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Polyfunctional Derivatives of Isocytosine: I.[1] Intramolecular Rearrangement of 6-Methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]aminodihydro-3*H*-pyrimidine

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Abstract—The reaction of 2-(2-hydroxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine with phenyl isocyanate yields 6-methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]dihydro-3*H*-pyrimidine, which rearranges into 2-(2-hydroxyethyl)amino-6-methyl-4-oxo-5-phenylcarbamoyldihydro-3*H*-pyrimidine under the action of HCl.

The carbamoyl group can be introduced into the ring or a side chain of pyrimidines by their direct reaction with isocyanates or with a mixture of phosgene and an amine, or under conditions of in situ generation of the carbamoylating agent [2]. Uracils are selectively carbamoylated at the N^1 atom of the ring, and cytosine, with the participation of the amino group [3]. A specific feature of carbamoylation of hydroxyaminopyrimidines is formation of O- or N-carbamoyl derivatives depending on the structure of the substrate [4, 5]. An example of carbamoylation of N^2-disubstituted isocytosines is their successive treatment with phosgene and secondary amines to obtain 2-amino-4-carbamoyloxypyrimidines [6].

In this study we examined the structure and acid hydrolysis of products formed by carbamoylation of polyfunctional isocytosine derivatives, 2-(2-hydroxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine **I** and 5-bromo-2-(2-hydroxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine **II**, with phenyl isocyanate.

The carbamoylation of pyrimidylaminoethanol **I** occurs in DMF at 120°C and yields 6-methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]aminodihydro-3*H*-pyrimidine **III**. The yield of **III** drastically decreases at lower reaction temperatures or with DMF replaced by pyridine. The preferential carbamoylation of **I** at the exocyclic hydroxy group follows from the set of the spectral data. In going from **I** to **III**, the ^{1}H NMR signal of the hydroxyl proton at 4.85 ppm disappears, but signals of protons in the exocyclic amino group and at the N^3 atom (6.42 and 10.54 ppm, respectively) are preserved. The IR spectrum contains strong bands of the C=O stretching vibrations at 1740 (NHCOO) and 1675 cm^{-1} (C^4=O), stretching vibrations of the double bonds in the pyrimidine ring at 1615–1600 cm^{-1}, and NH bending vibrations at 1555–1545 cm^{-1} (Fig. 1). The UV spectrum contains ab-

