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Polymethylene Derivatives of Nucleic Bases with ω-Functional Groups: V.[1] Pyrimidine- and Purine-Containing γ-Butyrophenones

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Abstract—New polymethylene derivatives of nucleic bases containing a keto function in the ω-position were synthesized by alkylation of nucleic bases with 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane and the subsequent deblocking of the keto group; their physicochemical properties were studied.

Key words: *alkylation, butyrophenones, nucleosides, polymethylene analogues*

INTRODUCTION

Some practically important antiviral agents have been found among acyclic nucleoside analogues, including polymethylene derivatives of nucleic bases.[3] A number of comprehensive reviews [2–5] are devoted to the preparation and properties of such widely used in medicine drugs as acyclovir, valacyclovir, gancyclovir, bucyclovir, pencyclovir, femcyclovir, and others. Acyclic nucleoside analogues are also interesting for studying action mechanisms of enzymes, whereas their structure–function relationships serve a rational basis for the design of medicines of new generations [6–8].

HBG specifically inhibits HSV-1 and HSV-2 viral thymidine kinases and does not affect the cellular thymidine kinase [9, 10]. The molecule of this acyclic nucleoside analogue contains a polymethylene chain of four carbon atoms, which is terminated with the functional hydroxyl group.

A series of highly active neuroleptics of the butyrophenone family (haloperidol, trifluperidol, droperidol, etc.) are known [11]. They belong to antipsychotic agents heavily blocking the dopamine receptors and, as a rule, lacking a hypnotic sedative activity because of a stimulating component. A modified piperidine heterocycle with a *p*-fluorobutyrophenone residue at its N atom serves as an analogue of nucleic base in these structures.

It appeared therefore interesting to synthesize and study physicochemical properties of pyrimidine and pyrine-containing γ-butyrophenones within the frames of our systematic studies of acyclic nucleoside analogues bearing various functional groups in ω-position of polymethylene chain.

RESULTS AND DISCUSSION

Alkylation of heterocyclic bases with γ-chlorobutyrophenone (**I**) is an evident method for the preparation of pyrimidine γ-butyrophenones. The starting alkylating agent was obtained using the reported procedures [12] (Scheme 1). The treatment of γ-butyrolactone with thionyl chloride converted it into γ-chlorobutyryl chloride. This was used to acylate benzene under the Friedel–Crafts conditions. An attempt to alkylate thymine with butyrophenone (**I**) in the presence of DBU according to the procedure we developed earlier [13] resulted in cyclopropylphenylketone (**II**) in 55% yield rather than in the expected N^1-mono- and N^1,N^3-bis-derivatives; the products of nucleic base alkylation were not found in the reaction mixture. A comparable yield (78%) of (**II**) was obtained under the classical conditions of synthesis of cyclopropane derivatives by the treatment of γ-chloroketones with aqueous alkali [12]. We supposed that, in this case, nitrogen-containing organic bases (e.g., DBU) exert a similar effect and the reaction course is not affected by nucleic base. This hypothesis was confirmed by the fact that the heating of equimolar amounts of (**I**) and DBU in DMF at 80–100°C for 20 h led to ~60% yield of cyclopropylphenone (**II**). We found in this manner that the oxo group of alkylating agent should be protected. The dioxolane group proved to be convenient for this aim. It was easily introduced by the reflux of γ-chlorobutyrophenone (**I**) in toluene with excess ethylene glycol in the presence of triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid. The reaction resulted in 84% yield of (**III**) (Scheme 2), which was used for the alkylation of nucleic bases.

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[3] Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; HBG, 9-(4-hydroxybutyl)guanine.

