Kinetic Study on the Anelation of Heterocycles. 2. Pyrido[2,3-*b*]pyrazine and Pyrido[3,4-*b*]pyrazine Derivatives Synthesized by the Hinsberg Reaction

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The regioselective synthesis of pyrido[2,3-*b*]- and [3,4-*b*]pyrazine derivatives **II** by the Hinsberg reaction is reported starting from 2,3 and 3,4-diaminopyridine and excess of pyruvic acid or ethyl pyruvate as reactants. Good yields (higher than 90%) were obtained for pyrido[2,3-*b*]pyrazine derivatives at room temperature using anhydrous methanol and chloroform as solvents which promote regioselective reactions to give 2-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (**3a**) and 3-methylpyrido[2,3-*b*]pyrazin-2(1*H*)-one (**4a**) respectively. On the other hand, when the same procedure was applied to 3,4-diaminopyridine results were not so encouraging for the formation of 2-methylpyrido[3,4-*b*]pyrazin-3(4*H*)-one (**3b**) and 3-methylpyrido[3,4-*b*]pyrazin-2(1*H*)one (**4b**). Kinetic studies were performed in aqueous buffers (*p*H −0.89 to 11.5) and different organic solvents trying to improve yields and achieve regioselectivity. The course of the reactions was followed by uv spectrophotometry being those with ethyl pyruvate 2 to 800 times faster than with pyruvic acid. This investigation involves the kinetics and mechanism of this reaction studying its factibility when π-deficient substrates are used and its regioselectivity according to the position of the pyridine nitrogen atom.

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Two years ago our interest turned to the regioselective synthesis of substituted quinoxalinones [1] as precursors of siamese bis-aminoquinoxalines. These derivatives had shown certain antineoplastic activity, possibly by a DNA bis-intercalative process [2].

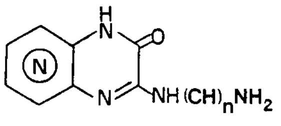
Recently we noted that a diaminoalkylenquinoxaline has more neoplasm inhibiting activity [3] (presumably by another biological mechanism) and several authors have recently reported that the anticancer activity increases if one or two carbon atoms of the quinoxaline benzene ring are replaced by nitrogen atoms, **I** [4-7].

Therefore, we report here the study of the regioselective synthesis of four pyridopyrazines **II** by the Hinsberg reaction using 2,3- or 3,4-diaminopyridine **1a-b** and excess of pyruvic acid (**2a**) or ethyl pyruvate (**2b**) as reactants. This investigation involves the kinetics and mechanism of this reaction, studying its feasibility when π-deficient substrates are used, and its regioselectivity according to the position of the pyridine nitrogen atom, when different experimental conditions are employed.

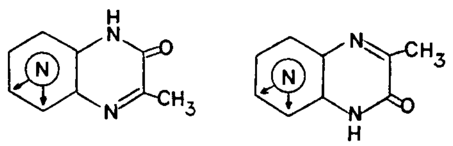
1) Synthesis of Pyrido[2,3-*b*]pyrazine Derivatives.

a) Reaction of 2,3-Diaminopyridine (**1a**) with Pyruvic Acid (**2a**) or Ethyl Pyruvate (**2b**) in Aqueous Buffer Solutions.

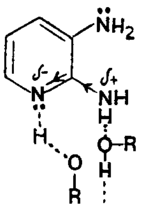
Reactions of **1a** with **2a** or its ethyl ester **2b** were followed by uv spectrophotometry in buffers of *p*H values between -0.89 and 11.5. Reactions occurred according to Scheme I and pyrido[2,3-*b*]pyrazine derivatives **3a** and **4a**



