REACTION OF 2-AMINO-5-HALOPYRIDINES WITH METHYL ACRYLATE

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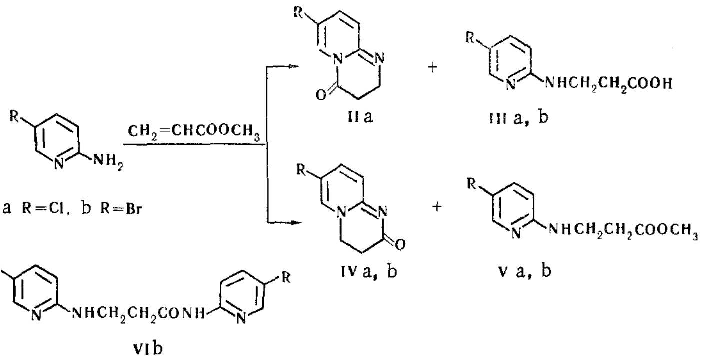
Two isomeric bicyclic dihydropyridopyrimidinones (II and IV), the methyl esters of the corresponding N-pyridyl-β-alanines (V), and a number of other compounds are formed during the reaction of methyl acrylate with 2-amino-5-halopyridines in the presence of acid catalysts. Compounds II and IV were hydrolytically cleaved, and some derivatives of N-(5-halo-2-pyridyl)-β-alanines were obtained.

2-Aminopyridine and 2-amino-5-methylpyridine give mono- and bicyclic compounds [1-3] in the nucleophilic addition of methyl acrylate to the double bond. In this paper we have studied the reaction of 2-amino-5-chloro(bromo)pyridines with methyl acrylate.

Compounds IIa and IIIa were isolated by heating 2-amino-5-chloropyridine (Ia) in an ampule with methyl acrylate in the presence of acetic acid, while IVa and Va were formed when the reaction was carried out at room temperature. Monocyclic compounds IIIb and Vb and pyridylamide VIb were isolated under similar conditions by the reaction of methyl acrylate with 2-amino-5-bromopyridine (Ib).



Bicyclic product IVb can be obtained when acetic anhydride is used as the catalyst in the reaction of methyl acrylate with Ib. Alkaline hydrolysis of VIb gives N-(5-bromo-2-pyridyl)-β-alanine (IIIb) and Ib. The hydrobromide of IIa, which is obtained by passing dry HBr through a solution of IIa, is isolated by the reaction of bromine with IIa in acetic acid [4]. Alanines III are also obtained by the hydrolysis of ester V, amide VII, bicyclic compound II, and from III. The corresponding N-nitroso compounds are obtained by the action of sodium nitrite in hydrochloric acid on III.

1-(3-Pyridyl)dihydrouracil [5] is formed by fusion of N-(3-pyridyl)-β alanine with urea, while III form amides VII under the same conditions, which indicates the very low reactivity of the hydrogen of the amine group of β-alanines III. VIIa is also obtained by the action of ammonia on IIa and Va, and from IIIa through the corresponding acid chloride.

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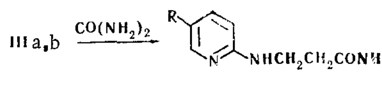
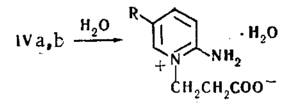


VII a,b

Dihydropyridopyrimidin-2-ones IV are decomposed to starting amines I by the action of alkalis [1] or ammonia in an ampule, while, like IIa, they form hydrobromides of IV on bromination. The dihydropyrimidine ring is opened to form betaines VIIIa and b by refluxing IV with water. Heating of VIIIa and b with HCl again gives hydrochlorides of IV.



VIII a,b

The structures of the synthesized compounds were confirmed by spectroscopic data. A band at 1580-1590 cm^{-1}, which corresponds to the valence vibrations of the aromatic system of bonds of the pyridine ring, is observed in the IR spectra (Fig. 1) of IIIa and Va. The bands at 1330, 1294, and 1250 cm^{-1} indicate the C–N–C grouping [6, 7]. These data indicate that the addition of the aminopyridine to methyl acrylate occurred at the nitrogen atom of the amino group. The absence of a band at 1404 cm^{-1} in the IR spectrum of IIIa indicates that the COOH group in the latter is not free [6]. The absorptions at 3240-3360 cm^{-1} in the spectrum of IIIa can be ascribed to the valence vibrations of the N–H group, which participates in the formation of a hydrogen bond.

