1,2,3,4-TETRAHYDRO-1,6-NAPHTHYRIDINES. PART 2. FORMATION AND UNEXPECTED REACTIONS OF 1,2,3,4-TETRAHYDRO-7*H*-PYRANO[4,3-*b*]PYRIDINE-2,7-DIONES

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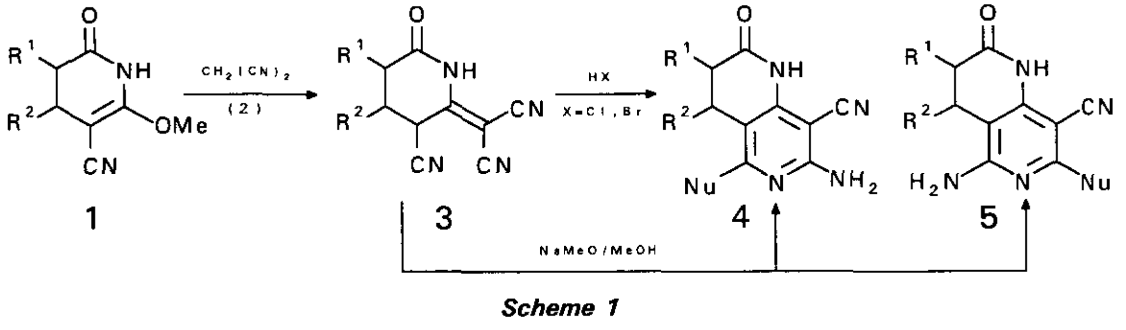
Abstract- The nucleophilic substitution of the enol methoxy group of pyridones (**1**) by methyl cyanoacetate led to (*Z*)-5-cyano-6-cyanomethoxycarbonylmethylenepiperidones (**6**), which underwent cyclization in acid medium to 1,2,3,4-tetrahydro-7*H*-pyrano[4,3-*b*]pyridine-2,7-diones (**7**). Surprisingly, the treatment of **7** with ammonia yielded the 5-cyano-6-cyanomethyl substituted pyridones (**11**) which were not accessible by reaction of **1** with $NaCH_2CN$.

INTRODUCTION

In a recent paper our group has reported a new synthesis of 3,4-dihydro-1,6-naphthyridine-2(1*H*)-ones by cyclization of dinitriles both in acid and basic medium[1]. Thus, the treatment of the pyridones **1** with malononitrile (**2**) yielded the corresponding substitution products **3** which underwent cyclization in acid medium (HCl or HBr in dioxane/benzene) to afford the 7-amino-5-halo-8-cyano-1,2,3,4-tetrahydro-1,6-naphthyridin-2-ones (**4**) (Nu = Cl, Br). The direction of the cyclization is independent of the thermal level employed and the nature and position of the substituents R^1 and R^2. On the other hand, when the cyclization was carried out in basic medium (NaOMe/MeOH), the two possible isomers **4** and **5** (Nu = MeO) were obtained but the proportion of **4** to **5** decreased when R^2 is not H.

