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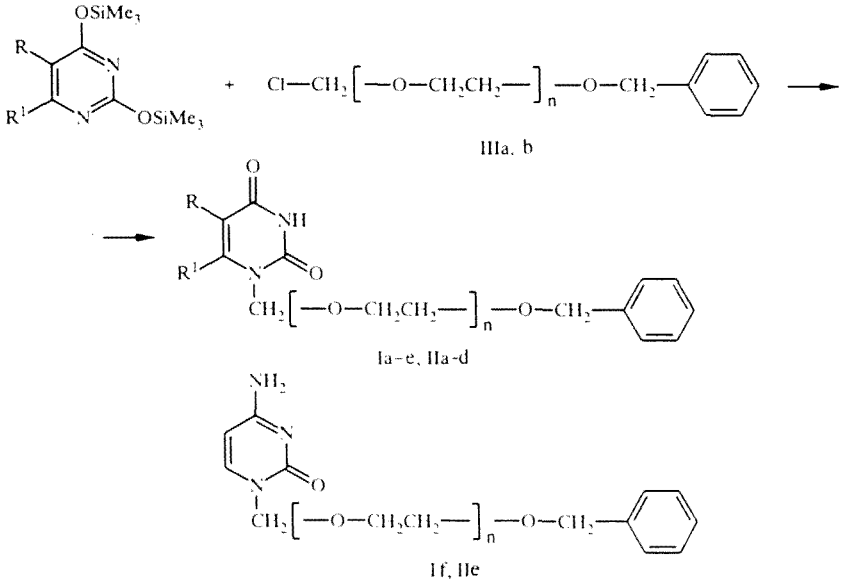
SYNTHESIS OF ACYCLIC ANALOGS OF PYRIMIDINE NUCLEOSIDES WITH AROMATIC UNITS IN THE SIDE CHAIN

**M. S. Novikov, A. A. Ozerov, A. K. Brel',
G. N. Solodunova, and T. P. Ozerova**

The synthesis of some pyrimidine acyclonucleotides with aromatic units in the side chain has been accomplished. Their physicochemical and spectroscopic properties have been studied. These compounds may be described as the substances with potential as antiviral and anticancer activity.

We have previously synthesized a variety of unsaturated derivatives of pyrimidine bases: 1-allyloxymethyl- [1], 1-[2-(allyloxy)ethyl]-, 1-[2-(vinyloxy)ethyl]- [2] and 1-(2-allyloxy)ethoxymethyl derivatives of uracil, thymine, and cytosine, some of which had considerable antiviral activity *in vitro*. It was also shown that the presence of high electron density at the end of the acyclic chain was a prerequisite for the appearance of virus inhibiting properties in compounds of this type. In the current work we present the synthesis of a number of aromatic analogs of the substances prepared earlier [1-3] in which the unsaturated fragment (allyl or vinyl) is replaced by a benzene ring.

The synthesis of 1-(benzyloxymethyl)-(Ia-f) and 1-[2-(benzyloxy)ethoxymethyl]pyrimidines (IIa-e) was carried out using Gilbert and Johnson's silyl method by treating the corresponding 2,4-bis(trimethylsiloxy)pyrimidine with benzyloxymethyl chloride (IIIa) or with 2-(benzyloxy)ethoxymethyl chloride (IIIb) in an inert aprotic solvent (Method A).



IIIa, b

Ia-e, IIa-d

If, IIe

Ia-f, n = 0; IIa-e, n = 1; Ia, Ic, If, IIa, IIc, IIe R = H; I, IIb R = CH_3; Id, Ie, IIf R = Br; Ia, Ib, Ie, If, IIa, IIb, IIe R^1 = H; I, IIc, IId R^1 = CH_3.

