Short Communication

Studies on the Alkylation of Guanine. 2.* The Synthesis of Acyclic Guanosine Analogs via the Precursor 7-Methyl-10-oxo-9,10-dihydropyrimido[1,2-a]purine

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In connection with our work on the antiherpes compound buiclovir ((R)-9-(3,4-dihydroxybutyl)guanine) we studied the alkylation of various types of guanine precursors. Buciclovir and the analogous compound 9-(4-hydroxybutyl)guanine (4) were prepared by condensation of 2-amino-6-chloropurine and the proper halide. As part of our studies on the regioselective alkylation of guanine precursors we followed Leonard’s procedure2 for preparing 7-methyl-10-oxo-9,10-dihydropyrimido[1,2-a]purine (I) by condensation of guanine and methylmalondialdehyde3,4 in 1 M HCl. This tricyclic aromatic structure was alkylated with 4-bromobutyl acetate in the presence of different bases and a 1:1 mixture of the N9-isomer (2) and the N7-isomer (3) were obtained.

This result seemed to be independent of the choice of base in contrast to related alkylations reported by us,4 where we found a strong influence of the base on the relative formation of the N9- and the N7-isomers. We obtained high yields (>90 %) by using one or three equivalents of potassium carbonate or sodium hydride. The alkylations in the presence of triethylaline, thallium (I) ethoxide or lithium disopropyl amide were performed under similar conditions. The yields were lower (about 20 % according to RP-HPLC; MeOH/H2O 50/50) but the distribution between the two isomers was not changed.

The products (2 and 3) were separated by flash column chromatography and readily hydrolyzed to 9-(4-hydroxybutyl)guanine (4)* and 7-(4-hydroxybutyl)guanine (5). The antiviral activity of compound 4 has been described.7

Experimental

Melting points were obtained on a Büchi 510 and are uncorrected. The NMR spectra were recorded by a Jeol JNM-FX 200. The mass spectra were recorded on an LKB 9000 (70 eV). For RP-HPLC analysis we used a Waters 440, RCM-100. The elementary analysis was performed by Novo Microanalytical Laboratory, Novo Allé, DK-2880 Bagsværd, Denmark. All bases, solvents and starting materials were of highest purity available. The solvents were dried over molecular sieves and triethylaline was distilled before use. The reactions were performed under dry nitrogen atmosphere. Sodium hydride (55 % dispersed in oil) was treated with hexane (2 ml) before use. Lithium diisopropylamide was generated in situ from freshly distilled diisopropylamine (1 eq.) and BuLi (1 eq., 15 % in n-hexane) in tetrahydrofuran (5 ml) at −20°C in 20 min. Thallium (I)-ethoxide (98 %) was purchased from Aldrich-Chemie.

General procedure: One half mmol (101 mg) of I was dissolved in 20 ml of N,N-dimethylformamide (DMF). The base (1 eq. or 3 eq.) and,

*Part 1. See Ref. 4.
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after 15 min, the halide (4-bromobutyl acetate, 1 eq.) were added. The condensation took place at 20°C overnight and was monitored by TLC (CHCl₃/McOH 7:1) and HPLC.

7-Methyl-10-oxo-9,10-dihydropyrimido[1,2-al]purine (I) was prepared in accordance with Mosc and Leonard.³ To a solution of 1.2 g of guanine in 80 ml of 1 M HCl was added 3.5 eq. of methylmalondialdehyde and the resulting solution was stirred at 45°C for 24 h. The yellow precipitate was washed with EtOH and water to give 1.1 g (69%) of I.

³¹H NMR (DMSO-d₆) δ 2.40 (d, 3H, 7-CH₃), δ 8.30 (s, 1H, 2-H), δ 8.93 (d, 1H, 6-H), δ 9.15 (q, 1H, 8-H); ³¹C NMR (DMSO-d₆) δ 14.84 (6-CH₃), δ 115.69 (C10a), δ 119.37 (C7), δ 133.60 (C8), δ 142.35 (C2), δ 147.95 (C3a), δ 151.82 (C4a), δ 152.84 (C10), δ 163.35 (C6); Found: C 53.49; H 3.49; N 34.15. Calcd. for C₉H₁₇N₃O: C 53.73; H 3.51; N 34.81. MS; m/z = 201; UV(nm) λ_max = 218, 247, 312, 342 (pH 1).

Synthesis of 3-(4-acetoxybutyl)-7-methyl-10-oxo-9,10-dihydropyrimido[1,2-a]purine (2) and 1-(4-acetoxybutyl)-7-methyl-10-oxo-9,10-dihydropyrimido[1,2-a]purine (3). One half mmol (101 mg) of I was dissolved in 20 ml of DMF. Potassium carbonate (2.5 mmol, 345 mg) and 4-bromobutyl acetate (0.5 mmol, 144 µl) were added. The suspension was stirred under nitrogen for 16 h after which no starting material was left according to RP-HPLC (MeOH/H₂O, 50/50). The two products separated completely and were formed in equivalent amounts. The inorganic salts were filtered off and the solvent was removed in vacuo. The residue was suspended in ethyl acetate (10 ml) and a brown solid precipitated. This insoluble part was filtered off. Ethyl acetate was removed by evaporation and the mixture of 2 and 3 was separated on a silica gel column by flash chromatography (eluent CHCl₃/MeOH 10:1) to give 74 mg (47%) of compound 2 and 74 mg (47%) of compound 3.