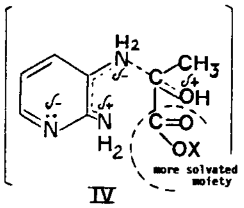
I



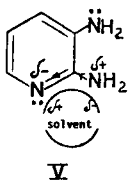
II



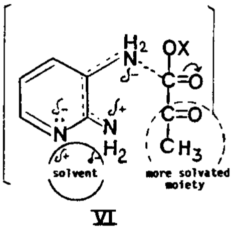
III



IV

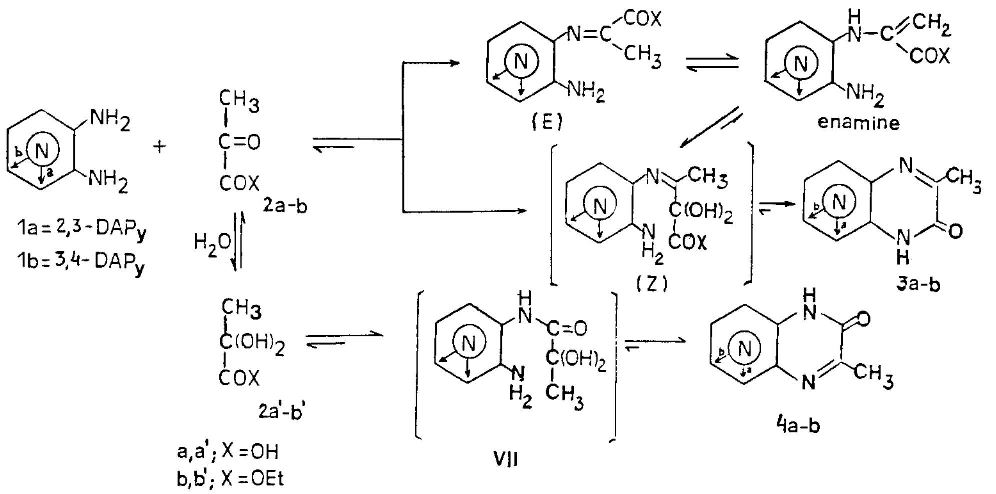


V

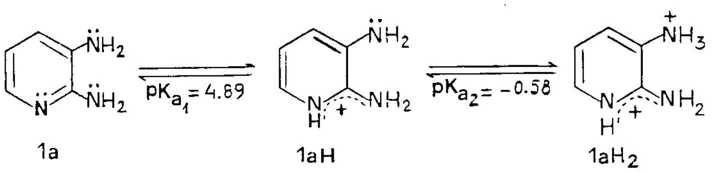


VI

Scheme I



Scheme II



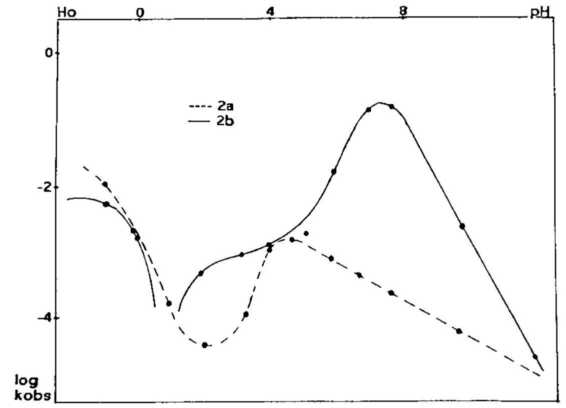


Figure 1. Dependence of observed rate constants for the attainment of 2-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (**3a**) on *p*H at 25° starting from 2,3-diaminopyridine (**1a**) and pyruvic acid (**2a**) or ethyl pyruvate (**2b**).

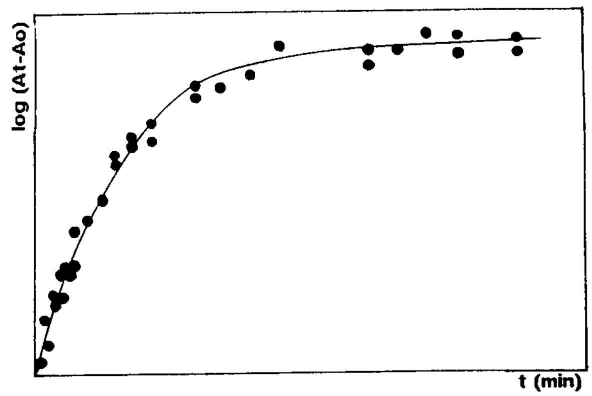


Figure 2. Characteristic profiles of log of absorbance *vs.* time for the attainment of mixtures of pyrido[2,3-*b*]pyrazine and pyrido[3,4-*b*]-pyrazine derivatives in aqueous buffers or in organic solvents at 25°.

were separated and identified by hplc.