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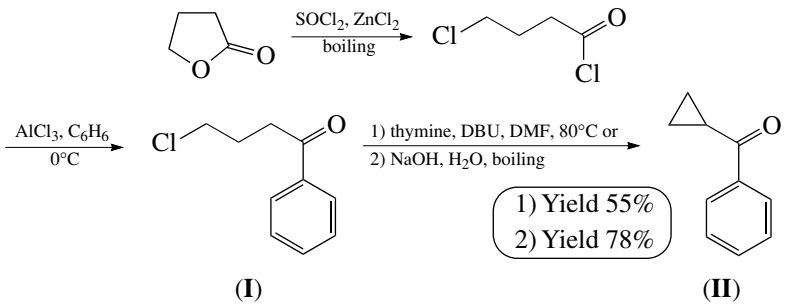
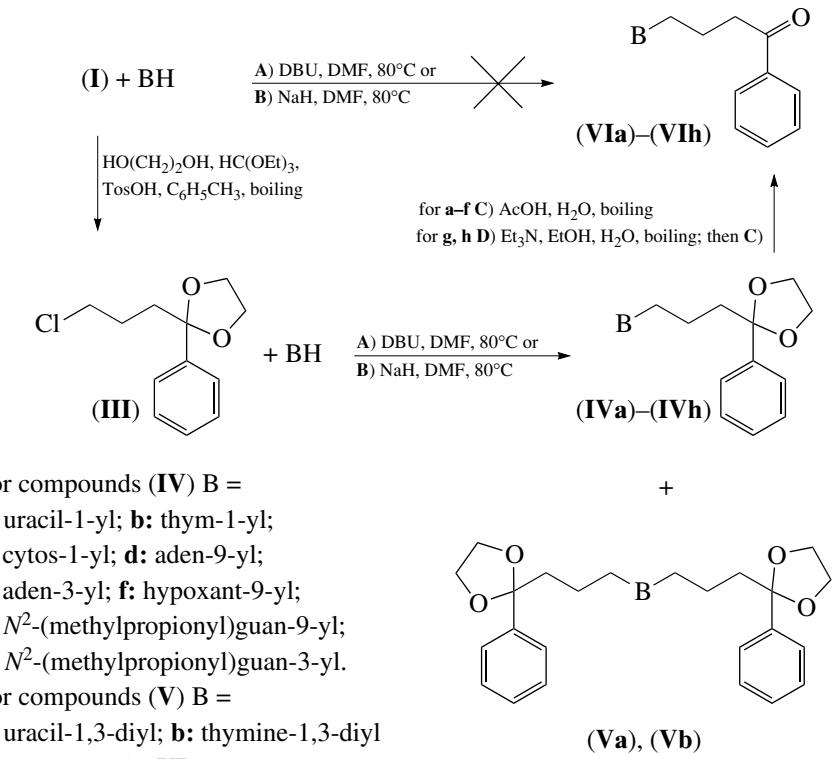


Scheme 1.



For compounds (**IV**) B =
a: uracil-1-yl; **b:** thym-1-yl;
c: cytos-1-yl; **d:** aden-9-yl;
e: aden-3-yl; **f:** hypoxant-9-yl;
g: N^2-(methylpropionyl)guan-9-yl;
h: N^2-(methylpropionyl)guan-3-yl.
For compounds (**V**) B =
a: uracil-1,3-diyl; **b:** thymine-1,3-diyl
For compounds (**VI**) B =
a–f: as for compounds (**IV**);
g: guan-9-yl; **h:** guan-3-yl

Scheme 2.

Thymine and uracil interacted with chlorophenone (**III**) under the standard conditions we described in [13] using DBU as a base (method **A**). N^1-Alkylated (**IVa**) and (**IVb**) and N^1,N^3-bisalkylated (**Va**) and (**Vb**) derivatives of uracil and thymine were obtained by this method. Cytosine was alkylated by method **B**: the nucleic base was preliminarily converted into sodium salt by the reaction with sodium hydride in DMF and then coupled with (**III**) to give 31% of the target (**IVc**) [13].

The resulting pyrimidine derivatives were isolated and purified by column chromatography on silica gel. Their structures were confirmed by elemental analysis, mass, UV, and NMR spectra (see Tables 1, 2, and the Experimental section).

Reagent (**III**) was also used for alkylation of hypoxantine, N^2-(2-methylpropionyl)guanine, and adenine. The reaction with hypoxantine by method **A** in DMF resulted in ~50% yield of N^9-derivative (**IVe**), which was isolated by column chromatography on silica gel.

Table 1. ^{1}H NMR spectra of the synthesized compounds (**VIa**)–(**VIh**)

Protons	Compounds (**VI**), δ, ppm							
	a	**b***	**c**	**d**	**e**	**f**	**g**	**h**
1 H, H1 or H3	11.17, s	11.12, s	–	–	–	12.26, s	10.52, s	10.67, s
1 H, H2 or H5	5.50, d**	–	5.63, d***	8.10, s	7.76, s	7.85, s	–	–
1 H, H6 or H8	7.63, d**	7.49, s	7.15, d***	8.15, s	8.35, s	8.18, s	7.69, s	7.89, s
2 H, 2-NH_2 or 4-NH_2 or 6-NH_2	–	–	6.91 s	7.14, s	7.90, s	–	6.36, s	6.03, s
2 H, *J* 7.16, H1'	3.74, t	3.71, t	3.70, t	4.23, t	4.41, t	4.48, t	4.03, t	4.25, t
2 H, H2'	1.94, m	1.94, m	1.91, m	2.18, m	2.26, m	2.17, m	2.10, m	2.14, m
2 H, *J* 6.88, H3'	3.07, t	3.07, t	3.02, t	3.06, t	3.10, t	3.07, t	3.04, t	3.00, t
2 H, *J* 7.48, H6' and H10'	7.93, d	7.94, d	7.93, d	7.91, d	7.90, d	7.92, d	7.90, d	7.90, d
2 H, H7' and H9'	7.51, m	7.51, m	7.52, m	7.50, m	7.51, m	7.50, m	7.50, m	7.50, m
1 H, *J* 7.16, H8'	7.61, t	7.62, t	7.63, t	7.62, t	7.62, t	7.60, t	7.61, t	7.62, t

Notes: * For (**VIb**), the resonances of 5-CH_3 group are: 1.73, 3 H, s.
** *J* 7.8.
*** *J* 7.16.

