REACTION OF 2-AMINOPYRIDINES WITH α, β-UNSATURATED ACIDS

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The reaction of 2-amino- and 2-amino-5-halopyridines with acrylic, methacrylic, and crotonic acids forms N-(2-pyridyl)- and N-(5-halo-2-pyridyl)-β-alanines and the betaines 2-amino-1-(2-carboxylatoethyl)pyridinium or 3,4-dihydropyrido[1,2-a]pyrimidin-2-ones, or their homologs.

It is known that the reaction of 2-aminopyridine with acrylic acid forms 2-amino-1-(2-carboxylatoethyl)pyridinium betaine (IIa), its cyclization product, 3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one (IIIa), or a mixture of these products; i.e., compounds obtainable through the reaction of the endocyclic nitrogen atom with an electrophilic double bond [1-5]. When 2-aminopyridine is reacted with methyl acrylate in the presence of 2,5-di(*tert*-butyl)hydroquinone, a mixture of the methyl ester of N-(2-pyridyl)-β-alanine (IVa) and compound IIIa is obtained [6]. In this case, both nitrogens of the 2-aminopyridine participate in the reaction. 2-Amino-5-halopyridines form a still more complex mixture with methyl acrylate in the presence of acetic acid or its anhydride [7].

The data concerning the reaction of 2-aminopyridine with methacrylic acid are contradictory. According to [8], 3-methyl-3,4-dihydropyrido[1,2-*a*]-pyrimidin-2-one obtained from the reaction of methacrylic acid with 2-aminopyridine in the presence of *tert*-butylpyrocatechol melts at 199-200°C; the same substance as described in a Japanese patent [9] has a melting point of 248-250°C. It is also noted in [8] that 2-aminopyridine does not react with crotonic acid and its derivatives.

Water soluble derivatives of N-(5-halo-2-pyridyl)-β-alanine are of interest as plant growth regulators [10, 11], and compounds in the hydropyrido[1,2-*a*]pyrimidin-2-one series, as contrasting agents [9].

In order to establish regiospecificity of reaction of 2-aminopyridine and its halogen derivatives with α,β-unsaturated acids, we have studied the effects of solvent and temperature on the outcome of the reaction. Regardless of temperature, the reactions of 2-aminopyridines Ia-c with acrylic, methacrylic, and crotonic acids in water, alcohols, dioxane, and chloroform all give the corresponding 2-amino-1-(2-carboxylatoethyl)pyridinium betaines (IIa-c) or their derivatives Va-c and VIa in the form of hydrates. It should be noted that pyridine Ia does not react with crotonic acid in water. Adducts of the endocyclic nitrogen atom are formed when the reaction is carried out in benzene or toluene at room temperature. When aminopyridine Ia and acrylic acid are gradually heated to boiling, the reaction gives a mixture of N-(2-pyridyl)-β-alanine (VIIa) and betaine IIa or pyrimidinone IIIa. The introduction of acrylic acid into a boiling solution of aminopyridine Ia in benzene leads to the formation of β-alanine VIIa in a 40% yield, while the gradual introduction of acrylic acid into a boiling solution of Ia in toluene gives N-(2-pyridyl)-β-alanine (VIIa) in a 90% yield. The same compound, VIIa, is obtained when the hydrochloride of 2-aminopyridine is used, or even when the reaction is carried out in the presence of acetic acid. Compounds VIIb, c and VIIIa are obtained in analogous fashion.

Note that even boiling (2-3 days) aminohalopyridines Ib, c with methacrylic or crotonic acids does not give results.

It was established by TLC that β-alanine VIIa is formed in 5-7 min after the introduction of acrylic acid into a boiling toluene solution of 2-aminopyridine. The formation of VIIa is the immediate consequence of the reaction of the endocyclic nitrogen of amine Ia with the acrylic acid. This is confirmed by the fact that betaine IIa does not isomerize under these conditions to the isomeric β-alanine VIIa, although alkylated pyridines can so isomerize.

N-(2-Pyridyl)-β-alanine is also obtained by the hydrolysis of methyl ester IVa, synthesized in turn in 90% yield when pyridine Ia is heated with methyl acrylate in acetic acid. It should be noted that ester IVa was synthesized earlier [6] in low yield by heating 2-aminopyridine with methyl acrylate in the presence of a catalyst.

On the reaction of 2-aminopyridine (Ia) with methacrylic acid in boiling toluene, 3-methyl-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one (IXa) with mp 199°C is evolved. With crotonic acid, the oily betaine is formed.

