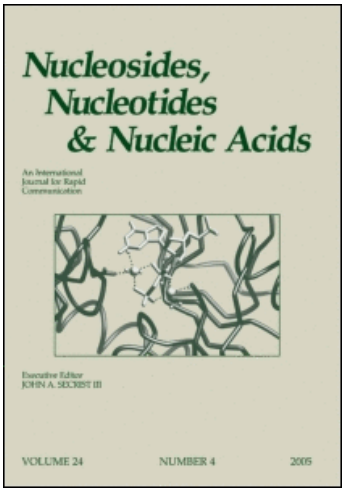

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Addition of 2,3-Dihydrofuran to N_2-Acetyl-8-bromoguanine

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ADDITION OF 2,3-DIHYDROFURAN TO N_2-ACETYL-8-BROMOGUANINE

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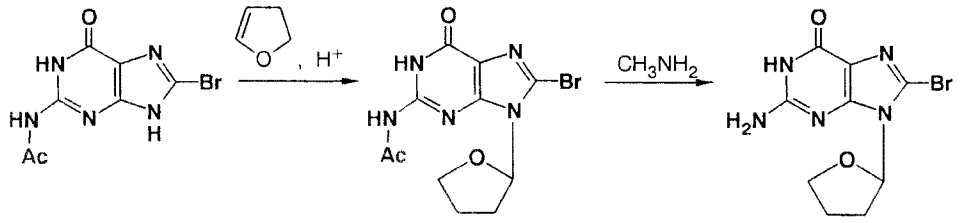
Abstract: N_2-Acetyl-8-bromoguanine has been found to react readily with 2,3-dihydrofuran in DMF in the presence of acid catalyst at room temperature to give 9-(tetrahydrofuryl-2)-8-bromo-N_2-acetylguanine in high yield. The structures of this compound and its deacetylated derivative were assigned by ^1H and ^{13}C NMR spectroscopy.

Some 9-substituted 8-bromo- and 8-aminoguanines as well as 9-deazaguanines have been found to be potent inhibitors of PNP and to possess immunomodulating properties [1,2]. Recently the inhibition of human O^6-Alkylguanine DNA-alkyltransferase by 9-substituted and 9,8-disubstituted O^6-benzylguanines has been established [3]. The biological activities of 7-substituted guanines are far less studied although it has been shown that 7-β-D-ribosides of guanine and hypoxanthine are substrates for PNP from human erythrocytes, calf spleen and E-coli and some 7-substituted guanines are twofold more potent PNP inhibitors than their N_9-counterparts [4].

This encouraged us to search more convenient routes for the synthesis of substituted guanines with special emphasis on 7,8-disubstituted compounds and to evaluate them for immunosuppressive and anticancer activities. We studied the alkylation of N_2-acetyl-8-bromoguanine under different reaction conditions. It has been shown that alkylation of N_2-acetyl-8-bromoguanine with benzylbromide or α-chloroethers with or without K_2CO_3 as well as with α-acetoxyethoxyethers in the presence of p-toluenesulfonic acid results in high yields (70-80%) of N-alkylated-N_2-acetyl-8-bromoguanines [5]. Unfortunately, the reactions lacked regioselectivity and yielded mixtures of 7- and 9-monoalkyl as well as bisalkyl derivatives of N_2-acetyl-8-bromoguanine. Besides, the hydrolysis of 8-bromo atom to oxo group as well as bromine substitution for chlorine were observed under certain

reaction conditions. 6-Substituted purines with electron acceptor groups in the position 6 have been shown to react with 2,3-dihydrofuran and 2,3-dihydropyran under acid conditions to afford 9-alkoxyalkyl-6-substituted purines [6]. We have used the reaction of 6-chloro- and 6-methylthiopurines with α-vinylethyl and α-vinylbutyl ethers to obtain 9-(1-alkoxyethyl-1)-6-substituted purines [7]. However, corresponding guanine derivatives could be obtained only indirectly via 2-acetamido-6-chloropurine [8].