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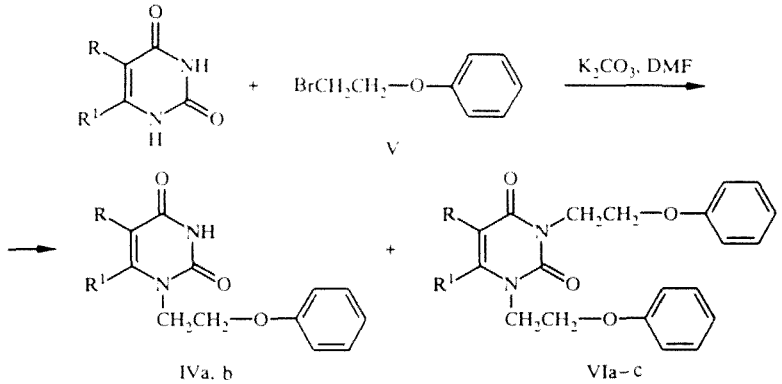
Synthesis of Ia-If and IIa-IIe by alkylation of pyrimidine salts was considerably less effective. For example, treatment of the sodium salt of thymine with the α-haloether IIIa in anhydrous DMF gave mixture of the N^1-mono and N^1,N^3-disubstituted products which were separated chromatographically [4]. The N^1-monosubstituted compound was the only product with the Gilbert-Johnson method.

Comparison of the yields of compounds Ia-If and IIa-IId obtained under identical conditions (Table 1) shows that the presence of the electron releasing CH_3 group at position 5 of the pyrimidine ring facilitates an increased yield of the benzoyloxymethyl derivatives (Ib and IIb). The notable relative decrease in the alkylation products from the trimethylsiloxy derivatives of 6-methyluracil and 6-methyl-5-bromouracil is probably a result of steric hindrance to alkylation resulting from the 6-methyl group.

We synthesized 1-(benzyloxymethyl)- (If) and 1-[2-(benzyloxy)ethoxymethyl]cytosine (IIe) analogously by the Gilbert–Johnson method.

The following steps were used in the synthesis of the derivatives of 1-(2-phenoxyethyl)uracil (IVa-c) which are hydrolytically more stable than their isomers Ia-Ic. The pyrimidine base was treated with an equimolar quantity of 1-bromo-2-phenoxyethane (V) in boiling anhydrous DMF in the presence of freshly calcined potassium carbonate (method B).

Alkylation of the potassium salts of uracil, thymine and 6-methyluracil with the bromide V is characterized by the formation of considerable amounts of 1,3-disubstituted products and an increased importance of steric factors as a result of which only trace amounts of the N^1-monosubstituted 6-methyluracil IVc were observed by TLC, the basic product being 1,3-di(2-phenoxyethyl)-6-methyluracil (VIc). This apparently results from a combination of the steric effect of the exocyclic methyl group in position 6 of the pyrimidine ring, the impossibility of an S_{N1} substitution and the increased reactivity of the α-haloethers IIIa and IIIb.



IVa, VIa, c R = H; IV, VId R = Me; IV, VIa, b R^1 = H; VIc R^1 = Me

Ia + V → IVa

Unsatisfactory results of alkylation of salts of the pyrimidine bases with bromide V persuaded us to use the Gilbert–Johnson silyl method, which permitted selective introduction of the alkyl substituent at position 1 of the pyrimidine ring.

Maintaining O-trimethylsilyl derivatives of uracil and thymine in an alkyl bromide medium at room temperature for 7-10 days is known to give the corresponding N^1-alkylated derivatives [5]. However, N^1-alkylation of 2,4-bis(trimethylsiloxy)pyrimidines with iodomethane occurs considerably more effectively (1-3 h) on raising the temperature [6]. 1-Bromo-2-phenoxyethane (V) is less reactive than the alkylating agents mentioned above, so we heated an equimolar mixture of 2,4-bis(trimethylsiloxy)pyrimidine and V at 180°C for 6 h (method C). However, the yield of the desired product did not exceed 30% (Table 1) since the reaction was accompanied by the formation of considerable amounts of polymeric products. Apparently, under these conditions HBr elimination occurs to give the readily polymerized vinyl phenyl ether. The isolation of the polymers during the reaction with uracil is an indirect confirmation of this.

