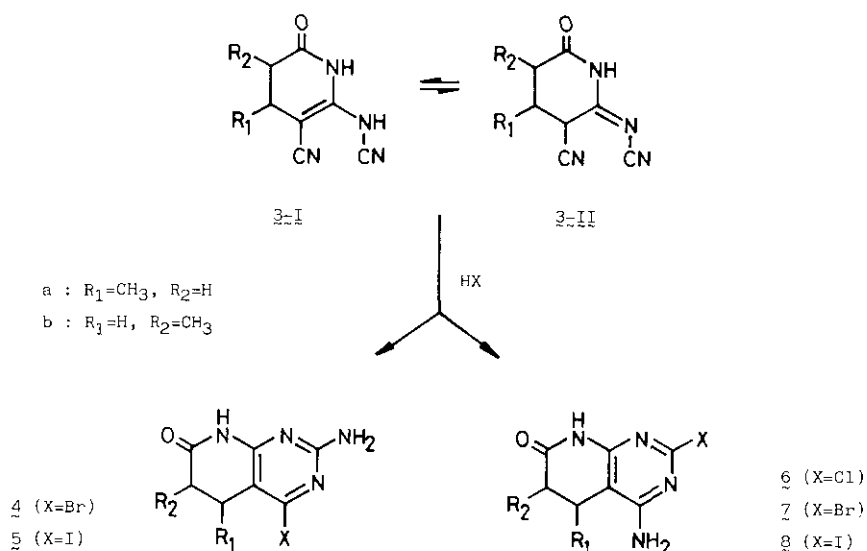
Dinitriles of the type 1 have received small attention although they are excellent precursors of the aminopyrimidines 2 (Scheme 1). In this case either or both of the two possible isomers could be expected since each cyano group of 1 fits with one of the above conditions, the direction of cyclization being unpredictable. However, in most of the few reported cases the reaction with hydrogen chloride is regiospecific leading to one or the other isomer depending on the substituent G_1 , being G_2 a cyano^{5,6} or a phenylsulphonyl group.⁷ None of the authors proposes an interpretation of these facts.

Scheme 1



We have recently reported⁸ the synthesis of 6-cyanamino-5-cyano-3,4-dihydro-2-pyridones (3) which are new particular cases of 1, and we have studied the cyclization of 3a¹ and 3b⁹ by addition of hydrogen halides. We found that hydrogen chloride always affords the 4-amino-2-chloro substituted pyrimidines 6 whereas hydrogen bromide and hydrogen iodide lead to both isomers, the direction of the cyclization depending on the thermal level. Thus, 4 and 5 are obtained at low temperature¹⁰ whereas 7 and 8 are the reaction products at high temperature. (Scheme 2).

Scheme 2



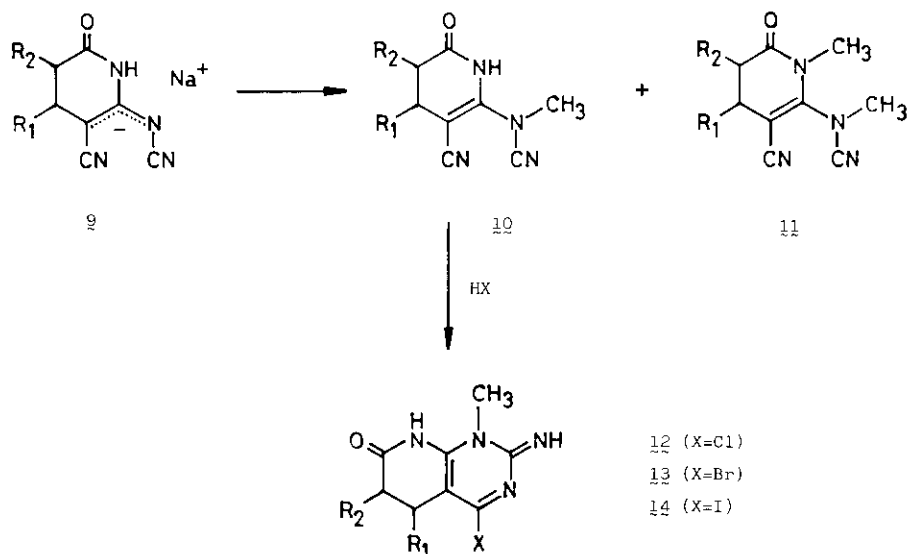
The complexity of these results cannot be easily explained by the sole effect of the temperature and the influence of the halide. It would rather seem that it is the tautomerism I-II which increases the possible reaction pathways. So, in order to achieve a better understanding of this type of cyclizations, we report here the synthesis of 10 -in which the structure of the tautomer I has been kept fixed- and the study of its cyclization reactions with hydrogen halides.

