ANOMALOUS NUCLEOSIDES AND RELATED COMPOUNDS

XXXI.* N,N'-BIS(6-AZA-5-URACILYL)ETHYLENEDIAMINE AND ITS DIGLUCOPYRANOSIDE

I. V. Alekseeva, A. S. Shalamai, V. I. Kobylinskaya, and V. P. Chernetskii

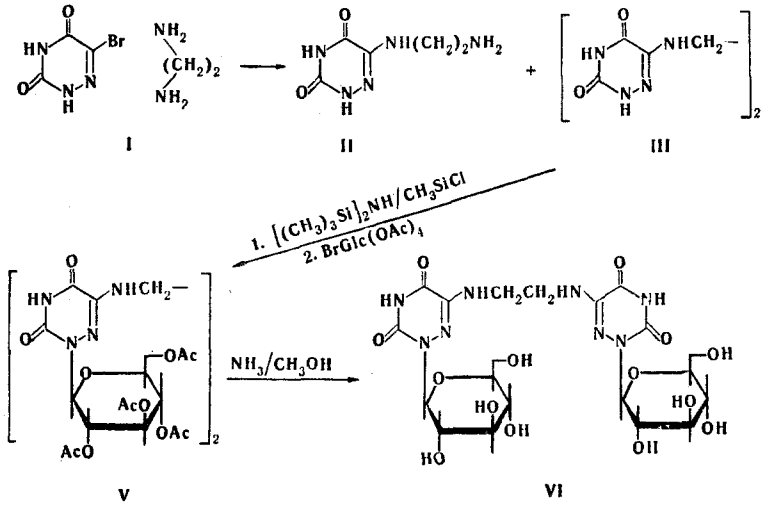
UDC 547.873'963.3

N-(6-Aza-5-uracilyl)- and symmetrical N,N'-bis(6-aza-5-uracilyl)ethylenediamines were obtained by reaction of 1-bromo-6-azauracil with ethylenediamine. N,N'-Bis(1-β-D-glucopyranosyl-6-aza-5-uracilyl)ethylenediamine was synthesized by condensation of the silylated dibase with α-acetobromoglucose and subsequent deacylation of the resulting octaacetyl derivative of a "dinucleoside."

In order to obtain new antimetabolites of nucleic exchange and inhibitors of protein biosynthesis we made an attempt to synthesize an unusual "dinucleoside" containing two 6-azauracil bases bonded covalently through an ethylenediamine bridge.

Syntheses of "dinucleosides" of this type, particularly those that are connected at the N_6 position of two adenosines, are known [2, 3].

The synthesis of a symmetrical 6-azauracil diaglycone was accomplished by a modified method for the preparation of 5-amino-substituted 6-azauracils [4]. N-(6-Aza-5-uracilyl)-ethylenediamine (II) and N,N'-bis(6-aza-5-uracilyl)ethylenediamine (III) in a ratio of 10:1 were obtained by reaction of 5-bromo-6-azauracil (I) [5] with ethylenediamine in the presence of copper bromide and various hydrogen acceptors (sodium carbonate, triethylamine). The isolation of the symmetrical diaglycone was based on the different solubilities of the products in aqueous solutions at pH < 6.



I II III V VI

Compounds II and III are high-melting substances that are only slightly soluble in organic solvents and have different chromatographic mobilities (Table 1).

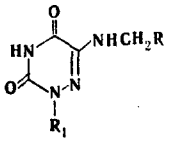
The UV spectra of II and III are similar to the spectra of a model compound — 5-methylamino-6-azauracil (IV); at pH 1 they had close absorption maxima at 303-308 nm, whereas a

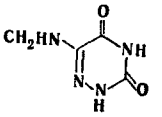
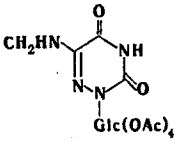
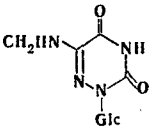
*See [1] for communication XXX.

Institute of Molecular Biology and Genetics, Academy of Sciences of the Ukrainian SSR, Kiev 252627. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1561-1563, November, 1978. Original article submitted November 9, 1977; revision submitted April 4, 1978.

