8. A. F. Oleinik, E. V. Adamskaya, G. Ya. Shvarts, and R. D. Syubaev, Article deposited in the Central Office of Scientific and Technical Information for the Medical Industry, No. 128, July, 1982.
9. A. F. Oleinik, E. V. Adamskaya, K. Yu. Novitskii, and N. P. Solov'eva, Khim. Geterotsikl. Soedin., No. 9, 1170 (1982).

SYNTHESIS OF N-(1-URACILYLALKYL)POLYMETHYLENEDIAMINES

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The alkylation of polymethylenediamines with 2-(1-uracilyl)ethyl bromide and 3-(1-uracilyl)propyl bromide yields the corresponding N-(1-uracilylalkyl)polymethylenediamines.

Biogenic polyamines, such as putrescine, cadaverine, spermidine, and spermine, take direct part in biophysical and biochemical processes taking place both in microorganisms and in plants and animals [1]. It is noteworthy that putrescine modified by a nucleic-acid nitrogenous base, viz., 5-(4-aminobutylaminomethyl)uracil, which appears in DNA, has been successfully isolated from bacteriophage FW-14 and characterized [2]. The antitumor properties of N,N'-bis(6-purinyl)ethylenediamine are known [3]. N-Alkylputrescines have hypotensive properties [4].

The present work was devoted to the synthesis of derivatives of diamines containing bases of nucleic acids. In order to preserve the basic properties inherent in biogenic polyamines, our purpose was to synthesize monosubstituted diamines, i.e., N-(1-uracilylalkyl)polymethylenediamines. 2-(1-Uracilyl)ethyl bromide and 3-(1-uracilyl)propyl bromide were selected as the reagents for alkylating the diamines [5, 6]. It was found that in the case of the reaction of the bromides with diamines (putrescine, cadaverine, trimethylenediamine, and hexamethylenediamine) in dimethylformamide, a mixture of mono- and diaklylated diamines which is difficult to separate forms even with a large excess of the diamine. In other words, in order to obtain only monoalkyldiamines, it is necessary to protect one amino group in the diamine. We selected the benzyloxycarbonyl grouping for the protection of the amino group. When the diamines are reacted with carbobenzoxy chloride in 0.1 N NaOH, the corresponding N,N'-biscarbobenzoxy derivatives form. The elimination of one carbobenzoxy group was carried out in glacial acetic acid with an equimolar amount of hydrochloric acid. It was not possible to rid the monocarbobenzoxypolymethylenediamine hydrochlorides obtained from the admixtures of the polymethylenediamine dihydrochlorides by recrystallization, as was proposed in [7]. Chromatographically pure products could be obtained only with the aid of column chromatography. The purified monocarbobenzoxypolymethylenediamines are converted into the corresponding hydrochlorides by treating them with a 1:1 mixture of absolute ethanol and concentrated hydrochloric acid. The physicochemical characteristics of the monocarbobenzoxypolymethylenediamine hydrochlorides obtained correspond to the data in [7].

The reaction of 2(or 3)-(1-uracilyl)ethyl(or propyl) bromide (I, II) with monocarbobenzoxypolymethylenediamines readily takes place in dimethylformamide at room temperature and gives the corresponding N-[2(or 3)-(1-uracilyl)ethyl)or propyl)]-N'-carbobenzoxypolymethylenediamine hydrobromides (IIIa-d, IVa-d) with good yields.

After the elimination of the carbobenzoxy group by a 33% solution of hydrogen bromide in glacial acetic acid, the N-[2(or 3)-(1-uracilyl)ethyl(or propyl)]polymethylenediamine dihydrobromides (Va-d, VIa-d) were obtained.

The structures of compounds III-VI were confirmed by data from the PMR, IR, and UV spectra. The UV spectra recorded at pH 1, 7, and 10 show an absorption maximum at 265-267 nm, which is characteristic of N_1-substituted uracils with a lactam structure.

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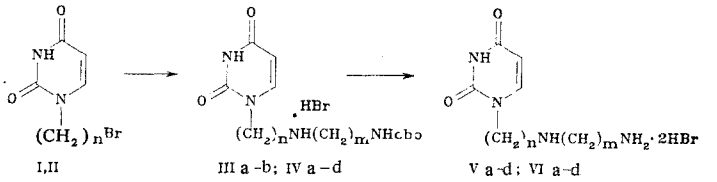
TABLE 1. N-[2-(1-Uracilyl)ethyl]- and N-[3-(1-Uracilyl)propyl]-N'-Carbobenzoxydiamine Hydrobromides