The preparation of 10 was carried out by the treatment of the sodium salts 9⁸ with dimethyl sulphate in refluxing acetone. Distillation of the solvent followed by extraction with dichloromethane gives a mixture from which 10 and the unavoidable dimethyl derivative 11 can be separated by column chromatography. The overall yield of 10 was 20%.

Spectroscopic data confirm the structure of 10a and 10b as that of the N-methylcyanamino substituted derivatives. So, the ir spectra in the solid state exhibit two stretching N-H bands (3200, 3115 and 3210, 3165 cm⁻¹ respectively) due to the cis associated amide, a C=O band (1695 and 1710 cm⁻¹), a C=C band (1635 and 1630 cm⁻¹), and two sharp C≡N bands (2235,

2200 and 2240, 2210 cm^{-1}) that can be assigned to the N-cyano and C-cyano group respectively.¹¹ Moreover, an only methyl group singlet appears at 3.40 and 3.33 ppm respectively in the ^1H -nmr spectra.

Scheme 3



The reaction of **10a** and **10b** with hydrogen chloride, hydrogen bromide and hydrogen iodide¹² using dioxane as the solvent affords, in each case, only one product independently of the thermal level (Scheme 3). Yields are lower (50-70%) than in the case of **3**, when the tautomerism is possible, and the reaction times required are longer, particularly for hydrogen chloride. The cyclization products **12a**, **13a** and **14a** show the same pattern in the ir and uv spectra, suggesting that the same isomer has been obtained. The same thing was found to be the case for **12b**, **13b** and **14b**.¹³

The ^{13}C -nmr spectra allow to determine the structure of the isomers obtained as that of the 4-halogeno-2-imino substituted compounds **12**, **13** and **14**. Spectral data are presented in table 1.

The regiospecificity of the cyclization of **10** shows that in the absence of tautomerism the conjugated cyano group is that which finally bears the halogen atom in the cyclized product in front of the N-bonded one, settling up the uncertainty which α,ω -dinitriles of the type **1** have presented, as regards the direction of cyclization. Furthermore, the influence of the other factors becomes null proving that they only have an effect when there are different reaction pathways because of tautomerism.

These new results allow to undertake a first tentative interpretation of the cyclization process when there is tautomerism considering the role of the tautomers themselves to-

Table 1. ^{13}C -nmr spectral data.^{14,15}

		C-2	C-4	C-4a	C-5	C-6	C-7	C-8a	CH ₃	NCH ₃
<u>12a</u>	(4-Cl)	160.6	153.7	106.2	28.1	37.7	178.4	153.6	18.1	30.5
<u>13a</u>	(4-Br)	159.7	147.7	108.8	30.2	37.8	178.4	153.2	18.0	30.4
<u>14a</u>	(4-I)	157.1	130.8	113.9	33.8	38.1	178.4	152.5	18.1	30.7
<u>12b</u>	(4-Cl)	161.2	153.5	101.6	30.0	33.7	181.9	153.7	15.8	30.6
<u>13b</u>	(4-Br)	159.7	147.8	104.5	32.1	33.9	181.3	153.1	15.5	30.8
<u>14b</u>	(4-I)	158.0	130.0	109.8	36.1	34.5	181.9	152.4	15.6	30.4

gether with the effect of the temperature and the nature of the halide involved.