Table 2. ^{13}C NMR spectra of the synthesized compounds (**VIa**)–(**VIh**)

Carbon atoms	Compounds (**VI**), δ, ppm							
	a	**b***	**c**	**d**	**e**	**f**	**g**	**e**
C2	151.0	150.9	155.8	152.3	143.4	147.7	153.5	154.5
C4	163.7	164.2	165.9	149.6	149.7	148.8	151.2	152.6
C5	101.0	108.5	93.2	118.8	120.4	114.5	116.7	108.1
C6	145.5	141.2	145.9	155.9	155.0	153.0	156.8	159.9
C8	–	–	–	140.8	152.4	139.5	137.4	143.1
C1'	47.0	46.7	48.0	42.4	48.93	48.5	42.2	45.6
C2'	23.0	23.0	23.5	24.1	23.4	24.1	24.0	25.1
C3'	34.7	34.7	34.9	34.9	34.9	34.5	34.9	34.7
C4'	199.0	199.0	199.2	198.9	198.9	200.1	198.9	198.9
C5'	136.6	136.6	136.6	136.5	136.1	135.7	136.6	136.6
C6' and C10'	128.6	128.6	128.7	128.6	128.6	128.7	128.6	128.6
C7' and C9'	127.8	127.8	127.8	127.8	127.8	127.8	127.8	127.7
C8'	133.0	133.0	133.1	133.1	133.1	133.5	133.1	133.0

* The 5-CH_3 group of (**VIb**) resonates at 11.8 ppm.

The alkylation of N^2-(2-methylpropionyl)guanine yielded a mixture of N^9- (**IVg**) and N^7-acylated (**IVh**) guanine derivatives smoothly separated by column chromatography on silica gel.

The N^9-derivative (**IVd**), isolated in a rather low yield (29%), was the product of the reaction of adenine sodium salt with (**III**) by the method **B**. No product of N^3-alkylation was in this reaction (cf. [1]). However, the yield of N^9-isomer considerably increased (up to 56%) when adenine was alkylated by method **A**. A small amount of very contaminated N^3-isomer (**IVe**) was also isolated from the reaction mixture [1, 14]; it was purified by ion-exchange chromatography on a sulfated cation-exchanger Dowex 50 × 8 (H^+ form). The 1,3-dioxolane group was quantitatively removed during the purification process. The yield of homogeneous N^3-isomer (**IVe**) was 6%.

The structures of the resulting purine bases were confirmed by elemental analyses, mass, UV, and NMR spectra (see Tables 1, 2 and the Experimental section).

The protective dioxolane group was quantitatively removed from the nucleic base derivatives by reflux with 50% acetic acid for 30 min (method **C**). This

method enabled the preparation of compounds (**VIa**)–(**VIf**). The target guanine derivatives (**VIg**) and (**VIh**) were obtained by the preliminary deblocking the 2-amino group in (**IVg**) and (**IVh**) by a prolonged reflux in a water–alcohol mixture in the presence of triethylamine (method **D**).

The solvents were evaporated in a vacuum, and the mixture of intermediates was hydrolyzed under acidic conditions described above for the removal of the 1,3-dioxolane fragment. Derivatives (**VIg**) and (**VIh**) were obtained in good yields.

The UV spectra of the compounds synthesized exhibit the absorption band at 245 nm (ε 13000 M^{-1} cm^{-1}) resulting from the electron transfer from carbonyl group to phenyl radical, which, for most compounds, is overlapped with the absorption band of the nucleic base chromophore. This makes the UV spectra low informative.

The structures of the compounds synthesized were convincingly confirmed by ^1H and ^{13}C NMR spectroscopy (Tables 1, 2). Three groups of signals are present in the NMR spectra: the resonances from the corresponding atoms of nucleic base, those of atoms of polymethylene chain, and the signals of terminal functional group. The structures of isomeric pairs (**VId**) and (**VIe**) and (**VIg**) and (**VIh**) were assigned on the basis of the presence of characteristic "alkylation effects" in the ^{13}C NMR spectra [1, 14]. An upfield shift of the C2 resonance (~8.9 ppm) and a downfield shift of C8 (~11.6 ppm) are observed for the N^9-isomer (**VIe**) in comparison with the N^3-isomer (**VId**). Unlike the N^9-isomer (**VIg**), the C5 resonance in the N^7-isomer (**VIh**) is shifted upfield (~8.6 ppm) and the C8 resonance, downfield (~5.7 ppm) (Table 2).

