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Dedicated to Professor Valer Fărcăşan at his 85th anniversary

REACTIONS OF THE 3-CYANO-10-METHYL-PYRIDO[3,2-g]QUINOLIN-4-ONE

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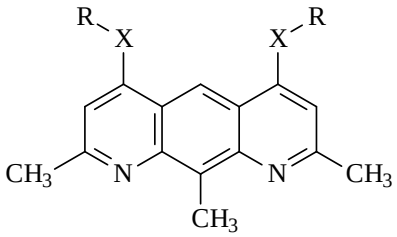
ABSTRACT. The reaction of 3-cyano-10-methyl-pyrido[3,2-g]quinoline-4-one **1** with alkylhalides in alkaline conditions under PTC conditions is described. A mixture of N-alkyl- and O-alkyl-3-cyano-10-methyl-pyrido[3,2-g]quinoline was obtained in low yields as a consequence of an ambident nucleophile generated by **1,** while the main competitive reaction appears to be the hydration of the carbonyl bond in alkaline medium.

INTRODUCTION

Interesting biological activity of symmetrically 4,6-bis-alkylated-pyrido[3,2-g]quinoline derivatives was previously reported [1-5]. The chemical synthesis of these compounds was performed starting with 2,8,10-trimethyl-pyrido[3,2-g]quinoline-4,6-dione and various alkylhalides under phase transfer catalysis (PTC) conditions.

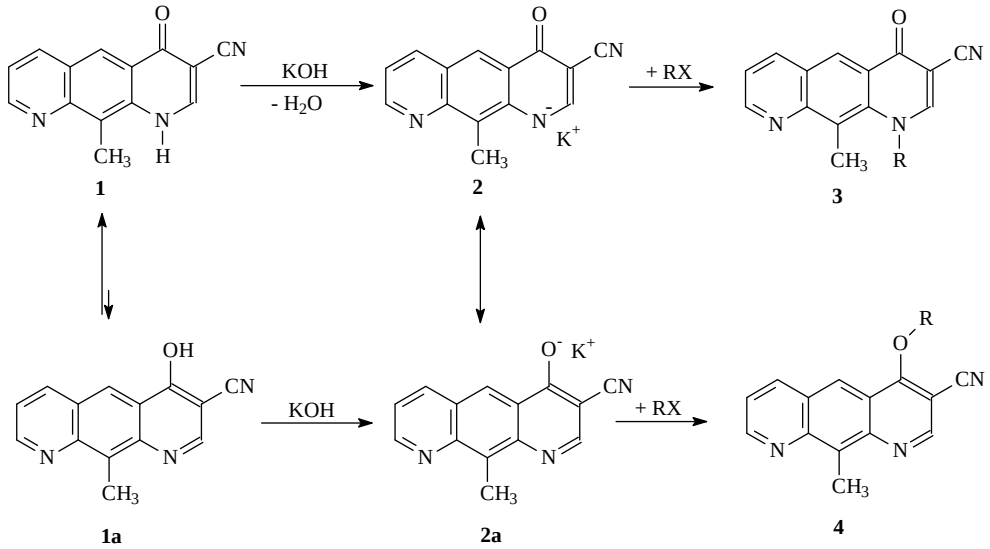


X = O, N, S
R = $-CH_2-CH_2-CH_2-N(CH_3)_2$
$-CH_2-CH_2-N(C_2H_5)_2$

Attempts to synthesize new 4-alkoxy-3-cyano-10-methylpyrido[3,2-g]quinoline **4** by the same method (S_N reaction of alkylhalides using 3-cyano-10-methylpyrido[3,2-g]quinoline-4-one **1** as a nucleophile under PTC conditions) are discussed.

RESULTS AND DISCUSSIONS

3-Cyano-10-methyl-pyrido[3,2-g]quinoline-4-one **1**, synthesized as previously reported and analyzed by NMR and IR spectroscopy [6], was found to present in DMSO solution only one of the two possible tautomeric forms shown in Scheme 1.



Scheme 1

The acidity of **1**, suggested by the low field signal of the proton (δ = 12.2 ppm in DMSO-d_6 solution) enabled us to propose the formation of the two potassium salts **2** and **2a** (Scheme 1). A high electron density could be expected either to the nitrogen atom in structure **2** or to the oxygen atom in the resonance structure **2a**. This ambident nucleophile could be the reagent in S_N reaction of several alkylchlorides.