Firstly, we have to consider the four cyano groups of 3 independently of whatever the equilibrium ratio between the tautomers may be,¹⁶ assuming a fast enough interconversion rate in the strong acidic medium. The N-cyano group of II and the C-cyano group of I are the most suitable to undergo the attack (Scheme 4). In fact, the C-cyano group of II is bonded to an sp^3 carbon and it is known that in these cases the other cyano group is that which undergoes the attack, as mentioned above. On the other hand, the N-cyano group of I has never shown any reactivity when this tautomer has been kept fixed in front of the conjugated one, the reaction having always taken place by the attack to the latter.

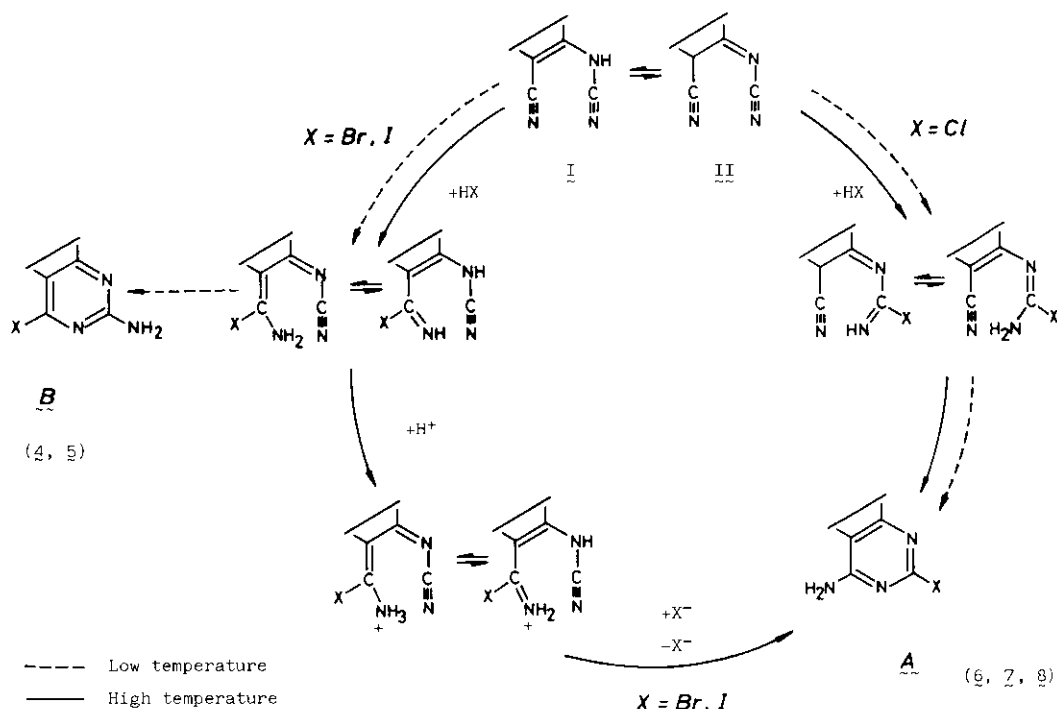
With regard to the results of the cyclization it is worth pointing out that hydrogen chloride, normally less reactive, yields, at low temperature, the same isomer which hydrogen bromide only does at high temperatures. It seems reasonable to assume that there are two different ways to arrive to A and it is the rise in temperature which allows to surpass an energy barrier generating the change of mechanism.¹⁷ This is the hypothesis presented in the scheme 4.

