SYNTHESIS AND PROPERTIES OF 1-(5-HALO-1-URACILYL)-β-D-GLUCOFURANURONIC ACIDS

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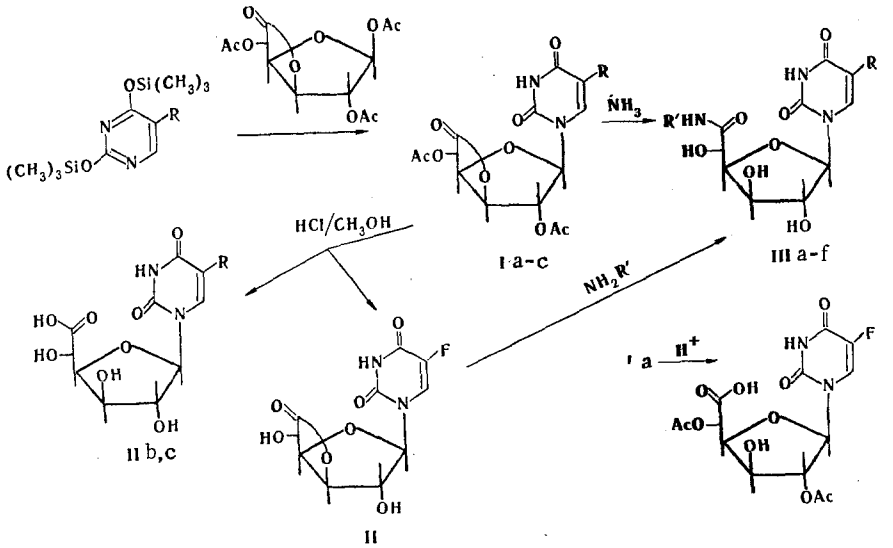
UDC 547.854.5'455.623.07

1-(5-Halo-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactones were obtained by condensation of 2,4-bis(trimethylsilyl)-5-halouracils with 1,2,5-tri-O-acetyl-β-D-glucofuranurono;-6,3-lactone. The chemical transformations of these compounds were studied. The structure of the glucuronides was proved by the IR, UV, circular dichroism, and NMR spectra.

Research involving the synthesis and study of nucleosides of uronic acids has undergone extensive development in recent years; however, up until now chief attention has been directed to the synthesis of 1-(9-purinyl)- and 1-(1-pyrimidinyl)-β-D-glucopyranuronic acids [1-4]. Only a relatively small amount of data on the corresponding derivatives of hexafuranuronic acids are available [1, 5].

The present research was devoted to the synthesis of 1-(5-halo-1-uracilyl)-β-D-glucofuranuronic acids. The preparation of 1-(5-fluoro-1-uracilyl)glucofuranuronic acid is of particular interest. The search for new antimetabolites among 5-fluorouracil derivatives that have a selective effect on cancerous cells and low toxicity is an urgent problem, since the 5-fluorouracil derivatives used up to now have a number of disadvantages. In addition, it is known that the biological activity of tetrahydrofuran derivatives of pyrimidine and purine bases is always higher than that of tetrahydropyranyl derivatives [6].

To obtain 1-(5-halo-1-uracilyl)-β-D-glucofuranuronic acids we selected glycosylation of trimethylsilyl derivatives of 5-fluoro-, 5-bromo-, and 5-iodouracil



I a R=F; b R=Br; c R=I; II b R=Br; c R=I; III a R=F; R′=H; b R=Br; R′=H; c R=I; R′=H; d R=F; R′=$(CH_2)_2CH_3$; e R=F; R′=$(CH_2)_6CH_3$; f R=F; R′=$CH_2C_6H_5$

with 1,2,5-tri-O-acetyl-β-D-glucofuranurono-6,3-lactone in the presence of stannic chloride in aprotic solvents.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1532-1537, November, 1981. Original article submitted January 13, 1981.

