TRANSFORMATION OF β-(5-BROMOURACIL-1-YL)-α-ALANINE INTO AN IMIDAZO[1,2-c]PYRIMIDINE

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In the reaction of β-(5-bromouracil-1-yl)-α-analine with primary or secondary amines an imidazo[1,2-c]pyrimidine is formed.

We have shown previously that on halogenation β-(uracil-1-yl)-α-alanine forms β-(5-halouracil-1-yl)-α-alanines readily and with good yield [1]. Continuing investigations of the chemical properties of β-(uracil-1-yl)-α-alanine we have studied the possibility of synthesizing β-(5-aminouracil-1-yl)-α-alanine derivatives by the reaction of β-(5-bromouracil-1-yl)-α-alanine with primary and secondary amines.

It is reported in the literature that when 5-bromouracil or 5-bromo-1,3-dimethyl-6-methylaminouracil is heated with an excess of a primary or secondary amine, the corresponding 5-aminouracil is formed [2-6]. The replacement of halogen by an amino group takes place similarly in the case of 5-bromouridine [7].

However, we have established that the reaction of β-(5-bromouracil-1-yl)-α-alanine (I) with primary or secondary amines, always gives the same product in the form of the salt of the corresponding amine. After the neutralization of its aqueous solution with hydrochloric acid and crystallization, a chromatographically pure product was isolated and its least elementary composition was established — $C_7H_7N_3O_4$, which corresponds to a reaction product obtained from compound (I) with the splitting out of HBr. The compound did not give the reaction with ninhydrin that is characteristic for amino acids. The UV spectrum taken in aqueous solution and in 0.1 N caustic soda solution showed the absorption at 265 nm that is characteristic for 1-N-substituted uracils. A study of the reaction of compound (I) with an aqueous solution of sodium bicarbonate by means of UV spectroscopy showed that after only 2 h at room temperature the absorption at 277 nm characteristic for 1-substituted 5-bromouracils had diminished and an absorption maximum had appeared at 265 nm (Fig. 1).

The IR spectrum of the compound obtained showed absorption bands at 1710-1640 cm^{-1} which are characteristic for the vibrations of the carbonyl groups of 2,4-dioxopyrimidines; C═C and C═N stretching vibrations absorb at 1580-1520 cm^{-1}, and the deformation vibrations of C—H atoms of the ring of a nitrogen heterocycle at 850-800 and 1010 cm^{-1}. Absorption bands at 3250 and 3120 cm^{-1} may relate to the stretching vibration of the N—H and C—H groups of a pyrimidine ring, respectively.

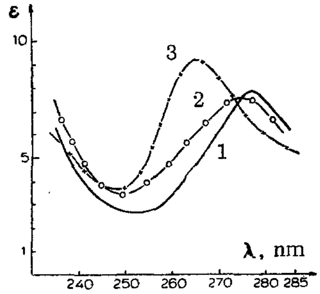

Fig. 1. UV spectrum of β-(5-bromouracil-1-yl)-α-alanine (I) in 0.1 N $NaHCO_3$ solution: 1) after 10 min; 2) after 30 min; 3) after 2 h.

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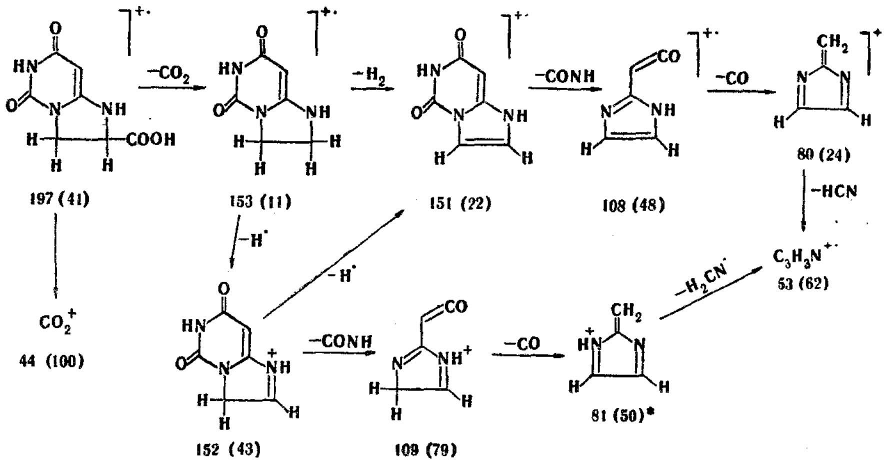
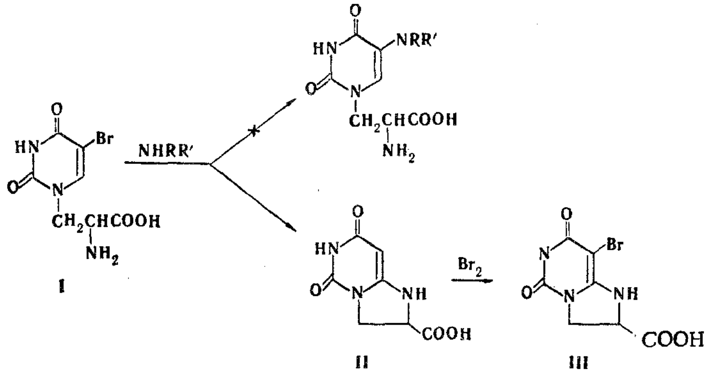
In the mass spectrum of this compound there is a peak of molecular ions with m/e 197[†] the decomposition of which proceeds with the successive elimination of a CO_2 molecule (decarboxylation) and of two hydrogen atoms (ions 153, 152, and 151, respectively). Subsequent fragmentation leads to the destruction of the pyrimidine ring in the manner described by Rice et al. [8]. On the basis of IR, UV, and mass-spectroscopic characteristics, for the compound obtained we have suggested the structure of 5,7-dioxoimidazo[1,2-c]pyrimidine-2-carboxylic acid (II).