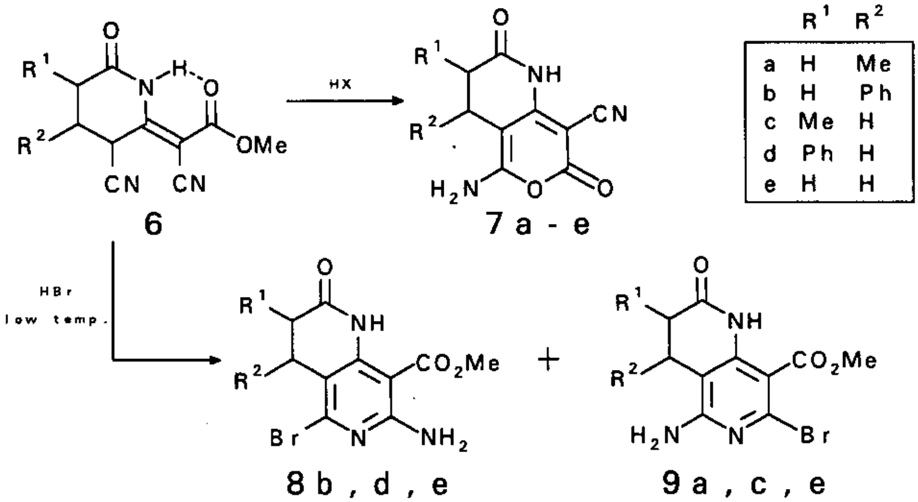


Scheme 1

RESULTS AND DISCUSSION

These results prompted us to assay the substitution of the enol methyl ether of **1** by carbon nucleophiles such as these corresponding to phenylacetonitrile, malonamide, dimethyl malonate, ethyl acetoacetate, acetonitrile, ethyl acetate, cyanoacetic acid, monomethyl malonic acid, and nitromethane, but no reaction took place. Only when **1a-e** were treated with methyl cyanoacetate in NaOMe/MeOH, the corresponding substitution products **6a-e** were obtained[2] which exhibit a strong intramolecular hydrogen bond between the ester carbonyl group and the cyclic N-H group.

Now we wish to report some singular and even unexpected results obtained in the study of the reactivity of **6a-e**. Thus, while the treatment of **6a-e** in basic medium (aqueous KOH, NaOMe/MeOH) gave complex crude materials, the treatment in acid media (HCl, HBr, CF_3CO_2H) yielded[3] the corresponding 5-amino-8-cyano-1,2,3,4-tetrahydro-7*H*-pyrano[4,3-*b*]pyridine-2,7-diones (**7a-e**) by cyclization of the ester group and the cyano group linked to the ring[4], independently of the nature and position of the substituents R^1 and R^2 (Scheme 2).