 0009-3122/81/1711-1120$07.50

TABLE 1. Parameters of the PMR Spectra of I-IV

Compound	Chemical shifts, δ, ppm									SSCC, J, Hz					
	6-H	1′-H	2′-H	3′-H	4′-H	5′-H	CH_3CO	N_3H	NH	1′2′	2′3′	3′4′	4′5′	1′-HF	6-HF
Ia	7,69	5,95	5,46	5,13	5,01	5,83	2,13 and 2,08	12,0	—	4,4	0,3	4,0	4,8	0,9	6,6
Ib	7,83	5,91	5,51	5,14	5,03	5,83	2,14 and 2,08	11,9	—	3,9	~0	4,0	4,8	—	—
Ic	7,85	5,94	5,52	5,13	5,03	5,85	2,15 and 2,09	11,9	—	3,8	~0	4,0	4,8	—	—
IIa	7,69	5,72	4,38	4,74	4,89	4,63	—	11,8	—	1,5	<0,4	3,9	4,5	1,3	8,0
IIb	8,07	5,54	4,07	4,00	4,14	4,38	—	11,8	—	<1,0	~1,0	2,2	8,5	—	—
IIc	8,14	5,52	4,00	3,98	4,14	4,36	—	11,7	—	<1,0	~1,0	2,7	8,5	—	—
IIIa	8,07	5,57	3,96	3,94	4,07	4,23	—		7,4 6,9	1,0	1,0	2,2	6,5	1,0	7,4
IIIb	8,27	5,58	3,98	3,96	4,14	4,22	—		7,4 7,2	<1,0	1,0	2,3	8,0	—	—
IIIc	8,31	5,56	3,97	3,97	4,12	4,22	—		7,8 7,4	<1,0	1,0	3,0	8,0	—	—
IV	8,16	5,79	4,69	4,16	4,24	5,09	2,00 and 2,04	—	—	3,0	2,0	4,5	2,3	1,5	8,0

It has been shown [1] that it is necessary to use the stannic chloride catalyst in a threefold excess as compared with the acylated sugar in order to unambiguously obtain only the N_1 isomers of 1-(1-uracilyl)-β-D-glucofuranuronic acid. In our case we found that a decrease in the ratio of stannic chloride to the acylated glucuronolactone to 1.34:1 does not affect the yield of the N_1 anomer and that the isolation of the desired product from the reaction mixture is simplified.

Deacetylation occurs when lactone Ia is treated with a 3% solution of hydrogen chloride in methanol, and 1-(5-fluoro-1-uracilyl)-β-D-glucofuranurono-6,3-lactone (IIa) is isolated after recrystallization from water. Similar treatment of Ib,c leads to cleavage of the lactone ring and to the formation of the corresponding 1-(5-bromo-1-uracilyl)- and 1-(5-iodo-1-uracilyl)-β-D-glucofuranuronic acids (IIb, c). Upon reaction with ammonia or primary amines Ia-c undergo cleavage of the lactone ring to give 1-(5-halo-1-uracilyl)-β-D-glucofuranuronic acid amides (IIIa-h).

The stability of 1-(5-halo-1-uracilyl)-β-D-glucuronides was investigated in the case of 1-(5-fluoro-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactone (Ia). We found that Ia is unstable in water, methanol, and acetone and undergoes partial hydrolysis at the glycoside bond even at 20°C. In a 0.01 N aqueous solution of sodium hydroxide (pH 8) lactone Ia undergoes 16% cleavage at the glycoside bond after 1 h at 37°C, whereas in hydrochloric acid solution (pH 2) the lactone ring is cleaved after 8 h to give 1-(5-fluoro-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranuronic acid (IV).

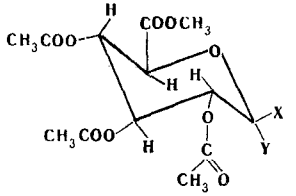
The structure of I-IV was proved by means of data from the UV, NMR, IR, and circular dichroism spectra. A bathochromic shift of the absorption maximum is not observed in the UV spectra of I-IV on passing from neutral to alkaline media, and this constitutes evidence that the substituent is attached to the N_1 atom of the uracil ring.

In addition to the absorption bands that are characteristic for the pyrimidine ring (stretching vibrations of C=O groups at 1695-1710 cm^{-1} and of C=C and C=N groups at 1520-1560 cm^{-1}), characteristic absorption bands of a γ-lactone ring (νC=O 1810-1820 cm^{-1}) are retained in the IR spectra. Consequently, glycosylation takes place with retention of the lactone ring. The absorption band at 1810-1820 cm^{-1} is retained in the IR spectrum of IIa but vanishes in the case of IIb, c; in the latter case absorption bands that are characteristic for carboxy groups appear at 1700-1705 cm^{-} .