Compound	T, mp, deg C	R_f in systems		Found, %			Empirical formula	Calculated, %			Yield, %
		A	B	C	H	N		C	H	N	
IIIa	245—246	0,85	0,38	47,5	5,6	12,9	$C_{17}H_{22}N_4O_4 \cdot HBr$	47,7	5,4	13,1	58
IIIb	228—229	0,84	0,37	48,6	5,7	12,4	$C_{18}H_{24}N_4O_4 \cdot HBr$	49,0	5,8	12,7	62
IIIc	223—225	0,85	0,40	50,0	6,0	12,0	$C_{19}H_{26}N_4O_4 \cdot HBr$	50,2	5,9	12,3	64
IIId	215—218	0,87	0,38	51,3	6,4	11,7	$C_{20}H_{28}N_4O_4 \cdot HBr$	51,1	6,2	11,9	56
IVa	222—223	0,83	0,35	48,7	5,7	12,4	$C_{18}H_{24}N_4O_4 \cdot HBr$	49,0	5,8	12,7	65
IVb	210—211	0,82	0,35	49,9	5,2	11,9	$C_{19}H_{26}N_4O_4 \cdot HBr$	50,2	5,9	12,3	68
IVc	214—215	0,80	0,35	50,8	6,5	11,6	$C_{20}H_{28}N_4O_4 \cdot HBr$	51,1	6,2	11,9	65
IVd	203—205	0,80	0,35	51,9	6,6	11,3	$C_{21}H_{30}N_4O_4 \cdot HBr$	52,2	6,4	11,6	58

The data from the IR spectra support the lactam structure of compounds III-VI (the absorption band at 1700-1670 cm^{-1} is assigned to stretching vibrations of the NC=O group, and the band in the 3115-3000-cm^{-1} region is assigned to the $N_{(3)}$—H vibration).



I, III, V n=2; II, IV, VI n=3; III—VI a m=3, b m=4, c m=5, d m=6; cbo — carbobenzoxy

Compounds V and VI produce a violet color with ninhydrin, which is characteristic of a primary amino group.

The study of amines Va, Vc, VIa, and VIb as inhibitors of the biosynthesis of DNA in tumor cells (of strain L-1210 and Erhlich adenocarcinoma) demonstrated that like putrescine, all the compounds studied have no influence on the biosynthesis of DNA in Erhlich adenocarcinoma cells and slightly inhibit its biosynthesis in L-1210 cells.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90 (90 MHz) instrument in DMSO-d_6 with HMDS as an internal reference. The UV spectra were recorded on a Specord UV-vis spectrophotometer, and the IR spectra were recorded on a UR-20 spectrometer in liquid petrolatum. The melting point was determined on a Boetius microstage (East Germany).

The monocarbobenzoxylpolymethylenediamine hydrochlorides were purified with the use of column chromatography (12 × 300 mm, LKB, Sweden) with the Silasorb 600 sorbent having a grain diameter equal to 30 μ from Chemapol (Czechoslovakia) and an LKB Ultra-Rac fraction collector (Sweden). The eluent was fed with the aid of an LKB Varioperpecs peristaltic pump (Sweden) at the rate of 0.2 ml/min. All the vaporization operations were carried out in a vacuum in a rotary evaporator with a bath temperature no greater than 60°C. The individuality of the compounds obtained was monitored with the aid of TLC on Silufol UV-254 planes. The following development systems were used 7:1:2 isopropanol—25% ammonia—water (A); 8:1:2 n-butanol—acetic acid—water (B). Fluorescence under UV irradiation and a ninhydrin reagent were used for the detection of the substances on the chromatograms.

Purification of Monocarbobenzoxypolymethylenediamines. A maximal quantity (0.4-0.45 g) of a mixture of the respective monocarbobenzoxypolymethylenediamine hydrochloride and polymethylenediamine dihydrochloride is dissolved in 1.5 ml of system A, introduced into a column with the sorbent, and eluted by system A. The eluate is collected in 5-ml fractions, which are analyzed with the aid of TLC. The R_f values of the monocarbobenzoxypolymethylenediamines are 0.7 to 0.8, and those of the polymethylenediamines are 0.05 (system A).

The fractions containing the monocarbobenzoxypolymethylenediamine are combined and evaporated in a vacuum to dryness. The residue is dissolved in 5 ml of a 1:1 mixture of absolute ethanol with 36% hydrochloric acid and left in a refrigerator for 24 h. The precipitate formed is filtered and washed with 20 ml of absolute ether. The filtrate is evaporated

TABLE 2. N-[2-(1-Uracilyl)ethyl]- and N=[3-(1-Uracilyl)propyl]polymethylenediamine Dihydrobromides