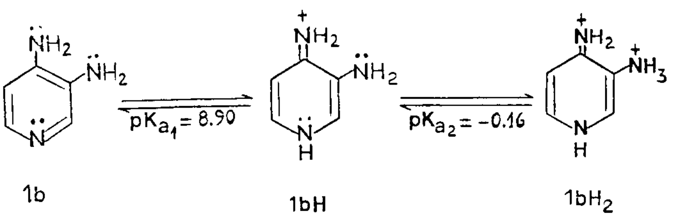
The appearance of **3a** and **4a** was followed at 330 nm where open intermediates did not absorb. Working with excess of **2a** or **2b** and initial **1a** concentrations 10^{-3} to 10^{-5} *M* a first order dependence on the latter was observed. In every case reactions with **2b** were 5 to 100 times faster than with **2a** (Figure 1).

Plotting log k_{obs} *vs.* pH/H_o (Figure 1) maximum rate of reaction for **2a** is observed at *p*H 4-5. This is in accord with the maximum stability of the intermediate Schiff base [1] in this medium.

The fact that two products are obtained, **3a** and **4a**, (Scheme I) as it can be deduced from hyperbolic curves as that shown for example in Figure 2, cannot be attributed to a similar nucleophilicity of both amino groups (Scheme II) [8], thus we are able to postulate that the hydrate form of **2a** or **2b** (Scheme I) is responsible for the attainment of compound **4a**.

The hydrate formation of **2a** and **2b** was proved to be thermodynamically favoured in other compounds such as

Scheme III



glyoxylic acid and it is catalysed by H^+ or OH^- [9]. Decomposition constants of the hydrate form of **2a**, **2b** and pyruvate anion (Pyr^-), (0.42, 0.32 and 18 respectively) were calculated by ^{17}O nmr [9-10]. According to the concentration of **2a** and **2b** used in our experiments ($\sim 2.7\text{-}8.7 \times 10^{-2}$ *M*) hydrate/2 relationships could be calculated: a) 2a'/2a = 2.3/1; b) 2b'/2b = 3.17/1; c) $Pyr^-(H_2O)/Pyr^-$ = 1/15.7.

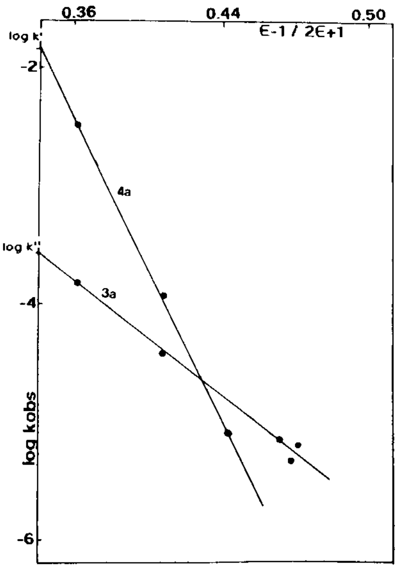


Figure 3. Dependence of observed rate constants on the dielectric constant of the organic solvent for the formation of 2-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (**3a**) and 3-methylpyrido[2,3-*b*]pyrazin-2(1*H*)-one (**4a**) at 25°.

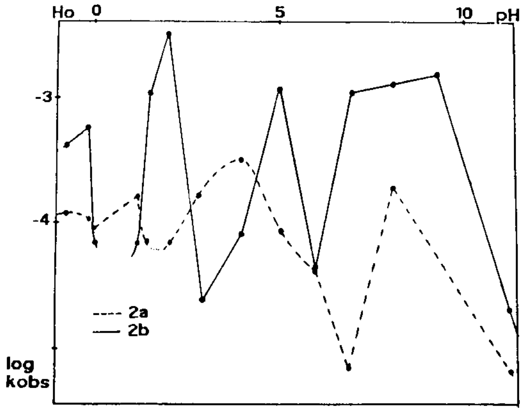


Figure 4. Dependence of observed rate constants for the attainment of 3-methylpyrido[3,4-*b*]pyrazin-2(1*H*)-one (**4b**) on *p*H at 25° starting from 3,4-diaminopyridine (**1b**) and pyruvic acid (**2a**) or ethyl pyruvate (**2b**).