In the case of the reaction of 2-amino-5-chloropyridine with acrylic acid, a considerable amount of β-alanine VIIc is formed along with the hydrate of betaine Vc (yield 14 and 62%, respectively). When boiled in hydrochloric acid, the hydrates of betaines II, V, and VI cyclize into the hydrochlorides of dihydro[1,2-*a*]pyrimidin-2-ones (X, XI).

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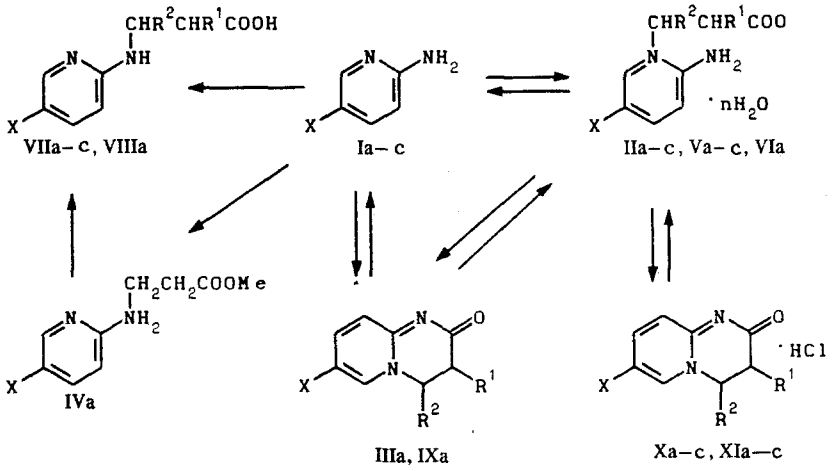
In contrast to betaines IIa and Va, halogen-containing betaines IIb, c and Vb do not cyclize to the corresponding pyridopyrimidin-2-ones when boiled in toluene. Under the influence of moisture, pyridopyrimidin-2-ones decyclize to the corresponding betaines. Treatment of hydrochloride Xa with sodium hydrogen carbonate in water leads to decyclization with the formation of 2-amino-1-(2-carboxylato-1-methylethyl)pyridinium (VIa).



I—XI a X=H, b X=Br, c X=Cl; IIa—c R^1=R^2=H; IIIa R^1=R^2=H; Va—c R^1=Me, R^2=H; VIa R^1=H, R^2=Me; VIIa—c R^1=R^2=H; VIIIa R^1=H, R^2=Me; IXa R^1=Me, R^2=H; Xa—c R^1=H; XIa—c R^1=Me, R^2=H

Betaines IIa-c, Va-c, VIa, pyridopyrimidin-2-ones IIIa, IXa, and their hydrochlorides Xa-c, XIa-c are decomposed by strong bases to starting amines Ia-c [2, 4]. Under these conditions, the isomeric pyridopyrimidin-4-ones form the corresponding N-pyridyl-β-alanines [7].

Derivatives of N-(2-pyridyl)-β-alanine containing substituents on the C_6 atom of the heterocycle are converted to naphthyridine derivatives under the influence of polyphosphoric acid [12-14]. The N-substituted β-alanines we have studied do not cyclize under such conditions.

In the PMR spectra (in CF_3COOH) of β-alanines VIIa-c, one finds the characteristic triplets or broadened singlets of the α- and β-methylene group protons at 2.53-2.55 and 3.43-3.44 ppm, respectively. The signals from the 4-H and 5-H protons of the pyridine nucleus occur at 6.45-6.90 ppm, and those from the 3-H and 6-H protons at 7.28-7.75 ppm.

In the PMR spectra of betaines IIb, c, the signals of the 1-H protons of the methylene group are shifted to lower fields by 0.77-0.80 ppm compared to these same protons in β-alanines VIIb, c. Apparently this is due to the decreased screening constants of the methylene group protons under the influence of the pyridinium nucleus. In the spectra of betaines Va-c, the protons of the methyl groups appear as doublets at 1.04-1.08, of the methine groups at 2.78-3.22, and of the methylene groups at 3.90-4.52 ppm. In the spectra of betaines IIb, c and Va-c, the signals of the 4-H proton (and of the 5-H proton in the spectrum of Va, also) of the pyridinium nucleus are found in the 6.40-7.18 ppm range, and those of the 3-H and 6-H protons appear at 7.35-7.85 ppm.

