REACTION OF AMINOQUINOLINES WITH METHYL ACRYLATE AND TRANSFORMATIONS OF SOME OF THE PRODUCTS OBTAINED

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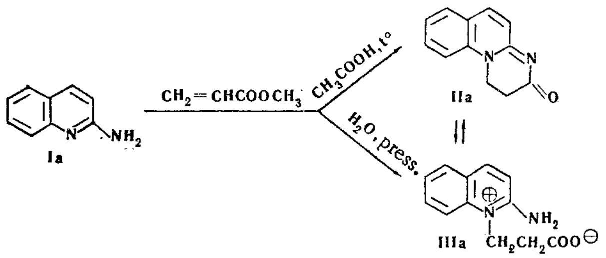
3H,4H-Quino[1,2-a]-2-pyrimidone, 1-(2-carboxyethyl)aminoquinolinium betaines, and methyl esters of N-quinolinyl-β-alanines were isolated from the reactions of aminoquinolines with methyl acrylate. Hydrolysis of the latter yielded the corresponding amino acids, two of which were converted to 1-(3- and 6-quinolinyl)dihydrouracils, and the latter was reduced to 1-(6-quinolinyl)-2-oxohexahydropyrimidine.

It is known that several β-substituted alanines of the quinoline series have bactericidal properties [1], and N-(6-methoxy-8-quinolinyl)-β-alanine is a potential anticarcinogenic preparation [2]. These compounds were obtained by the reaction of the appropriate aminoquinolines with propiolactone and esters of α,β-unsaturated acids [2] or by the reaction of β-alanine with haloquinoline derivatives in the presence of phenol [3]. In this study we carried out the reactions of 2-, 3-, 4-, 5-, 6-, 7-, and 8-aminoquinolines with methyl acrylate in the presence of water, acetic acid, or acetic anhydride and converted some of the N-quinolinyl-β-alanines obtained to the corresponding pyrimidine derivatives.

The reaction of 2-aminoquinoline (Ia) with methyl acrylate proceeds smoothly when these compounds are heated in the presence of acetic acid or acetic anhydride [4] and results in the preparation of 3H,4H-quino[1,2-a]-2-pyrimidone (IIa). When water is used as the catalyst the reaction proceeds (at elevated pressures) to form 1-(2-carboxyethyl)-2-aminoquinolinium betaine (IIIa); the latter is a very unstable compound which on storage in air or on heating is converted to IIa, which gives IIIa on heating with water:



The reactions of 3-, 4-, 5-, 6-, 7-, and 8-aminoquinolines with methyl acrylate in the presence of acetic acid proceed with the formation of the corresponding methyl esters of N-quinolinyl-β-alanines (IVb-g), which give the corresponding N-quinolinyl-β-alanines (Vb-g) on hydrolysis:

$$\underset{\text{Ib-g}}{R-NH_2} + CH_2{=}CHCOOCH_3 \longrightarrow \underset{\text{IVb-g}}{R-NHCH_2CH_2COOCH_3} \longrightarrow \underset{\text{Vb-g}}{R-NHCH_2CH_2COOH}$$

I, IV, V b $R = 3\text{-}C_9H_6N$; c $R = 4\text{-}C_9H_6N$; d $R = 5\text{-}C_9H_6N$; e $R = 6\text{-}C_9H_6N$; f $R = 7\text{-}C_9H_6N$; g $R = 8\text{-}C_9H_6N$

During the hydrolysis of IVc, Vc is isolated from the reaction mixture as a hydrate, which on vacuum drying over phosphorus pentoxide is converted to the anhydride form. On melting (205-207°), the hydrate of Vc loses a molecule of water, begins to crystallize, and melts at a temperature which coincides with the melting point of Vc.

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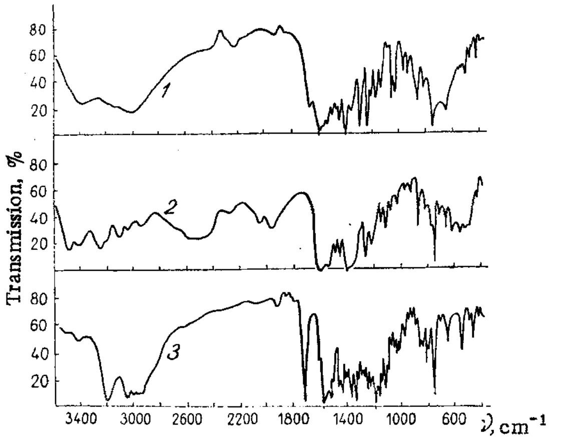


Fig. 1. IR spectra: 1) 1-(2-carboxyethyl)-4-aminoquinolinium betaine (IIIc); 2) N-(4-quinolinyl)-β-alanine (Vc); 3) methyl ester of N-(4-quinolinyl)-β-alanine (IVc).