When the *p*H of the reaction is two logarithmic units over the pK_a value of the pyruvic acid (pK_a 2.58) concentration of the hydrate in item c) is negligible so reaction occurs mainly through the formation of the Schiff base and **3a** is the principal product (Scheme I). Linear profiles are observed in these cases when absorbance is plotted against time.

The maximum rate using **2b** as reactant appears at *p*H ~ 7.5 but we cannot conclude that the mechanism in this case is exclusively by Schiff base formation because according to item b) a grate concentration of the hydrate form is present and both isomers, **3a** + **4a** are attained. Characteristic profiles of the mixtures are shown in Figure 2.

Curves in very acid media (*p*H ≤ 1) for **2a** and **2b** show an increase in rate constants (Figure 1) and only **4a** is obtained. This is explained considering that at these *p*H values both reactants are almost completely as the hydrate form and reaction presumably occurs *via* acyl carbonium $CH_3\text{-}C(OH)_2\text{-}C^+$ by a similar mechanism as that we have proposed in [1]. Similar results were obtained when diaminopyrimidines were treated with oxalacetic acid which is completely under the hydrate form below *p*H 1 as it was demonstrated by ^{13}C nmr [11] and the same was confirmed by us for **2a** in aqueous acid medium using also ^{13}C nmr and dioxane as internal reference {[δ 197.43 (C=O)], 175.75 $[-C(OH)_2-\overset{*}{C}O_2H]$, 163.98 $(\text{-CO-}\overset{*}{C}OOH)$, 93.79 $[-\overset{*}{C}(OH)_2]$, 26.71 $(-CH_3)$, 26.12 $(-CH_3)$}.

Rate constants for the formation of **3a** and **4a** in aqueous buffer solutions were calculated by a function that was adjusted to the experimental values by computational methods and their logarithms plotted in Figure 1.

b) Reaction of **1a** with **2a** or **2b** in Organic Solvents.

In protic dipolar organic solvents such as methanol or ethanol we can predict a solvated structure of **1a** like III. An attack of the less compromised 3-NH_2 group upon the C=O group of **2a-b** may occur this giving a transition state presumably like **IV**. Thus, according to Ingold's concepts [13] strongly solvated reactants would favour the initial state rather than the transition state **IV** in which dispersal of charge is observed, and then slow anelation reactions, releasing alcohol, might take place through the intermediate *Z* (Scheme I) to give **3a**. Really, much lower rate constants (2 to 800 times slower rates) are obtained in light alcohols compared with aprotic solvents (Table 1).

In a polar aprotic solvent such as dimethylformamide, positive charge density at 1-NH_2 level of **1a** in the initial state must be greatly solvated by this nucleophilic solvent so, a similar mechanism as that proposed for protic solvents is expected, to give compound **3a**. In fact, reactions between **1a** and **2a** or **2b** in DMF were regioselective and only **3a** was obtained.

Table 1

Observed Rate Constants at 25° for the Formation of Pyrido[2,3-*b*]pyrazine Derivatives **3a**,**4a** and Pyrido[3,4-*b*]pyrazine Derivatives **3b**,**4b** in Organic Solvents