In the spectra of the hydrochlorides of pyridopyrimidin-2-ones XIa-c, the characteristic doublets of the methyl group protons are found at 1.06 ppm, and multiplets of the methine and methylene groups in the 2.80-3.29 and 4.22-4.72 ppm range, respectively. In the spectra of the hydrochlorides of Xa-c, the signals of the methyl group protons (as doublets) are shifted to weaker fields by 0.33 ppm, and those of the methylene and methine group protons (as multiplets) lie in the 2.50-3.50 ppm range. The signals of the protons of the CH group of the pyridine nucleus in the spectra of the hydrochlorides of the pyridopyrimidin-2-ones (X, XI) are found in the 7.12-8.30 ppm region.

EXPERIMENTAL

The PMR spectra were taken on a Tesla-BS-487C (80 MHz) instrument with HMDS as an internal standard.

The elementary analyses for C, H, N, and Br correspond to the calculated values.

Hydrate of Betaine 2-Amino-5-bromo-1-(2-carboxylatoethyl)pyridinium (IIb, $C_8H_9BrN_2O_2 \cdot H_2O$). A mixture of 8.65 g (50 mmoles) of 2-amino-5-bromopyridine, 3.75 ml (55 mmoles) of acrylic acid, and 20 ml of water is boiled for 2 h and allowed to stand at 5°C. The precipitate is filtered off, washed with ether, and dried to obtain betaine IIb in a 10.8 g (88%) yield. Mp

159-160°C (ethanol). PMR spectrum (CF_3COOH): 2.78 (2H, br.s, CH_2CO), 4.20 (2H, br.s, NCH_2), 6.53-7.18 (1H, m, 4-H), 7.35-7.83 ppm (2H, m, 3-H, 6-H).

Methyl Ester of N-(2-Pyridyl)-β-alanine (IVa, $C_9H_{12}N_2O_2$). A mixture of 18.8 g (200 mmoles) of 2-aminopyridine, 20 ml (220 mmoles) of methacrylate, and 5 ml of acetic acid are heated at 100°C for 24 h. The liquid fraction is distilled off, and the residue is distilled, with the fraction with bp 165-170°C (10-15 mm Hg) being taken. Alanine IVa is obtained in a 34.2 g (90%) yield. Mp 50-51°C; 50-51°C according to [6]; an oily substance [15].

Dihydrate of Betaine 2-Amino-1-(2-carboxylato-2-methylethyl)pyridinium (Va, $C_9H_{12}N_2O_2 \cdot 2H_2O$). A mixture of 47.0 g (500 mmoles) of 2-aminopyridine, 40 ml (550 mmoles) of methacrylic acid, and 100 ml of water is boiled for 20 h, cooled, and 300 ml of acetone is added. The crystals forming are filtered off, washed with acetone, and dried. Mp 87-88°C (ethanol). PMR spectrum (CF_3COOH): 1.08 (3H, d, J = 8 Hz, CH_3), 2.82-3.22 (1H, m, CH), 3.97-4.52 (2H, m, CH_2), 6.50-7.00 (2H, m, 4-H, 5-H), 7.43-7.72 ppm (2H, m, 3-H, 6-H). Yield 55.2 g (51%).

Hydrate of Betaine 2-Amino-5-bromo-1-(2-carboxylato-2-methylethyl)pyridinium (Vb, $C_9H_{11}BrN_2O_2 \cdot H_2O$). A mixture of 8.65 g (50 mmoles) of 2-amino-5-bromopyridine, 4.0 ml (55 mmoles) of methacrylic acid, and 30 ml of water is boiled for 16 h and allowed to stand at 5°C for 1 day. The precipitate forming is filtered off, and the filtrate evaporated off under vacuum. The residue is dissolved in ethanol and filtered into ether. The precipitate forming is filtered off, washed with ether, and dried to obtain compound Vb in a 1.55 g (11%) yield. Mp 149°C (with decomposition, ethanol/ether). PMR spectrum (CF_3COOH): 1.04 (3H, d, J = 6 Hz, CH_3); 2.78-3.15 (1H, m, CH), 3.90-4.33 (2H, m, CH_2), 6.40-7.05 (1H, m, 4-H), 7.40-7.70 ppm (2H, m, 3-H, 6-H).