In the UV spectrum of IIIa and Va (Fig. 2), the bands with absorption maxima at 248-252 nm and 312-316 are close to the absorption maxima of 2-amino-5-chloropyridine at 240-244 nm and 308-310 nm, respectively. The UV spectrum of IIIb corresponds to that described in [6].

A comparison of the UV spectra of IIa and IVa with the UV spectra of compounds of analogous structure [1] also confirmed their structures.

EXPERIMENTAL

2,3-Dihydro-7-chloropyrido[1,2-a]pyrimidin-4-one (IIa) and N-(5-Chloro-2-pyridyl)-β-alanine Hydrate (IIIa). A mixture of 2 g (0.015 mole) of Ia, 2 g (0.023 mole) of methyl acrylate, and 0.1 ml of acetic acid was heated in an ampule at 100 deg for 8 h. The crystals that formed on cooling were filtered and crystallized three times from ethanol to give 0.3 g (11%) of a product with mp 168-168.5 deg. The compound was very slightly soluble in acetone but readily soluble in water. Found %: C 52.3; H 4.5; Cl 19.4; N 15.4. $C_8H_7ClN_2O$. Calc. %: C 52.3; H 4.4; Cl 19.3; N 15.3. The picrate had mp 202-207 deg (dec., from dioxane).

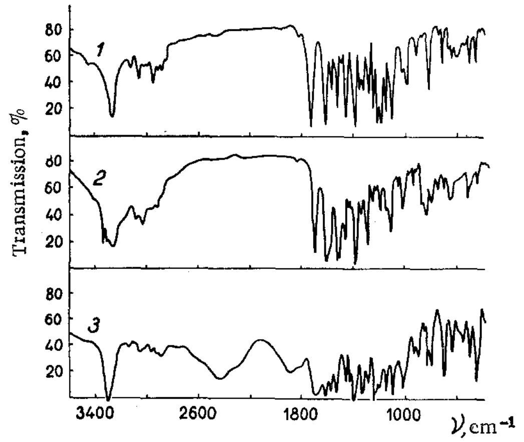


Fig. 1. IR spectra: 1) Va; 2) IIIa (hydrate); and 3) IIIa.

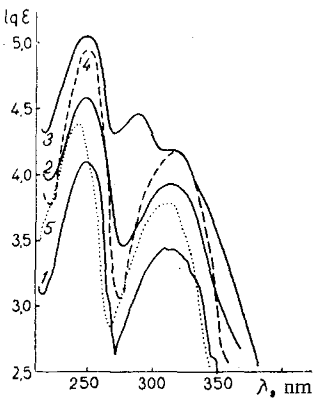


Fig. 2. UV spectrum [1 and 2) in 0.001% NaOH, 3 -5) in ethanol]: 1) IIIa; 2) IIIb; 3) IIIa (hydrate); 4) Va; and 5) Ia.

A total of 1 g (28%) of crystals of IIIa with mp 148.5-149 deg (from ethanol) precipitated from the filtrate on standing. Found %: C 43.8; H 5.2; Cl 16.2; N 12.7. $C_8H_9ClN_2O_2 \cdot H_2O$. Calc. %: C 43.7; H 5.1; Cl 16.2; N 12.8.

3,4-Dihydro-7-chloropyrido[1,2-a]pyrimidin-2-one (IVa) and N-(5-Chloro-2-pyridyl)-β-alanine Methyl Ester (Va). A mixture of 19.7 g (0.15 mole) of Ia, 15 ml (0.166 mole) of methyl acrylate, and 1.5 ml of acetic acid was allowed to stand at 30-35 deg for two months, after which the reaction mixture was poured into 100 ml of benzene. Fractional crystallization gave 7.91 g (24.7%) of IVa with mp 182-183 deg (from ethanol) and 3.6 g (18.6%) of starting amine Ia. Compound IVa was readily soluble in acetic acid and insoluble in ether. Found %: Cl 18.9; N 15.3. $C_8H_7ClN_2O$. Calc. %: Cl 19.3; N 15.3. The picrate had mp 172-173 deg (from methanol).