The alkylation reaction of **1** was experimented under PTC conditions, using aromatic hydrocarbon solvent (toluene, xylene), concentrated aqueous potassium hydroxide and tetrabutylamonium bromide (TBAB) as phase transfer agent. From the organic layer of the PTC reaction mixture, two alkyl-derivatives were identified by TLC chromatography and analyzed by means of ^{1}H-NMR spectroscopy. After 72 hours reaction time, a mixture of alkyl-derivatives **3** and **4** was obtained (table 1). The overall yield of the alkylation reaction was found to be very low (5%).

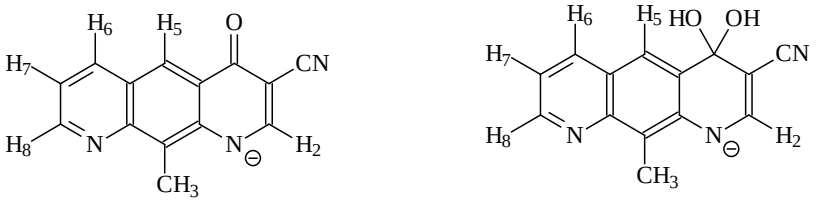
Table 1.

Alkylation of **1** under PTC conditions

Alkyl halide RX	**4** :**3** ratio	Solvent (reaction temperature)
Cl-CH_2-CH_2-N(Et)$_2$	1 : 3	toluene (110ºC)
	1 : 3	xylene (130ºC)

In contrast, a large amount of another reaction product separated as a precipitate between the two layers of the PTC reaction mixture. After filtration the precipitate was found to be highly soluble in water. The ^{1}H-NMR analysis of

this reaction product revealed a mixture of two compounds with similar coupling patterns characteristic to 4-substituted-3-cyano-10-methyl-pyrido[3,2-g]quinoline structures separated by slightly different shielding effects ($\Delta\delta_{similar\ H}$= 0.1 ppm) These two compounds, **6** and **2**, were found in 5:1 ratio according to their ^{1}H-NMR signals integrals. A detail containing the aromatic protons region of ^{1}H-NMR spectrum is shown in fig. 1.



2 **6**

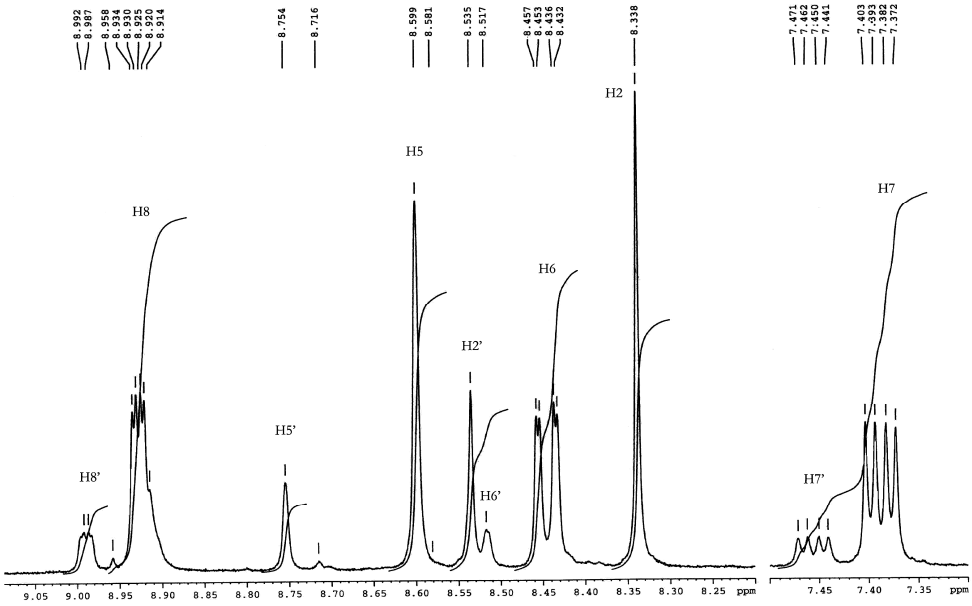
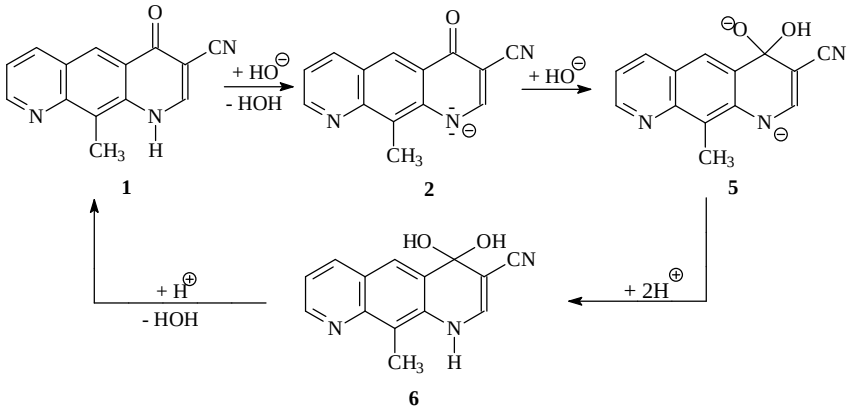


Fig. 1. 400 MHz ^{1}H-RMN of the by-products of PTC reaction.