A comparison of the parameters of the PMR spectra of I-IV (Table 1) with those for model compounds, viz., with the spectra of 1,2,4,5-tetra-O-acetyl-β-D-glucopyranuronic acid (V), 1,2,4,5-tetra-O-acetyl-α-D-glucopyranuronic acid (VI) [7], and 1-(5-fluoro-1-uracilyl)-β-D-glucopyranuronic acid (VII) [8] (Table 2), makes it possible to reliably prove retention of the furanose ring. The pronounced difference in the spin–spin coupling constants (SSCC) between the protons of the sugar part of the molecule constitutes evidence for this.

One's attention is directed to the fact that the chemical shift of the 6-H proton is shifted markedly to weak field in the case of destruction of the lactone ring (compare Ib, IIb, and IIIb or Ic, IIc, and IIIc in Table 1). This may constitute evidence for the effect of the anisotropy of this ring on the shielding of 6-H, since the circular-dichroism method distinctly indicates that the base has a β configuration.

TABLE 2. Parameters of the ^1H NMR Spectra



Compound	X	Y	Chemical shifts, of the protons, δ, ppm								SSCC, J, Hz			
			1′-H	2′-H	3′-H	4′-H	5′-H	$OCOCH_3$	$COOCH_3$	H_x	1′-H—2′-H	2′-H—3′-H	3′-H—4′-H	4′-H—5′-H
V	$OCOCH_3$	H	5,98	4,92	5,47	4,98	4,61	1,94 1,97 1,98	3,61	2,03	8,1	9,1	9,1	9,5
VI	H	$OCOCH_3$	6,09	5,43	5,56	5,24	4,67	1,93 1,97 1,98	3,63	8,32 (6-H) 11,83 (NH)	8,0	8,8	8,7	9,0
VII	R*	H	6,72	4,94	5,38	5,14	4,42	1,98 (2×) 2,03	3,66	2,03	3,6	9,0	9,0	9,1

*Where R is a 5-fluorouracil residue.

TABLE 3. Parameters of the ^{13}C NMR Shifts

Compound	Chemical shifts, δ, ppm										SSCC, J, Hz											
	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	C_6O	C_2	C_4	C_5	C_6	C_6H_6	$C_{1'}H_{1'}$	$C_{2'}H_{2'}$	$C_{3'}H_{3'}$	$C_{4'}H_{4'}$	$C_{5'}H_{5'}$	C_5H_5	$C_2H_{1'}$	C_2H_6	C_4H_6	C_5H_3	$C_6H_{1'}$
Ia*	91,2	77,8	76,3	82,6	69,3	170,3	148,8	157,0	140,2	125,1	181,6	167,7	160,7	168,4	168,4	150,4	4,8	3,3	8,8	7,0	7,7	3,7
IIb	91,9	79,8	73,5	83,9	67,7	172,6	149,9	159,3	94,6	140,9	—	—	—	—	—	—	—	—	—	—	—	—
IIc	91,7	79,8	73,5	83,6	67,7	172,8	150,3	160,7	51,7	145,9	186,8	172,8	154,4	154,4	151,8	150,0	4,0	1,1	11,4	9,6	0	3,3
IIIa	91,5	80,3	74,6	83,4	69,2	174,6	150,3	158,8	139,9	125,6	182,7	171,0	154,1	154,1	150,0	146,7	4,4	0,7	8,0	6,6	0	3,7
IIa	93,7	77,5	80,4	83,1	69,2	175,0	149,0	157,1	139,9	124,2	181,6	173,2	154,4	167,6	166,6	142,5	4,4	0	8,1	7,0	6,0	3,3

*The chemical shifts of the remaining C atoms are 169.6 and 169.3 ppm (CO) and 20.3 and 20.0 ppm (CH_3).

A positive Cotton effect is observed at 270 nm in the circular dichroism (CD) spectra of lactone Ia; this is characteristic for pyrimidine nucleosides in the β-D-configuration [9]. Consequently, Ia-c have a β configuration. The $J_{1'-H-2'-H}$ SSC in the spectra of IIb, c and IIIa-c do not exceed 1 Hz, and this makes it possible to reliably assign these compounds also to β anomers.

