BRIEF COMMUNICATIONS

ANALOGS OF PYRIMIDINE NUCLEOSIDES

II. N_1-(α-Butyrolactono) Derivatives of 5-Substituted Uracils*

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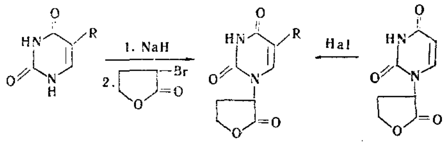
A number of N_1-(α-butyrolactono) derivatives of 5-substituted uracils have been synthesized by condensing the sodium derivatives of the corresponding bases with α-bromobutyrolactone or by the halogenation of N_1-(α-butyrolactono)uracil.

We have previously [1] described the synthesis of N_1-(α-furanidyl) derivatives of 5-substituted uracils with properties extremely similar to those of the pyrimidine nucleosides. It was found that these compounds are cleaved by nucleoside phosphorylases, although to a smaller extent than natural nucleosides.

In order to investigate the connection between chemical structure and biochemical properties in the N_1-derivatives of the pyrimidine bases, we have synthesized N_1-(α-butyrolactono) derivatives of 5-substituted uracils I-VI [2]; these have configurations close to those of the nucleosides but possess markedly differing chemical properties.

To obtain I-VI we studied the reaction of the sodium derivatives of uracil, thymine, and 5-halouracils with α-bromobutyrolactone. The sodium derivatives were obtained by the reaction of the bases with sodium hydride in dimethylformamide and were used for condensation without isolation from the reaction mixture [3].



I-VI I

I R=H; II R=CH_3; III R=F; IV R=Cl; V R=Br; VI R=I

Compounds I-VI are white crystalline substances soluble in polar solvents such as ethanol and, especially, water and dimethylformamide. The structure of I-VI as N_1-derivatives was confirmed by their UV spectra (absence of a bathochromic shift of the absorption maximum on passing from an acid medium to an alkaline one). The presence of a lactone ring explains the appearance of an absorption band in the 1780 cm^{-1} region in the IR spectra which is characteristic for the stretching vibrations of C=O in γ-lactones, together with γ_{CO} of a uracil at 1680 and 1715 cm^{-1}.

In the case of 5-bromouracil and, particularly, 5-iodouracil, halogen is eliminated under the reaction conditions. Consequently, the 5-halouracil derivatives were also obtained by the direct halogenation of N_1-(α-butyrolactono)uracil I with N-halosuccinimides or with free halogen in the presence of nitric acid [4].

The compounds obtained are potential inhibitors of nuclein metabolism and they also may be used for starting materials for the synthesis of new N_1-substituted pyrimidine bases.

EXPERIMENTAL

N_1-(α-Butyrolactono)uracil (I). To a suspension of 11.2 g (0.1 mole) of uracil in 125 ml of dry dimethylformamide was added 2.4 g (0.1 mole) of sodium hydride, and the mixture was stirred at room temperature for 2 hr and was cooled to –10° C, after which 33 g (0.2 mole) of α-bromobutyrolactone in 15 ml of dimethylformamide was added. The temperature was gradually raised to room temperature, and then the mixture was heated at 80° C for 1 hr, another 16.5 g (0.1 mole) of α-bromobutyrolactone was added, and it was heated at 150° C for 30 min. The solvent was distilled off in vacuum and the residue was extracted with boiling ethanol. The insoluble residue consisted of a mixture of uracil and sodium bromide. Its recrystallization from water gave 3.4 g of uracil (30% of that taken for the reaction). The ethanolic solution yielded 5.9 g of N_1-(α-butyrolactono)uracil

Characteristics of the Compounds Obtained

Compound	Mp, °C	UV spectrum						Empirical formula	Found, %				Calculated, %			
		pH 2—3		pH 7—8		pH 9—10										
		λ_{max}, nm	$E \cdot 10^{-3}$	λ_{max}, nm	$E \cdot 10^{-3}$	λ_{max}, nm	$E \cdot 10^{-3}$		C	H	N	halogen	C	H	N	halogen
I	238—240	261	9.80	260	7.56	264	7.30	$C_8H_8N_2O_4$	48.67	4.18	14.86	—	48.98	4.08	14.28	—
II	260—261	267	9.44	267	8.80	270	7.36	$C_9H_{10}N_2O_4$	51.09	4.96	13.38	—	51.43	4.81	13.32	—
III	240—242	268	8.22	267	7.54	271	6.20	$C_8H_7FN_2O_4$	44.37	3.49	12.70	9.33	44.86	3.29	13.08	8.87
IV	>300 (decomp.)	275	8.86	276	8.42	278	6.28	$C_8H_7ClN_2O_4$	41.11	2.91	12.65	15.52	41.64	3.06	12.15	15.38
V	>300 (decomp.)	278	9.50	278	8.82	282	7.30	$C_8H_7BrN_2O_4$	34.78	2.52	10.41	29.50	34.94	2.56	10.19	29.05
VI	>280	286	7.32	285	6.90	282	5.22	$C_8H_7IN_2O_4$	29.56	2.27	8.39	38.46	29.83	2.19	8.69	39.41

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*For part I, see [1].