The interpretations of the ³¹H NMR spectra of the compounds 2 and 3 were somewhat complicated. The peak from the 7-methyl group was split to a doublet (J ± 1.2 Hz). The 6-H peak was also split to a doublet by long-range coupling (J = 3.0 Hz, compound 2; J = 2.8 Hz, compound 3). The 8-H signal showed double quartets (J = 1.2 Hz), which indicates long-range coupling both to the 7-methyl group and to the proton attached to C8. The protons and the carbon atoms were assigned by off-resonance measurements and were consistent with published data.⁸
2. 'H NMR (CDCl₃) δ 1.60-2.05 (m, 4H, CH₂CH₂), δ 2.00 (s, 3H, COCH₃), δ 2.43 (d, 3H, 7-CH₃), δ 4.06 (t, 3H, OCH₃), δ 4.30 (t, 3H, NCH₃), δ 7.91 (s, 1H, 2-H), δ 8.81 (d, 1H, 6-H), δ 9.20 (o, 1H, 8-H); ¹³C NMR (CDCl₃) δ 15.32 (7-CH₃), δ 20.95 (COCH₃), δ 26.05 (C₃), δ 27.07 (C₂), δ 43.69 (C₁), δ 63.56 (C₄), δ 118.68 (C₁₀a), δ 119.39 (C₇), δ 134.45 (C₈), δ 141.67 (C₂), δ 148.58 (C₃a), δ 150.09 (C₄a), δ 152.59 (C₁₀), δ 163.00 (C₆), δ 170.96 (C₁₀); Anal. for C₇H₁₇N₂O₃; m/z = 315. m.p. = 122°C; UV(nm) λₘₐₓ = 220, 249, 313 (pH 1).

3. 'H NMR (CDCl₃) δ 1.61-2.12 (m, 4H, CH₂CH₂), δ 2.02 (s, 3H, COCH₃), δ 2.44 (d, 3H, 7-CH₃), δ 4.09 (t, 3H, OCH₃), δ 4.51 (t, 3H, NCH₃), δ 8.08 (s, 1H, 2-H), δ 8.83 (d, 1H, 6-H), δ 9.03 (o, 1H, 8-H); ¹³C NMR (CDCl₃) δ 15.47 (7-CH₃), δ 21.02 (COCH₃), δ 25.74 (C₃), δ 28.29 (C₂), δ 47.19 (C₁), δ 63.59 (C₄), δ 110.28 (C₁₀a), δ 119.24 (C₇), δ 132.52 (C₈), δ 146.58 (C₂), δ 147.92 (C₃a), δ 150.43 (C₄a), δ 159.09 (C₁₀), δ 162.56 (C₆), δ 171.03 (C₁₀); Anal. for C₇H₁₇N₂O₃; m/z = 315. m.p. = 130°C; UV(nm) λₘₐₓ = 220, 248, 313 (pH 1). Synthesis of 9-(4-hydroxybutyl)guanine (4). One tenth mmol (32 mg) of compound 2 was treated with 0.1 M NaN₃ (10 ml) overnight. After neutralization with 1 M HCl white crystals of 9-(4-hydroxybutyl)guanine (18 mg, 80%) were isolated by filtration. The retention time (RP-HPLC, MeOH/H₂O 20/80) of 3 was identical with an authentic sample.

4. 'H NMR (DMSO-d₆) δ 1.3-1.5 (m, 2H, CH₂), δ 1.6-1.8 (m, 2H, CH₂), δ 3.97 (t, 2H, OCH₂), δ 4.50 (t, 2H, NCH₂), δ 6.49 (s, 2H, NH₂), δ 7.72 (s, 1H, H-8); ¹³C NMR (DMSO-d₆) δ 26.9 (C₂), δ 30.0 (C₃), δ 43.1 (C₁), δ 60.7 (C₄), δ 117.1 (C₅), δ 138.0 (C₆), δ 151.6 (C₄), δ 153.9 (C₂), δ 157.4 (C₆); Anal. for C₇H₁₇N₂; m/z = 223. UV(nm) λₘₐₓ = 253, 278 (pH 1), λₘₐₓ = 268 (pH 13).

The method for synthesis of 4 above was followed to give 14 mg (63%) of 7-(4-hydroxybutyl)guanine (5).

5. 'H NMR (DMSO-d₆) δ 1.2-1.5 (m, 2H, CH₂), δ 1.7-1.9 (m, 2H, CH₂), δ 3.39 (t, 2H, OCH₂), δ 4.19 (t, 2H, NCH₂), δ 6.05 (s, 2H, NH₂), δ 7.87 (s, 1H, H-8); ¹³C NMR (DMSO-d₆) δ 27.5 (C₂'), δ 29.4 (C₃'), δ 46.2 (C₁'), δ 60.4 (C₄'), δ 108.3 (C₅), δ 143.2 (C₈), δ 152.9 (C₂), δ 154.7 (C₆), δ 160.0 (C₄); Anal. for C₇H₁₇N₂; m/z = 223. UV(nm) λₘₐₓ = 250 (pH 1), λₘₐₓ = 279 (pH 13).

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