The reaction is always kinetically controlled and the direction of the cyclization depends on the nature of the halide. Thus, hydrogen chloride adds to the N-cyano of II whereas hydrogen bromide and hydrogen iodide react faster with the C-cyano of I. At low temperature the mechanism is always the same but the addition of a hydrogen halide takes place on different cyano groups leading to different isomers. However, from certain thermal level upwards the reaction involves the addition-elimination of halide raising A through a more energetic pathway. At the same time, hydrogen chloride still reacts the same way, probably due to the fact that the difference in reaction rate with the two active cyano groups is in this case greater than for the other halides, because neither its lower acidity provides sufficient concentration of I nor the less nucleophilic character of its anion can afford the addition-elimination step.

ACKNOWLEDGEMENTS

Support of this work by a grant from the Comisión Asesora de Investigación Científica y Técnica (0622/81) is gratefully acknowledged. One of us (M. G.) would like to thank the Ministerio de Educación y Ciencia of Spain for a grant within the Plan de Formación de Personal Investigador.

Scheme 4



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8. P. Victory, R. Nomen, O. Colomina, M. Garriga, and A. Crespo, *Heterocycles*, **23**, 1135 (1985).
9. P. Victory and M. Garriga, unpublished results.
10. Low temperature and high temperature refer to the ranges 10-15°C and 95-100°C due to the use of dioxane as the solvent.
11. T. Itaya and K. Ogawa, *Tetrahedron*, **38**, 1767 (1982), have reported compounds with N-methyl substituted cyanamino groups in which the C≡N stretching band appears at 2225 cm⁻¹.