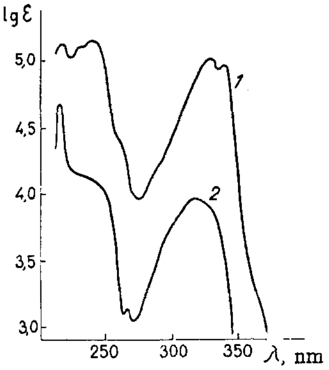
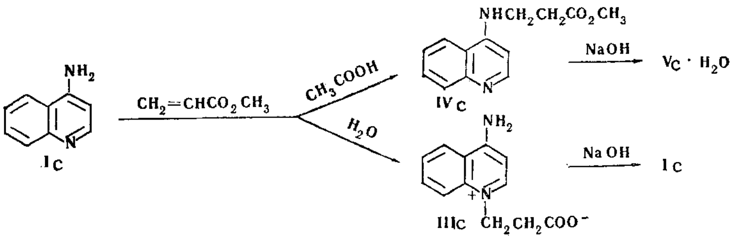


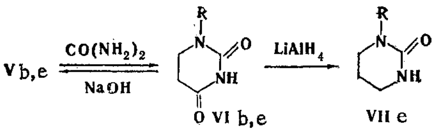
Fig. 2. UV spectra in 0.001% NaOH: 1) 1-(2-carboxyethyl)-4-aminoquinolinium betaine (IIIc); 2) N-(4-quinolinyl)-β-alanine (Vc).

In the presence of water, 4-aminoquinoline (Ic) reacts with methyl acrylate to form 1-(2-carboxyethyl)-4-aminoquinolinium betaine (IIIc), which decomposes during alkaline hydrolysis to form the starting material:



Compound Vb is not acylated by acetyl chloride, acetic anhydride, or benzoyl chloride.

The corresponding 1-quinolinyldihydrouracils (VIb and VIe) are isolated only from Vb and Ve by the action of urea [4, 5] on the N-quinolinyl-β-alanines (Vb-g). The fact that β-alanines V, which are derivatives of 4-, 5-, 7-, and 8-aminoquinolines, are not inclined to form dihydrouracils can be explained by the amino–imino tautomerism [6-8] of these compounds. Attempts to obtain 1-(3- and 6-quinolinyl)-2-thiodihydrouracils by the action of potassium or ammonium thiocyanates on Vb and Ve were unsuccessful, and the starting β-alanines and their hydrochlorides or hydrothiocyanates were isolated from the reaction mixture.



1-(6-Quinolinyl)-2-oxohexahydropyrimidine (VIIe) was isolated by the reduction [9] of dihydrouracil VIe with lithium aluminum hydride in ether. Only the hydrobromide of dihydrouracil VIe was isolated by bromination of VIe with bromine in acetic acid at room temperature. Compounds VIb and VIe are decomposed to the starting β-alanines (Vb and Ve) by alkali.

The IR spectra of Vb-g and IVc contain the characteristic frequencies of NH valence vibrations at 3150-3450 cm^{-1} and bands of the valence vibrations of the $=C-H$ group of the quinoline ring at 3000-3100 cm^{-1}. The bands at 1680-1730 cm^{-1} correspond to the valence vibrations of the $C=O$ group. The carbonyl absorption at 1720 cm^{-1}, which is present in the spectrum of IVc, disappears in the IR spectra of IIIc and Vc (Fig. 1); this indicates the formation of a carboxylate ion in IIIc and Vc [10].

The differences in the UV spectra of IIIc and Vc are illustrated in Fig. 2. While IIIc has maxima at 217, 237-239, 327, and 340 nm, Vc is characterized by only two maxima at 214-216 and 316-318 nm.

EXPERIMENTAL

The purity of the substances was monitored by means of thin-layer chromatography on a loose layer of aluminum oxide.

Starting Materials. 7-Nitroquinoline was synthesized according to the method in [11]; the 5-, 6-, 7-, and 8-aminoquinolines were obtained from the corresponding nitroquinolines [12].