Solvent	Reactants	Products	k_1	log k_1	k_2	log k_2	ϵ-1/2ϵ+1	
MeOH	**1a** + **2a**	**3a**	4.68×10^{-6}	-5.33	----	----	32.70	0.477
EtOH	**1a** + **2a**	**3a**	6.92×10^{-6}	-5.16	----	----	24.55	0.470
DMF	**1a** + **2a**	**3a**	6.31×10^{-6}	-5.20	----	----	36.71	0.480
Py	**1a** + **2a**	**4a**	7.94×10^{-6}	-5.10	----	----	12.40	0.442
THF	**1a** + **2a**	**4a** + **3a**	1.15×10^{-4}	-3.94	3.80×10^{-5}	-4.42	7.58	0.407
$CHCl_3$	**1a** + **2a**	**4a** + **3a**	3.63×10^{-3}	-2.44	1.58×10^{-4}	-3.80	4.81	0.359
MeOH	**1a** + **2b**	**3a** + **4a**	4.89×10^{-5}	-4.31	1.17×10^{-5}	-4.93		
EtOH	**1a** + **2b**	**3a** + **4a**	3.39×10^{-2}	-1.47	2.63×10^{-6}	-5.58		
DMF	**1a** + **2b**	**3a**	7.41×10^{-5}	-4.13	----	----		
Py	**1a** + **2b**	**4a** + **3a**	1.20×10^{-5}	-4.92	3.80×10^{-6}	-5.42		
THF	**1a** + **2b**	**4a** + **3a**	1.35×10^{-3}	-2.87	2.19×10^{-4}	-3.66		
$CHCl_3$	**1a** + **2b**	**4a**	3.23×10^{-6}	-5.49	----	----		
MeOH	**1b** + **2a**	**4b**	5.01×10^{-5}	-4.30	----	----		
ETOH	**1b** + **2a**	**4b**	Uncertain					
DMF	**1b** + **2a**	**4b** + **3b**	6.61×10^{-3}	-2.18	2.14×10^{-4}	-3.67		
Py	**1b** + **2a**	**3b** + **4b**	1.15×10^{-2}	-1.94	5.75×10^{-5}	-4.24		
THF	**1b** + **2a**	**3b** + **4b**	3.02×10^{-3}	-2.52	5.75×10^{-4}	-3.24		
$CHCl_3$	**1b** + **2a**	**3b**	6.02×10^{-3}	-2.22	----	----		
MeOH	**1b** + **2b**	**4b**	2.09×10^{-6}	-5.68	----	----		
EtOH	**1b** + **2b**	**4b**	3.47×10^{-6}	-5.46	4.68×10^{-7}	-6.33		
DMF	**1b** + **2b**	**4b**	2.75×10^{-6}	-5.56	----	----		
Py	**1b** + **2b**	**3b** + **4b**	4.17×10^{-6}	-5.38	4.36×10^{-7}	-6.36		
THF	**1b** + **2b**	**3b**	6.61×10^{-5}	-4.18	----	----		
$CHCl_3$	**1b** + **2b**	**3b**	1.74×10^{-6}	-5.76	----	----		

In organic non-polar solvents (chloroform, pyridine) major solvation is expected around the more lipophilic moiety CH_3-CO of **2a** and a polarized accommodation of the solvent between N-1 and 2-NH_2 groups (**V**). Thus again 3-NH_2 group would attack, in this case the more electrophilic carboxylic function giving presumably a transition state like **VI** to give finally **4a** by a slow Schiff base formation through a non-hydrated intermediate **VII**.

This would be in accord with the reported higher rate constants for aminolysis of activated esters ($k \sim 10^{-2}$) [14] than for cetimine formation ($k \sim 10^{-3}$) [1].

We can conclude that in organic solvents regioselective reactions and very good yields (> 90%) are achieved using **1a** and **2b** in anhydrous methanol or ethanol to obtain **3a** (Table I) while anhydrous chloroform results the solvent of election when the synthesis of **4a** is intended. When non-anhydrous solvents are employed reaction always leads to Hinsberg's mixture (**3a** + **4a**).

Several calculations with k_{obs} as a function of different solvent parameters allow us to point out that the attainment of pyrido[2,3-*b*]pyrazine derivatives depends fundamentally on the dielectric constant of the organic solvent. A quantitative treatment may be done through the Kirkwood approach [15] plotting log k_{obs} *vs.* ϵ-1/2ϵ + 1. In fact, straight lines for the attainment of **3a** and **4a** are obtained (Figure 3), in which log k' and log k" are the rate constants in media of dielectric constant $\epsilon = 1$ and the "apparent value" of the slopes are approximately 1/ 2.303 k_{obs} T.

2) Synthesis of Pyrido[3,4-*b*]pyrazine Derivatives.

a) Reaction of 3,4-Diaminopyridine (**1b**) with **2a** or **2b** in Aqueous Buffer Solutions.

The same kinetic procedure described in item 1a) was used to follow the appearance of pyrido[3,4-*b*]pyrazine derivatives **3b** and **4b** (Scheme I) which were also isolated and identified by hplc.