12. C. J. Hoffmann, *Inorg. Synth.*, **7**, 180 (1963).
13. All of the products gave satisfactory elemental and spectral analysis. Selected data:
 - 10a: mp 137-138°C; ^{13}C -nmr (DMSO- d_6), δ 169.9 (C-2), 146.4 (C-6), 115.7 (CN), 111.6 (N-CN), 81.8 (C-5), 38.6 (N-CH $_3$), 37.6 (C-3), 26.7 (C-4), 18.0 ppm (CH $_3$); ms, 190 (M $^+$, 38), 175 (100).
 - 10b: mp 149.5-150°C; ^{13}C -nmr (DMSO- d_6), δ 172.8 (C-2), 146.4 (C-6), 116.3 (CN), 111.5 (N-CN), 75.2 (C-5), 38.7 (N-CH $_3$), 33.8 (C-3), 28.5 (C-4), 13.8 ppm (CH $_3$); ms, 190 (M $^+$, 90), 135 (60), 56 (100).
 - 12a: mp 232-233°C; ir (KBr), 3335, 3240, 3170, 1655, 1580, 1565 cm^{-1} ; ^1H -nmr (DMSO- d_6), δ 7.81 (br s, 2H, NHCO and NH), 3.49 (s, 3H, N-CH $_3$), 3.13 (dxq, J_{cb} = 6.5 Hz, J_{cd} = 6.9 Hz, 1H, C $_5$ -H $_c$), 2.50 (dxd, J_{ba} = 15.8 Hz, J_{bc} = 6.5 Hz, 1H, C $_6$ -H $_b$), 2.18 (d, J_{ab} = 15.8 Hz, 1H, C $_6$ -H $_a$), 1.01 ppm (d, J_{dc} = 6.9 Hz, 3H, CH $_3$); ms, 226 (M $^+$, 43), 228 (15), 211 (26), 198 (19), 183 (100).
 - 13a: mp 234-236°C; ir (KBr), 3325, 3240, 3180, 1650, 1580, 1560 cm^{-1} ; ^1H -nmr (DMSO- d_6), δ 7.75 (br s, 2H, NHCO and NH), 3.45 (s, 3H, N-CH $_3$), 3.05 (dxq, J_{cb} = J_{cd} = 7 Hz, 1H, C $_5$ -H $_c$), 2.50 (dxd, J_{ba} = 15 Hz, J_{bc} = 7 Hz, 1H, C $_6$ -H $_b$), 2.15 (d, J_{ab} = 15 Hz, 1H, C $_6$ -H $_a$), 1.00 ppm (d, J_{dc} = 7 Hz, 3H, CH $_3$); ms, 270 (M $^+$, 60), 272 (59), 255 (28), 242 (29), 227 (100).
 - 14a: mp 235-237°C; ir (KBr), 3320, 3230, 3150, 1665, 1645, 1550 cm^{-1} ; ^1H -nmr (DMSO- d_6), δ 7.78 (br s, 2H, NHCO and NH), 3.43 (s, 3H, N-CH $_3$), 2.93 (dxq, J_{cb} = 6.2 Hz, J_{cd} = 6.8 Hz, 1H, C $_5$ -H $_c$), 2.50 (dxd, J_{ba} = 14.9 Hz, J_{bc} = 6.2 Hz, 1H, C $_6$ -H $_b$), 2.20 (d, J_{ab} = 14.9 Hz, 1H, C $_6$ -H $_a$), 0.96 ppm (d, J_{dc} = 6.8 Hz, 3H, CH $_3$); ms, 318 (M $^+$, 28), 304 (40), 303 (23), 290 (23), 289 (100), 275 (28).
 - 12b: mp 233-235°C; ir (KBr), 3330, 3230, 3160, 1665, 1650, 1580 cm^{-1} ; ^1H -nmr (DMSO- d_6), δ 7.79 (br s, 2H, NHCO and NH), 3.45 (s, 3H, N-CH $_3$), 2.90-2.30 (m, 3H, CH and CH $_2$), 1.07 ppm (d, J = 5.3 Hz, 3H, CH $_3$); ms, 226 (M $^+$, 32), 228 (11), 211 (15), 198 (18), 183 (100).
 - 13b: mp 234-236°C; ir (KBr), 3500, 3330, 3150, 1670, 1570 cm^{-1} ; ^1H -nmr (DMSO- d_6), δ 7.22 and 6.00 (br s, 2H, NHCO and NH), 3.42 (s, 3H, N-CH $_3$), 2.88-2.16 (m, 3H, CH and CH $_2$), 1.16 ppm (d, J = 5.9 Hz, 3H, CH $_3$); ms, 270 (M $^+$, 43), 272 (43), 255 (13), 242 (28), 227 (100).
 - 14b: mp 237-238°C; ir (KBr), 3380, 3310, 3220, 3140, 1660, 1645, 1550 cm^{-1} ; ^1H -nmr (DMSO- d_6), δ 7.65 (br s, 2H, NHCO and NH), 3.41 (s, 3H, N-CH $_3$), 2.80-2.26 (m, 3H, CH and CH $_2$), 1.07 ppm (d, J = 5.2 Hz, 3H, CH $_3$); ms, 318 (M $^+$, 22), 304 (30), 290 (15), 275 (32), 142 (100).
14. Recorded in a Varian XL-200/F-19 and a Bruker AC-80 apparatus using DMSO- d_6 as the solvent.
15. In the table 1 of our last report (ref. 1, p. 2856), the chemical shifts of carbons C-4 and C-4a of compounds 5 and 7 must be interchanged.
16. Although we first reported a 1:1 equilibrium ratio between the tautomers I-II, a more detailed study has shown that only II is present in solution of dioxane. Furthermore, in the ^{13}C -nmr spectra there are no signals which could be assigned to the carbons C-5 and C-6 of 3-II on the basis of the chemical shifts observed for 10.
17. This seems to be in good agreement with the observations of F. Klages, R. Ruhnau, and W. Hauser, *Ann. Chem.*, **626**, 60 (1959), who found that the temperature determines which of the salts is formed -nitrilium or imonium salt- in the reaction between hydrogen chloride and benzonitrile-antimony pentachloride adduct.

Received, 21st July, 1986