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REGIOSELECTIVE ALKYLATION OF 6-(β-METHOXYETHOXY)GUANINE TO GIVE THE 9-ALKYLGUANINE DERIVATIVE

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Abstract. In the presence of lithium hydride 6-(β-methoxyethoxy)guanine reacts regioselectively with 4-bromobutyl acetate to give the 9-alkylguanine derivative.

In connection with our work on the antiherpes compound buciclovir ((R)-9-(3,4-dihydroxybutyl)guanine)[1] we have studied the alkylation of various types of guanine precursors. Alkylation of 6-chloroguanine with 1-bromobutanes containing various functional groups as well as alkylation with other halides gave a 4:1 mixture of the 9- and 7-isomers[2]. Recently we have reported the regioselective alkylation of guanine via diacyloxyglyoxal-N^2-acetylguanine to obtain 7-alkylguanine derivatives[3].

We now present a selective way of synthesizing 9-(4-hydroxybutyl)guanine[4] (4), a compound with antiviral properties[5]. We have studied the alkylation of 6-butoxyguanine (1a), 6-(β-methoxyethoxy)guanine (1b) and 6-benzyloxyguanine (1c) with 4-bromobutyl acetate under various conditions and we have found the distribution between the two N9 and N7 alkylated products to be strongly dependent on the substituent at the 6-position of guanine, the choice of the base used in the reaction, and on the reaction temperature. Alkylation of 6-(β-methoxyethoxy)guanine with 4-bromobutyl acetate in the presence of lithium hydride at 80 °C gave the desired 9-substituted compound in an excess of 15:1 relative to the 7-substituted isomer. Hydrolysis in 3 M HCl gave 4 in high yield (~90 %).

The compounds 1a and 1b were prepared from 6-chloroguanine[6] by nucleophilic displacement of the chlorine by sodium n-butoxide or sodium β-methoxyethoxide (Reflux 18 h, 7 eq of Na in n-butanol/β-methoxyethanol). Removal of inorganic salts by filtration and neutralization (pH 5) with 1 M HCl followed by evaporation and purification (flash chromatography, EtOAc with increasing amounts of EtOH) gave 3.0 g (83 %) of 1a[7] and 2.8 g (75 %) of 1b[8], respectively. The analogous compound 1c was prepared according to described methods[9],[10].

For the reaction with 4-bromobutyl acetate, alkali metal hydrides and carbonates were used as bases and the reaction conditions and results are summarized in the table. The alkylations were followed by TLC (Merck 60 F, $CHCl_3$/MeOH 9:1) and after 2-14 h no starting material was left. The alkylations were performed in analogy with the following two examples.

Alkylation of 1a in the presence of potassium carbonate: One mmol of 1a was dissolved in dry DMF (25 ml) and potassium carbonate (5 eq) was added. After stirring at 20 °C for 0.5 h 4-bromobutyl acetate (1 eq) was added and the reaction took place overnight at 80 °C under N_2.

The salts were filtered off and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml) and filtered. After evaporation of the solvent the product was analyzed by ^1H NMR[11] and the ratio of the N9 and N7 isomers were determined from the integral values of their respective NH_2 and H-8 signals. The two alkylated products were separated on a silica gel column by flash chromatography (gradient eluent 0-10 % MeOH in $CHCl_3$) to give 121 mg (38 %) of 9-(4-acetoxybutyl)-6-butoxyguanine, 2a[12], and 116 mg (36 %) of 7-(4-acetoxybutyl)-6-butoxyguanine, 3a[13].

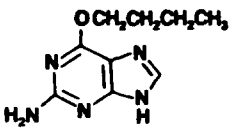
Alkylation of 1b in the presence of lithium hydride: One mmol of 1b was dissolved in dry DMF (25 ml) and lithium hydride (~1.5 eq) was added under dry N_2. The suspension was stirred for 0.5 h at 20 °C and then 4-bromobutyl acetate (1 eq) was added. The reaction was heated (80 °C) for 2 h. Water (~3 ml) was added and the solvent was removed under reduced pressure. The residue was treated with ethyl acetate (10 ml) and insoluble material was removed. NMR showed that the two products 2b[14] and 3b[15] were formed in a ratio 15:1. After chromatography the yield of 2b[14] was 198 mg (61 %).
A substantial amount of the compound 3b[15] was isolated by flash chromatography (gradient eluent 0-10 % MeOH in $CHCl_3$) from the reaction mixture where sodium hydride had been used as a base.

The synthesis of 2c[16] and 3c[17] were performed similarly.