Hydrate of betaine 2-amino-1-(2-carboxylato-2-methylethyl)-5-chloropyridine (Vc, $C_9H_{11}ClN_2O_2 \cdot H_2O$) is obtained from 6.42 g (50 mmoles) of 2-amino-5-chloropyridine, 4.0 ml (55 mmoles) of methacrylic acid, and 50 ml of water in analogous fashion to compound Vb in a 2.4 g (23%) yield. Mp 159°C (with decomposition, ethanol/ether). PMR spectrum (CF_3COOH): 1.06 (3H, d, J = 6 Hz, CH_3), 2.82-3.20 (1H, m, CH), 3.95-4.39 (2H, m, CH_2), 6.58-7.00 (1H, m, 4-H), 7.35-7.65 ppm (2H, m, 3-H, 6-H).

Betaine 2-Amino-1-(2-carboxylato-1-methylethyl)pyridinium (IVa, $C_9H_{12}N_2O_2$). A 5.94 g (30 mmoles) sample of Xa hydrochloride is dissolved in 20 ml of water, 2.52 g (30 mmoles) of $NaHCO_3$ is added, and the solution heated 20 min until CO_2 evolution ceases. The liquid fraction is distilled off under vacuum and the residue boiled in 30 ml of ethanol and filtered into 150 ml of ether. The material that separates out is dissolved in 10 ml of chloroform and added to 100 ml of dry ether to obtain 4.2 g (74%) of betaine VIa. Mp 145-146°C. PMR spectrum (CF_3COOH): 1.32 (3H, d, J = 8 Hz, CH_3), 2.52-3.37 (2H, m, CH_2), 4.70-5.07 (1H, m, CH), 7.12-7.47 (2H, m, 4-CH, 5-CH), 7.87-8.17 ppm (2H, m, 3-CH, 6-CH).

N-(2-Pyridyl)-β-alanine (VIIa, $C_8H_{10}N_2O_2$). A. To a boiling solution of 18.8 g (200 mmoles) of 2-aminopyridine in 30 ml of toluene 15 ml (220 mmoles) of acrylic acid is added gradually and the boiling continued for another hour. During the heating an oil separates which crystallizes on cooling. To the reaction mixture 100 ml of acetone is added, the mixture heated to boiling, and the crystals that form are filtered off, washed with acetone, and recrystallized from ethanol to obtain 29.1 g (88%) of compound VIIa. Mp 139-140; according to [15], mp 139°C. PMR spectrum (CF_3COOH): 2.55 (2H, t, J = 6 Hz, CH_2CO), 3.44 (2H, t, J = 6 Hz, NCH_2), 6.42-6.84 (2H, m, 4-H, 5-H), 7.30-7.80 ppm (2H, m, 3-H, 6-H).

B. A solution of 17.0 g (100 mmoles) of compound IV in 25 ml of ethanol to which 35 ml of 15% NaOH has been added is heated to boiling and acidified with acetic acid to pH 5. After the solution has stood at 5°C, 15 g (88%) of alanine VIIa separates out.

N-(5-Bromo-2-pyridyl)-β-alanine (VIIb, $C_8H_9BrN_2O_2$). A mixture of 17.3 g (100 mmoles) of 2-amino-5-bromopyridine and 7.5 ml (110 mmoles) of acrylic acid in 20 ml of toluene is boiled for 6 h and allowed to stand for 20 h at 16°C. The toluene layer is decanted off and the remaining solid is dissolved in 60 ml of a 10% sodium hydroxide solution. This is filtered and the filtrate acidified with acidic acid to pH 5-6. After having stood for 2 h at 5°C, the alanine VIIb that separates is filtered off, washed with water, then ether, and dried. Mp 219.5-220°C (ethanol); according to [7], mp 220°C. PMR spectrum (CF_3COOH): 2.23 (2H, t, J = 6 Hz, CH_2CO), 3.43 (2H, t, J = 10 Hz, NCH_2), 6.66 (H, d, J = 10 Hz, 4-H), 7.40-7.68 ppm (2H, m, 3-H, 6-H). Yield 18.0 g (7.5%).