EXPERIMENTAL

Guanine, adenine, uracil, thymine, cytosine, and hypoxantine were from Sigma (United States); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), from Aldrich (United States); sodium hydride (80% suspension in mineral oil) and aluminum chloride, from Fluka (Switzerland); *p*-toluenesulfonic acid, from Pierce (United States); triethyl orthoformate and ethylene glycol, from Acros Organics (Belgium), and Dowex 50 × 8, from Serva (Germany).

Solvents were purified and dried by standard procedures [12]. UV-spectra were registered on a Cary 50 spectrophotometer (Varian, Australia) at pH 1, 7 and 14; λ_{max} are given in nm and ε, in M^{-1} cm^{-1}. Mass spectra were registered on a MS-30 mass spectrometer (Kratos, Japan) at electron impact ionization. NMR spectra were registered on a Bruker AMXIII-400 (Germany) with a working frequency of 400.13 MHz for ^1H and 100.6 MHz for ^{13}C NMR nuclei. The spectra were obtained at 300 K in DMSO-d_6 or $CDCl_3$ (Acros Organics, Belgium). Chemical shifts are given in ppm; coupling constants, in Hz; tetramethylsilane was an internal standard. TLC was carried out on precoated Kieselgel 60 F_{254} plates (Merck, Germany) using chloroform–ethanol elution systems at the following ratios: (A) 1 : 0, (B) 19 : 1, (C) 18 : 2, (D) 17 : 3, and (E) 17.5 : 2.5. For column chromatography, silica gel L 40/100 (Chemapol, Czech Republic) was used.

4-Chloro-1-phenylbutan-1-one (I). Anhydrous aluminum chloride (28 g, 0.21 mmol) was portionwise added for 25 min to a stirred solution of 4-chlorobutanoyl chloride [12] (28.2 g, 0.2 mmol) in dry benzene (40 ml) cooled to 0°C. The resulting solution was stirred for 1 h at 0°C and for 1 h at 20°C and then poured on ice (200 g). The organic layer was separated; the aqueous layer was extracted with benzene (2 × 30 ml); and the combined extracts were dried with anhydrous sodium sulfate and evaporated. The residue was distilled in a vacuum to give 31.3 g (85.9%) of (**I**); bp 145–147°C/8 mmHg; MS, *m/z*: 182.6 $[M]^{+\cdot}$, calc. for $C_{10}H_{11}ClO$: 182.6; ^1H NMR ($CDCl_3$): 2.08 (2 H, m, $C\underline{H}_2CH_2Cl$), 3.01 (2 H, t, *J* 7.0, $COC\underline{H}_2$), 3.54 (2 H, t, *J* 6.2, $C\underline{H}_2Cl$), 7.33 (2 H, m, *m*-H of Ph), 7.43 (1 H, t, *J* 7.5, *p*-H of Ph), and 7.84 (2 H, d, *J* 8.1, *o*-H of Ph); ^{13}C NMR ($CDCl_3$): 26.78 ($\underline{C}H_2CH_2Cl$), 35.21 ($CO\underline{C}H_2$), 44.61 ($\underline{C}H_2Cl$), 127.89 (2 C), 128.54 (2 C), 133.04, and 136.69 ($\underline{C}_6H_5$), and 198.69 ($\underline{C}O$).

2-(3-Chloropropyl)-2-phenyl-1,3-dioxolane (III). 4-Chloro-1-phenylbutan-1-one (30 g, 0.164 mol) (**I**), ethylene glycol (21 ml, 0.378 mol), *p*-toluenesulfonic acid monohydrate (3 g, 0.015 mol), and triethyl orthoformate (68.4 ml, 0.411 mol) were added to dry toluene (250 ml). The solution was refluxed with a Dean–Stark trap for 8 h, and evaporated in a vacuum of a water jet pump. Cold dichloromethane (50 ml) was added to the residue, the precipitated *p*-toluenesulfonic acid was filtered off, dichloromethane was evaporated, and the residue was distilled in a vacuum to give 31.3 g (84%) of the product; bp 126–127°C/1 mm Hg; MS, *m/z*: 226.7 $[M]^+$, calc. for $C_{12}H_{15}ClO_2$: 226.7; ^1H NMR (DMSO-d_6): 1.74 (2 H, m, $C\underline{H}_2CH_2Cl$), 1.96 (2 H, t, *J* 7.5, $C\underline{H}_2CH_2CH_2Cl$), 3.59 (2 H, t, *J* 6.9, $C\underline{H}_2Cl$), 3.68 and 3.97 (2 H × 2, 2 m, $OC\underline{H}_2C\underline{H}_2O$), 7.28–7.42 (5 H, m, Ph); ^{13}C NMR (DMSO-d_6): 26.86 ($\underline{C}H_2CH_2Cl$), 37.14 ($\underline{C}H_2CH_2CH_2Cl$), 45.21 ($\underline{C}H_2Cl$), 64.19 (2C, $O\underline{C}H_2\underline{C}H_2O$), 109.29 ($O\underline{C}O$), 125.29 (2 C), 127.78 and 128.10 (2 C), and 142.24 (Ph).