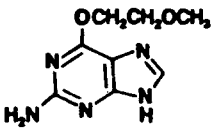
Base[e,f]	Temp. (°C)	Ratio N9/N7[a] 2a/3a	2b/3b	2c/3c
LiH[b]	20	10	10	-
LiH	80	8	15	6
NaH[b]	20	1.5	2	-
NaH[b]	80	2	3	4
KH[b]	80	1.5	3	-
Na_2CO_3[c,d]	20	1	1.5	2
K_2CO_3[c,d]	20	1	2	4
K_2CO_3	80	1	3	-
CaH_2[b]	20	1	3	-

[a] Determined by ^1H NMR (H-8, integral value). [b] Performed as for lithium hydride at 80 °C. [c] Performed as for potassium carbonate at 80 °C. [d] The reactions at 20 °C were slow and the conversions were 50-80 % after 14 h. [e] No sign of reaction in the presence of N,N'-dimethylpiperazine. [f] The reactions in the presence of Li_2CO_3 were very slow.

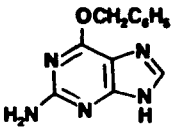
These alkylated 6-substituted guanine precursors were readily hydrolyzed in 3 M HCl at 85 °C for 3 h to give the deprotected nucleosides 4[4] and 5[18]. They were purified by recrystallization from water and analyzed by NMR, UV and MS[19].



1a

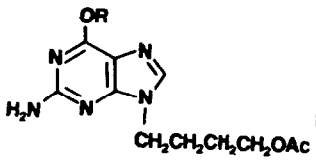


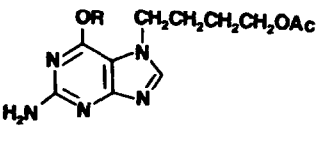
1b

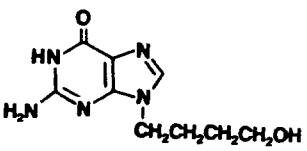


1c

2a 3a R = $CH_2CH_2CH_2CH_3$
2b 3b R = $CH_2CH_2OCH_3$
2c 3c R = $CH_2C_6H_5$







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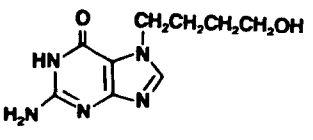

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References and Notes

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3. J. Kjellberg and N.G. Johansson. Manuscript submitted for publication in J. Heterocyclic Chem.
4. A. Yamazaki, Chem. Pharm. Bull. 17, 1268 (1969).
5. A. Larsson, S. Alenius, N.G. Johansson and B. Öberg. Antiviral Res. 3, 77 (1983).
6. Purchased from Sigma, Chemical Company, P.O. Box 14508, St. Louis, MO 63178, U.S.A.
7. 1a, ^{1}H NMR δ 0.94 (t, 3H, CH_3), δ 1.45 (m, 2H, CH_2), δ 1.74 (m, 2H, CH_2), δ 4.39 (t, 2H, OCH_2), δ 6.18 (s, 2H, NH_2), δ 7.80 (s, 1H, H-8); ^{13}C NMR δ 13.87 (C4''), δ 18.90 (C3''), δ 30.73 (C2''), δ 66.17 (C1''), δ 111.00 (C5), δ 139.65 (C8), δ 154.83 (C4), δ 159.09 (C6), δ 160.01 (C2); UV (nm) λ_{max} = 286 (pH 1), λ_{max} = 239,281 (pH 7), λ_{max} = 283 (pH 13); m.p. (°C) = 124-126; MS m/e = 207.
8. 1b, ^{1}H NMR δ 3.31 (s, 3H, OCH_3), δ 3.69 (t, 2H, OCH_2), δ 4.52 (t, 2H, OCH_2), δ 6.63 (s, 2H, NH_2), δ 7.80 (s, 1H, H-8); ^{13}C NMR δ 58.36 (C3''), δ 64.78 (C2''), δ 70.42 (C1''), δ 113.74 (C5), δ 138.02 (C8), δ 155.37 (C4), δ 159.92 (C6), δ 160.31 (C2); UV (nm) λ_{max}= 287 (pH 1), λ_{max} = 240,281 (pH 7), λ_{max} = 289 (pH 13), m.p. (°C) = 203-204; MS m/e = 209.
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11. The NMR spectra were recorded with a Jeol JNM-FX 200 in DMSO-d_6.

12. 2a, ^{1}H NMR δ 0.92 (t, 3H, CH_3), δ 1.35-1.51 (m, 4H, CH_2), δ 1.68-1.80 (m, 4H, CH_2), δ 1.98 (s, 3H, $COCH_3$), δ 3.99 (m, 4H, NCH_2 and CH_2OCO), δ 4.39 (t, 2H, OCH_2) δ 6.37 (s, 2H, NH_2), δ 7.87 (s, 1H, H-8); ^{13}C NMR δ 13.77 (C4''), δ 18.88 (C3''), δ 20.80 ($\underline{C}H_3CO$), δ 25.54 (C3'), δ 26.06 (C2'), δ 30.77 (C2''), δ 42.45 (C1'), δ 63.44 (C4'), δ 65.54 (C1''), δ 114.09 (C5), δ 139.77 (C8), δ 154.42 (C4), δ 159.94 (C6), δ 160.72 (C2), δ 170.50 (CO); UV (nm) λ_{max} = 241, 290 (pH 1), λ_{max} = 250, 282 (pH 7), λ_{max} = 289 (pH 13); m.p. (°C) = 82.5-84.5; MS m/e = 321.