The proof of the structure of IIa requires additional commentary. The observation of 6-H resonance, as in the case of lactones I, constitutes evidence for retention of the lactone ring in IIa. In addition, the expected shift to strong field in the case of deacetyla- as compared with Ia is observed only with respect to the 5'-H and 2'-H resonances and not with respect to the 3'-H resonance. This also indicates retention of the lactone ring in IIa. The same conclusions follow from a study of the $^1J_{^{13}C-H}$ values in the furanose ring. It is apparent from the data in Table 3 that if the $C_{4'}$ and $C_{3'}$ atoms are found in the lactone ring, the algebraic $^1J_{^{13}C-H}$ value is increased markedly (Ia). The same principle is also observed in the case of IIa, and this also indicates retention of the lactone ring in the IIa molecule. Information regarding the preferred conformation of the base relative to the glycoside bond can be obtained by means of the $^3J_{^{13}C_2-N-C-H^{1'}}$ and $^3J_{^{13}C_6-N-C_3-H_{1'}}$ SSCC [10]; for the preferred anti conformation $^3J_{^{13}C_6-H_{1'}} > {}^3J_{^{13}C_2-H_{1'}}$, whereas just the opposite is observed for the syn conformation. The results obtained (Table 3) constitute evidence that the percentage of the syn conformer in the investigated compounds increases in the order IIa<IIIa<IIc<Ia.

The antitumorigenic activity of 1-(5-fluoro-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactone (Ia) was investigated in seven test systems. It was found that Ia has a strong antitumorigenic effect on five strains of grafted tumors. Compound Ia retards the growth of melanoma B_{16} by 75%, of adenocarcinoma 755 by 75%, and of Walker carcinosarcoma by 80% and prolongs the life of mice with hemocytoblastoma La by 148% and the life of mice with leucosis L-1210 by 70%. The LD_{50} value for Ia for mice is 2400 mg/g.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Spectromom 204 spectrophotometer. The NMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Brucker WH spectrometer (90 MHz) with hexamethyldisiloxane as the internal standard. The circular dichroism spectra of solutions in methanol (c $4 \cdot 10^{-4}$ mole/liter) were recorded with a JASCO-20 spectropolarimeter (JASCO, Japan). The specific rotation was measured with a Perkin-Elmer 141 polarimeter. The course of the reaction and the individuality of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in a benzene—ethyl acetate—acetate system (2:1:1).

1-(5-Fluoro-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactone (Ia). A 28.5-g (0.103 mole) sample of 2,4-bis(trimethylsilyl)-5-fluorooouracil was added to a solution of 30.2 g (0.1 mole) of 1,2,5-tri-O-acetyl-β-D-glucofuranurono-6,3-lactone [10] in 200 ml of anhydrous methylene chloride, after which 35.17 g (0.135 mole) of stannic chloride was added dropwise in the course of 2 min, and the mixture was heated at 40°C for 7 h. It was then poured slowly with stirring into a suspension of 79.0 (0.921 mole) of sodium bicarbonate in 120 ml of methylene chloride, and the precipitate was removed by filtration. A saturated aqueous solution of sodium bicarbonate was added to the filtrate to bring the pH to 5-6, and the organic layer was separated and dried over anhydrous sodium sulfate. Compound Ia was precipitated from the solution by means of ether to give 28.2 g (75%) of a product with mp 138-140°C (ethyl acetate—ether) and $[\alpha]_D^{20}$ +109.5° (c 1.0; MeOH). UV spectrum (MeOH): λ_{max} 267 nm (ε 6620). Circular dichroism: λ_{max} 270 nm (θ = +3029). Found: C 45.2; H 3.8; N 7.7%. $C_{14}H_{13}FN_2O_9$. Calculated: C 54.2; H 3.5; N 7.6%.

1-(5-Bromo-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactone (Ib). This compound was obtained in 60% yield from 2,4-bis(trimethylsilyl)-5-bromouracil and 1,2,5-tri-O-acetyl-β-D-glucofuranurono-6,3-lactone by the method used to obtain lactone Ia. The product had mp 131-133°C and $[\alpha]_D^{20}$ + 98.7° (c 1.0; MeOH). UV spectrum (in ethanol): λ_{max} 279 nm (ε 6720). Found: C 38.7; H 3.4; N 6.1%. $C_{14}H_{13}BrN_2O_9$. Calculated: C 39.0; H 3.0; N 6.4%.