Reactions were followed by uv spectrophotometry at 350 nm at which wavelength open products do not absorb. Similar results, in general, as those achieved in item 1a) were obtained working with excess of **2a** or **2b** in aqueous buffers of *p*H values -0.89-11.5 and reactions with **2b** were 10 to 100 times faster than with **2a** (Figure 4).

In the case of using **1a** as reactant the following structures must be considered on varying *p*H (Scheme III).

Structure **1bH** accounts for the major nucleophilicity of the 3-NH_2 group which is always responsible for the attack upon the $-COX$ function of the hydrate form of **2a** or **2b** to give mainly **3b** under acid conditions.

Working with **1b** + **2b** mixtures of **3b** + **4b** are obtained at every *p*H buffer due to the equilibrium **2b** $\rightleftharpoons$ **2b**', and especially in alkaline media where the 3-NH_2 and 4-NH_2 groups of pyridine have both chances to perform a nucleophilic attack upon the other reactant.

The Hinsberg mixture [16] can be avoided using **1b** + **2a** in buffers of *p*H <6 (Scheme III) but yields are not very good ($<20\%$).

When log (A_r-A_o) were plotted against time linear profiles (when only one product was obtained) accounted for pseudo-first order kinetics, and hyperbolic profiles (when a mixture of pyridopyrazines was obtained) accounted for bi-exponential curves according to the equation quoted in the Experimental.

b) Reaction of **1b** with **2a** or **2b** in Organic Solvents.

Reaction of **1b** + **2a** or **2b** in organic solvents proceeds similarly those starting with **1a** to achieve **4b** and **3b** (Table I). However, in this case we cannot find a linear relationship between log k_{obs} and the dielectric constant of the solvent. Trying to look for an acceptable correlation other solvent parameters were considered such as polarization, dipolar moment, donnor number, acceptor number, solvent nucleophilicity, *etc.* but no correlations with rate constants could be found. This is not surprising if we note that is very difficult to state "*a priori*" theoretical models of solvated forms of **1b**. However, solvents must have an important roll in the solvation of **1b** at the initial state since reaction with 3,4-diaminopyridine (**1b**) instead of 2,3-diaminopyridine (**1a**) at room temperature are very slow and give much lower yields when the Hinsberg reaction is applied, ($<20\%$).

EXPERIMENTAL

The ultraviolet spectra and kinetic measurements were performed with a Jasco 7850 uv/visible spectrophotometer. The nmr spectra were obtained on a Varian FT 80A spectrometer with tetramethylsilane as the internal reference. The ir spectra were recorded on a Beckman IR-20A spectrophotometer using potassium bromide pellets. The hplc spectra were recorded on a Beckman 110B apparatus. Analytical samples of the starting materials were used to perform the kinetic studies.

2-Methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (**3a**).

Compound **3a** was synthesized from 0.5 g of **1a** (4.58 mmoles) and 5 ml of **2b** (45.6 mmoles) in anhydrous methanol (10 ml) at room temperature with stirring. The resulting solid crystallized from ethanol (white needles) affording **3a** (94% yield), mp 240° dec, lit [12]; ir: (cm^{-1}) 1700 (C=O), 2700 (N-H), 2900-3040 (C-H); ^{1}H nmr (DMSO-d_6): δ 8.5-8.6 (dd, 1, py), 8.1-8.25 (dd, 1, py), 7.3-7.5 (q, 1, py), 2.5 (s, 3, CH_3); uv (methanol): λ max nm 223, 321, 329; hplc: (C_8, mobile phase PO_4H_2Na-TEA-AcN 5%, λ 330, Q 1.7 ml/min), t_r: 16.22 min; $pK_{a1} = 0.82$, $pK_{a2} = 7.72$.

3-Methylpyrido[2,3-*b*]pyrazin-2(1*H*)-one (**4a**).

Compound **4a** was synthesized by the same procedure as above using anhydrous chloroform as solvent instead of methanol, pale yellow powder from ethanol, mp 279° dec, 270° [12]; ir: (cm^{-1}) 1650 (C=O), 2650 (N-H), 2960 (C-H); ^{1}H nmr (DMSO-d_6): δ 8.5-8.6 (dd, 1, py), 7.7-7.9 (dd, 1, py-4-aromatic), 7.4-7.6 (q, 1, py), 2.5 (s, 3, CH_3); uv (methanol): λ max nm 225, 325, 336; hplc: (same experimental conditions as above), t_r: 3.9 min., $pK_{a1} = 1.98$, $pK_{a2} = 8.27$.