Alkylation of nucleic bases with 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane (III) using DBU as a base (method A). Alkylating agent (**III**) (3.4 g, 15 mmol) and DBU (2.3 g, 15 mmol) were added to a suspension of nucleic base or its protected derivative (10 mmol) in dry DMF (25 ml), and the mixture was heated at 80–100°C for 20 h (TLC monitoring). The reaction mixture was cooled and evaporated in a vacuum to dryness. The residue was suspended in minimal volume of chloroform and chromatographed on a silica gel column (5 × 28 cm, 200 g), eluted with a gradient of

ethanol in chloroform (0 to 20%). The target fractions were evaporated, and the residue was recrystallized from ethanol or an ethyl acetate–octane mixture.

Alkylation of adenine and cytosine sodium salts with 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane (III) (method B). Sodium hydride (80% suspension in mineral oil, 0.33 g, 11 mmol) was added to a stirred suspension of nucleic base (10 mmol) in dry DMF (25 ml), the mixture was stirred for 30 min at 20°C, and (**III**) (2.7 g, 12 mmol) was added. The reaction mixture was heated at 80–100°C for 20 h (TLC monitoring). DMF was removed in a vacuum, and the residue was shaken with water (20 ml) and chloroform (50 ml). The organic layer was separated, and the water layer was extracted with chloroform (5 × 30 ml). The combined extracts were dried with anhydrous sodium sulfate, evaporated, and the residue was chromatographed on a silica gel column as described in method **A**. The target fractions were evaporated and the residue was recrystallized from alcohol or an ethyl acetate–octane mixture.

1-[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]uracil (IVa) was obtained by method **A**; yield 41%; R_f 0.78 (B); mp 186–187°C (EtOAc–octane); MS, *m*/*z*: 302.3 $[M]^+$, 303.3 $[M + H]^+$, calc. for $C_{16}H_{18}N_2O_4$: 302.3; ^{1}H NMR (DMSO-d_6): 1.59 (2 H, m, H2'), 1.82 (2 H, t, *J* 7.5, H3'), 3.61 (2 H, t, *J* 7.16, Hl'), 3.68 and 3.97 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 5.50 (1 H, d, *J* 7.8, H5), 7.29–7.39 (5 H, m, Ph), 7.58 (1 H, d, *J* 7.8, H6), and 11.14 (1 H, s, H1); ^{13}C NMR (DMSO-d_6): 22.87 (C2'), 36.52 (C3'), 47.34 (C1'), 64.10 (2 C, O$\underline{C}$H$_2$$\underline{C}H_2$O), 106.65 (C5), 109.18 (C4'), [125.13 (2 C), 127.62, 127.91 (2 C), 142.19] (Ph), 145.41 (C6), 150.71 (C2), and 163.45 (C4).

1,3-Bis[3-(2-phenyl-1,3-dioxolan-2-yl)propyl]uracil (Va) was obtained by method **A** in 13% yield; R_f 0.9 (B); oil; UV: 266 (8300) at pH 1, 266 (8300) at pH 7, and 266 (8300) at pH 14; MS, *m*/*z*: 492.6 $[M]^+$, 493.6 $[M + H]^+$; calc. for $C_{28}H_{32}N_2O_6$: 492.6; ^{1}H NMR ($CDCl_3$): 1.73 (4 H, m, H2' and H2"), 1.92 (4 H, m, H3' and H3"), 3.71 (2 H, t, *J* 7.48, Hl'), 3.75 and 3.99 (4 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 3.92 (2 H, t, *J* 7.48, Hl"), 5.63 (1 H, d, *J* 7.8, H5), 7.04 (1 H, d, *J* 7.8, H6), and 7.23–7.44 (10 H, m, Ph); ^{13}C NMR ($CDCl_3$): 22.00 (C2'), 23.32 (C2"), 36.95 (C3'), 37.86 (C3"), 41.26 (C1'), 49.57 (C1"), 64.62 (2 C) and 64.67 (2 C) (O$\underline{C}$H$_2$$\underline{C}H_2$O), 101.52 (C5), 110.01 (C4'), 110.2 (C4"), [125.69 (2 C), 125.78 (2 C), 127.82 (2 C), 128.13 (2 C), 128.35 (2 C), and 142.23 (2 C)] (Ph), 142.79 (C6), 151.38 (C2), and 163.13 (C4).

