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New "sp^2-Bonded" Carbanucleosides

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Abstract—By reaction of 2,3-dichloro-, 2,3,5-trichloro-, 2,5-dichloro-3-phenylsulfonyl-, 2-chloro-3-phenylsulfonyl-4,4-ethylenedioxycyclopent-2-en-1-ones with uracyl 3- and 2-uracyl derivatives were obtained of the corresponding chlorocyclopentenone.

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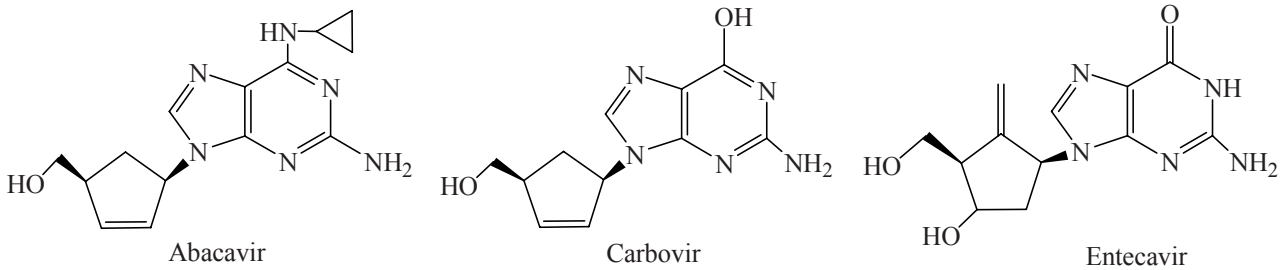
The steady growth and the pandemic character of HIV/AIDS-disease, the fast adaptability of the pathogens to the applied drugs stimulate the search for new pharmaceuticals for the treatment of these and probable concurrent infections. Nowadays the most important in the treatment of viral infections remain the drugs based on nucleosides that regretfully are not free of disadvantages. The main among the latter are metabolic instability and cytotoxicity. In this respect carbanucleosides are preferable where an oxygen in the furanose part of the molecule is replaced by a methylene fragment. This modification supplied them, in contrast to the parent nucleosides, with a higher metabolic stability with respect to phosphorylases and hydrolases which quickly cleave the glycoside bond in the nucleosides. Among them can be cited the permitted anti-HIV drugs: Carbovir [1], Abacavir [2], Entecavir [3] [for the treatment of HSV-infections (virus of a simple herpes)] (see scheme).

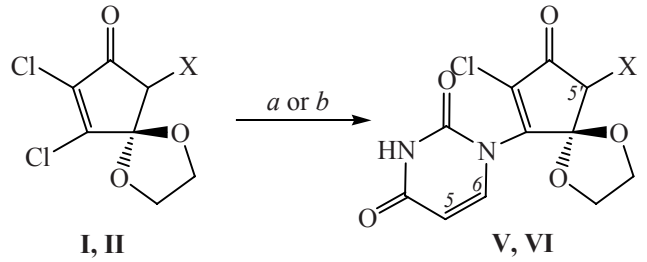
The cyclopentenone blocks **I–IV** we have formerly synthesized [4, 5] seem suitable objects for the Ad_NE reaction with nucleic bases and a way to new types of polyheterofunctionalized carbanucleosides.

We first studied the uracyl reaction with the basic trichlorocyclopentenone **I**. Inasmuch as the uracyl was a weak nucleophile, we used as a base sodium hydride to attain more complete proceeding of the reaction. The experiment showed that the Ad_NE reaction proceeded quickly and with a complete conversion of the initial chlorocyclopentenone. However we met some difficulties in further workup of the reaction mixture and in isolation of the products. Because of the poor solubility of the uracyl in the most organic solvents we added DMSO as a cosolvent to create a homogeneous medium. This fact complicated the isolation and purification of target product **V**. It turned out that the chromatographic mobility (R_f) of DMSO, uracyl, and the reaction product were nearly identical, and therefore the purification of the reaction product by column chromatography on silica gel was very difficult. Besides the reaction product possessed low solubility comparable with uracyl, therefore at the chromatographic separation the reaction mixture was applied to the column as a dispersion, and this also negatively affected the separation quality.