Compound	mp, deg C	R_f in system A	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Va	262—263	0,21	29,0	4,4	15,3	$C_9H_{16}N_4O_2 \cdot 2HBr$	28,8	4,8	15,0	88
Vb	249—250	0,20	30,7	5,4	14,3	$C_{10}H_{18}N_4O_2 \cdot 2HBr$	31,0	5,2	14,5	90
Vc	231—232	0,20	32,6	5,7	13,7	$C_{11}H_{20}N_4O_2 \cdot 2HBr$	32,9	5,5	13,9	80
Vd	215—216	0,18	34,4	6,2	13,2	$C_{12}H_{22}N_4O_2 \cdot 2HBr$	34,6	5,8	13,4	74
VIa	205—206	0,16	30,8	5,5	14,0	$C_{10}H_{18}N_4O_2 \cdot 2HBr$	31,0	5,2	14,5	85
VIb	193—194	0,15	32,6	5,9	13,6	$C_{11}H_{20}N_4O_2 \cdot 2HBr$	32,9	5,5	13,9	76
VIc	175—176	0,15	34,2	6,0	13,0	$C_{12}H_{22}N_4O_2 \cdot 2HBr$	34,6	5,8	13,4	80
VId	170—173	0,15	36,0	6,5	12,8	$C_{13}H_{24}N_4O_2 \cdot 2HBr$	36,4	6,1	13,1	75

TABLE 3. Proton-Magnetic-Resonance Spectra of N-(1-Uracilylalkyl)-N'-carbobenzoxypolymethylenediamine Hydrobromides in DMSO-d_6

Compound	Chemical shifts, δ, ppm						
	$N_{(3)}H$ (s, 1H)	$C_{(6)}H$ (d, 1H)	$C_{(5)}H$ (d, 1H)	Phe* (s, 5H)	Bzl—CH_2*, (s, 2H)	α-CH_2 (t, 2H)	aliphatic chain
IIIa	11,18	7,53	5,53	7,22	4,89	3,85	3,06—2,67 (β-, 1-, 3-CH_2, m 6H); 1,90—1,55 (2-CH_2, m 2H)
IIIb	11,18	7,55	5,50	7,20	4,89	3,86	3,28—2,69 (β-, 1-, 4-CH_2, m 6H); 1,63—1,21 (2-, 3-CH_2, m 4H)
IIIc	11,16	7,57	5,51	7,24	4,91	3,94	3,13—2,62 (β-, 1-, 5-CH_2, m 4H); 1,72—1,11 (2-, 3-, 4-CH_2, m 6H)
IIId	11,18	7,57	5,53	7,22	4,91	3,97	3,14—3,06 (β-, 1-, 6-CH_2, m 6H); 1,74—1,13 (2-, 3-, 4-, 5-CH_2, m 8H)
IVa	11,20	7,55	5,44	7,16	4,89	3,64	3,06—2,65 (γ-, 1-, 3-CH_2, m 6H), 1,52—2,12 (β-, 2-CH_2, м, 4H)
IVb	11,16	7,57	5,48	7,24	4,85	3,33	3,02—2,67 (γ-, 1-, 4-CH_2, m 6H); 1,90 (β-CH_2, m 2H); 1,32—1,74 (2-, 3-CH_2, m 4H)
IVc	11,20	7,55	5,48	7,22	4,91	3,68	3,04—2,60 (γ-, 1-, 5-CH_2, m 6H); 1,90 (β-, 2-CH_2, m 2H); 1,77—1,06 (2-, 3-, 4-CH_2, m 6H)
IVd	11,18	7,53	5,46	7,22	4,89	3,70	3,04—2,60 (γ-, 1-, 6-CH_2, m 6H); 1,89 (β-CH_2, m 2H); 1,74—1,08 (2-, 3-, 4-, 5-CH_2, m 8H)

*Protons of the benzene ring (Phe) and the methylene group (Bzl—CH_2) in the benzyloxycarbonyl grouping.

TABLE 4. Proton-Magnetic-Resonance Spectra of N-(1-Uracilylalkyl)polymethylenediamine Dihydrobromides Va-d and VIa-d

Compound	Chemical shifts, δ, ppm				
	$N_{(3)}H$ (s, 1H)	$C_{(6)}H$ (d, 1H)	$C_{(5)}H$ (d, 1H)	α-CH_2 (t, 2H)	aliphatic chain
Va	11,20	7,44	5,52	3,92	3,04—2,71 (β-, 1-, 3-CH_2, m, 6H); 1,95—1,70 (2-CH_2, m, 2H)
Vb	11,18	7,46	5,57	3,90	3,26—2,67 (β-, 1-, 4-CH_2, m, 6H); 1,59—1,26 (2-, 3-CH_2, m 4H)
Vc	11,18	7,53	5,54	3,92	3,09—2,58 (β-, 1-, 5-CH_2, m, 6H); 1,70—1,11 (2-, 3-, 4-CH_2, m, 6H)
Vd	11,20	7,63	5,59	4,01	3,26—3,02 (β-, 1-, 6-CH_2, m, 6H); 1,79—1,17 (2-, 3-, 4-, 5-CH_2, m, 8H)
VIa	11,20	7,64	5,53	3,72	3,09—2,65 (γ-, 1-, 3-CH_2, m, 6H); 2,12—1,70 (β-, 2-CH_2, m, 4H)
VIb	11,18	7,42	5,55	3,68	3,00—2,60 (γ-, 1-, 4-CH_2, m, 6H); 2,10—1,35 (β-, 2-, 3-CH_2, m 6H)
VIc	11,18	7,66	5,33	3,70	3,00—2,62 (γ-, 1-, 5-CH_2, m, 6H); 2,12—1,33 (β-, 2-, 3-, 4-CH_2, m 8H)
VId	11,13	7,59	5,34	3,70	3,02—2,58 (γ-, 1-, 6-CH_2, m, 6H); 2,14—1,06 (β-, 2-, 3-, 4-, 5-CH_2, m, 10H)