0009-3122/78/1411-1273$07.50

TABLE 1. UV Spectra and Chromatographic Mobilities of 5-Ethylenediamine Derivatives of 6-Azauracil



Compound	R[a]	UV spectrum, λmax, nm (ε·10⁻³)			Rf in system	
		0,1 N HCl	H_2O	0,1N KOH	A	B
II	CH_2NH_2	303 (4,62)	297 (4,35)	297 (3,76)	0,34	0,48
III		—	307 (8,67)	296 (7,42)	0,0	0,16
IV	H	308 (4,58)	308 (4,07)	298 (3,73)	0,57	0,80
V			311 (11,27)[b]		0,42[c]	
VI		309 (11,23)	309 (11,17)	298 (9,17)	0,15	0,58
VII	H	311 (5,02)	311 (5,09)	299 (4,79)	0,43	0,65

a) For II, III, and IV R_1 = H, for V R_1 = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl [Glc(OAc)$_4$], and for VI and VII R_1 = β-D-glucopyranosyl (Glc). b) In ethanol. c) On Silufol in benzene—acetone (2:1).

hypsochromic shift of 6-10 nm was observed in alkaline media, and considerably higher absorption intensity was observed for the symmetrical dibase. In the PMR spectrum of bis(6-aza-5-uracilyl)ethylenediamine the resonance signals of the protons of the —NH—CH_2— bridge pairs are nonequivalent, which can apparently be explained by nonequivalence of the indicated protons in connection with the difference in their spatial environment in the case of the most favorable configuration of the molecule, which is stabilized by intramolecular hydrogen bonds.

The corresponding acyldinucleoside V was synthesized by condensation of silylated dibase III with two equivalents of α-acetobromoglucose in the presence of an HgO/$HgBr_2$ catalyst (see the previous scheme). The isolation of V and its deacetylation and the purification of the free "dinucleoside" were accomplished by the method described in [6]. The structures of glycosides V and VI were confirmed by the results of elementary analysis and by a comparison of their UV spectra with the spectra of the previously synthesized 5-methylamino-6-azauracil N_1-β-D-glucopyranoside (VI) [6] (see Table 1). The close values of the absorption maxima of VI and VII in solutions with different pH values and the higher (by a factor of two) extinction of VI with respect to VII constitute evidence for the diglycoside structure of the synthesized "dinucleoside." The absence of signals of protons attached to N_1 and the presence of an N_3—H resonance band in the PMR spectrum of V indicate the N_1 position of the glucoside residues in the azapyrimidine rings. The anomeric protons are represented by two doublet signals for V and one doublet for VI (evidently because of the effect of the solvent) with the same spin—spin coupling constant (9 Hz), which confirms the β configuration of the glycoside centers.

EXPERIMENTAL

The UV spectra of solutions ($2\cdot10^{-5}$-$6\cdot10^{-5}$ M) of the compounds in water or ethanol were recorded with a Specord UV-vis spectrophotometer. The specific rotation was determined with a Spectropol-1 apparatus. The PMR spectra of solutions of the compounds in d_6-DMSO (for III), $CDCl_3$ (for V), and D_2O (for VI) were recorded with a Telsa BS-487B spectrometer (80 MHz) at

30°C with hexamethyldisiloxane as the internal and external standard. Chromatography was carried out on Filtrak FN-12 paper in n-butanol—acetic acid—water (5:2:3) (A) and isopropyl alcohol—25% ammonia—water (7:1:2) (B) systems and on Silufol in a benzene—acetone (2:1) system (C).

N-(6-Aza-5-uracilyl)- and N,N'-Bis(6-aza-5-uracilyl)ethylenediamines (II and III). A 3-ml sample of a 1% solution of copper bromide and 2.4 ml of 70% (21 mmole) aqueous ethylenediamine were added to 30 ml of an aqueous solution of 7.68 g (40 mmole) of I and 2 g of sodium carbonate, and the mixture was heated in an autoclave at 140°C for 3 h. It was then cooled, and the precipitate (4.64 g) was removed by filtration and dissolved in 50 ml of hot water and 10 ml of concentrated ammonium hydroxide. The solution was decolorized with charcoal and filtered, and the filtrate was concentrated in vacuo to half its original volume. The concentrate was acidified to pH 3, and the resulting cream-colored precipitate was removed by filtration and washed with water to give 0.59 g (5%) of III. An analytical sample was obtained by additional reprecipitation of III from an alkaline solution by addition of acid to give a product that decomposed above 320°C. PMR spectrum, δ: 11.07 (s, N_1—H), 6.82 (s, N_3—H), 3.97 [m, N—H attached to $C_{(5)}$], and 3.60 and 3.57 ppm (d, CH_2, J = 2.5 Hz). Found: C 33.9; H 3.4; N 39.5%. $C_8H_{10}N_8O_4$. Calculated: C 34.0; H 3.4; N 39.7%.