3H,4H-Quino[1,2-a]-2-pyrimidone (IIa). A mixture of 14.4 g (0.1 mole) of 2-aminoquinoline (Ia), 10 ml (0.11 mole) of methyl acrylate, and 0.1 g of acetic anhydride was heated at 120° for 8 h, and the volatile

TABLE 1. N-Quinolinyl-β-alanines and Their Derivatives

Comp.	Mp (crystallization solvent)	N found, %*	Hydrochlorides			Yield, %
			mp (crystallization solvent)	found %,†		
				Cl	N	
IVb	103—103,5 (ethanol)	12,33	202—205 (dec., ethanol – ether)	13,25	10,35	31,5
IVc	94,2—95,2 (petroleum ether)	12,27	161—162 (ethanol)	13,26	10,54	98,0
IVd	39,5—40 (petroleum ether)	12,35	191—191,5 (methanol)	13,25	10,57	45,0
IVe	63,5—64 (ether)	12,17	145—146 (methanol – ether)	13,44	10,42	80,0
IVf	61,5—62,5 (petroleum ether)	12,22				5,0
IVg	69—69,5 (petroleum ether)	12,27	157—158 (methanol)	13,38	10,59	50,0
Vb	190 (ethanol)	12,87	222—223 (ethanol – ether)	14,08	11,05	70,0
Vc	260—260,5 (ethanol)	12,88	277—278 (ethanol – ether)	14,00	10,95	
Hydrate Vc	205—207 (dec., ethanol)	11,91				93,5
Vd	194,5—195 (ethanol)	12,93	238,5—239 (ethanol)	13,98	10,96	86,0
Ve	210,5—211 (dioxane)	13,09	184—186 (ethanol – ether)	14,20	10,98	93,5
Vf	162—162,5 (ethanol)	12,80	212,5—214 (ethanol – ether)	13,95	11,20	80,0
Vg	147,2—148 (benzene)	13,12	188—189 (ethanol – ether)	14,08	11,15	83,0

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* The empirical formula of IVb-g is $C_{13}H_{14}N_2O$. Calculated %: N 12.16. The empirical formula of Vb-g is $C_{12}H_{12}N_2O_2$. Calculated %: N 12.95. The empirical formula of the hydrate of Vc is $C_{12}H_{12}N_2O_2 \cdot H_2O$. Calculated %: N 11.90.

† The following values were calculated for the hydrochlorides of IVb-g: Cl 13.29; N 10.50. The following values were calculated for the hydrochlorides of Vb-g: Cl 14.02; N 11.08.

fractions were vacuum distilled. The residual viscous mass began to crystallize in a vacuum desiccator to give 13.5 g (68%) of a product with mp 167-168° (from absolute ethanol). Compound IIa was soluble in hot absolute ethanol and slightly soluble in water and ether. Found %: C 72.96; H 5.20; N 13.95. $C_{12}H_{10}N_2O$. Calculated %: C 72.96; H 5.20; N 14.14.

1-(2-Carboxyethyl)-2-aminoquinolinium Betaine (IIIa). A mixture of 14.4 g (0.1 mole) of Ia, 10 ml (0.11 mole) of methyl acrylate, and 2 ml of water was heated in an ampule at 120° for 8 h. The excess methyl acrylate was distilled from the reaction mass, and 15.8 g (73%) of IIIa with mp 167-168° precipitated on standing (24 h). Found %: C 66.75; H 5.52; N 12.95. $C_{12}H_{12}N_2O_2$. Calculated %: C 66.66; H 5.55; N 12.95.

1-(2-Carboxyethyl)-4-aminoquinolinium Betaine (IIIc). A mixture of 1.44 g (0.01 mole) of Ic, 1 ml (0.011 mole) of methyl acrylate, and 1 ml of water was heated at 100° for 1.5 h, cooled, and filtered to give 1.39 g (60.5%) of IIIc with mp 233-234° (from ethanol). Found %: N 12.97. $C_{12}H_{12}N_2O_2$. Calculated %: N 12.95. The hydrochloride of IIIc melted at 230° (decomp., from methanol–ether). Found %: Cl 13.96. $C_{12}H_{12}N_2O_2 \cdot HCl$. Calculated %: Cl 14.02.

Methyl Esters of N-Quinolinyl-β-alanines (IVb-g). A mixture of 1.44 g (0.01 mole) of Ib-g, 1 ml (0.011 mole) of methyl acrylate, and 0.05 ml of acetic acid was heated for 10-60 h, and the excess methyl acrylate was removed by distillation. The reaction mixture was dissolved in chloroform, and the solution was passed through a column filled with aluminum oxide. The chloroform was evaporated, and IVb-g were crystallized from appropriate solvents (Table 1).