The benzene filtrate was vacuum-evaporated, and 9.3 g (34%) of Va distilled at 160-165 deg (1 mm). Three crystallizations from petroleum ether gave a product with mp 51-52.5 deg. Found %: C 50.7; H 5.2; Cl 16.5; N 13.0. $C_9H_{11}ClN_2O_2$. Calc. %: C 50.4; H 5.2; Cl 16.5; N 13.1.

5-Bromo-2-pyridylamide of N-(5-Bromo-2-pyridyl)-β-alanine (VIb), N-(5-Bromo-2-pyridyl)-β-alanine Hydrate (IIIb), and N-(5-Bromo-2-pyridyl)-β-alanine Methyl Ester (Vb). A mixture of 17.3 g (0.1 mole) of Ib, 9.5 ml (0.105 mole) of methyl acrylate, and 0.4 ml of acetic acid was heated in an ampule at 110-115 deg for 24 h; the contents were cooled; and 5.72 g (14%) of VIb with mp 172-173 deg (from ethanol) was filtered. The compound was insoluble in water. Found %: Br 39.5; N 14.1. $C_{13}H_{12}Br_2N_4O$. Calc. %: Br 39.9; N 14.0.

The filtrate was vacuum-evaporated and the viscous residue was dissolved in ethanol and poured into ether to give 0.95 g (4%) of IIIb with mp 158 deg (dec., from ethanol). Found %: Br 30.3; N 10.6. $C_8H_9BrN_2O_2 \cdot H_2O$. Calc. %: Br 30.4; N 10.64.

The ether–ethanol solution was evaporated to dryness, the residual viscous mass was extracted with petroleum ether, and the extract was vacuum-evaporated to give 10.1 g (39%) of Vb with mp 57.5-58 deg (from petroleum ether). Found %: Br 31.1; N 11.0. $C_9H_{11}BrN_2O_2$. Calc. %: Br 30.8; N 10.8.

3,4-Dihydro-7-bromopyrido[1,2-a]pyrimidin-2-one (IVb). A mixture of 8.65 g (0.05 mole) of Ib, 8 ml (0.088 mole) of methyl acrylate, and 0.5 ml of acetic anhydride was allowed to stand at 30-35 deg for a month. The resulting crystals (5.9 g) were filtered, washed with ether, and crystallized from chloroform–ether to give 3.6 g (32%) of a product with mp 171.5-172 deg. Found %: Br 34.9; N 12.2. $C_8H_7BrN_2O$. Calc. %: Br 35.2; N 12.3.

N-(5-Chloro-2-pyridyl)-β-alanine IIIa). A) A mixture of 0.5 g (2.7 mmole) of IIa, 10 ml of ethanol, and 1 g of KOH was heated for 3 h at 60-70 deg; 15 ml of water was added; and the mixture was filtered. The filtrate was acidified with acetic acid, and 0.31 g (61%) of IIIa with mp 200-201 deg (from ethanol) was filtered. Found %: C 47.9; H 4.5; N 14.0. $C_8H_9ClN_2O_2$. Calc. %: C 47.9; H 4.6; N 14.0.

B) Compound VIIa [0.5 g (2.5 mmole)] was treated as in method A to give a quantitative yield of IIIa.

C) The hydrate of IIIa [1 g (4.5 mmole)] was dissolved in 5 ml of 10% NaOH, the solution was filtered, and IIIa was precipitated in quantitative yield with acetic acid.

D) Va [0.43 g (2 mmole)] was dissolved in 5 ml of ethanol, 10 ml of 15% NaOH was added, and IIIa was precipitated in quantitative yield with acetic acid.

Mixtures of samples of IIIa obtained via methods A-D did not give melting-point depressions.

The hydrochloride of IIIa had mp 178-188 deg (dec., from ethanol–ether). Found %: N 11.7. $C_8H_9ClN_2O_2 \cdot HCl$. Calc. %: N 11.8.

N-(5-Bromo-2-pyridyl)-β-alanine (IIIb). A) Vb [2.59 g (0.01 mole)] was dissolved in 10 ml of ethanol, 15 ml of 15% NaOH was added, and a quantitative yield of IIIb with mp 219.5-220 deg (mp 221 deg [6]) was precipitated with acetic acid after 30 min. Found %: Br 32.7; N 11.4. $C_8H_9BrN_2O_2$. Calc. %: Br 32.6; N 11.4.