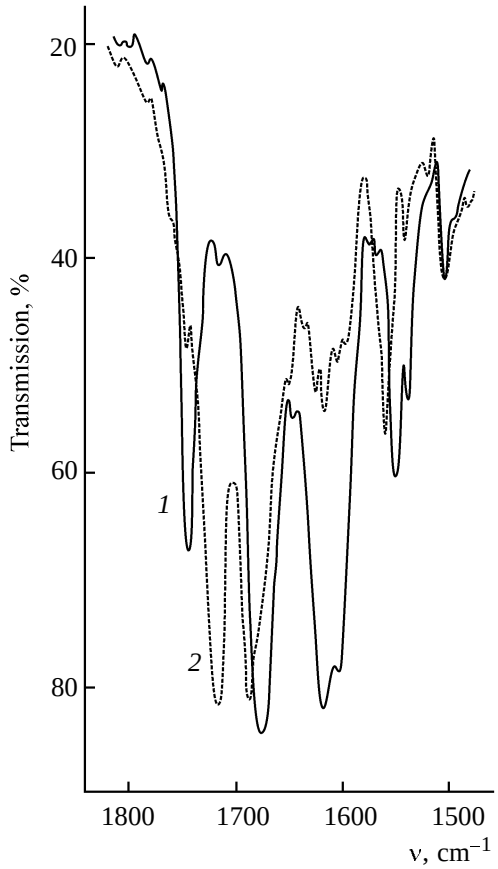


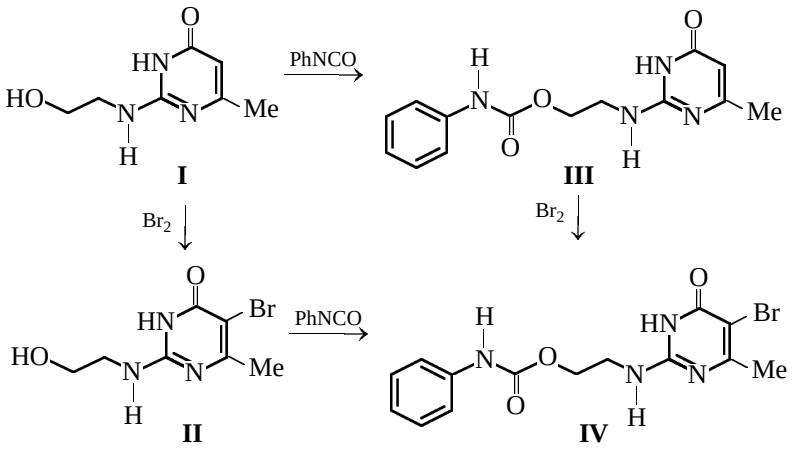
Fig. 1. Range of absorption of double bonds in the IR spectra of (*1*) 6-methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]aminodihydro-3*H*-pyrimidine **III** and (*2*) 2-(2-hydroxyethyl)amino-6-methyl-4-oxo-5-phenylcarbamoyldihydro-3*H*-pyrimidine **V**.

[1] For the preliminary communication, see [1].

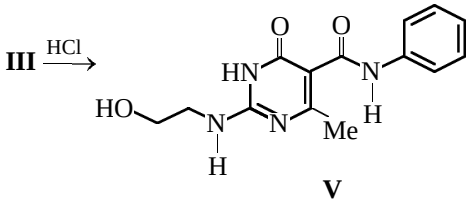
sorption bands with maxima at 233 (log ε 4.34) and 289 nm (log ε 3.93), coinciding with those in the model compounds, ethyl phenylcarbamate [λ_{max} 235 nm (log ε 4.16)] and pyrimidylaminoethanol **I** [λ_{max} 289 nm (log ε 3.93)], and hence corresponding to the isolated chromophores of the phenylcarbamoyl and pyrimidine moieties (Fig. 2).

The selectivity of the carbamoylation of **I** at the exocyclic hydroxy group is indirectly confirmed by the inertness of 2-(2-acetoxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine to phenyl isocyanate under the above-described conditions.

5-Bromo derivative **II**, which is readily prepared by the reaction of **I** with bromine in glacial acetic acid, is carbamoylated similarly to **I**, but chromatographically pure 5-bromo-6-methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]aminodihydro-3*H*-pyrimidine **IV** was obtained only after threefold recrystallization from ethanol in a yield not exceeding 10%. To increase the yield of **IV**, we chose an alternative synthesis route, bromination of **III** in glacial acetic acid at 30–35°C, and obtained compound **IV** as hydrobromide in 59% yield (in terms of the free base). As judged from the ^{1}H NMR spectrum (C^5H signal at 5.36 ppm, characteristic of **III**; integral intensity of aromatic protons corresponding to 5H), bromination of **III** occurs exclusively at the 5-position of the pyrimidine ring.



Hydrolysis of phenylcarbamate **III** with concentrated HCl at 100°C does not yield pyrimidylaminoethanol I or 6-methyluracil as we initially expected, but is accompanied by an intramolecular rearrangement of the substrate. This is indicated by different chromatographic mobility of the above-mentioned compounds and equal molecular weights of **III** and its hydrolysis product. Based on the spectral data, we identified the hydrolysis product as 2-(2-hydroxyethyl)amino-6-methyl-4-oxo-5-phenylcarbamoyldihydro-3H-pyrimidine **V**.