The hydrochlorides of the methyl esters of the N-quinolinyl-β-alanines (IVb-g) were obtained by passing dry HCl through methanol solutions of IVb-g (Table 1).

N-Quinolinyl-β-alanine (Vb-g). A. A mixture of 1.15 g (5 mmole) of IVb-g and 5 ml of 15% sodium hydroxide was heated at 60-70° for 1.5 h, cooled, the salts were separated by filtration, and Vb-g were isolated by acidification with acetic acid.

B. A mixture of 0.24 g (1 mmole) of VIb or VIe and 3 ml of 10% sodium hydroxide was heated at 100° for 1.5 h, cooled, and 3 ml of water was added. The mixture was filtered, acidified with acetic acid, and the practically quantitative precipitates of Vb or Ve were filtered (Table 1). The hydrochlorides of Vb-g were obtained by vacuum evaporation of solutions of Vb-g in hydrochloric acid with subsequent crystallization (Table 1). The hydrothiocyanate of Vb melted at 172-172.5° (from ethanol). Found %: C 56.88; H 4.78; N 15.52. $C_{12}H_{12}N_2O_2 \cdot HCNS$. Calculated %: C 56.88; H 4.77; N 15.31.

1-(3-Quinolinyl)dihydrouracil (VIb). A. A total of 0.75 g (3.5 mmole) of Vb was dissolved in 1.5 ml of acetic acid, 0.8 g (13 mmole) of urea was added, the mixture was heated at 100° for 6 h, 1 ml of concentrated HCl was added, and the mixture was heated for another 2 h. The reaction mixture was cooled, diluted with water (1 : 2), and neutralized with sodium carbonate. The resulting crystals were filtered and crystallized from ethanol to give 0.37 g (45%) of a product with mp 270-271°. Found %: N 17.67. $C_{13}H_{11}N_3O_2$. Calculated %: N 17.43.

B. A mixture of 0.21 g (1 mmole) of Vb and 0.7 g of urea was heated at 135-140° for 4 h. The mixture was cooled, the glassy mass was treated with water, and the resulting precipitate (0.22 g) was filtered and crystallized from ethanol to give 0.1 g (42.5%) of product. A sample of this product did not depress the melting point of a sample of VIb obtained via method A.

1-(6-Quinolinyl)dihydrouracil (VIe). A mixture of 1.8 g (80 mmole) of Ve and 5.5 g (91 mmole) of urea was heated at 140-150° for 9 h. After cooling, the reaction mass began to crystallize and was dissolved in water and repeatedly extracted with chloroform. The extract was evaporated, and the residue was crystallized from ethanol to give 0.7 g (35%) of a product with mp 251-252°, which was slightly soluble in ethanol and soluble in chloroform. Found %: C 64.66; H 4.46; N 17.62. $C_{13}H_{11}N_3O_2$. Calculated %: C 64.72; H 4.52; N 17.43. The hydrobromide of VIe was prepared as follows. A total of 0.24 g (1 mmole) of VIe was dissolved in 5 ml of acetic acid, 0.2 g of sodium acetate was added, and 0.1 ml of bromine in 2 ml of acetic acid was added dropwise to this solution. A quantitative yield of yellow crystals of the hydrobromide with mp 298° (decomp., from ethanol) precipitated from the solution. Found %: Br 24.75. $C_{13}H_{11}N_3O_2 \cdot HBr$. Calculated %: Br 24.95.

1-(6-Quinolinyl)-2-oxohexahydropyrimidine (VIIe). A total of 1.5 g (0.037 mole) of lithium aluminum hydride was dissolved in 150 ml of absolute diethyl ether, 2.4 g (0.01 mole) of VIe was added in small portions, and the mixture was refluxed with stirring for 40 h. The excess lithium aluminum hydride was decomposed with ethanol–ether, the solvents were removed by distillation, and the residue was extracted with acetone in Soxhlet apparatus. Evaporation of the acetone yielded 0.22 g (10%) of VIIe with mp 191-192° (from acetone). Found %: N 18.50, 18.60. $C_{13}H_{13}N_3O$. Calculated %: N 18.44.

The IR spectra of the solids were obtained with a UR-10 spectrometer. The UV absorption spectra for concentrations of $0.5 \cdot 10^{-3}$ to $2 \cdot 10^{-3}$ M were measured with an SF-4 spectrophotometer.

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