to dryness, and the residue is washed with 10 ml of absolute ether, filtered out, and added to the main precipitate. This gives 0.25-0.30 g (60-70%) of the monocarbobenzoxypolymethylenediamine hydrochloride.

N-[2-(1-Uracilyl)ethyl]-N'-carbobenzoxytrimethylenediamine (IIIa). A solution of 0.37 g (18 mmole) of monocarbobenzoxytrimethylenediamine hydrochloride in 8 ml of DMFA is given an addition of 1.8 g (18 mmole) of triethylamine and 0.4 g (18 mmole) of 2-(1-uracilyl)ethyl bromide (I) and held for 24 h at 20°C. The precipitate of triethylamine hydrochloride is filtered out and washed with 5 ml of DMFA. The filtrates are evaporated in a vacuum to dryness, and the residue is washed with 5 ml of isopropanol and filtered out. The yield is 0.33 g (58%), and the mp is 245-246°C (absolute ethanol). The hydrobromides of N-[2-(1-uracilyl)-ethyl]-N'-carbobenzoxytetramethylenediamine (IIIb), N-[2-(1-uracilyl)ethyl]-N'-carbobenzoxy-pentamethylenediamine (IIIc), N-[2-(1-uracilyl)ethyl]-N'-carbobenzoxyhexamethylenediamine (IIId), N-[3-(1-uracilyl)propyl]-N'-carbobenzoxytrimethylenediamine (IVa), N-[3-(1-uracilyl)-propyl]-N'-carbobenzoxytetramethylenediamine (IVb), N-[3-(1-uracilyl)propyl]-N'-carbobenzoxy-pentamethylenediamine (IVc), and N-[3-(1-uracilyl)propyl)]-N'-carbobenzoxyhexamethylenediamine (IVd) are obtained in analogy to compound IIIa from the corresponding starting compounds (Tables 1 and 3).

N-[2-(1-Uracilyl)ethyl]trimethylenediamine Dihydrobromide (Va). A 0.3-g portion (8 mmole) of compound IIIa is dissolved in a mixture of 1.5 ml of glacial acetic acid with 6 ml of a 33% solution of hydrogen bromide in glacial acetic acid and held at 20°C for 1 h. The precipitate formed is filtered out and washed with 30 ml of absolute ethyl ether. The yield is 0.23 g (88%). The product is recrystallized from a mixture of absolute methanol with absolute ethyl ether.

The dihydrobromides of N-[2-(1-uracilyl)ethyl]tetramethylenediamine (Vb), N-[2-(1-uracilyl)ethyl]pentamethylenediamine (Vc), N-[2-(1-uracilyl)ethyl]hexamethylenediamine (Vd), N-[3-(1-uracilyl)propyl]trimethylenediamine (VIa), N-[3-(1-uracilyl)propyl]tetramethylenediamine (VIb), N-[3-(1-uracilyl)propyl]pentamethylenediamine (VIc), and N-[3-(1-uracilyl)propyl]hexamethylenediamine (VId) are obtained in analogy to compound Va from the corresponding starting compounds (Tables 2 and 4).

LITERATURE CITED

1. H. Tabor and C. W. Tabor, Pharmacol. Rev., 16, 245 (1964).
2. A. M. B. Kropinski, R. J. Bose, and A. J. Warren, Biochemistry, 12, 151 (1973).
3. H. Ettre and H. Ballweg, Naturwissenschaften, 45, 364 (1958).
4. A. A. Ryabinin, A. D. Panashchenko, and I. L. Anisimova, Zh. Obshch. Khim., 10, 577 (1974).
5. I. Zh. Lulle, R. A. Paégle, and M. Yu. Lidak, Khim., Geterotsikl. Soedin., No. 4, 535 (1983).
6. Fol-Siong Tjoeng, E. K. Krass, E. Breitmaier, and G. Jung, Chem. Ber., 109, 2615 (1976).
7. W. B. Lawson, M. D. Leafer, A. Tewes, and G. J. S. Rao, Z. Physiol. Chem., 349, 258 (1968).