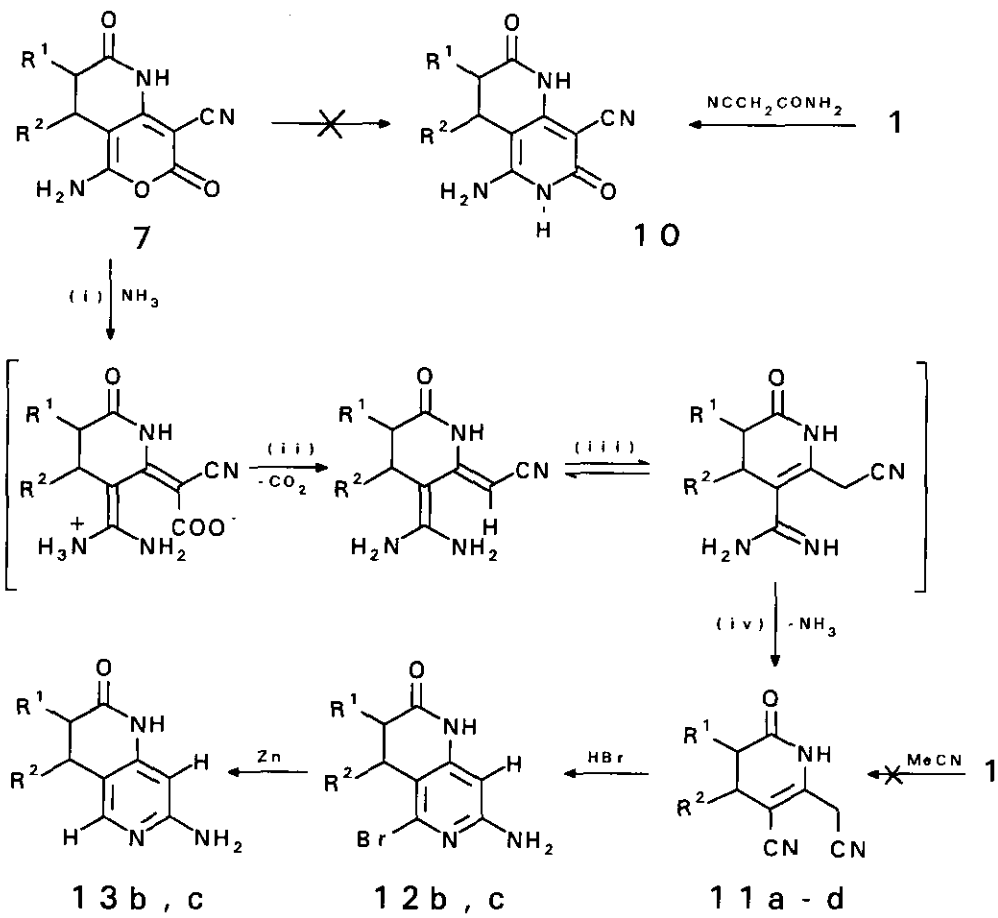


Scheme 2

Although the reaction was mainly independent of the nature of the hydrogen halide and the reaction temperature employed, a mixture of **7** and the 1,6-naphthyridines **8** and **9** was obtained when it was carried out using HBr at low temperature. However, if the temperature or the polarity of the solvent were increased, the formation of **7** was favored.

As for the direction of the cyclization that leads to the 1,6-naphthyridines **8** and **9**, it strongly depends on the nature of the substituents $R^1$and R^2. Thus, **6b** and **6d** (R =Ph) afforded the 7-amino-5-bromo substituted isomers **8b** and **8d**, while **6a** and **6c** (R =Me) yielded the 5-amino-7-bromo-1,6-naphthyridines **9a**[5] and **9c**. However, when R^1 = R^2 = H (**6e**) both isomers **8e** and **9e** were obtained, what has been of great value for the spectroscopic assignment[6] of the cyclization products, once the position of the halogen in structures **9** was established[7]. Studies are being carried out in order to cast light on the substituents effect.

On the other hand, in order to confirm chemically their structure, the treatment of the pyranopyridines **7** with NH_3 was assayed[8] to obtain the previously described[1] 1,6-naphthyridines **10**. Surprisingly, the pyridones **11a-d** were obtained instead of **10a-d**. These compounds formally correspond to the substitution product of the enol methyl ether of **1a-d** by $NaCH_2CN$ and were not directly accessible. Their formation could be rationalized as follows: (i) Nucleophilic attack at C-5 which opens the pyrane ring[9], (ii) decarboxylation, (iii) tautomerization (amidine formation), and (iv) elimination of NH_3 from the unstable amidine[10] which is converted into the nitrile linked to C-5[11].