Scheme.



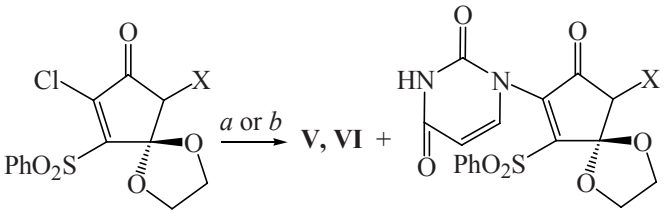
Another mode of reaction turned out the be more convenient, namely, the boiling of the initial substrate with 1.5 equiv of uracyl in aqueous alkali for 5 h. The crystalline substance that precipitated in the course of the reaction was isolated by recrystallization from aqueous methanol. As a result of this reaction modification target compound **V** was obtained in 67% yield. Dichlorocyclopentenone **II** proved to be less active: the comparable yield of compound **VI** was attained in 18 h.



I, II **V, VI**

a: 1.5 equiv of uracyl, NaH, DMSO–THF, 20°C; *b*: 1.5 equiv of uracyl, NaOH, THF–H_2O, 80°C; X = Cl (**I, V**), H (**II, VI**).

In attampt to optimize the synthesis and design of the product we studied the uracyl reaction with phenylsulfonyl-substituted chlorocyclopentenones **III** and **IV**. It was expected that highly active cyclopentenone blocks **III** and **IV** containing Cl and $PhSO_2$ would easier react with the weak N-nucleophiles like uracyl and its derivatives. The presence in the cyclopentenones of two reaction sites suggested that the reaction might proceed along two directions (Ad_NE-replacement of a vinyl Cl atom or SO_2Ph group and S_N2-substitution of sp^3-Cl adjacent to the carbonyl) and might yield respectively three types of products. We isolated from the reaction only the products of replacement of the vinyl Cl atom and the SO_2Ph group in the ratio 3:1. Interestingly, in contrast to the above described reactions of these compounds with C-nucleophiles, in this case we observed a prevailing formation of the products of substitution of vinyl Cl atom: vinylsulfones **VII** and **VIII**.



III, IV **VII, VIII**

a: 1.5 equiv of uracyl, NaH, DMSO–THF, 20°C; *b*: 1.5 equiv of uracyl, NaOH, THF–H_2O, 80°C; X = Cl (**III, VII**), H (**IV, VIII**).

The structure and composition of compounds obtained were established from IR, ^1H and ^{13}C NMR spectra, and also from the elemental analysis. The singlet signals of amide group protons in the ^1H NMR spectra of adducts obtained **V–VIII** appearing in a very weak field (8–11 ppm) indicate the N^1-substitution in the uracyl ring.

Thus as a result of the reactions of chlorocyclopentenones **III** and **IV** with uracyl we obtained the corresponding 3- and 2-uracyl cyclopentenone derivatives. The most active were in this reaction 2,5-dichloro-3-phenylsulfonyl- and 2,3,5-trichloro-4,4-ethylenedioxycyclopent-2-en-1-ones (**III**) and (**I**), evidently because of the activating effect of the Cl atom at $C^{5'}$.

The developed method of the reaction of chlorocyclopentenones with uracyl is an efficient way of building up structures of new vinyl (sp^2-bonded) carbanucleosides, and the combining in their structure of pharmacophore fragments, uracyl and chlorocyclopentenone, gives a hope to find in them an interesting biological activity.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 (from films or mulls in mineral oil). ^1H and ^{13}C NMR spectra were recorded on a spectrometer Bruker AM-300 (at operating frequencies 300.13 and 75.47 MHz respectively); internal reference TMS, solvent DMSO-d_6. The reaction progress was monitored and the purity of compounds obtained was checked by TLC and HPLC. TLC was performed on Sorbfil PTSKh-AF-A plates, spots visualized by alkaline solution of $KMnO_4$ [6]. The chromatographic analysis was carried out on a system Staier (Akvilon, Russia) with the use of a column 250×4.6 mm with a stationary phase Luna C 18 (Phenomenex, USA) with particle size 5 μm. Eluent water–acetonitrile, gradient elution, flow rate 1 ml/min. Detection was performed at λ 215 nm.