1-[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]thymine (IVb) was obtained by method **A** in 54% yield; R_f 0.47 (A); mp 167–168°C (EtOAc–octane); MS, *m*/*z*: 316.3 $[M]^+$, 317.3 $[M + H]^+$; calc. for $C_{16}H_{18}N_2O_4$: 316.3; ^{1}H NMR (DMSO-d_6): 1.57 (2 H, m, H2'), 1.73 (3 H, s, 5-C$\underline{H}_3$), 1.81 (2 H, t, *J* 7.5, H3'), 3.58 (2 H, t, *J* 7.16, Hl'), 3.66 and 3.96 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 7.29–7.38 (5 H, m, Ph), 7.46 (1 H, s, H6), and 11.10 (1 H, s, H1); ^{13}C NMR (DMSO-d_6): 11.80 (5-$\underline{C}$H$_3$), 23.09 (C2'), 36.73 (C3'), 47.20 (C1'), 64.20 (2 C, O$\underline{C}$H$_2$$\underline{C}H_2$O), 108.42 (C5), 109.29 (C4'), [125.30 (2 C), 127.80, 128.10 (2 C), and 142.30] (Ph), 141.39 (C6), 150.80 (C2), and 164.23 (C4).

1,3-Bis[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]thymine (Vb) was obtained by method **A** in 22% yield; R_f 0.87 (A); oil; UV: 273 (7600) at pH 1, 273 (7600) at pH 7, and 273 (7600) at pH 14; MS, *m*/*z*: 506.6 $[M]^+$, 507.6 $[M + H]^+$; calc. for $C_{29}H_{34}N_2O_6$: 506.6; ^{1}H NMR (DMSO-d_6): 1.52 and 1.61 (2 H × 2, 2 m, H2' and H2"), 1.77 (3 H, s, 5-C$\underline{H}_3$), 1.83 (4 H, m, H3' and H3"), 3.66 (2 H, t, *J* 6.88, Hl'), 3.66 and 3.95 (4 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 3.77 (2 H, t, *J* 6.88, Hl"), 7.37 (10 H, m, Ph), and 7.50 (1 H, s, H6); ^{13}C NMR (DMSO-d_6): 12.49 (5-$\underline{C}$H$_3$), 21.70 (C2'), 22.96 (C2"), 36.68 (C3'), 37.37 (C3"), 40.40 (C1'), 48.36 (C1"), 64.18 (4 C, O$\underline{C}$H$_2$$\underline{C}H_2$O), 107.6 (C5), 109.29 (C4'), 109.35 (C4"), [125.29 (4 C), 127.70, 127.78, 128.03 (2 C), 128.07 (2 C), 142.29, 142.40] (Ph), 139.92 (C6), 150.69 (C2), and 162.99 (C4).

1-[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]cytosine (IVc) was obtained by method **B** in 31% yield; R_f 0.19 (C); mp 230–231°C (ethanol); MS, *m*/*z*: 301.3 $[M]^+$, 302.3 $[M + H]^+$; calc. for $C_{16}H_{19}N_3O_3$: 301.3; ^{1}H NMR (DMSO-d_6): 1.57 (2 H, m, H2'), 1.80 (2 H, t, *J* 7.5, H3'), 3.60 (2 H, t, *J* 7.16, Hl'), 3.67 and 3.97 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 5.61 (1 H, d, *J* 7.16, H5), 6.83 (2 H, br. s, 4-N$\underline{H}_2$), 7.27–7.38 (5 H, m, Ph), 7.48 (1 H, d, *J* 7.16, H6). ^{13}C NMR (DMSO-d_6): 23.34 (C2'), 36.92 (C3'), 48.54 (C1'), 64.21 (2 C, O$\underline{C}$H$_2$$\underline{C}H_2$O); 93.05 (C5), 109.41 (C4'), [125.30 (2 C), 127.73, 128.06 (2 C), and 142.42] (Ph), 145.91 (C6), 155.72 (C2), and 165.82 (C4).

9-[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]adenine (IVd) was obtained by method **A** in 56% yield; R_f 0.65 (E); mp 151–152°C (EtOAc–octane); MS, *m*/*z*: 325.4 $[M]^+$, 326.4 $[M + H]^+$; calc. for $C_{17}H_{19}N_5O_2$: 325.4; ^{1}H NMR (DMSO-d_6): 1.82 (4 H, m, H2' and H3'), 3.64 and 3.93 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 4.13 (2 H, t, *J* 7.16, Hl'), 7.19 (2 H, br. s, 6-N$\underline{H}_2$), 7.25–7.33 (5 H, m, Ph), 8.08 (1 H, s, H2), and 8.28 (1 H, s, H8); ^{13}C NMR (DMSO-d_6): 24.14 (C2'), 36.87 (C3'), 42.78 (C1'), 64.12 (2 C, O$\underline{C}$H$_2$$\underline{C}H_2$O), 109.29 (C4'), 118.74 (C5), 125.21 (2 C), 127.70, 127.99 (2 C), and 142.17 (Ph), 140.73 (C8), 149.45 (C4), 152.31 (C2), and 155.89 (C6).

By method **B**, the yield was 29%. Physicochemical characteristics were identical to those reported for the substance obtained by method **A**.