Aprotic nonpolar and poorly polar are frequently used for the alkylation of 2,4-bis(trimethylsiloxy)pyrimidines with alkyl halides both at room temperature [8] and on heating [9]. We have previously described the successful alkylation of O-trimethylsilyl derivatives of uracil and thymine with epoxides [10] and 1-chloro-2-vinyloxyethane [2] in anhydrous DMF at 80-155°C. Boiling an equimolar mixture of O-trimethylsilyl derivatives of uracil and bromide V for 10 h in anhydrous DMF gave a considerably larger yield of IVa (54%) (method B) than when the reaction was carried out without a solvent, and N^1,N^3-disubstituted products were absent.

The physico-chemical properties of compounds Ia-If, IIa-IIe, IVa, IVb and VIa-VIc are given in Table 2. The structures of the products were confirmed by ^1H NMR spectroscopy (Table 3).

TABLE 1. Dependence of the Yield of the N^1-Monoalkylation Products Ia-If, IIa-IIe, and IVa-IVc on the Substrate, the Alkylating Agent, and the Reaction Conditions

Compound	Alkylating agent	Method	Yield*, %
Ia	IIIa	A	77
Ib	IIIa	A	80
Ic	IIIa	A	70
Id	IIIa	A	67
Ie	IIIa	A	72
If	IIIa	A	77
IIa	IIIb	A	47
IIb	IIIb	A	67
IIc	IIIb	A	58
IId	IIIb	A	61
IIe	IIIb	A	66
IVa	V	C	30 (0)
IVa	V	D	54 (0)
IVa	V	B	36 (16)
IVb	V	B	52 (12)
IVc	V	B	0 (48)

*The yields of the corresponding 1,3-disubstituted products are given in brackets.

TABLE 2. Physico-Chemical Properties of Compounds Ia-If, IIa-IIe, IVa, IVb, and VIa-VIc

Compound	M.p., °C	R_f (system A)	Molecular formula	(Found, %) / (Calculated, %)		
				C	H	N
Ia	138...140	0,22	$C_{12}H_{12}N_2O_3$	62,33 62,06	5,53 5,21	11,78 12,06
Ib	114...116	0,34	$C_{13}H_{14}N_2O_3$	63,67 63,40	5,95 5,73	11,47 11,78
Ic	184...186	0,21	$C_{13}H_{14}N_2O_3$	63,19 63,40	5,98 5,73	11,95 11,78
Id	159...161	0,52	$C_{13}H_{13}BrN_2O_3$	48,30 48,02	4,32 4,03	8,39 8,62
Ie	151...153	0,51	$C_{12}H_{11}BrN_2O_3$	46,53 46,32	3,71 3,56	8,89 9,00
If	180...181	0,40*	$C_{12}H_{13}N_3O_2$	62,51 62,33	5,89 5,67	17,98 18,17
IIa	63...66	0,15	$C_{14}H_{16}N_2O_4$	61,03 60,86	5,62 5,84	9,99 10,14
IIb	71...73	0,25	$C_{15}H_{18}N_2O_4$	62,27 62,06	6,34 6,25	9,39 9,65
IIc	96...98	0,17	$C_{15}H_{18}N_2O_4$	62,30 62,06	6,31 6,25	9,82 9,65
IId	97...99	0,40	$C_{15}H_{17}BrN_2O_4$	49,02 48,81	4,88 4,64	7,40 7,59
IIe	116...119	0,39*	$C_{14}H_{17}N_3O_3$	60,96 61,08	6,39 6,22	15,07 15,26
IVa	156...158	0,15	$C_{12}H_{12}N_2O_3$	62,28 62,06	5,46 5,21	11,85 12,06
IVb	193...195	0,25	$C_{13}H_{14}N_2O_3$	63,65 63,40	5,90 5,73	11,51 11,78
VIa	112...114	0,49	$C_{20}H_{20}N_2O_4$	68,22 68,17	5,91 5,72	7,88 7,95
VIb	126...127	0,68	$C_{21}H_{22}N_2O_4$	68,76 68,84	6,13 6,05	7,52 7,65
VIc	137...140	0,63	$C_{21}H_{22}N_2O_4$	68,97 68,84	6,16 6,05	7,54 7,65

*System B.