We have found that N_2-acetyl-8-bromoguanine (I) reacts readily with 2,3-dihydrofuran in DMF in the presence of p-toluenesulfonic acid or hydrogen chloride at room temperature to give 85% yield of 9-(tetrahydrofuryl-2)-8-bromo-N_2-acetylguanine (II). No other alkylation products have been detected in this case. Deacetylation of the guanine II with methylamine water solution afforded 9-(tetrahydrofuryl-2)-8-bromo-guanine (III).



I II III

The structures of II and III were assigned by ^1H and ^{13}C NMR spectroscopy. ^{13}C Chemical shifts of C-5 and C-8 when compared with N_9- and N_7-benzyl-8-bromoguanines confirmed the structure of compound II as the N_9-substituted guanine. We failed to perform similar reactions with 2,3-dihydropyran or α-vinylalkylethers so far.

Although the substitution of hydrogen at the imidazole nitrogen for the tetrahydrofuryl moiety was expected to increase the solubility of the product II compared with that of the substrate I this appeared not to be the case. Guanine II was less soluble in DMF than the starting compound I and precipitated readily from the reaction mixture. Moreover, it was hardly soluble both in water and in any organic solvent used. The compounds obtained may serve as intermediates for 8-substituted-9-(tetrahydrofuryl-2)guanines possessing useful biological properties.

EXPERIMENTAL

9-(Tetrahydrofuryl-2)-8-bromo-N_2-acetyl-guanine (II). 2,3-Dihydrofuran (1.75 g; 25 mmol) was added to the solution of I (1.36 g; 5 mmol) and p-toluenesulfonic acid monohydrate (0.14 g; 0.7 mmol) in 30 ml of DMF. After 10 minutes at room temperature a white precipitate appeared. The mixture was stirred at room temperature overnight and neutralized by 2 ml of $(C_2H_5)_3N$. The precipitate was filtered, washed thoroughly with cold water, dried to provide 1.33 g of II (85% yield): m.p.>300°C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 2.04 (1H, m, CH-4'), 2.23 (3H, s, CH_3), 2.45 (1H, m, CH-3'), 2.52 (1H, m, CH-4'), 2.66 (1H, m, CH-3'), 3.94 (1H, m, CH-5'), 4.23 (1H, m, CH-5'), 6.16 (1H, m, NCH-2'), 11.48 (1H, br.s, NH), 12.13 (1H, br.s, NH). ^{13}C NMR (400 MHz, DMSO-d_6) δ, ppm 23.9 (CH_3), 25.1 (C-4'), 29.7 (C-3'), 69.4 (C-5'), 86.9 (C-2'), 120.9 (C-5), 123.4 (C-8), 147.4 (C-2), 149.2 (C-4), 153.5 (C-6), 173.5 (CO). Anal.Calcd. for $C_{11}H_{12}N_5BrO_3$: C, 38.61; H, 3.54; N, 20.47. Found: C, 38.52; H, 3.47; N, 20.40.

9-(Tetrahydrofuryl-2)-8-bromo-guanine (III). The compound II (0.2 g; 0,6 mmol) was dissolved in 20 ml of 40% CH_3NH_2 water solution. The reaction mixture was stirred at room temperature for 2 h, and evaporated to dryness in vacuo. The residue was crystallized from ethanol to produce 0.15 g of III (86% yield): m.p.>300°C (decomp.). ^{1}H NMR (90 MHz, DMSO-d_6) δ, ppm 2.00 (1H, m, CH-4'), 2.48 (3H ,m, 2xCH-3', CH-4'), 3.88 (1H, m, CH-5'), 4.17 (1H, m, CH-5'), 6.04 (1H, m, NCH-2'), 6.48 (2H, s, NH_2), 10.69 (1H, br.s, NH). Anal.Calcd. for $C_9H_{10}N_5BrO_2$: C, 36.00; H, 3.36; N, 23.33. Found: C, 35.83; H, 3.18; N, 23.01.

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