B) A mixture of 1.2 g (3 mmole) of VIb, 12 ml of ethanol, and 6 ml of 20% KOH was heated for 2 h at 70-80 deg; extracted with ether (five 30-ml portions); and the ether extract was evaporated to give 0.4 g (92.5%) of Ib. Acidification of the alkaline solution with acetic acid gave 0.6 g (97.5%) of IIIb.

Amide of N-(5-Chloro-2-pyridyl)-β-alanine (VIIa). A) A mixture of 5 g (0.025 mole) of IIIa and 7.5 ml of PCl_3 was held at 18-20 deg for 2-3 h and then vacuum-evaporated. The semicrystalline residue was triturated in ether, and dry ammonia was passed through the mixture with cooling. The resulting VIIa was filtered and recrystallized twice from water–alcohol (2:1) to give 2 g (40%) of a product with mp 148 deg. Found %: C 48.3; H 5.5; Cl 17.7; N 20.9. $C_8H_{11}ClN_3O$. Calc. %: C 48.3; H 5.5; Cl 17.7; N 20.9.

B) A mixture of 0.86 g (0.04 mole) of Va and 8 ml of concentrated ammonium hydroxide was heated for 10 h in an ampule at 100 deg. Cooling yielded 0.32 g (39.5%) of VIIa.

C) A mixture of 1.83 g (0.01 mole) of IIa and 20 ml of concentrated ammonium hydroxide was heated in an ampule at 150-160 deg for 9 h. Cooling yielded 1.2 g (60%) of VIIa.

D) A mixture of 2 g (0.01 mole) of IIIa and 10 g of urea was heated at 135-140 deg for 4 h. The reaction mass was dissolved in water, and cooling of the solution yielded 1.4 g (70%) of VIIa.

Mixtures of samples of the amide obtained via methods A-D did not give melting-point depressions. The picrate had mp 254-255 deg (from dioxane). Found %: N 19.5. $C_8H_{11}ClN_3O \cdot C_6H_3N_3O_7$. Calc. %: N 19.6.

Amide of N-(5-Bromo-2-pyridyl)-β-alanine (VIIb). A mixture of 1.77 g (7.2 mmole) of IIIb and 5.31 g of urea was heated for 3.5 h at 140-145 deg. The VIIb was isolated in the same way as VIIa via method D and was obtained in a yield of 1.27 g (72%) and had mp 140.5-141.5 deg (from water). Found %: Br 32.6; N 17.5. $C_8H_{11}BrN_3O$. Calc. %: Br 32.7; N 17.2.

Dimethylamide of N-(5-Chloro-2-pyridyl)-β-alanine. Phosphorus trichloride (3 ml) was added to 1 g (5 mmole) of IIIa, and the mixture was allowed to stand for 2-3 h. After vacuum distillation, the semicrystalline residue was cooled and treated with 5 ml of dimethylamine, the excess of the latter was removed by distillation, and the residue was crystallized from ethanol to give 0.92 g (80%) of a product with mp 122-123 deg. Found %: Cl 15.2; N 18.3. $C_{10}H_{15}ClN_3O$. Calc. %: Cl 15.5; N 18.4.

N-Nitroso-N-(5-chloro-2-pyridyl)-β-alanine IIIa [0.5 g (2.5 mmole)] was dissolved in 3 ml of concentrated HCl, the solution was poured into ice water, and 0.4 g (6 mmole) of sodium nitrite was added with stirring. The precipitated product was removed by filtration and washed with water to give 0.52 g (91%) of a product with mp 98.5-100 deg (from ethanol–water). Found %: Cl 15.4; N 18.1. $C_8H_8ClN_3O_3$. Calc. %: Cl 15.4; N 18.3.