Reactions of chlorocyclopentenones I–IV with uracyl. *a.* To a suspension of 0.62 mmol of NaH in 2 ml of THF was added 1 ml of DMSO and 0.62 mmol of uracyl, and the mixture was stirred for 30 min at room temperature, then to the reaction mixture was added dropwise a solution of 0.41 mmol of an appropriate chlorocyclopentenone in 5 ml of THF. The reaction mixture was stirred for 30 min, excess NaH was quenched with water at cooling (0–5°C), 10 ml of chloroform was added and 10% HCl to pH 7, the mixture was stirred for 20 min, reaction products were extracted into $CHCl_3$. The organic extracts were washed with a saturated NaCl

solution, dried with $MgSO_4$, and concentrated in a vacuum. The reaction products were isolated by column chromato-graphy on SiO_2.

b. To a solution of 1.23 mmol of NaOH in 4 ml of water was added 1.23 mmol of uracyl, the mixture was stirred for 40 min at room temperature, and then thereto was slowly added dropwise a solution of 0.82 mmol of chlorocyclopentenone in 4 ml of THF. The reaction mixture was boiled at stirring till complete consumption of the initial compound (5–6 h). On completion of the reaction into the reaction mixture 10% water solution of HCl was added till pH 7, the mixture was stirred for 30 min and evaporated in a vacuum to dryness. The reaction products either were isolated by column chromatography on SiO_2 or the precipitated reaction product was filtered off and recrystallized from a mixture MeOH–H_2O, 20:1.

1-(2,5-Dichloro-4,4-ethylenedioxycyclopent-2-en-1-one-3-yl)-1,3-dihydropyrimidine-2,4-dione (V) was obtained from chloroenone **I**, complete conversion within 8 h. Yield 30% (*a*), 67% (*b*). Colorless crystals, mp 254°C (MeOH–H_2O, 20:1), R_f 0.40 (chloroform–methanol, 9:1, double elution). IR spectrum, ν, cm^{-1}: 3530 (C–N), 3110, 3095, 3055 (C–N), 1747 (C=O), 1718 (C=O), 1640 (C=O), 1590 (C=C). ^1H NMR spectrum, δ, ppm: 3.94–4.22 m (4H, $2CH_2O$), 5.45 s (1H, H^{52}), 5.76 d (1H, H^5, *J* 8.0 Hz), 7.52 s (1H, H^6, *J* 8.0 Hz), 11.74 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 60.78 (C^{52}), 64.90 and 65.22 ($2CH_2O$), 101.65 (C^5), 106.17 (C^{42}), 132.47 (C^{22}), 139.24 (C^6), 149.50 (C^{32}), 145.36 (C^2), 185.55 (C^{12}). Found, %: C 41.59; H 2.39; Cl 22.38; N 8.89. $C_{11}H_8Cl_2N_2O_5$. Calculated, %: C 41.40; H 2.53; Cl 22.22; N 8.78.

1-(2-Chloro-4,4-ethylenedioxycyclopent-2-en-1-one-3-yl)-1,3-dihydropyrimidine-2,4-dione (VI) was obtained from chloroenone **II**, complete conversion within 18 h. Yield 62% (*b*). Colorless crystals, mp 240–242°C (MeOH–H_2O, 20:1), R_f 0.39 (chloroform–methanol, 5:1). IR spectrum, ν, cm^{-1}: 3527 (C–N), 3117 (C–N), 1747 (C=O), 1735 (C=O), 1715 (C=O), 1650 (C=C), 1624 (C=C). ^1H NMR spectrum, δ, ppm: 3.01 s (2H, H^{52}), 3.91–4.15 m (4H, $2CH_2O$), 5.81 d.d (1H, H^6, J_1 8.0, J_2 2.0 Hz), 7.63 s (1H, H^5, J_1 8.0 Hz), 11.78 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 46.25 (C^{52}), 65.84 ($2CH_2O$), 102.77 (C^5), 108.37 (C^{42}), 135.25 (C^{22}), 141.85 (C^6), 147.15 (C^{32}), 153.18 (C^2), 162.93 (C^4), 192.74 (C^{12}). Found, %: C 46.58; H 3.35; Cl 12.68; N 9.99. $C_{11}H_9ClN_2O_5$. Calculated, %: C 46.41; H 3.19; Cl 12.45; N 9.84.