Alcohol (10 ml) was added to the mother liquor, the mixture was cooled, and the crystals of the hydrochloride of II were removed by filtration to give 4.46 g (54%) of a product with mp 272-274°C (from aqueous alcohol). Found: C 26.8; H 5.2; Cl 16.2; N 30.7%. $C_5H_{10}ClN_5O_2 \cdot H_2O$. Calculated: C 26.6; H 5.4; Cl 15.8; N 31.1%. Free II was obtained by dissolving 3.8 g of the hydrochloride in 500 ml of methanol and passing dry ammonia through the solution. Workup gave 3.0 g (95%) of a product with mp 268-276°C (dec., from water). Found: C 34.7; H 5.1; N 40.8%. $C_5H_9N_5O_2$. Calculated: C 35.1; H 5.3; N 40.9%.

N,N'-Bis[1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-6-aza-5-uracilyl]ethylenediamine (V). A mixture of 0.28 g (1 mmole) of III, 18 ml of hexamethyldisilazane, and 5 ml of trimethylchlorosilane was heated for 9 h, after which the solvent was removed by vacuum distillation. Solvent residues were removed by evaporation with benzene (two 15 ml samples), and the oily residue was dissolved in 15 ml of absolute benzene. The solution was treated with 0.25 g samples of mercuric oxide and mercuric bromide and 0.85 g (2.06 mmole) of α-acetobromoglucose [7], and the mixture was maintained at room temperature for 6 days. Alcohol (5 ml) was added to it, the resulting precipitate was removed by filtration, and the filtrate was evaporated in vacuo. The residue was dissolved in 200 ml of chloroform, and the solution was purified to remove mercury residues [6]. The solvent was removed by vacuum evaporation, and the residue was crystallized from ethyl acetate to give 0.81 g (86%) of a product with mp 157-159°C. PMR spectrum, δ: 6.12 (s, N_3—H), 4.32 [m, N—H attached to $C_{(5)}$], 3.88 and 3.80 (d, CH_2, J = 5.5 Hz), and 5.30 and 5.18 ppm [d, $C'_{(1)}$—H, $J_{1',2}$ = 9 Hz]. Found: C 45.1; H 4.9; N 11.7%. $C_{30}H_{46}N_8O_{22}$. Calculated: C 45.0; H 4.8; N 11.9%.

N,N'-Bis(1-β-D-glucopyranosyl-6-aza-5-uracilyl)ethylenediamine (VI). A 0.21-g sample of octaacetate V was dissolved in 25 ml of methanol, and the solution was saturated with dry ammonia at —5°C. It was then maintained at 4°C for 2 days, after which the ammonia and the solvent were removed by vacuum evaporation, and the residue was crystallized from aqueous alcohol to give 0.12 g (92%) of a product with mp 291-292°C and $[\alpha]_D^{20}$ +6° (c 0.5, H_2O). PMR spectrum δ: 5.81 ppm [$C'_{(1)}$—H, $J_{1',2}$ = 9 Hz]. Found: C 39.6; H 4.9; N 18.5%. $C_{20}H_{28}N_8O_{14}$. Calculated: C 39.7; H 4.7; N 18.5%.

LITERATURE CITED

1. I. V. Alekseeva, V. P. Chernetskii, A. S. Shalamai, D. V. Semenyuk, V. A. Gladkaya, L. S. Usenko, V. I. Kobylinskaya, E. G. Sidorenko, V. L. Makitruk, T. G. Mustyatsa, and F. F. Salontai, News in the Chemistry of Nucleosides and Nucleotides. Summaries of Papers Presented at the First All-Union Conference on the Chemistry of Nucleosides and Nucleotides, Zinatne, Riga (1978), p. 126.
2. J. Zemlicka and J. Owens, J. Org. Chem., 42, 517 (1977).
3. J. Smrt, Coll. Czech. Chem. Commun., 42, 1890 (1977).
4. C. Cristescu and J. Marcus, Pharmazie, 16, 135 (1961).
5. P. K. Chang, J. Org. Chem., 26, 1118 (1961).
6. I. V. Alekseeva, A. S. Shalamai, V. L. Makitruk, and V. P. Chernetskii, Khim. Geterotsikl. Soedin., No. 9, 1260 (1977).
7. L. Gatterman and H. Wieland, Practical Works in Organic Chemistry [Russian translation], Goskhimizdat, Moscow—Leningrad (1948), p. 436.