N-Nitroso-N-(5-bromo-2-pyridyl)-β-alanine. This was similarly obtained from 2.45 g (0.01 mole) of IIIb, 10 ml of concentrated HCl, and 1.4 g (0.02 mole) of sodium nitrite. The product was obtained in a yield of 1.15 g (42%) and had mp 118-119 deg (from petroleum ether). Found %: Br 29.3; N 15.0. $C_8H_8BrN_3O_3$. Calc. %: Br 29.2; N 15.3

2-Amino-5-chloro-1-(2-carboxyethyl)pyridinium Betaine Hydrate (VIIIa). Compound IVa [0.37 g (2 mmole)] was refluxed for 2 h with 10 ml of water, the water was evaporated, and the residue was crystallized from ethanol to give 0.35 g (80%) of a product with mp 158 deg (dec.). Found %: Cl 16.1; N 12.6. $C_8H_9ClN_2O_2 \cdot H_2O$. Calc. %: Cl 16.2; N 12.8.

2-Amino-5-bromo-1-(2-carboxyethyl)pyridinium Betaine Hydrate (VIIIb). Compound VIIIb was similarly obtained in a yield of 0.43 g (82%) with mp 160 deg (dec., from ethanol) from 0.45 g (2 mmole) of IVb. Found %: Br 30.5; N 10.4. $C_8H_9BrN_2O_2 \cdot H_2O$. Calc. %: Br 30.4; N 10.4.

2,3-Dihydro-7-chloropyrido[1,2-a]pyrimidin-4-one Hydrobromide. Compound IIa [0.37 g (2 mmole)] was dissolved in 2 ml of acetic acid, 0.05 g of sodium acetate was added, and a solution of 0.6 ml (0.011 mole) of bromine in 1.5 ml of acetic acid was added dropwise. The precipitated crystals were removed by filtration and crystallized from ethanol to give 0.5 g (96%) of a product with mp 290-291 deg that was soluble in water and insoluble in ether. Found %: Br + Cl 44.4; N 11.0. $C_8H_7ClN_2O \cdot HBr$. Calc. %: Br + Cl 44.1; N 10.7. A sample of this hydrobromide did not depress the melting point of the hydrobromide obtained by passage of dry HBr through an ethanol solution of IIa.

3,4-Dihydro-7-chloropyrido[1,2-a]pyrimidine-2-one Hydrobromide. This compound was similarly obtained from 1 g (5.5 mmole) of IVa in 10 ml of acetic acid, 0.7 g of sodium acetate, and 0.7 ml (0.0136 mole) of bromine in 3 ml of acetic acid. The yield of product with mp 303-304 deg (from ethanol) was 0.92 g (65%). Found %: Br + Cl 44.0; N 10.7. $C_8H_7ClN_2O \cdot HBr$. Calc. %: Br + Cl 44.1; N 10.7.

3,4-Dihydro-7-bromopyrido[1,2-a]pyrimidin-2-one Hydrobromide. This compound was similarly obtained from 0.45 g (2 mmole) of IVb (dissolved in 15 ml of acetic acid), 0.16 g of sodium acetate, and 0.1 ml (2 mmole) of bromine in 2.5 ml of acetic acid. The yield of product with mp 315 deg (dec., from ethanol) was 0.4 g (56%). Found %: Br 52.0; N 9.2. $C_8H_7BrN_2O \cdot HBr$. Calc. %: Br 52.2; N 9.2.

3,4-Dihydro-7-chloropyrido[1,2-a)pyrimidin-2-one Hydrochloride. A) This compound was obtained by passage of dry HCl through an alcohol solution of IVa and had mp 306-308 deg (from ethanol). Found %: Cl 32.4; N 12.8. $C_8H_7ClN_2O \cdot HCl$. Calc. %: Cl 32.4; N 12.8.

B) VIIIa was refluxed with concentrated HCl, the solution was evaporated to dryness, and the residue was crystallized from ethanol to give a compound that was identical to that obtained via method A.

3,4-Dihydro-7-bromopyrido[1,2-a]pyrimidin-2-one Hydrochloride. This was similarly obtained from IVb and VIIIb and had mp 292 deg (dec., from ethanol–ether). Found %: Br + Cl 44.0; N 10.7. $C_8H_7BrN_2O \cdot HCl$. Calc. %: Br + Cl 44.0; N 10.7.

The IR spectra in the solid state were obtained with a UR-10 spectrometer. The UV spectra of solutions with concentrations of $2.7 \cdot 10^{-5}$ to $0.6 \cdot 10^{-3}$ mole/liter were obtained with an SF-4 spectrophotometer.

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