13. 3a, ^{1}H NMR δ 0.95 (t, 3H, CH_3), δ 1.45-1.60 (m, 4H, CH_2), δ 1.72-1.85 (m, 4H, CH_2), δ 1.98 (s, 3H, $COCH_3$), δ 4.00 (t, 2H, CH_2OCO), δ 4.22 (t, 2H, NCH_2), δ 4.44 (t, 2H, OCH_2), δ 6.10 (s, 2H, NH_2), δ 8.08 (s, 1H, H-8); ^{13}C NMR. δ 13.67 (C4''), δ 18.88 (C3''), δ 20.75 ($\underline{C}H_3CO$), δ 25.28 (C3'), δ 27.30 (C2'), δ 30.48 (C2''), δ 46.61 (C1'), δ 63.37 (C4'), δ 66.24 (C1''), δ 105.96 (C5), δ 145.32 (C8), δ 157.58 (C4), δ 158.80 (C6), δ 160.86 (C2), δ 170.40 (CO); UV (nm) λ_{max} = 288 (pH 1), λ_{max} = 289 (pH 7), λ_{max} = 289 (pH 13); m.p. (°C) = 99-101; MS m/e = 321.

14. 2b, ^{1}H NMR δ 1.56-1.81 (m, 4H, CH_2CH_2), δ 1.99 (s, 3H, $COCH_3$), δ 3.31 (s, 3H, OCH_3), δ 3.69 (t, 2H, $\underline{CH_2}OCH_3$), δ 3.97-4.07 (m, 4H, NCH_2 and CH_2OCO), δ 4.53 (t, 2H, OCH_2), δ 6.45 (s, 2H, NH_2), δ 7.93 (s, 1H, H-8); ^{13}C NMR δ 20.95 (CH_3CO), δ 25.59 (C3'), δ 26.10 (C2'), δ 42.57 (C1'), δ 58.36 (C3''), δ 63.54 (C4'), δ 64.90 (C2''), δ 70.38 (C1''), δ 113.75 (C5), δ 140.16 (C8), δ 154.52 (C4), δ 159.96 (C6), δ 160.40 (C2), δ 170.64 (CO); UV (nm) λ_{max} = 242-290 (pH 1), λ_{max} = 249, 281 (pH 7), λ_{max} = 249, 281 (pH 13); m.p. (°C) = 103-105; MS m/e = 323.

15. 3b, ^{1}H NMR δ 1.55-1.90 (m, 4H, CH_2CH_2), δ 1.98 (s, 3H, $COCH_3$), δ 3.31 (s, 3H, OCH_3), δ 3.70 (t, 2H, $\underline{CH_2}OCH_3$), δ 3.99 (t, 2H, CH_2OCO), δ 4.18 (t, 2H, NCH_2), δ 4.53 (t, 2H, OCH_2). δ 6.12 (s, 2H, NH_2), δ 8.08 (s, 1H, H-8); ^{13}C NMR δ 20.80 ($\underline{C}H_3CO$), δ 25.33 (C3'), δ 27.34 (C2'), δ 46.39 (C1'), δ 58.26 (C3''), δ 63.47 (C4'), δ 64.78 (C2''), 70.28 (C1'), δ 105.89 (C5), δ 145.56 (C8), δ 156.71 (C4), δ 159.72 (C6), δ 164.20 (C2), δ 170.47 (CO); UV (nm) λ_{max} = 287 (pH 1), λ_{max} = 288 (pH 7), λ_{max} = 289 (pH 13: m.p. (°C) = 95.5-98; MS m/e = 323.

16. 2c, ^{13}C NMR δ 20.8 ($\underline{C}H_3CO$), δ 25.6 (C3'), δ 26.1 (C2'), δ 42.5 (C1'), δ 63.5 (C4'), δ 68.5 (C1''), δ 113.7 (C5), δ 126.5-137.0 (6 benzylic), δ 140.1 (C8), δ 155.0 (C4), 160.4 (C2), δ 160.4 (C6), δ 170.5 (CO).

17. 3c, ^{13}C NMR δ 21.0 ($\underline{C}H_3CO$), δ 25.5 (C3'), δ 27.5 (C2'), δ 46.6 (C1'), δ 63.3 (C4'), 67.3 (C1''), δ 107.8 (C5), δ 126.8-136.9 (6 benzylic), δ 146.5 (C8), δ 157.0 (C6), δ 160.3 (C2), δ 165.1 (C4), δ 170.4 (CO).

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