2-Methylpyrido[3,4-*b*]pyrazin-3(4*H*)-one (**3b**).

Compound **3b** was obtained from **1b** (4.6 mmoles) and **2b** (46 mmoles) in anhydrous chloroform (10 ml) at room temperature with stirring during two days. The reaction mixture solution was purified by plc (precoated silica gel F_{254} plates, $CHCl_3$/MeOH 10:1 as eluent) and identified by mp 280° dec, lit 276-278°; hplc (same experimental conditions); t_r: 6.44 min; $pK_{a1} = -0.94$, $pK_{a2} = 8.21$.

3-Methylpyrido[3,4-*b*]pyrazin-2(1*H*)-one (**4b**).

Compound **4b** was obtained from the reaction between **1b** (4.6 mmoles) and **2b** (46 mmoles) in anhydrous methanol at room temperature with stirring during three days. The reaction mixture solution was purified by plc (as above) and **4b** was identified by mp 265° dec, lit 262-263°; hplc (as above) t_r: 7.1 min. Spectral properties of compounds **3b** and **4b** are described in the literature [17-18].

Kinetic Measurements.

Reactions were performed at 25° using buffers over the *p*H range $1-8.50$ and sulphuric acid-water mixtures for reactions below *p*H 1.0. The *p*H of each solution above 0.40 was measured at 25° in a Metrohm E632 *p*H meter using a standardized glass electrode. Values of H_o were taken from Hine [19]. Reactions performed with initial concentrations 2×10^{-2} to 2×10^{-4} *M* of **1a-b** showed a first-order dependence on the pyridine derivative at every hydrogen concentration at which anelation occurred. All rate constants were obtained from 1.76×10^{-4} *M* initial concentrations of **1a-b** and 9.80×10^{-2} *M* of **2a-b**. The appearance of **3a-b** and **4a-b** was followed by uv spectrophotometry at wavelengths above 330 nm at which wavelength only pyridopyrazines absorb.

Rate constants were obtained from data of log (A_r-A_o) as a function of time by computational treatments. Linear profiles accounted for pseudo-first order kinetics and hyperbolic profiles (Figure 2) accounted for bi-exponential curves according to:

$(A_r\text{-}A_o) = K_1\,[1\text{-}\exp(\text{-}k_1t)] + K_2\,[1\text{-}\exp(\text{-}k_2t)]$ which was solved and adjusted to our experimental values by a software developed by us to obtain k_1 and k_2. Logarithms of k_1 and k_2 are plotted in Figures 1 and 4. K_1 and K_2 in the equation above are preexponential constants and k_1 and k_2 are exponential factors related to the observed rate constants for the attainment of **3a-b** and **4a-b** when competitive reactions take place.

General Kinetic Procedure.

Solutions (1.76×10^{-4} *M*) of **1a-b** and (9.80×10^{-2} *M*) of **2a-b** in the buffers or organic solvents were prepared and thermostated at 25° ±0.1°. Both solutions were mixtured and the appearance of the reaction product was followed by uv spectrophotometry until 70-80% of its final concentration was achieved.

Experimental data were subjected to computational treatments.

Adjustment of p*K*$_a$ and k$_{obs}$ Values by Computational Treatments.

For the adjustment of pK_a values drugs were dissolved in buffers of different *p*H values and changes in the uv spectrum were registered. This system carries out a) a statistical treatment of the total spectrum, b) an adjustment of the different estimated pK values, successively and within the same data process. This method is based on Nagano-Metzler algorithms [20] and was improved by us i) to adjust very close pK values because by successive iterations results undergo an autocorrection to reach the best estimation and ii) to obtain molar extinction coefficients data (ϵM) of each individual ionic species at every wave length.

In order to adjust the observed rate constants to the corresponding equation we developed a software that uses the Gauss and Newton-Raphson algorithms. It persues an iterative improvement of assumptive rate constant values (which are not necessarily close to the real constants) promoting a decrease in the convergence values to achieve the optimum one [21].

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