TABLE 3. ^{1}H NMR Spectrum of the Compounds Synthesized, δ, ppm (J_{H-H}, Hz)

Compound	R (s)	R^1 (s)	N—CH_2—O (s)	—CH_2—CH_2—O (m)	O—CH_2—Ph (s)	—C_6H_5 (s)	Solvent
Ia	5,52 d (8 Hz)	7,52 d (8 Hz)	5,16	—	4,54	7,22	Acetone-D_6
IIb	1,75	7,34	5,12	—	4,52	7,22	Acetone-D_6
Ic	5,36	2,20	5,22	—	4,49	7,20	CD_3CN
Id	—	2,45	5,30	—	4,50	7,21	CD_3CN
Ie	—	7,95	5,16	—	4,54	7,19	DMSO-D_6
If	6,14 d (7,5 Hz)	8,00 d (7,5 Hz)	5,37	—	4,74	7,44	DMSO-D_6
IIa	5,75 d (8 Hz)	7,80 d (8 Hz)	5,25	3,54...3,96	4,62	7,43	DMSO-D_6
IIb	1,96	7,68	5,22	3,50...3,95	4,62	7,44	DMSO-D_6
IIc	5,72	2,47	5,43	3,55...3,96	4,66	7,46	DMSO-D_6
Id	—	2,72	5,54	3,53...4,01	4,66	7,48	DMSO-D_6
IIe	6,35 d (8 Hz)	8,20 d (8 Hz)	5,37	3,65...4,00	4,64	7,43	DMSO-D_6
IVa	5,53 d (8 Hz)	—*	—	3,79...4,37	—	6,59...7,27 m	$CDCl_3$
IVb	1,74	7,36	—	3,88 t (7 Hz) 4,12 t (7 Hz)	—	6,60...7,29 m	Acetone-D_6
VIa	5,58 d (8 Hz)	7,57 d (8 Hz)	—	3,97...4,37	—	6,71...7,33 m	Acetone-D_6
VIb	1,75	7,38	—	3,82...4,30	—	6,60...7,30 m	Acetone-D_6
VIc	5,45	2,22	—	3,94...4,30	—	6,66...7,28 m	$CDCl_3$

*The signal is covered by the aromatic multiplet.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Tesla BS-567A (100 MHz) machine in acetone-D_6, acetonitrile-D_3, chloroform-D or DMSO-D_6. Purity of compounds was monitored by TLC on Silufol UV-254 sheets using ethyl acetate (system A) or chloroform–methanol 7:1 (system B) as eluant, and also by HPLC with a Milichrom-2 machine with a KaX-1 column and 3:1 chloroform–ethyl acetate as eluant. Silica gel L40/100 was used for preparative column chromatography. Melting points were recorded in glass capillary tubes and were not corrected.

Elemental analyses for C, H, and N agreed with calculated values.

Benzyloxymethyl Chloride (IIIa). A stream of dry HCl gas was passed through a vigorously stirred mixture of benzyl alcohol (20 cm^3, 0.193 mol), paraformaldehyde (6.3 g, 0.21 mol) and methylene chloride (100 cm^3) at 0°C for 3 h. The water formed was removed with a separatory funnel, the organic layer was dried over $MgSO_4$, filtered, and the filtrate evaporated in vacuum to give benzyloxymethyl chloride (29.0 g, 95.8%) as a colorless liquid, n_D^{20} 1.5295.

2-Benzyloxyethoxymethyl chloride (IIIb) was prepared and isolated analogously to IIIa. Yield 96.1%, n_D^{20} 1.5169.