The intensities of the peaks of the ions in per cent of the maximum ion are given in parentheses. The asterisk denotes that the composition of the ion was determined with the aid of high resolution (~25,000).

Compound (II) is readily brominated in position 8:



The structure of compound (II) was also confirmed by its PMR spectra, in which two singlet signals are observed at 10.25 and 8.28 ppm; they can be ascribed to the NH protons in the pyrimidine and imidazole rings, respectively. In the 3.8-4.5 ppm region a ABX multiplet system is observed that is due to the $3CH_2$—$2CH$ fragment of the molecule. The C_8H proton gives a singlet signal at 4.53 ppm. On the bromination of compound (II), this signal disappeared. After the addition of D_2O, the singlet at 4.53 likewise disappeared completely, which shows the rapid exchange of the hydrogen on the C_8 atom with deuterium. The ease of this exchange is explicable if one considered compound (II) as an enamine derivative that can exist in two tautomeric forms — lactam and lactim.

It is known from the literature that in the reaction of 5-halouridines with nucleophiles the first stage is the addition of the nucleophile to the C_6 atom. It has also been reported that in place of a nucleophile the 5′-hydroxy group of a nucleoside may add to this atom with the formation of a O^6,5′-cyclonucleoside [9]. It may be assumed that the amination of β-(5-bromouracil-1-yl)-α-alanine takes place by the same route. In a similar manner to the 5′-hydroxy group of a nucleoside, in our case the amino group of the alanine (I) adds to the C^6 ring atom of the uracil and, after the splitting out of the molecule of HBr, an imidazo[1,2-c]pyrimidine is formed.

[†] Here and below the numbers characterizing ions specify the ratio of the mass of the ion to its charge.

EXPERIMENTAL

Ir spectra were taken on a UR-20 spectrophotometer in paraffin oil, UV spectra on a Spectramom-240 instrument in water and 0.1 N NaOH solution, and PMR spectra on a Bruker instrument (90 MHz) in DMSO-d_6 and D_2O solutions, with HMDS as internal standard. The mass spectrum was taken on a AEI MS-50 instrument with direct introduction of the sample into the ion source at an energy of the ionizing electrons of 70 eV and a temperature of the ionization chamber of 300°C. The individuality of the compounds was checked with the aid of TLC on Silufol UV-254 plates in the n-butanol—acetic acid—water (8 : 1 : 2) system. The substances were detected on the chromatograms from their absorption in UV light and were also revealed with ninhydrin.

5,7-Dioxyimidazo[1,2-c]pyrimidine-2-carboxylic acid (II). A mixture of 2.78 g (0.01 mole) of β-(5-bromouracil-1-yl)-α-alanine (I) and 5 ml of an amine (sec.-butylamine, benzylamine, cyclopentylamine, morpholine, piperidine) was heated with stirring until the solid matter had dissolved (1-3 h). The solution was evaporated to dryness in vacuum and the residue was washed with ether. It was then recrystallized from methanol, which gave the corresponding amine salt of 5,7-dioxoimidazo[1,2-c]pyrimidine-2-carboxylic acid. The salts were dissolved in water and neutralized with hydrochloric acid to pH 7. The white precipitate that deposited was recrystallized from water. Yield 89-91%, mp 337-339°C (decomp.), R_f 0.45. PMR spectrum (in DMSO-d_6), ppm: 10.25 (1 H, s, 6NH); 8.28 (1 H, s, 1NH); 4.53 (1 H, s, 8CH); 4.51 (1 H, dd, J = 8.0 and 5.6 Hz, 2CH); 4.06 (1 H, dd, J = 10.0 and 8.0 Hz, 3CH); 3.88 (1 H, dd, J = 10.0 and 5.6 Hz). Found: C 42.35; H 3.73; N 20.92%. $C_7H_7N_3O_4$. Calculated: C 42.35; H 3.50; N 21.37%.

8-Bromo-5,7-dioxoimidazo[1,2-c]pyrimidine-2-carboxylic acid (III). A suspension of 0.197 g (0.01 mole) of compound (II) in 3 ml of glacial acetic acid was treated, with stirring, with 0.1 ml bromine and the mixture was left overnight. The resulting solution was evaporated to dryness in vacuum and the residue was recrystallized from water. Yield 0.21 g (76.1%). mp >350°C, R_f 0.13. UV spectrum, λ_{max}, nm (logε); pH 7: 277 (3.94); pH 1: 275 (3.83). Found: C 26.41; H 3.19; N 13.30%. $C_7H_6BrN_3O_4 \cdot 2H_2O$. Calculated: C 26.93; H 3.21; N 13.46%.

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