N-(5-Chloro-2-pyridyl)-β-alanine (VIIc) and the Hydrate of Betaine 2-Amino-1-(2-carboxylatoethyl)-5-chloropyridinium (IIc, $C_8H_9ClN_2O_2 \cdot H_2O$). A. A mixture of 3.85 g (30 mmoles) of 2-amino-5-chloropyridine, 2.25 ml (33 mmoles) of acrylic acid, and 45 ml of toluene is boiled for 10 h. The solvent is distilled off under vacuum, the residue dissolved in 20 ml of ethanol, 20 ml of 10% sodium hydroxide solution is added, and the mixture boiled for 15 min. After cooling, the starting amine Ic that precipitates is filtered off, and the filtrate is acidified with acetic acid to pH 4-5. The precipitate of alanine VIIc that separates is filtered off, washed with water, and dried to obtain a 3.7 g (61%) yield of alanine VIIc. Mp 200-201°C (ethanol); according

to [7], mp 200-201°C. PMR spectrum (CF_3COOH): 2.23 (2H, t, J = 6 Hz, CH_2O), 3.43 (2H, t, J = 6 Hz, NCH_2), 6.71 (H, d, J = 10 Hz, 4-H), 7.33-7.63 ppm (2H, m, 3-H, 6-H).

B. A mixture of 6.42 g (50 mmoles) of 2-amino-5-chloropyridine, 4 ml (50 mmoles) of acrylic acid, and 30 ml of water is boiled for 20 h. After cooling, the crystals of VIIc that have separated are filtered off. Yield 6.2 g (62%). The filtrate is evaporated under vacuum and the residue recrystallized from a 1:5 ethanol:ether mixture to obtain 1.5 g of betaine IIc (14%). Mp 157-158°C (ethanol/ether, with decomposition); according to [7], mp 158°C (with decomposition). PMR spectrum (CF_3COOH): 2.82 (2H, br.s, CH_2CO), 4.24 (2H, br. s, NCH_2), 6.62-7.03 (H, m, 4-H), 7.35-7.80 ppm (2H, m, 3-H, 6-H).

N-(2-Pyridyl)-β-methyl-β-alanine (VIIIa, $C_9H_{12}N_2O_2$). A solution of 17.2 g (200 mmoles) of crotonic acid in 50 ml of toluene is poured into a boiling solution of 18.8 g (200 mmoles) of 2-aminopyridine in 75 ml of toluene and the boiling continued for 20 h. The toluene is then distilled off under vacuum, and the residue chromatographed on a column with Silpearl 254 silica gel and a 1:1 acetone:chloroform eluent. The fraction with R_f 0.88 is taken to obtain 6.3 g (15%) of alanine VIIIa. PMR spectrum (CF_3COOH): 1.38 (3H, d, J = 8 Hz, CH_3), 2.30-3.10 (2H, m, CH_2), 4.60-4.90 (1H, m, CH), 6.63-7.98 ppm (4H, m, ArH).

3-Methyl-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one (IXa, $C_9H_{10}N_2O$). A. A mixture of 47.0 g (500 mmoles) of 2-aminopyridine, 46.7 ml (550 mmoles) of methacrylic acid, and 100 ml of toluene is boiled for 20 h in a flask with a Lynn—Stark absorption column. The reaction mixture is cooled and the precipitate that separates is filtered off and recrystallized from 2-propanol. Mp 199°C; according to [8], mp 199-200°C; according to [9], mp 248-250°C. PMR spectrum ($CDCl_3$): 1.23 (3H, d, J = 8 Hz, CH_3), 2.50-2.85 (1H, m, CH), 3.75-4.43 (2H, m, CH_2), 6.45-7.65 ppm (4H, m, ArH). Yield 39.0 g (48%).

B. A mixture of 3.6 g (20 mmoles) of betaine Va and 20 ml of toluene is boiled for 1 h in a flask with a Lynn—Stark absorption column. The crystals forming after cooling are filtered off, washed with 2-propanol, and dried to obtain 3.0 g (93%) of compound IXa.

4-Methyl-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one Hydrochloride (Xa, $C_9H_{10}N_2O \cdot HCl$). A mixture of 47.0 g (500 mmoles) of 2-aminopyridine Ia, 43.0 g (500 mmoles) of crotonic acid, and 100 ml of toluene is boiled in a flask with a Lynn—Stark absorption column for 20 h, after which 13 ml of concentrated HCl is added and heating continued for another hour. The liquid fraction is distilled off under vacuum and the residue dissolved in 50 ml of ethanol and filtered into 200 ml of ether to obtain 37.5 g (38%) of salt Xa. Mp 219-220°C (ethanol/ether). PMR spectrum (CF_3COOH): 1.36 (3H, d, J = 6 Hz, CH_3), 2.57-3.47 (2H, m, CH_2), 4.80-5.17 (1H, m, 4-H), 7.22-7.53 (2H, m, 7-H, 8-H), 7.91-8.27 ppm (2H, m, 6-H, 9-H).