(30%, calculated on the uracil taken for the reaction). It was crystallized from ethanol.

N_1-(α-Butyrolactono)-5-chlorouracil (IV). A suspension of 1 g (0.005 mole) of I in 60 ml of glacial acetic acid containing 1.2 ml of acetic anhydride was heated at 80° C until the I had dissolved and was then cooled to 55° C and treated with 0.8 g (0.006 mole) of N-chlorosuccinimide, after which the mixture was kept at 50°-55° C for 9 hr and cooled, and the precipitate that deposited was filtered off. Yield 0.74 g (60%). It was crystallized from water.

N_1-(α-Butyrolactono)-5-bromouracil (V). A suspension of 1 g (0.005 mole) of I in 50 ml of acetic acid was heated to 55° C and a solution of 1 g (0.006 mole) of bromine in 5 ml of glacial acetic acid was added, after which the mixture was kept at 55° C for 1 hr and was cooled and the precipitate that deposited was filtered off. Yield 1.1 g (71%). It was crystallized from water.

N_1-(α-Butyrolactono)-5-iodouracil (VI). To a solution of 1 g (0.005 mole) of I in 20 ml of dioxane containing 5 ml of 0.5 N nitric acid was added 2.6 g (0.01 mole) of iodine, and the reaction mixture was heated at 100° C for 1 hr. The solvent was distilled off in vacuum and 10-ml portions of ethanol were added to the residue and evaporated three times. It was crystallized from water. Yield 0.8 g (50%).

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THE CHEMICAL NATURE OF THE PRODUCTS OF THE ICROBIOLOGICAL TRANSFORMATION OF LATHYRINE

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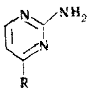
The chemical nature of the compounds formed in the microbiological transformation of α-amino-β-(2-amino-4-pyrimidyl)propionic acid (lathyrine) under the action of soil microorganisms capable of using pyrimidine bases as sources of carbon and nitrogen has been studied.

Recently, a new amino acid which has been given the name of lathyrine has been isolated from a number of plants of the family Leguminosae (Lathyrus tingitanus, Lathyrus japonicus, Lathyrus variegatus, etc.) [1-3]. From the chemical point of view, this amino acid is α-amino-β-(2-amino-4-pyrimidyl)propionic acid (I) [4-7]. Recently, we have carried out an investigation of the routes of the microbiological transformation of I under the action of soil microorganisms capable of using pyrimidine derivatives as sources of carbon and nitrogen. In the present communication we give some information on the chemical nature of the compounds formed in this process.



I $R = CH_2CH(NH_2)CO_2H$;
II $R = CH_3$,
III $R = CH_2COCO_2H$

As the starting material in the experiments on microbiological transformation we used racemic I obtained by chemical synthesis [8]. As the transforming organism we used a strain of Mycobacterium sp. 47 isolated from soil by the method of accumulative cultures [9]. The bacterial cells were incubated at 28° C under conditions of forced aeration in a synthetic medium of the following composition: DL-lathyrine—0.1%, KH_2PO_4—0.01%, $MgSO_4 \cdot 7H_2O$—0.02%, glycerol—0.4%, succinic acid—0.1%, yeast autolyzate—0.01%, distilled water—to 100% (pH 7.2). A 24-hour culture of the strain mentioned grown on MPA slopes was used as the seed material. The growth of the cultures was followed nephelometrically and the changes in the composition of the incubates were determined by chromatography and electrophoresis on paper.

The experiments performed showed that in the incubation of DL-lathyrine with growing cultures of Mycobacterium sp. 47 there is a gradual disappearance of part of the initial amino acid (I), although the degree of utilization of the latter does not exceed half its initial amount, and the remainder of the amino acid exhibits the optical activity characteristic for the D-form. These facts permit the conclusion that only the L-form of I undergoes microbiological transformation.

It was also established that as a result of the incubation three new substances (A, B, and C) regularly appear in the culture medium, these substances, in