The two compounds in the mixture are: the potassium salt **2** (scheme 1) and the *geminal*-diol **6** (scheme 2), both obtained in the presence of KOH strong base used in PTC reaction. The hydration of the heterogenous C=O bond could be taken into account, due to the stabilizing effect of the nitrile group which lies in the neighboring position and the electron withdrawing effect of the quinoline moiety in the structure of compound **6**.



Scheme 2

The diagnosis of hydration was proved by supplementary experimental data. Thus, by the titration of the mixture with NaOH and back titration with HCl a curve with the aspect of a hysteresis loop was obtained (fig. 2).

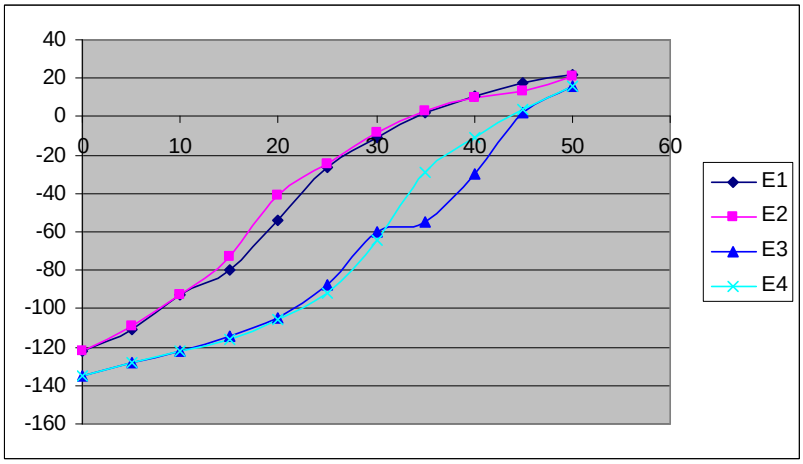


Fig. 2. Titration curve of reaction mixture. E_1: HCl 0,001N titration curve; E_2: HCl 0,001N titration curve registered after 5 min. equilibration time; E_3: NaOH 0,001N titration curve; E_4: NaOH 0,001N titration curve registered after 5 min. equilibration time.

The acido-basic properties of **1** make possible the anion structure **2** to be obtained by the ionization of the acidic N-H group in the presence of one equivalent of NaOH. Subsequently the nucleophilic addition of a OH^- to the heterogenous carbonyl double bond of **2,** may produce the hydrated 3-cyano-10-methyl-pyrido[3,2-g]quinoline-4-one anion **5**. During the back titration, in acidic media, the anion **5** is neutralized to 3-cyano-10-methyl-pyrido[3,2-g]dihydroquinolin-4,4-diol **6**, which regenerates the starting compound **1** by water elimination.

The recorded UV spectrum of the neutral solution (obtained by titration) contains three absorption bands situated at 198, 247 and 279 nm. The same pattern was obtained for the absorption bands of the solution in basic medium. In acidic medium a batochromic shift of 9 nm was recorded for the position of the absorption band situated at the highest wavelength (fig. 3).

According to these UV data we suggest the formation of compound **6** in acidic media; the batochromic shift could be expected for the structure **6** as compared to structures **1** and **2** because of the fact that the cross conjugation of the lone pair of electrons from the nitrogen atom with the carbonyl and nitrile groups is altered.