1-(5-Chloro-3-phenylsulfonyl-4,4-ethylene-dioxycyclopent-2-en-1-one-2-yl)-1,3-dihydro-pyrimidine-2,4-dione (VII) was obtained from sulfone **III**, complete conversion within 12 h, isolated by column chromatography on SiO_2 of the reaction mixture (eluent chloroform–methanol, 9:1). Yield 65% (*b*). Colorless crystals, mp 280–282°C, R_f 0.34 (chloroform–methanol, 7:3). IR spectrum, ν, cm^{-1}: 3527 (C–N), 3117 (C–N), 1747 (C=O), 1735 (C=O), 1715 (C=O), 1697(C_{arom}), 1650 (C_{arom}), 1624 (C=C), 1385 (SO_2), 1160 (SO_2). ^1H NMR spectrum, δ, ppm: 3.95–4.33 m (4H, $2CH_2O$), 4.24 s (2H, $H^{5'}$), 5.78 d (1H, H^5, *J* 7.9 Hz), 7.25 d (1H, H^6, *J* 7.9 Hz), 7.58–7.70 m (5H, H_{arom}), 7.85 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 63.71 ($C^{5'}$), 65.54 and 65.79 ($2CH_2O$), 105.75 (C^5), 106.99 ($C^{4'}$), 125.47 (C^O), 127.64 (cm), 128.54 (C^n), 127.35 (C^5), 129.00 (C^6), 137.14 (C^θ), 141.40 ($C^{2'}$), 147.94 ($C^{3'}$), 162.41 (C^4), 180.84 ($C^{1'}$). Found, %: C 48.13; H 3.16; Cl 8.14; N 6.40; S 7.42. $C_{17}H_{13}ClN_2O_7S$. Calculated, %: C 48.06; H 3.08; Cl 8.35; N 6.59; S 7.55.

1-(3-Phenylsulfonyl-4,4-ethylenedioxycyclopent-2-en-1-one-2-yl)-1,3-dihydropyrimidine-2,4-dione (VIII) was obtained from sulfone **IV**, complete conversion within 18 h, isolated by column chromatography on SiO_2 of the reaction mixture (eluent chloroform–methanol, 9:1). Yield 44% (*a*), 63% (*b*), Colorless crystals, mp 228–230°C, R_f 0.31 (chloroform–methanol, 7:3). IR spectrum, ν, cm^{-1}: 3190 (NH), 3099 (C–N), 1759 (C=O), 1726 (C=O), 1703 (C=O), 1620 (C_{arom}), 1360 (SO_2), 1150 (SO_2), 1043 (C–O–C). ^1H NMR spectrum, δ, ppm: 2.84 s (2H, $H^{5'}$), 4.05–4.50 m (4H, $2CH_2O$), 5.82 d (1H, H^5, *J* 7.9 Hz), 7.23 d (1H, H^6, *J* 7.9 Hz), 7.61–7.93 m (5H, H_{arom}), 9.25 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 46.44 (C^{52}), 65.20 and 65.42 ($2CH_2O$), 101.14 (C^5), 106.46 (C^{42}), 126.91 (C^O), 128.21 (C^m), 133.67 (C^n), 137.84 (C^θ), 148.15 (C^{22}), 142.10 (C^{32}), 142.15 (C^6), 147.36 (C^2), 162.41 (C^4), 187.20 (C^{12}). Found, %: C 52.41; H 3.77; N 7.35; S 8.03. $C_{17}H_{14}N_2O_7S$. Calculated, %: C 52.30; H 3.61; N 7.18; S 8.21.

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