1-(5-Iodo-1-uracilyl)-2,5-di-O-acetyl-β-D-glucofuranurono-6,3-lactone (Ic). This compound was obtained in 56% yield by condensation of 2,4-bis(trimethylsilyl)-5-iodouracil with 1,2,5-tri-O-acetyl-β-D-glucofuranurono-6,3-lactone by the method used to prepare Ia. The product had $[\alpha]_D$ -83.8° (c 1.0; MeOH). UV spectrum (in ethanol): λ_{max} 285 nm (ε 8440). Found: C 434.9; H 2.9; N 5.6%. $C_{14}H_{13}IN_2O_9$. Calculated: C 35.0; H 2.7; N 5.8%.

1-(5-Fluoro-1-uracilyl)-β-D-glucofuranurono-6,3-lactone (IIa). A 3.72-g (0.01 mole) sample of Ia was dissolved in 75 ml of dry methanol, 20 ml of a 3% solution of HCl in methanol was added, and the mixture was maintained at 20°C for 5 days. The methanol was removed by vacuum distillation, and the residue was recrystallized from water to give 0.8 g (45%) of a product with mp 223-225°C and $[\alpha]_D$ - 28.3° (c 1.0; H_2O). UV spectrum (in water): λ_{max} 272 nm (ε 5610). Circular dichroism: λ_{max} 271 nm (θ = +15217). Found: C 41.2; H 3.4; N 9.4%. $C_{10}H_9FN_2O_7$. Calculated: C 41.7; H 3.2; N 9.7%.

1-(5-Bromo-1-uracilyl)-β-D-glucofuranuronic Acid (IIb). This compound was obtained in 49% yield from lactone Ib as in the preceding experiment and had mp 201-203°C (from water) and $[\alpha]_D$ −69.4° (c 1.0; H_2O). UV spectrum (in water): λ_{max} 28; m, (ε 9300). Found: C 32.6; H 3.5; N 7.1%. $C_{10}H_{11}BrN_2O_8$. Calculated: C 32.7; H 3.0; N 7.6%.

1-(5-Iodo-1-uracilyl)-β-D-glucofuranuronic Acid (IIc). This compound was similarly obtained in 42% yield and had mp 208-210°C and $[\alpha]_D$ −21.8° (c 1.0; H_2O). UV spectrum (in water): λ_{max} 286 nm (ε 5680). Found: C 29.4; H 3.0; N 6.3%. $C_{10}H_{12}IN_2O_8$. Calculated: C 29.0; H 2.7; N 6.8%.

1-(5-Fluoro-1-uracilyl)-β-D-glucofuranuronic Acid Amide (IIIa). A 12.4-g (0.04 mole) sample of IIa was dissolved in 300 ml of methanol saturated with ammonia, and the mixture was maintained at 0°C for 2 days. The solution was evaporated *in vacuo*, and the residue was crystallized from a mixture of methanol with water (1:1) to give 7.1 g (59%) of a product with mp 129-131°C. UV spectrum (in water): λ_{max} 273 nm (ε 3200). Found: C 39.7; H 3.6; N 13.9%. $C_{10}H_{12}FN_3O_7$. Calculated: C 39.3; H 4.0; N 13.8%.

1-(5-Bromo-1-uracilyl)-β-D-glucofuranuronic Acid Amide (IIIb). This compound was obtained in 56% yield from lactone Ib as in the preparation of IIIa and had mp 216-218°C. UV spectrum (in water): λ_{max} 281 nm (ε 2250). Found: C 32.5; H 3.2; N 11.1%. $C_{10}H_{12}BrN_3O_7$. Calculated: C 32.8; H 3.3; N 11.5%.

1-(5-Iodo-1-uracilyl)-β-D-glucofuranuronic Acid Amide (IIIc). This compound was similarly obtained in 72% yield and had mp 226-228°C. UV spectrum (in water): λ_{max} 285 nm (ε 2400). Found: C 29.7; H 2.7; N 10.0%. $C_{10}H_{12}IN_3O_7$. Calculated: C 29.1; H 2.9; N 10.2%.

