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SYNTHESIS OF 9-(2,3-DIHYDROXY-1-PROPOXYMETHYL)GUANINE - A NEW POTENTIAL ANTIVIRAL AGENT

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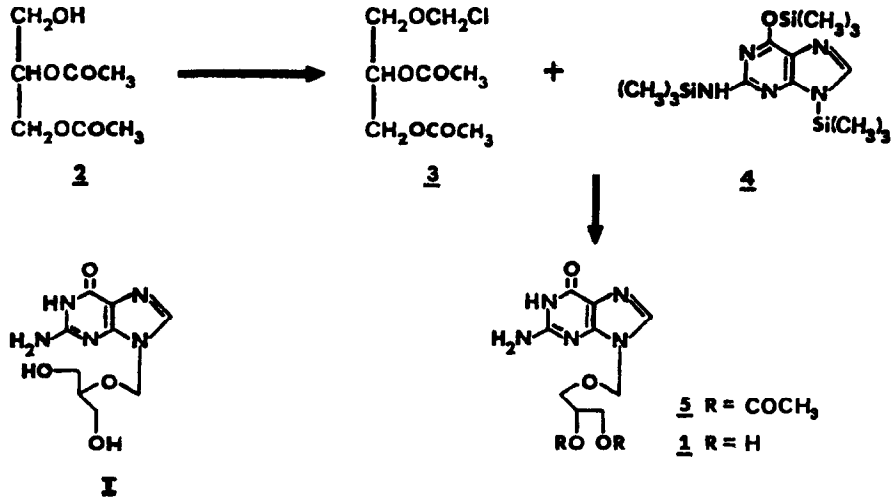
Coupling of tris(trimethylsilyl)guanine (4) with 1,2-di-O-acetyl-3-O-chloromethyl glycerol (3), followed by removal of the protecting groups afforded 9-(2,3-dihydroxy-1-propoxy)guanine (1). Compound 1 exhibited potent antiviral activity.

Recently, a novel guanine acyclic nucleoside analog, 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (I) (BIOLF-62, DHPG, 2'NDG), was reported by several independent groups of investigators[2-6] to have antiviral activity compatible to that of acyclovir which was approved by the FDA for the topical and i.v. treatment of primary genital herpes and for cutaneous herpes simplex infections in immunocompromised patients. It was also claimed that compound I has activity in vitro against some HSV-1 strains which are resistant to acyclovir[6]. Now we would like to report the synthesis of a new guanine acyclic nucleoside 1 which is the straight-cahin analog of I. Nucleoside 1 was found to possess potent antiviral activity. Recently, Ashton et al.[7] have independently reported the synthesis and antiherpetic activity of (R) and (S) enantiomers of 1.

The starting material, 1,2-di-O-acetyl-glycerol (2) which was prepared by a reported literature procedure[8], was converted to the chloromethyl derivative (3)[4] by treatment of 2 with paraformaldehyde and dry HCl in 1,2-dichloroethane at 0-5° for 1 hr. and after drying with $CaCl_2$ to remove the water formed, the reaction was continued for another hr. The reaction mixture was then dried with $CaCl_2$ again. The solvent was removed in vacuo to afford chloride 3 as a clear oil, which was used for the next step without further purification: NMR ($CDCl_3$) δ 1.97 (s, 6H, CH_3CO), 3.69 (d, 2H, CH_2O), 4.12 (d, 2H, CH_2OAc), 5.10 (m, 1H, CHOAc), 5.34 (s, 2H, OCH_2Cl). Alkylation[9] of tris(trimethylsilyl)guanine (4) with 3 in the presence of triethylamine in toluene gave 9-(2,3-diacetoxy-1-propoxymethyl)guanine (5) in 84% yield: mp 207-208° (from water); UV (H_2O) λ max 270 nm (sh) (ϵ 8694), λ max 253 nm (ϵ 12,618); mass spectrum m/e (relative intensity) 339 (8.9, M), 280 (3.5, M-OAc), 206 (13.4, M-CH_2OAc-HOAc), 189 (5.1, sugar portion), 180 [8.6, M-$CH_2CH(OAc)CH_2OAc$], 164 [41.3, M-$OCH_2CH(OAc)CH_2OAc$], 159 [41.9, $CH_2CH(OAc)CH_2OAc$], 151 (100, B + H), 73 (15.0, CH_2OAc); NMR (DMSO-d_6) δ 1.95 (s, 6H, CH_3COO), 3.56 (d, 2H, C-CH_2O), 4.03 (d, 2H, C-CH_2-OAc), 5.00 (m, 1H, C-CH-C), 5.26 (s, 2H, OCH_2N), 6.40 (s, 2H, NH_2-2, D_2O exchangeable), 7.67 (s, 1H, H-8), 10.47 (s, 1H, NH-1, D_2O exchangeable). The protecting group were removed by treatment of 5

with NH_3-CH_3OH solution at room temperature overnight. The final product, 9-(2,3-dihydroxy-1-propoxymethyl)guanine (1) was obtained in 89% yield: mp 235-236° (from water); UV (H_2O) λmax 272 nm (sh) (ϵ 6764), λmax 253 nm (ϵ 12,634); Mass spectrum m/e (relative intesity) 255 (0.2, M), 180 (0.5, M-$CH_2CHOHCH_2OH$), 164 (1.4, M-$OCH_2CHOHCH_2OH$), 151 (5.8, B + H), 150 (0.2, B), 105 (32.7, sugar portion), 75 (19.7, $CH_2CHOHCH_2OH$), 6.1 (100, $CHOHCH_2OH$); NMR (DMSO-d_6) δ 3.24-3.57 (m, 5H, glyceryl H's), 5.35 (s, 2H, N-CH_2-O), 6.52 (s, 2H, NH_2-2, D_2O exchangeable), 7.82 (s, 1H, H-8), 10.67 (s, 1H, NH-1, D_2O exchangeable).



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