The ^{1}H NMR spectrum of V contains signals of protons of the hydroxy and exocyclic amino groups at 5.04 and 5.82 ppm, respectively, and an N^3H doublet at 8.64–8.76 ppm, but does not contain a signal from the methine proton of the pyrimidine ring at 5.36 ppm, characteristic of **III**. The splitting and upfield shift of the proton signal from the cyclic amino group are caused by possible existence of the *E* and *Z*

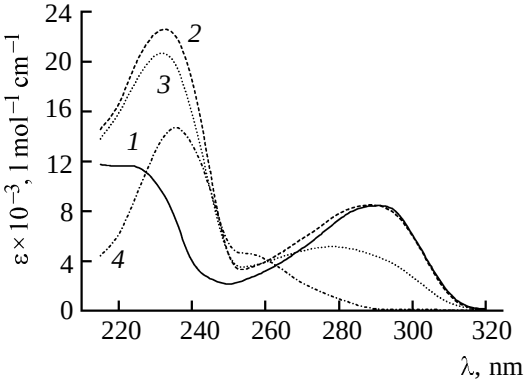
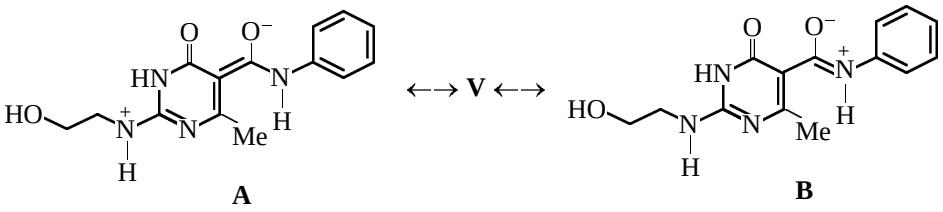


Fig. 2. UV spectra of (*1*) 2-(2-hydroxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine **I**, (*2*) 6-methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]aminodihydro-3*H*-pyrimidine **III**, (*3*) 2-(2-hydroxyethyl)amino-6-methyl-4-oxo-5-phenylcarbamoyldihydro-3*H*-pyrimidine **V**, and (*4*) ethyl phenylcarbamate.

isomers of **V**. The IR spectrum contains strong bands assignable to stretching vibrations of carbonyl groups at 1715 (NHCO) and 1685 cm^{-1} (C^4=O), and also to bending vibrations of NH groups at 1570–1540 cm^{-1} (Fig. 1). A considerable decrease in the intensity of the stretching vibration bands of the double bonds in the pyrimidine ring (1625–1615 cm^{-1}) suggests a significant contribution of pseudo-*p*-quinoid structure **A** to stabilization of **V**. Indeed, the UV spectrum contains a weak band with a maximum at 280 nm ($\log \varepsilon$ 3.71) corresponding to $n \rightarrow \pi^*$ transitions in the conjugated system of this resonance model. Preservation of the shorter-wave but stronger band of the phenylcarbamoyl moiety with a maximum at 232 nm ($\log \varepsilon$ 4.31) is indicative of the less significant contribution of structure **B** in which the charge delocalization is inefficient to the stabilization of **V** (Fig. 2).



In contrast to phenylcarbamate **III**, its 5-bromo derivative **IV** is incapable of intramolecular rearrangement under the above conditions, which indirectly confirms the isomerization of **III** involving 5-position of the pyrimidine ring. Furthermore, compound **IV** undergoes acid hydrolysis neither to bromopyrimidylaminoethanol **II** not to 5-bromo-6-methyluracil. After heating in concentrated HCl at 100°C for 1 h, compound **IV** is recovered unchanged, according to chromatography and to a mixing test which showed no melting point depression on mixing with the initial sample of **IV**. Such a behavior may be caused by extremely low solubility of **IV** in water: even traces of this compound were not detected in the filtrate.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer (KBr pellets). The ^{1}H NMR spectra were taken on a Bruker AC-200 spectrometer (200.13 MHz) in DMSO-d_6, with residual proton signal of the solvent as internal reference. The UV spectra were measured with an SF-26 spectrophotometer from 10^{-4} M solutions in methanol.

The elemental analysis was performed with a Perkin–Elmer-240 CHN analyzer.

The purity of the compounds was checked by TLC on Silufol UV-25 plates in the systems chloroform–methanol, 9 : 1 (A) and acetone–hexane, 2 : 1, + two drops of pyridine (B). The spots were developed by UV light.

The molecular weights were determined by the Rast method.

2-(2-Hydroxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine I and 2-(2-acetoxyethyl)-amino-6-methyl-4-oxodihydro-3*H*-pyrimidine were prepared as described in [1].