9-[3-(Phenyl-1,3-dioxolan-2-yl)propyl]hypoxantine (IVf) was obtained by method **A** in 29% yield; R_f 0.27 (B); mp 212–213°C (EtOAc–octane); MS, *m*/*z*:

326.3 $[M]^+$, 327.3 $[M + H]^+$; calc. for $C_{17}H_{18}N_4O_3$: 326.3; ^{1}H NMR (DMSO-d_6): 1.74–1.85 (4 H, m, H2' and H3'), 3.64 and 3.94 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 4.30 (2 H, t, *J* 6.84, Hl'), 7.25–7.35 (5 H, m, Ph), 7.95 (1 H, s, H2), 8.18 (1 H, s, H8), and 12.26 (1 H, s, H1); ^{13}C NMR (DMSO-d_6): 24.33 (C2'), 36.78 (C3'), 46.24 (C1'), 64.18 (2 C, O$\underline{C}$H$_2\underline{C}$H$_2$O), 109.21 (C4'), 114.77 (C5), [125.24 (2 C), 127.78, 128.07 (2 C), 142.22] (Ph), 140.22 (C8),145.40 (C2), 148.29 (C4), and 154.24 (C6).

***N*^{2}-(2-Methylpropionyl)-9-[3-(2-phenyl-1,3-dioxolan-2-yl)propyl]guanine (IVg)** was obtained by method **A** in 15% yield; R_f 0.52 (B); mp 171–172°C (EtOAc–octane); MS, *m/z*: 411.5 $[M]^+$, 412.5 $[M + H]^+$; calc. for $C_{21}H_{25}N_5O_4$: 411.5; ^{1}H NMR (DMSO-d_6): 1.10 (6 H, d, *J* 6.84, COCH(C$\underline{H}_3$)$_2$), 1.79 (4 H, m, H2' and H3'), 2.78 (1 H, m, COC$\underline{H}$(CH$_3$)$_2$), 3.64 and 3.94 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 4.03 (2 H, t, *J* 6.38, Hl'), 7.26–7.33 (5 H, m, Ph), 7.93 (1 H, s, H8), and 11.94 (2 H, br. s, H1 and 2-NH); ^{13}C NMR (DMSO-d_6): 18.84 (2 C, COCH(C$\underline{H}_3$)$_2$), 24.23 (C2'), 34.66 (CO$\underline{C}$H(CH$_3$)$_2$), 36.79 (C3'), 43.04 (C1'), 64.20 (2 C, O$\underline{C}$H$_2\underline{C}$H$_2$O), 109.17 (C4'), 120.10 (C5), [125.26 (2 C), 127.81, 128.10 (2 C), 142.15] (Ph), 139.75 (C8), 147.79 (C4), 148.52 (C2), 154.88 (C6), and 180.13 ($\underline{C}$OCH(CH$_3$)$_2$).

***N*^{2}-(2-Methylpropionyl)-7-[3-(2-phenyl-1,3-dioxolan-2-yl)propyl]guanine (IVh)** was obtained by method **A** in 10% yield; R_f 0.46 (B); mp 215–216°C (EtOAc–octane); MS, *m/z*: 411.5 $[M]^+$, 412.5 $[M + H]^+$; calc. for $C_{21}H_{25}N_5O_4$: 411.5; ^{1}H NMR (DMSO-d_6): 1.11 (6 H, d, *J* 6.84, COCH(C$\underline{H}_3$)$_2$), 1.73–1.83 (4 H, m, H2' and H3'), 2.74 (1 H, m, COC$\underline{H}$(CH$_3$)$_2$), 3.64 and 3.94 (2 H × 2, 2 m, OC$\underline{H}_2$C$\underline{H}_2$O), 4.25 (2 H, t, *J* 6.84, Hl'), 7.25–7.33 (5 H, m, Ph), 8.11 (1 H, s, H8), and 11.75 (2 H, br. s, H1 and 2-NH); ^{13}C NMR (DMSO-d_6): 18.85 (2 C, COCH(C$\underline{H}_3$)$_2$); 25.17 (C2'), 34.69 (C3'), 36.47 (CO$\underline{C}$H(CH$_3$)$_2$), 46.16 (C1'), 64.19 (2 C, O$\underline{C}$H$_2\underline{C}$H$_2$O), 109.22 (C4'), 111.17 (C5), [125.25 (2 C), 127.76, 128.07 (2 C), 142.24] (Ph), 144.24 (C8), 147.00 (C4), 152.46 (C2), 157.26 (C6), and 179.91 ($\underline{C}$OCH(CH$_3$)$_2$).

The removal of the 1,3-dioxolane protective group and the synthesis of derivatives (VIa)–(VIh) (method C). Glacial acetic acid (15 ml) and water (15 ml) were added to derivatives (**IVa**)–(**IVf**) (3 mmol), and the reaction mixture was refluxed for 30 min. The solvents were removed in a vacuum, the residue was stirred with a saturated sodium bicarbonate solution (30 ml), and the resulting precipitate was filtered and washed with water (~10 ml) and cold ethanol (5 ml).