General Method for the Preparation of 1-(Benzyloxymethyl)- (Ia-If), 1-(2-Benzyloxyethoxymethyl)- (IIa-IIe) and 1-(Benzyloxy-1-ethyl)uracils (IVa, IVb). A. The requisite chloroether (15 mmol) in methylene chloride (15 cm^3) was added to a solution silylated pyrimidine base (15.1 mmol) in methylene chloride (30 cm^3) at room temperature and the mixture was stirred for 20 h. 2-Propanol (20 cm^3) was added, the mixture was stirred for 1 h, filtered, the filtrate evaporated in vacuum, and the residue chromatographed on a silica gel column. The fraction containing the required product was collected and evaporated, and the residue was recrystallized from a suitable solvent (ethyl acetate, 2-propanol or acetone).

1-Bromo-2-phenoxyethane (V). Phenol (15.0 g, 0.159 mol) was dissolved in water (50 cm^3) containing KOH (9.5 g, 0.169 mol). 1,2-Dibromoethane (55 cm^3, 0.638 mol) and 18-crown-6 (0.1 g) were then added. The reaction mixture was heated on a boiling water bath with vigorous stirring for 16 h. It was then cooled, poured into chloroform (200 cm^3), and washed in a separating funnel with 5% KOH (3 × 50 cm^3) to remove traces of phenol. The organic layer was dried over $CaCl_2$, filtered and evaporated at low pressure. The residue was vacuum distilled to give a fraction boiling at 99-104°C/2

mm Hg, yield 52%, m.p. 30-33°C, R_f 0.63 (1:1 acetone–hexane). ^{1}H NMR spectrum (CCl_4): 3.43 (2H, t, J = 7 Hz, CH_2), 4.08 (2H, t, J = 7Hz, CH_2), 6.56-7.33 ppm (5H, m, C_6H_5).

1-(2-Phenoxyethyl)uracil (IVa). B. A mixture of uracil (3.0 g, 26.76 mmol) and K_2CO_3 (3.3 g, 23.88 mmol) in DMF (50 cm^3) was stirred at 80°C for 1 h, then a solution of VIc (4.9 g, 24.37 mmol) in DMF (10 cm^3) was added and the mixture was heated at 150°C for 5 h. The cooled reaction mixture was filtered, the filtrate was evaporated in vacuum, and the solid residue was extracted with chloroform (4 × 100 cm^3). The organic layer was evaporated in vacuum and chromatographed in portions on a silica gel column (40 × 1.6 cm). 1,3-Di(2-phenoxyethyl)uracil (VIa) was eluted with chloroform and subsequent elution with chloroform–methanol (7:1) gave 1-(2-phenoxyethyl)uracil (IVa).

C. Compound V (6.4 g, 31.83 mmol) was added to 2,4-bis(trimethylsiloxy)pyrimidine (9.8 g, 38.21 mmol). The mixture was heated at 180°C for 6 h, cooled, diluted with chloroform (20 cm^3), and hydrolyzed with ethanol (15 cm^3). The mixture was stirred for 1 h at room temperature, filtered, the filtrate evaporated in vacuum, and the residue chromatographed on a silica gel column (40 × 1.6 cm). Va (2.2 g) was eluted with chloroform–ethyl acetate (1:1).

D. Compound V (3.6 g, 17.90 mmol) was added at room temperature to a solution of 2,4-bis(trimethylsiloxy)-pyrimidine (4.6 g, 17.94 mmol) in anhydrous DMF (50 cm^3). The mixture was boiled for 8 h with the exclusion of moisture, cooled, and ethanol (15 cm^3) was added. The mixture was stirred for 1 h at room temperature, filtered, and the filtrate was evaporated in vacuum. The solid product was chromatographed on a silica gel column (40 × 1.6 cm) and compound Va (2.2 g) was eluted with chloroform–ethyl acetate (1:1).

1-(2-Phenoxyethyl)thymine (IVb), 1,3-Di(2-phenoxyethyl)thymine (IVb), and 1,3-Di(2-phenoxyethyl)-6-methyl-uracil (VIc) were prepared and isolated by method B as described for compound IVa.

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