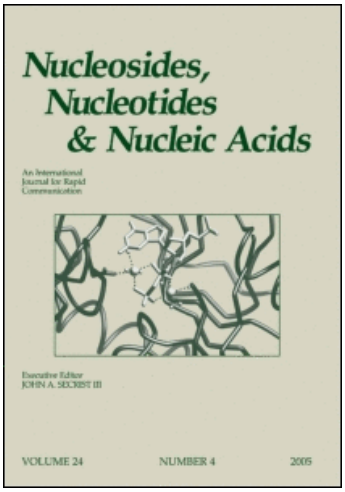

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DEPROTECTION STUDIES OF ETHANOIC ACID 5,6,7,9-TETRAHYDRO-3-/2-(ACETOXYETHOXY) METHYL-5-O-ACETYL-9-OXO-3H-IMIDAZO/1,2a/ PURINE-6,7-DIOYOL ESTER (1) AND RELATED GLYOXAL-GUANINE ADDUCTS

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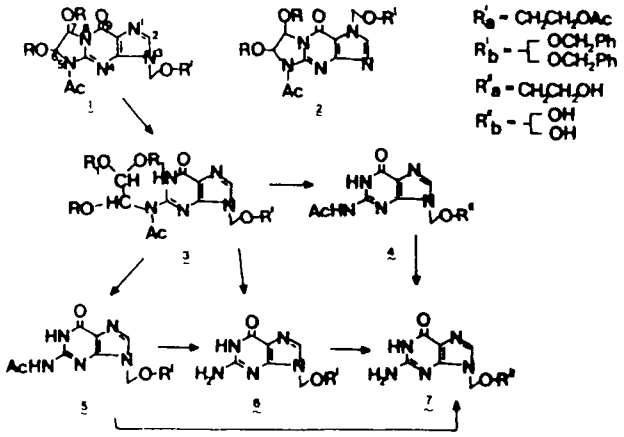
Abstract: *Selective deprotection of fully protected 1 was achieved via sodium methoxide or cyanide catalyzed removal of acetate groups. The glyoxal protecting group diminished nucleophylisity of N7 regardless of the blocking of N1 position in guanine.*

In current oligodeoxyribonucleotide synthesis the side reaction at the amide function of the guanine moiety was recently prevented by bis(isobutyryloxy)ethylene (Bibe) group which was very suitable for further processing either by phosphotriester methods or via phosphor amidite[2,3]. *Unconventional building blocks could be alternatively prepared by using protected heterocyclic bases as synthons. Thus bis(acetoxy)ethylene protecting group on guanine itself was used to yield intermediate 1, a fully protected acyclovir or gancyclovir in good yields*[1]. *These model intermediates were further selectively deprotected and the protonation studies were performed in order to investigate the efficiency of this protection of the guanine residue against an electrophile*[4].

A complete deprotection of 1 was readily achieved in conc. sodium hydroxide or methanolic ammonia. A search for milder conditions was initiated with final objective to selectively remove by subtle variations of conditions the different acyl groups. Thus sodium



methoxide (5) was used first and it resulted in 4a and 5a when used in cat. ammounts that was not in a satisfactory selectivity or speed. Therefore a cyanide catalyzed removal of acetate groups in KCN in MeOH was attempted [6]. The data promted a thorough NMR study

TABLE: ^{15} *N-chemical shifts in neutral and acidic media and coupling constants of compounds 1a, 1b, 2a and 2b*

Compound	N-3	N-4	N-1	N-8	N-5
1a	-206.80	-201.82	-130.28	-215.87	-229.10
	(8.51)	/	(11.4)	(2.4)	(2.2)
1 eq TFA	-205.60	-202.07	-152.86	-215.21	-229.16
1b	-204.70	-201.15	-131.49	-216.29	-229.37
	(8.5)	/	(12.5)	(2.2)	(2.4.)
1 eq TFA	-205.35	-203.72	(-152.97)*	-217.24	-230.84
2a	-127.63	-183.15	-208.36	-216.03	-229.38
	(11.5)	/	(7.3)	(1.5)	(2.3)
1 eq TFA	-187.9	-190.36	-208.34	-216.80	-230.85
2b	-130.10	-183.96	-207.53	-217.32	-230.35
	(12.16)	/	(7.5)	(1.8)	(2.3)
1 eq TFA	-164.22	-191.85	-205.24	-217.03	-230.83

Notes: Measurements were carried at RT in 0.55 M $CDCl_3$ solution for 1a, 0.6 M for 1b, 0.65 M for 2a and 0.66 M for 2b. Chemical shifts are reported in ppm with respect to $CH_3{}^{15}NO_2$, $^2J_{N,H}$ coupling constants are in Hz.

which revealed the following scheme via intermediate 3 as detected by ^{1}H NMR. 3 accordingly to scheme afforded 7 via 4a, 5a or 6a[7]. According to several earlier uses of cyanide - catalyzed esterifications O-acyl deprotection was expected to precede. Unexpectedly N-deacylation appeared to be the first step after the removal of glyoxal, what was proven by an independent experiment using 5 [7], which was followed by HPLC under this condition, and which clearly showed stepwise removing of acetyl group from 5a to 6a and finaly to 7a.

^{15}N assignments of protected models are shown in Table 1 including the protonation studies. The observed values of $^{2}J_{N(8)H(7)}$ or $^{2}J_{N(5)H(6)}$ in 1 and 2 are small suggesting a trans relationship between two protons in a fused 5 - membered ring in a nonplanar relation preventing a perfect delocalization of N5 lone pair to the rest of the system. The dependence of ^{15}N chemical shifts of the eqiv. of added CF_3COOH support these findings in terms of diminished nucleophylicity of the N7 position regardless of the blocking of N1 position in guanine, which is of a comparable magnitude to the N^2 acylated derivatives.

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7. Full deprotection: 540 mg (1 mmole) of 1 was added to a solution of 7 mmoles of NaOH in 15 ml H_2O and the resulting mixture stirred for 4 h, then neutralized with conc. HCl and the solid filtered to yield 182 mg (81 %) of 7a. Selective deprotection experiment: 5a (300 mg, 0.7 mmoles) was dissolved in 20 ml of 1:1 mixture of MeOH - acetone, KCN (8 mg, 0.12 mmoles) was added and the reaction immediatelly followed by injection in LDC/Milton Roy apparatus (Spherisorb Si) column on gradient solvent delivery system A (900 ml H_2O, 100 ml MeOH, 0.005 M PIC) and B (1000 ml of MeOH, 0.005 M PIC) from 5 % A to the 90 % of solvent B with 1.5 ml/min flow rate. Starting time (1 min., run time 10.13 for 3 (4.12 %) and for 1 12.08 (73 %), 3 h, (3, 11.92 %, 1, 58 %); 40 h (3, 40.7 %, 1, 33.58 %). Solvent was evaporated after 68 h to give a mixture of products with 3 (55 %), Mass, m/z=455 (M^+), consistent with ^1H assignment for 3: DMSO-d_6 δ -(7.95, s, 1H H8; 6.6, s 1H, CH; 5.42, s, 2H, H1'; 5.08, s, 1H, CH; 3.37, s, 6H, OCH_3; 2.11, 2.09, 1.96, 1.85, m, 9H, CH_3CO).