5-Bromo-2-(2-hydroxyethyl)amino-6-methyl-4-oxodihydro-3*H*-pyrimidine II. A 1.6-g portion of bromine was added dropwise with vigorous stirring to a solution of 1.69 g of **I** in 20 ml of glacial acetic acid. The resulting suspension was filtered off, and the precipitate was dissolved in 10% aqueous NaOH, reprecipitated with the calculated amount of acetic acid, washed with water, and dried at 80°C for 10 h; yield of compound **II** thus obtained 1.93 g (78%), mp 219°C (with decomposition) (published data: mp 236°C [7]), R_f 0.24 (A). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, Me), 3.33 t (2H, CH_2), 3.49 d (2H, CH_2), 4.74 br.s (1H, OH), 6.67 br.s (1H, NH_e), 11.03 br.s (1H, NH). Found, %: C 33.72; H 5.89; N 16.54. $C_7H_{10}BrN_3O_2$. Calculated, %: C 33.89; H 4.06; N 16.94.

6-Methyl-4-oxo-2-[2-(phenylcarbamoyloxy)-ethyl]aminodihydro-3*H*-pyrimidine III. A mixture of 1.69 g of **I** and 1.31 g of freshly distilled phenyl isocyanate in 3 ml of absolute DMF was heated at 120°C for 2 h. Then the solvent was distilled off to dryness in a vacuum, and the residue was crystallized by adding 10 ml of absolute acetonitrile. The precipitate was filtered off, recrystallized from ethanol, and vacuum-dried over phosphorus pentoxide; yield of compound **III** thus obtained 1.7 g (59%), mp 181°C, R_f 0.19 (B). ^{1}H NMR spectrum, δ, ppm 2.02 s (3H, Me), 3.58 d (2H, CH_2), 4.20 t (2H, CH_2), 5.36 s (1H, CH), 6.42 br.s (1H, NH_e), 6.90–7.47 m (5H, Ph),

9.56 s (1H, NHCO), 10.54 s (1H, NH). Found, %: C 58.42; H 5.45; N 19.56. *M* 284. $C_{14}H_{16}N_4O_3$. Calculated, %: C 58.33; H 5.56; N 19.44. *M* 288.

5-Bromo-6-methyl-4-oxo-2-[2-(phenylcarbamoyloxy)ethyl]aminodihydro-3*H*-pyrimidine IV. A 0.8-g portion of bromine was added dropwise with vigorous stirring to a solution of 1.44 g of phenyl carbamate **III** in 25 ml of glacial acetic acid, heated to 30–35°C. The precipitate formed in the process was filtered off, washed with glacial acetic acid, recrystallized from absolute ethanol, and vacuum-dried over phosphorus pentoxide; yield of compound **IV** thus obtained 0.98 g (40%), mp 188°C, R_f 0.67 (B). ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, Me), 3.60 d (2H, CH_2), 4.21 t (2H, CH_2), 6.94–7.46 m (6H, Ph + NH_e), 9.64 s (1H, NHCO). Found, %: C 37.70; H 3.45; N 12.62. $C_{14}H_{15}BrN_4O_3 \cdot HBr$. Calculated, %: C 37.50; H 3.57; N 12.50. Isolated as hydrobromide.

2-(2-Hydroxyethyl)amino-6-methyl-4-oxo-5-phenylcarbamoyldihydro-3*H*-pyrimidine V. A mixture of 0.65 g of **III** and 5 ml of concentrated HCl was refluxed for 1 h and then cooled to room temperature. The precipitate was filtered off, recrystallized from water, and vacuum-dried over phosphorus pentoxide; yield of compound **V** thus obtained 0.40 g (61%), mp 196°C, R_f 0.57 (A). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, Me), 3.77 d (2H, CH_2), 4.24 d (2H, CH_2), 5.04 br.s (1H, OH), 5.82 br.s (1H, NH_e), 6.90–7.47 m (5H, Ph), 8.64, 8.76 (1H, NH), 9.57 s (1H, NHCO). Found, %: C 58.45; H 5.68; N 19.52. *M* 294. $C_{14}H_{16}N_4O_3$. Calculated, %: C 58.33; H 5.56; N 19.44. *M* 288.

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