Scheme 3

The preliminary assays of cyclization with HBr of **11b,c**, which contrary to **3** present an endocyclic double bond, have solely yielded the 7-amino-5-bromo-1,6-naphthyridines **12b,c** independently of the thermal level employed. The structural assignment has been carried out by dehalogenation to **13b,c** where no coupling between the pyridine ring protons has been observed in ^{1}H nmr. Experiments are currently being undertaken to explode the synthetic utility of the **7** to **11** conversion procedure.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. P. J. Victory, J. Teixidó, and J. I. Borrell, *Heterocycles*, **1992**, *34 (10)*, in press.
2. In a typical experiment: A mixture of 0.050 mol of the pyridone **1a**[1], 0.050 mol of methyl cyanoacetate and 0.050 mol of sodium in 300 ml of anhydrous dioxane and 5 drops of methanol, was heated under reflux for 22 h. The dark solid obtained was filtered off, suspended in 60 ml of ethanol and neutralized with an equimolar amount of ethanolic HCl. The solid obtained was filtered and the mother liquor was concentrated *in vacuo* to give an extra crop of solid. The combined solids were washed with water, ethanol, and ether, and dried *in vacuo* over P_2O_5. The crude material was recrystallized from AcOEt/EtOH or AcOEt/hexane to give (*Z*)-5-cyano-6-cyanomethoxycarbonylmethylene-4-methylpiperidone (**6a**), yield: 74%, mp 158-159 °C. Ir ν: 3225, and 3190 (NH), 2250, and 2225 (CN), 1750, and 1735 (C=O), 1690, and 1615 cm^{-1} (C=C). ^{1}H Nmr (d_6-DMSO) δ: 1.20-1.40 (3H, m, Me), 2.30-3.00 (3H, m, H-3 and H-4), 3.80 (3H, s, CO_2Me), 4.70-4.90 (1H, m, C<u>H</u>-CN, exchangeable with D_2O), and 11.00 (1H, bs, NH, exchangeable with D_2O). ^{13}C Nmr (d_6-DMSO) δ: 167.5 (C-2), 35.1 (C-3), 27.1 (C-4), 34.4 (C-5), 158.3 (C-6), 81.2 [<u>C</u>CNCO$_2$Me], 113.8, and 112.7 (CN), 164.6 (<u>C</u>O$_2$Me), 52.9 (CO$_2$<u>Me</u>), and 17.1 (Me). Ms, m/z (relative intensity): 233 (M$^+$, 8), 69 (100). *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C , 56.65; H, 4.75; N, 18.02. Found: C, 56.66; H, 4.68; N, 18.10.
3. In a typical experiment: A stream of anhydrous hydrogen bromide was bubbled through a suspension of 0.01 mol of the piperidone **6b** in 150 ml of dioxane at reflux temperature until saturation (1-2 h). The stream was maintained for 0.5-1 h, then was stopped and the mixture was stirred at room temp. for 1 h and for 24 h in a closed vessel. The hydrobromide of the cyclization product was filtered and the solution was concentrated *in vacuo* to give a crude solid. Both solids were treated separately as follows. The solid is suspended in methanol and neutralized with methanolic ammonia solution. The solid obtained was filtered, washed with water, cold ethanol, and ether, and dried *in vacuo* over P_2O_5. The crude material was recrystallized from ethanol/acetone to give 5-amino-8-cyano-1,2,3,4-tetrahydro-4-phenyl-7*H*-pyrano[4,3-*b*]pyridine-2,7-dione (**7b**), yield: 94%, mp 247-249 °C. Ir ν: 3400, 3310, 3200, and 3140 (NH), 2220 (CN), 1705, and 1680 (C=O), 1635 cm^{-1}. ^{1}H Nmr (d_6-DMSO) δ: 2.70-4.24 (3H, m, H-3 and H-4), 7.20 (5H, m, Ph), and 8.90 (3H, bs, NH, exchangeable with D_2O). ^{13}C Nmr (d_6-DMSO) δ: 169.5 (C-2), 38.7 (C-3), 33.3 (C-4), 83.0 (C-4a), 157.0 (C-5), 162.2 (C-7), 65.5 (C-8), 159.5 (C-8a), 115.3 (CN), 140.5, 128.7, 127.1, and 126.7 (Ph). Uv (EtOH): 244 nm (log ε, 4.30), 350 (4.00). Ms, m/z (relative intensity): 281 (M$^+$, 16), 237 (30), 44 (100). *Anal.* Calcd for $C_{15}H_{11}N_3O_3$: C , 64.05; H, 3.94; N, 14.94. Found: C, 63.86; H, 4.03; N, 15.00. When the reaction was carried out at room temperature using benzene as solvent, a mixture of **7b** (10%) and the naphthyridine **8b** (57%) was obtained, but if a mixture of benzene/dioxane (1:1) was used the yields were 25% of **7b** and 47% of 7-amino-5-bromo-

1,2,3,4-tetrahydro-8-methoxycarbonyl-4-phenyl-1,6-naphthyridin-2-one (**8b**), mp 254-256 °C. Ir ν: 3440, 3385, 3280, and 3170 (NH), 1715, and 1695 (C=O), 1615 cm^{-1}. ^1H Nmr (d_6-DMSO) δ: 2.60-3.40 (2H, m, H-3), 3.90 (3H, s, OMe), 4.50 (1H, d, *J* = 5 Hz, H-4), 7.30 (5H, m, Ph), 7.40 (2H, bs, NH_2, exchangeable with D_2O) and 10.50 (1H, bs, NH, exchangeable with D_2O). ^{13}C Nmr (d_6-DMSO) see Table 1. Ms, m/z (relative intensity): 375 (M^+, 49), 377 (M^+ +2, 50), 298 (100), 300 (95). *Anal.* Calcd for $C_{16}H_{14}N_3O_3Br$: C , 51.08; H, 3.75; N, 11.17; Br, 21.24. Found: C, 50.98; H, 3.77; N, 11.03; Br, 21.05. The use of a mixture of CF_3CO_2H and ethanol at room temperature afforded **7b** in 94% yield.