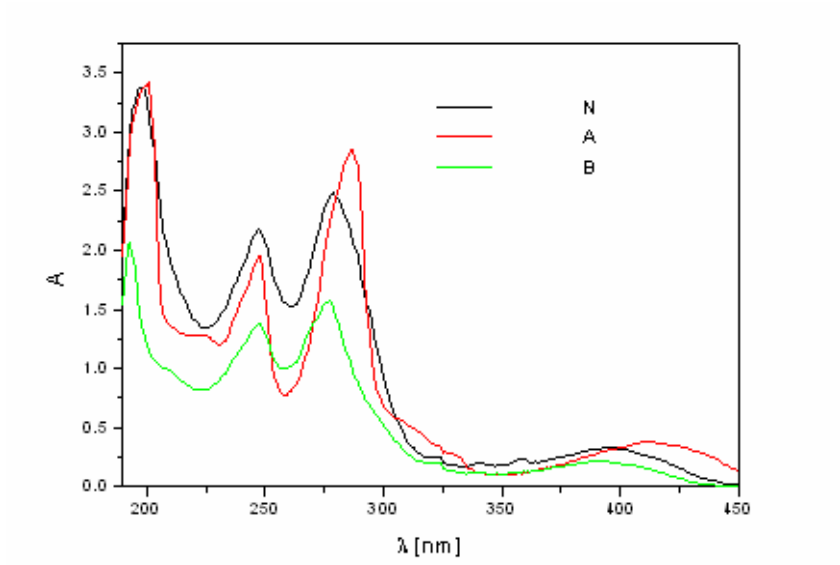


Fig. 3. UV-spectrum of compounds 1, 2 and 6.
N (neutral solution, pH 7), λ[nm] / (ε): 193 (2059), 248 (1373), 277 (1571)
A (acidic solution, pH 1), λ[nm] / (ε): 201 (3424), 248 (1956), 286 (2850)
B (basic solution pH 10), λ[nm] / (ε): 198 (3367), 247 (2174), 279 (2448)

The alkylation reaction of **1** performed under classical conditions (using alkylhalides in the presence of K_2CO_3 in DMF solvent) generated a product completely soluble in water, a fact that enabled us to suggest that a hydration reaction took place.

CONCLUSIONS

Under PTC conditions, in the presence of strong bases such as KOH and NaOH, the hydration of the carbonyl bond in the substrate **1** occurs as the main reaction. As a consequence of an ambident nucleophile structure generated by **1**, the alkylation reaction generates a mixture of N- and O-alkyl-derivatives in low yields.

EXPERIMENTAL

*General procedure for hydration/alkylation reaction of **1** under PTC conditions*

Compound **1** (5 mmol), 2-diethylamino-ethylchlorid hydrochlorid (7 mmol), TBAB (0.2g) were solved in aromatic hydrocarbon solvent (50 mL) and mixed with 25 mL KOH 50% aqueous solution. The reaction mixture was heated under vigorous stirring for 72 hours. After cooling, the abundant precipitate separated between the two layers was filtered off. A white powder (1.03 g, 80% yields) was obtained and it was found to be highly soluble in water.

The two layers of the reaction mixture were separated. The organic layer was washed with water, then dried over anhydrous $MgSO_4$ and the solvent was evaporated in vacuum. 0.08 g, yield 5% crude reaction product was obtained.

3-cyano-10-methyl-pyrido[3,2-g]dihydroquinolin-4,4-diol 6

^{1}H-NMR (DMSO-d_6 solution): 3.01 ppm (s, 3H, -CH_3), 8.92 ppm (dd, 1H, H_8), 7.38 ppm (m, 1H, H_7), 8.44 ppm (dd, 1H, H_6), 8.59 ppm (s, 1H, H_5), 8.33 ppm (s, 1H, H_2)

3-Cyano-1-(2'-diethylaminoethyl)-10-methyl-pyrido[3,2-g]quinolin-4-one 3

^{1}H-RMN ($CDCl_3$ solution): 2.49 ppm (s, 3H, -CH_3), 8.65 ppm (dd, 1H, H_8), 6.92 ppm (m, 1H, H_7), 7.8 ppm (dd, 1H, H_6), 7.42 ppm (s, 1H, H_5), 7.40 ppm (s, 1H, H_2), 3.55 ppm (t, 2H, -CH_2), 3.05 ppm (t, 2H, -CH_2), 2.95 ppm (q, 4H, -CH_2), 2.99 ppm (t, 6H, -CH_3).

3-Cyano-4-(2'-diethylaminoethoxy)-10-methyl-pyrido[3,2-g]quinoline 4

^{1}H-NMR ($CDCl_3$ solution): 2.99 ppm (s, 1H, -CH_3), 8.9 ppm (dd, 1H, H_8), 7.3 ppm (m, 1H, H_7), 8.19 ppm (dd, 1H, H_6), 8.62 ppm (s, 1H, H_5), 8.75 ppm (s, 1H, H_2), 4.4 ppm (t, 2H, -CH_2), 2.38 ppm (t, 2H, -CH_2), 2.14 ppm (q, 4H, -CH_2), 0.51 ppm (t, 6H, -CH_3).

The hysterezis curve was obtained by potentiometric titration of 0.117 g precipitate solved in 50 mL of distilled water, with HCl solution (0.001N). The back titration was performed with NaOH solution 0.001N.

The UV spectra were recorded on a UNICAM Helios β spectrophotometer.

NMR spectra were recorded on a 400 MHz Bruker spectrometer.

ACKNOWLEDGMENT

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