1-(4-Oxo-4-phenylbutyl)uracil (VIa) was obtained by method **C** in 98% yield; R_f 0.78 (B); mp 165–166°C (ethanol); UV: 251 (14 000) at pH 1, 249 (13100) at pH 7, and 249 (12 800) at pH 14; MS, *m/z*: 258.3 $[M]^+$, 269.3 $[M + H]^+$; calc. for $C_{14}H_{14}N_2O_3$: 258.3.

1-(4-Oxo-4-phenylbutyl)thymine (VIb) was obtained by method **C** in 97% yield; R_f 0.47 (A); mp 182–183°C (ethanol); UV: 249 (12 500), 272 (8700) (shoulder) at pH 1, 249 (12 500), 272 (8700) at pH 7, and 249 (12 200), 272 (7200) (shoulder) at pH 14; MS, *m/z*: 272.3 $[M]^+$, 273.3 $[M + H]^+$; calc. for $C_{15}H_{16}N_2O_3$: 272.3.

1-(4-Oxo-4-phenylbutyl)cytosine (VIc) was obtained by method **C** in 99% yield; R_f 0.19 (C); mp 232°C (dec., ethanol); UV: 247 (11 200), 283 (11300) at pH 1, 245 (13700), 274 (8000)(shoulder) at pH 7, and 245 (13700), 274 (8000) (shoulder) at pH 14; MS, *m/z*: 257.3 $[M]^+$, 258.3 $[M] + H]^+$, calc. for $C_{14}H_{15}N_3O_2$: 257.3.

9-(4-Oxo-4-phenylbutyl)adenine (VId) was obtained by method **C** in 96% yield; R_f 0.65 (E); mp 220–221°C (ethanol); UV, 253 (18600) at pH 1, 253 (18600) at pH 7; and 253 (18600) at pH 14; MS, *m/z*: 281.3 $[M]^+$, 282.3 $[M + H]^+$, calc. for $C_{15}H_{15}N_5O$: 281.3.

3-(4-Oxo-4-phenylbutyl)adenine (VIe) was obtained during purification of (**IVe**) on a Dowex 50 × 8 (H^+) column. The fraction containing (**IVe**) obtained by method **A** was dissolved in ethanol (30 ml) and loaded on a Dowex column. The column was successively washed with ethanol, water, and 5% ammonia. The target (**VIe**) was eluted with EtOH, the solvent was evaporated in a vacuum, and the residue was crystallized from a 5 : 1 EtOAc–octane mixture to give 6% of (**VIe**); R_f 0.45 (E); mp 210°C (dec); UV, plateau 249 (13300)–278 (14300) at pH 1, plateau 249 (12100)–275 (11700) at pH 7, and plateau 249 (11700)–275 (10900) at pH 14; MS, *m/z*: 281.3 $[M]^+$, 282.3 $[M + H]^+$, calc. for $C_{15}H_{15}N_5O$: 281.3.

9-(4-Oxo-4-phenylbutyl)hypoxantine (VIf) was obtained by method **C** in 98% yield; R_f 0.17 (B); mp 225°C (ethanol); UV, 248 (14 000) at pH 1, 248 (16600) at pH 7, and 248 (13 000) at pH 14; MS, *m/z*: 282.3 $[M]^+$, 283.3 $[M + H]^+$, calc. for $C_{15}H_{14}N_4O_2$: 282.3.

The removal of isobutyroyl group in the guanine derivatives (method D). Triethylamine (0.23 ml, 1.6 mmol) was added to a solution of protected guanine derivatives (**IVg**) or (**IVh**) (0.33 g, 0.8 mmol) in ethanol (9 ml) and water (1.5 ml). The resulting solution was refluxed (TLC monitoring), and the solvents were removed in a vacuum. The crude products were used without further purification.

9-(4-Oxo-4-phenylbutyl)guanine (VIg) was obtained in 73% yield from (**IVg**) successively using methods **D** and **C**; R_f 0.25 (D); mp 255–256°C (ethanol); UV: 250 (18 900) and 279 (7500) (shoulder) at pH 1, 249 (19 500) and 272 (8800) (shoulder) at pH 7, 248 (19 500) and 271 (10 500) (shoulder) at pH 14; MS,

m/z: 297.3 $[M]^+$, 298.3 $[M + H]^+$, calc. for $C_{15}H_{15}N_5O_2$: 297.3.

7-(4-Oxo-4-phenylbutyl)guanine (VIh) was obtained in 46% yield from (**IVh**) successively using methods **D** and **C** followed by chromatography on a silica gel column; R_f 0.36 (D); UV: 248 (24 400) and 279 (8200) (shoulder) at pH 1, 245 (15 800) and 285 (7200) at pH 7, and 243 (16 900) and 283 (7100) at pH 14; MS, *m/z*: 297.3 $[M]^+$, 298.3 $[M + H]^+$, calc. for $C_{15}H_{15}N_5O$: 297.3.

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