4. This kind of cyclization has been previously reported by H. Kristinsson, T. Winkler, G. Rihs, and H. Fritz, *Helv. Chim. Acta,* **1985**, *68*, 1155.
5. Trace levels of **8a** have been detected in the reaction crudes.
6.

	8a	8b	8d	8e	9a	9c	9e
C-2	169.5	168.6	170.3	170.1	169.8	172.3	170.0
C-3	36.4	39.8	44.3	29.1	36.6	33.0	28.9
C-4	29.9	37.7	31.4	23.7	24.3	26.3	18.4
C-4a	111.3	108.8	106.6	106.8	103.1	100.1	98.2
C-5	145.1	146.2	144.9	145.0	157.0	157.1	157.1
C-7	157.7	158.0	157.6	157.6	137.5	137.4	137.1
C-8	90.9		90.5	90.6	106.0	105.0	105.7
C-8a	148.3	149.1	148.6	149.1	144.4	145.4	145.2
CO	167.3	167.1	167.1	167.3	165.9	165.6	165.6
OMe	52.6	52.3	52.4	52.5	52.5	52.2	52.4
R	18.7	141.0 128.6 126.7 126.5	137.9 128.3 127.9 127.0		17.1	15.0	

Table 1: ^{13}C nmr spectral data of naphthyridines 8 and 9

7. The position of the halogen in structures **9** has been confirmed chemically by reaction with hydrazine, which afforded a dihydropyrazole ring by substitution of the bromine in C-7 and cyclization with the ester group in C-8.
8. The treatment of pyranes with RNH_2 is a common method for the synthesis of pyridines. In particular, V, K. Jhalani, L. P. Ghalsasi, S. P. Acharya, and R. N. Usgaonkar, *Indian J. Chem. Sect. B.*, **1989**, 173, describe the synthesis of 1,6-naphthyridines using this procedure.
9. The nucleophilic attack at C-5 instead of at C-7 is easily understandable according to the principle of vinylology (C-5 is linked to two heteroatoms and to two electron withdrawing groups, CN and CO). In other words, this reaction is a vinylogous extension of the nucleophilic substitutions carried on **1**.
10. Unsubstituted amidines can be prepared in the form of hydrochlorides by treatment of nitriles with NH_3/NH_4Cl under pressure. However, amidines are usually unstable and regenerate the original nitrile (For a review of amidines, see J. Gautier, M. Miocque, and C. C. Farnoux, in: *The Chemistry of Amidines and Imidates*; S. Patai (Ed.); New York: John Wiley and Sons, 1975; pp 283-348).
11. In a typical experiment: 0.01 mol of **7b** and 30 ml of aqueous ammonia were stirred at room temperature for 2-3 h. The solvent was eliminated *in vacuo*,the residue was neutralized with 6 M HCl, extracted with 3x30 ml of

CH_2Cl_2 and dried with $MgSO_4$. After solvent elimination, the crude material was recrystallized from CH_2Cl_2/hexane (1:10) to give 5-cyano-6-cyanomethyl-4-phenyl-1,2,3,4-tetrahydro-2-pyridone (11b), yield: 74%, mp 117-118 °C. Ir ν: 3240, and 3185 (NH), 2265, and 2215 (CN), 1715 (C=O), 1650 cm^{-1} (C=C). ^1H Nmr ($CDCl_3$) δ: 2.40-3.75 (3H, m, H-3 and H-4), 3.50 (2H, s, C<u>H</u>$_2$-CN), 7.10 (5H, m, Ph), and 8.90 (1H, bs, NH, exchangeable with D_2O). ^{13}C Nmr ($CDCl_3$) δ: 169.0 (C-2), 39.2 (C-3), 36.9 (C-4), 92.1 (C-5), 141.5 (C-6), 20.8 [<u>C</u>H_2CN], 116.5, and 113.7 (CN), 138.7, 129.2, 128.1, and 126.6 (Ph). Uv (EtOH): 275 nm (log ε, 4.08). Ms, m/z (relative intensity): 237 (M^+, 97), 77 (100). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C , 70.87; H, 4.67; N, 17.71. Found: C, 70.82; H, 4.56; N, 17.85.

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