7-Bromo-4-methyl-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one Hydrochloride (Xb, $C_9H_9BrN_2O \cdot HCl$). A mixture of 8.65 g (50 mmoles) of 2-amino-5-bromopyridine Ib, 4.73 g (55 mmoles) of crotonic acid, and 30 ml of water are boiled for 20 h, after which the solution is extracted with ether (3 × 50 ml). Five milliliters of concentrated HCl is added to the solution and it is boiled for 1 h and the liquid phase distilled off under vacuum. The residue is dissolved in 30 ml of ethanol, filtered into 150 ml of ether, and kept for 1 day at 5°C. The precipitate that forms is filtered off, washed with ether, and dried. Mp 286-288°C (with decomposition, ethanol/ether). PMR spectrum (CF_3COOH): 1.38 (3H, d, J = 7 Hz, CH_3), 2.53-3.00 (2H, m, 3-H), 3.86 (1H, br. s, 4-H), 7.30 (1H, d, J = 10 Hz, 8-H), 8.11 (1H, d, J = 10 Hz, 6-H), 8.30 ppm (1H, s, 9-H). Yield 7.8 g (56.1%).

4-Methyl-7-chloro-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one hydrochloride (Xc, $C_9H_{10}ClN_2O \cdot HCl$) is obtained from 12.86 g (100 mmoles) of 2-amino-5-chloropyridine Ic, 9.46 g (110 mmoles) of crotonic acid and 30 ml of water in analogous fashion to compound Xb in a yield of 2.35 g (10%). Mp 282-283°C (with decomposition, 2-propanol/ether). PMR spectrum (CF_3COOH): 1.38 (3H, d, J = 4 Hz, CH_3), 2.50-3.40 (2H, m, 3-H), 4.70-5.15 (1H, m, 4-H), 7.30 (1H, d, J = 8 Hz, 8-H), 7.95 (1H, d, J = 8 Hz, 6-H), 8.15 ppm (1H, s, 9-H).

3-Methyl-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one Hydrochloride (XIa, $C_9H_{10}N_2O \cdot HCl$). A mixture of 3.6 g (20 mmoles) of betaine Va or 3.24 g (20 mmoles) of compound IXa and 5 ml of concentrated HCl is boiled for 1 h. The liquid fraction is distilled off under vacuum, and the residue dissolved in 50 ml of ethanol and filtered into 200 ml of ether. Mp 288-289°C (ethanol/ether). PMR spectrum (CF_3COOH): 1.06 (3H, d, J = 8 Hz, CH_3), 2.80-3.20 (1H, m, CH), 4.22-4.72 (2H, m, CH_2), 7.12-7.43 (2H, m, 7-H, 8-H), 7.88-8.17 ppm (2H, m, 6-H, 9-H). Yield 3.8 g (97%).

7-Bromo-3-methyl-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one hydrochloride (XIb, $C_9H_9BrN_2O \cdot HCl$) is obtained from 1.8 g (7 mmoles) of betaine hydrate Vb and 2 ml of concentrated HCl in analogous fashion to compound XIa in a yield of 1.65 g (86%). Mp 229-230°C (with decomposition, 2-propanol/ether). PMR spectrum (CH_3COOH): 1.06 (3H, d, J = 6 Hz, CH_3), 2.86-3.29 (1H, m, 3-H), 4.23-4.72 (2H, m, 4-H), 7.28 (1H, d, J = 8 Hz, 8-H), 7.88-8.20 ppm (2H, m, 6-H, 9-H).

3-Methyl-7-chloro-3,4-dihydropyrido[1,2-*a*]pyrimidin-2-one hydrochloride (XIc, $C_9H_9ClN_2O \cdot HCl$) is obtained from 2.15 g (10 mmoles) of betaine hydrate Vc and 2 ml of concentrated HCl in analogous fashion to compound XIa in a 2.0 g (86%) yield. Mp 325°C (with decomposition, ethanol/ether). PMR spectrum (CF_3COOH): 1.06 (3H, d, J = 6 Hz, CH_3), 2.85-3.27 (H, m, 3-H), 4.22-4.72 (2H, m, 4-H), 7.26 (1H, d, J = 8 Hz, 8-H), 7.86-8.20 ppm (2H, m, 6-H, 9-H).

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