SYNTHESIS AND REACTIONS OF β-(5-HALO-3-URACYL) PROPIONIC ACIDS

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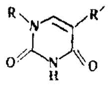
The reaction of elementary bromine and iodine with β-(3-uracyl)-propionic acid has given the corresponding β-(5-bromo-3-uracyl) and β-(5-iodo-3-uracyl)propionic acids. The methyl esters and amides of the acids have also been synthesized for the first time.

Continuing our investigations on the synthesis of N-substitued hydropyrimidine systems, we have carried out the synthesis of the previously unknown β-(5-bromo-3-uracyl)propionic acid (I), β-(5-iodo-3-uracyl)propionic acid (II), and their derivatives. Attempts to obtain compounds I and II by a known method of synthesis [1–3] based on the reaction of 5-bromouracil (III) and 5-iodouracil (IV) with acrylonitrile in liquid ammonia were unsuccessful, and it was found that after the treatment mentioned compounds III and IV were recovered unchanged.

It was, however, possible to obtain the acids I and II by direct halogenation of the β-(3-uracyl)propionic acid (V) synthesized previously [1].

On treatment with methanol in the presence of sulfuric acid, compounds I and II were smoothly converted into the corresponding methyl esters VI and VII.



I $R = CH_2CH_2CO_2H$, $R' = Br$;

II $R = CH_2CH_2CO_2H$, $R' = I$;

III $R = H$; $R' = Br$;

IV $R = H$; $R' = I$;

V $R = CH_2CH_2CO_2H$, $R' = H$;

VI $R = CH_2CH_2CO_2CH_3$, $R' = Br$;

VII $R = CH_2CH_2CO_2CH_3$, $R' = I$;

VIII $R = CH_2CH_2CONH_2$, $R' = Br$;

IX $R = CH_2CH_2CONH_2$, $R' = I$.

The aminolysis of the esters VI and VII with aqueous ammonia in the presence of ammonium chloride led to the amides of the β-(5-halo-3-uracyl)propionic acids (VIII and IX).

All the compounds obtained were colorless crystalline substances with high melting points. They were soluble in hot water and the lower alcohols but practically insoluble in ether and benzene. As was to be expected, all the substances obtained had strong absorption in the near UV region.

EXPERIMENTAL

Paper chromatography. Chromatography was carried out on paper of the Volodarskii Leningrad Mill. The following systems of solvents were used: n-butanol–acetic acid–water (4 : 1 : 5) (system 1); isopropanol–ammonia–water (7 : 1 : 2) (system 2); n-butanol–water (43 : 7) (system 3); ethanol–n-butanol–water (1 : 5 : 4) (system 4). The substances were revealed on the chromatograms by their absorption of UV light.

β-(5-Bromo-3-uracyl)propionic acid (I). A suspension of 1.8 g (0.01 mole) of β-(3-uracyl)propionic acid (V) [1] in 20 ml of water was treated dropwise with 1.8 ml (0.03 mole) of bromine, after which the mixture was boiled in the water bath for 45 min. After this time, it had become homogeneous. The resulting solution was evaporated to half bulk and cooled, and the precipitate that deposited was filtered off. The yield of I was 1.89 g (73.5%); mp 250° (from water). Found, %: C 32.03; H 2.83; Br 30.28; N 10.49. Calculated for $C_7H_7BrN_2O_4$, %: C 31.96; H 2.69; N 10.65; Br 30.38. R_f 0.69 (system 1); 0.31 (system 2); 0.23 (system 4). UV spectrum: λ_{max} 281 nm; lg ε 4.08 (0.1 N HCl); λ_{max} 280 nm; lg ε 3.68 (0.01 N NaOH).

β-(5-Iodo-3-uracyl)propionic acid (II). A solution of 1.8 g (0.01 mole) of compounds **V** in a mixture of 40 ml of water and 25 ml of dimethylformamide was treated with 0.98 g of mercuric nitrate and the mixture was stirred for 1 hr in the boiling water bath and was then cooled to 70° and a solution of 2.5 g (0.01 mole) of iodine in 10 ml of dioxane was added to it in drops. It was then stirred at room temperature for 1 hr, after which the solvent was distilled off in vacuum. The residue, which consisted of a reddish oil, crystallized upon prolonged storage. The crystals formed were transferred to a filter and carefully washed with 15% aqueous potassium iodide solution (to remove mercury salts) and then with cold water. This gave 2.0 g (80%) of compound **II** in the form of colorless crystals with mp 180–181° (from water). Found, %: C 27.53; H 2.55; N 9.07; I 40.34. Calculated for $C_7H_7IN_2O_4$, %: C 27.11; H 2.27; N 9.03; I 40.67. R_f 0.66 (system 1); 0.31 (system 4). UV spectrum: λ_{max} 289 nm, lg ε 3.97 (0.1 N HCl); λ_{max} 280–281 nm, lg ε 3.61 (0.01 N NaOH).

Methyl β-(5-bromo-3-uracyl)propionate (VI). To 2.6 g (0.01 mole) of V was added 2.8 ml of 98% sulfuric acid and 28 ml of methanol. The mixture was boiled in the water bath for 10 hr and was then evaporated in vacuum to one third of its bulk and cooled. The precipitate was filtered off and dried. The yield of VI was 2.7 g (94%), mp 159–160° (from methanol). Found, %: C 34.39; H 3.50; N 10.52; Br 28.49. Calculated for $C_8H_9BrN_2O_4$, %: C 34.68; H 3.20; N 10.11; Br 28.84. R_f 0.68 (system 1); 0.72 (system 2); 0.76 (system 4). UV spectrum: λ_{max} 281 nm, lg ε 3.94 (0.1 N HCl); λ_{max} 278 nm, lg ε 3.87 (0.01 N NaOH).

Methyl β-(5-iodo-3-uracyl)propionate (VII). This compound was obtained in a similar manner to the preceding one. Yield 40%, mp 185–186° (from methanol). Found, %: C 29.72; H 2.93; N 8.55; I 39.26. Calculated for $C_8H_9IN_2O_4$, %: C 29.64; H 2.79; N 8.64; I 39.16. R_f 0.89 (system 1); 0.81 (system 4). UV spectrum: λ_{max} 288–290 nm, lg ε 3.75 (0.1 N HCl); λ_{max} 281–282 nm, lg ε 3.77 (0.01 N NaOH).

β-(5-Bromo-3-uracyl)propionamide (VIII). A mixture of 2.77 g (0.01 mole) of the ester VI, 80 ml of 25% aqueous ammonia, and 46 g of ammonium chloride was heated at 40–50° for 10 hr, after which the solution was evaporated in vacuum to one third of its initial bulk and cooled. The while crystalline precipitate that deposited was filtered off, washed with cold water, and dried. Yield 2.34 g (91%), mp 281° (from water). Found, %: C 32.23; H 3.20; N 16.23. Calculated for $C_7H_8BrN_3O_3$, %: C 32.08; H 3.07; N 16.03. R_f 0.48 (system 1); 0.47 (system 4). UV spectrum: λ_{max} 282 nm, lg ε 3.82 (0.1 N HCl), λ_{max} 277 nm, lg ε 3.78 (0.01 N NaOH).

β-(5-Iodo-3-uracyl)propionamide (IX). The compound was obtained similarly to the preceding one. Yield 85%, mp 230° (from water). Found, %: C 27.20; H 2.60; N 13.59; I 41.06. Calculated for $C_7H_8IN_3O_3$, %: C 27.33; H 2.85; N 13.84; I 41.40. R_f 0.45 (system 1); 0.44 (system 4).

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