1-(5-Fluoro-1-uracilyl)-β-D-glucofuranuronic Acid N-Propylamide (IIId). A 0.86-g (0.003 mole) sample of IIa was suspended in 15 ml of methanol, after which 1.5 ml of a 20% aqueous solution of propylamine was added with stirring at −20°C, and the solution was maintained at 0°C for 12 h. It was then evaporated *in vacuo*, and the residue was washed with ether to give 0.47 g (47%) of a product with mp 110-112°C (from ethanol). UV spectrum (in water): λ_{max} 280 nm (ε 10500). Found: C 44.4; H 5.5; N 11.6%. $C_{13}H_{18}FN_3O_7$. Calculated: C 44.9; H 5.2; N 12.1%.

1-(5-Fluoro-1-uracilyl)-β-D-glucofuranuronic Acid N-Heptylamide (IIIe). This compound was similarly obtained from IIa and heptylamine. The analytically pure preparation was isolated by means of preparative TLC on Merck Kieselgel 60 UV-254 plates in a chloroform–ethanol–water system (47:40:5) and had mp 139-140°C. UV spectrum in water): λ_{max} 280 nm (ε 11500). Found: C 50.2; H 6.1; N 10.0%. $C_{17}H_{29}FN_3O_7$. Calculated: C 50.6; H 6.5; N 10.4%.

1-(5-Fluoro-1-uracilyl)-β-D-glucofuranuronic Acid N-Benzylamide (IIIf). A 3.06-g (0.01 mole) sample of IIa was suspended in 10 ml of anhydrous methanol, and 1.07 g (0.01 mole) of benzylamine was added slowly at 20°C. After 24 h, the resulting precipitate was removed by filtration and crystallized from water to give 1.56 g (39%) of a product with mp 118-119°C. UV spectrum (in water): λ_{max} 270 nm (ε 9100). Found: C 45.5; H 4.5; N 9.3%. $C_{17}H_{19}FN_3O_7$. Calculated: C 45.5; H 4.0; N 9.4%.

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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

6.* SYNTHESIS AND SOME PROPERTIES OF BENZO[f]-1,5-DIAZABICYCLO[3.2.2]NONENE AND BENZO[g]-1,6-DIAZABICYCLO[4.2.2]DECENE

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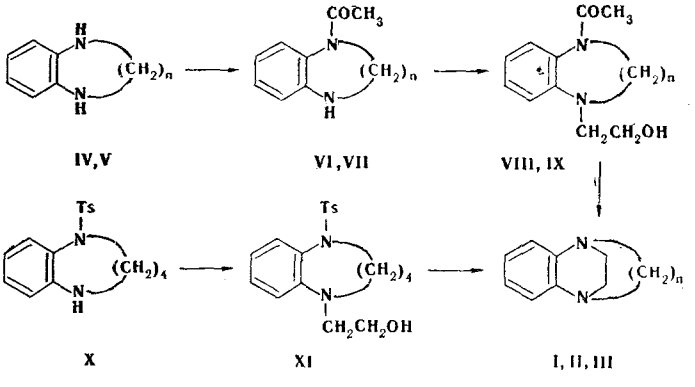
UDC 547.863.13'896/897.07

The reaction of N-acetyl derivatives of N,N'-trimethylene- and N,N'-tetramethylene-o-phenylenediamines with ethylene oxide gave the corresponding N-(β-hydroxyethyl)-N'-acetyl derivatives, the cyclization of which in refluxing hydrobromic acid leads to benzo[f]-1,5-diazabicyclo[3.2.2]nonene and benzo[g]-1,6-diazabicyclo[4.2.2.]decene.

We have previously obtained benzo[b]-1,4-diazabicyclo[2.2.2]octane (I) by cyclization of N-β-hydroxyethyl-1,2,3,4-tetrahydroquinoxaline [2]. In the present research we used a similar approach to synthesize benzo[f]-1,5-diazabicyclo[3.2.2]nonene (II) and benzo[g]-1,6-diazabicyclo[4.2.2]decene (III) in order to investigate the effect of the length of the polymethylene bridge on the properties of heterocyclic compounds of this type. N,N'-Trimethylene- and N,N'-tetramethylene-o-phenylenediamines (IV and V) were used as the starting compounds.



Compounds IV and V were acetylated under the conditions used for the monoacetylation of tetrahydroquinoxaline [3]. According to the results of analysis and the PMR spectra, the

*See [1] for Communication 5.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1538-1542, November, 1981. Original article submitted December 26, 1980.

0009-3122/81/1711-1125$07.50