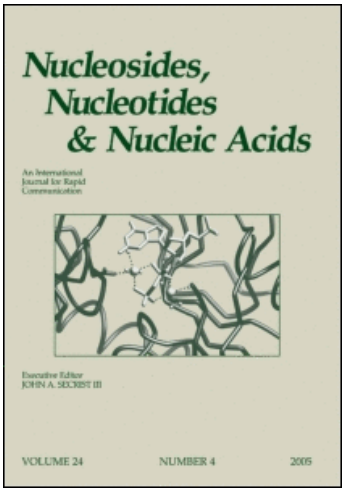

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Structure and Properties of 7,9-Diglycosylguanine - an Unstable Intermediate in Transglycosylation of Guanine Nucleosides

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STRUCTURE AND PROPERTIES OF 7,9-DIGLYCOSYLGUANINE - AN UNSTABLE INTERMEDIATE IN TRANSGLYCOSYLATION OF GUANINE NUCLEOSIDES

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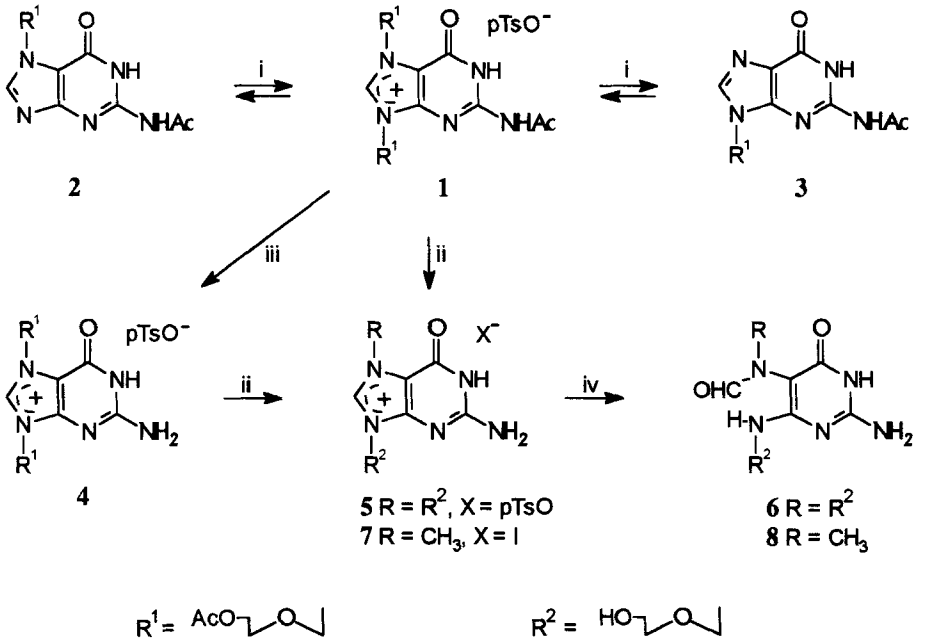
ABSTRACT: 7,9-*bis*[(2-Acetoxyethoxy)methyl]-N^2-acetylguanine (**1**), an unstable intermediate in the 7,→9 transglycosylation of acyclovir, has been isolated and characterized by spectroscopy and chemical degradation.

In line with the generally accepted mechanism, purine bases are initially glycosylated at N3, and the resulting kinetic product undergoes then an irreversible 3→9 transglycosylation *via* a 3,9-diglycosylpurine intermediate to the thermodynamically stable 9-regioisomer.[1] In the case of 6-oxopurine nucleosides, however, the N3 atom does not participate in glycosyl migration reactions.[2-4] Thus, protected derivatives of guanosine and inosine undergo a fully reversible 7,→9 transglycosylation, and only N7 and N9 of the imidazole ring may act as donors or acceptors of a glycosyl cation. Isolation of the reaction intermediate of an anticipated structure of 7,9-diglycosylpurine would be a strong evidence supporting this mechanism. In the ribo series, hipoxanthine derivative of this type was isolated and partially characterized, but a respective guanine analog was too unstable for further study.[5]

Here we report the synthesis of 7,9-*bis*[(2-acetoxyethoxy)methyl]-N^2-acetylguanine (**1**), postulated as a reaction intermediate in the synthesis of the antiviral drug acyclovir. This compound was reportedly present as a minor product in the transpurination of tetraacetyl-guanosine,[2,4] but attempted isolation of **1** from the reaction mixture was unsuccessful due to its instability. In the present work, reaction of 7-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine (**2**) with a 10-fold excess of 2-

acetoxyethyl acetoxymethyl ether using *p*-toluenesulfonic acid as a catalyst gave the fluorescent compound **1**[6] as a minor product (8% after silica gel chromatography), in addition to the main product, diacetylacyclovir (**3**; 28%). Compound **1** underwent decomposition to a mixture of **2** and **3** when heated without solvents (210°C, 5 min) or in chlorobenzene (70°C, 2 h). Deacetylation of **1** with methanolic ammonia gave the deprotected compound **5**,[7] more stable than **1**. Treatment of **5** with NH_4OH for 10 min yielded quantitatively an imidazole ring-opened product **6**.[8] The reaction was much faster than in the case of a model compound, 7-methylacyclovir (**7**),[9] which was completely converted to **8**[10] after 6 h.



SCHEME 1. i, $AcOCH_2OCH_2CH_2OAc$, *p*-TsOH, C_6H_5Cl, 130°; ii, NH_3/MeOH, rt; iii, MeOH, silica gel; iv, NH_4OH, rt.

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REFERENCES

1. Watanabe, K.A.; Hollenberg,, D.H.; Fox, J.J., *J. Carbohydrates Nucl. Nucl.* **1974**, *1* 1.
2. Boryski, J.; Golankiewicz, B., *Nucleosides Nucleotides,* **1989**, *8*, 529.

3. Boryski, J., *Nucleosides Nucleotides,* **1996**, *15*, 771.
4. Boryski, J., *J. Chem. Soc., Perkin Trans. 2,* **1997**, 649.
5. Dudycz, L.W., Wright, G.E., *Nucleosides Nucleotides,* **1984**, *3*, 33.
6. **1**: ^{1}H NMR (all samples in DMSO-d_6, TMS): δ 9.88 (s, 1, 8-H), 5.92 (s, 2, 7-CH_2), 5.68 (s, 2, 9-CH_2). ^{13}C NMR: 137.9 (C-8), 77.4 (7-CH_2), 74.5 (9-CH_2). LSIMS HR (glycerol) calcd. MH^+ for $C_{17}H_{24}N_5O_8$ 426.1625; found 426.1631.
7. **5**: λ_{max} (H_2O) 256, 281 nm. ^{1}H NMR: δ 9.48 (s, 1, 8-H), 5.86 (s, 2, 7-CH_2), 5.56 (s, 2, 9-CH_2). ^{13}C NMR: 135.3 (C-8), 77.3 (7-CH_2), 73.9 (9-CH_2). LSIMS HR (NBA) calcd. MH^+ for $C_{11}H_{18}N_5O_5$ 300.1308; found 300.1314.
8. **6**: λ_{max} (H_2O) 218, 270 nm. ^{1}H NMR: δ 8.27 and 7.85 (2s, total 1, NCHO – two rotamers).
9. Boryski, J., Golankiewicz, B., De Clercq, E., *J. Med. Chem.,* **1988**, 31, 1351.
10. **8**: λ_{max} (H_2O) 217, 271 nm. ^{1}H NMR: δ 8.04 and 7.72 (2s, total 1, NCHO – two rotamers).