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A NOVEL METHOD FOR THE SYNTHESIS OF 9-[[2-HYDROXY-1-(AMINOMETHYL)ETHOXY]METHYL]GUANINE - A POTENTIAL ANTIVIRAL AGENT[1]

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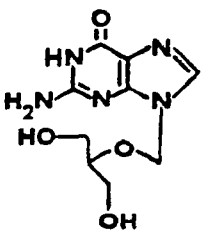
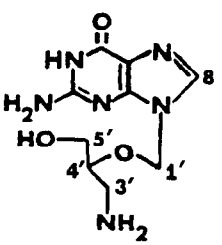
9-[[2-Hydroxy-1-(aminomethyl)ethoxy]methyl]guanine (1a), an amino analogue of 9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl]guanine (I) which is a potent antiviral agent, has been synthesized via a multistep-synthesis.

Recently, a novel guanine acyclic nucleoside analogue, 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (I) (BIOLF-62, 2'NDG, DHPG) has been reported independently by several laboratories[3-7] to have potent antiviral activity against both herpes simplex virus type 1 and 2 in vitro as well as in vivo at concentrations will below cytotoxic levels. Now we wish to report the synthesis of the amino analogue of I. Since the amino function is sterically and electronically similar to that of the hydroxy group, the modification of the acyclic sugar moiety with an amino group may lead to compounds with high antiviral activity and low host cytotoxicity. Furthermore, the amino analogue 1a can be readily converted to the corresponding hydrochloride, acetate or other salts. These salts should markedly enhance the water solubility, a factor critical for the formulation, which often limits the usefulness of new potential antiviral agents. Recently, Martin et al.[8], have also reported the synthesis of 1a by a completely different method.



I



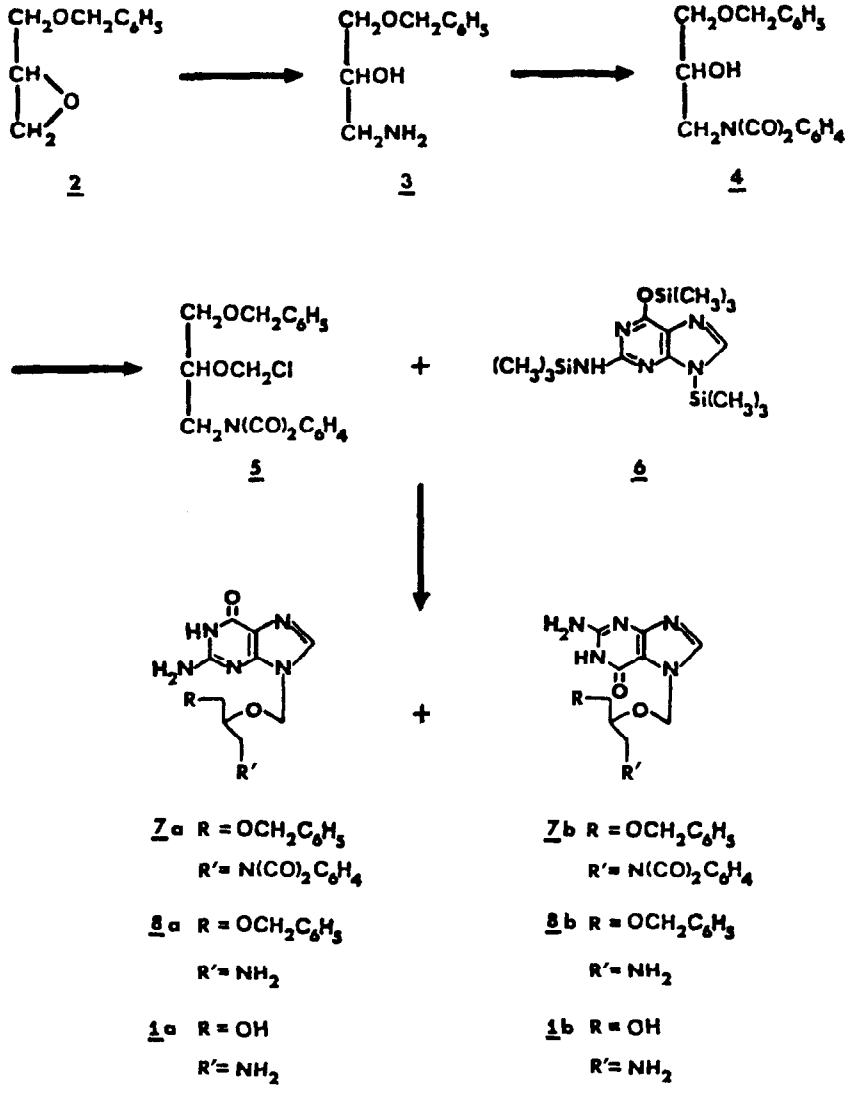
1a

The ether 2 which was prepared by a reported literature procedure[9], was stirred with concentrated (28%) NH_4OH at room temperature for 3 days to afford the desired 1-amino-3-benzoxy-2-propanol (3) in 72% yield: mp 76°C; NMR ($CDCl_3$) δ 2.38 (s, 3H, H_2N-1 and OH-2, D_2O exchangeable), 2.80 (d, 2H, CH_2N), 3.49 (d, 2H, OCH_2C), 3.80 (m, 1H, CH), 4.54 (s, 2H, $ArCH_2O$), 7.32 (m, 5H, C_6H_5). Compound 3 was reacted with phthalic anhydride to afford N-(3-benzoxy-2-hydroxypropyl) phthalimide (4) (65%): mp 79-80°C; NMR ($CDCl_3$) δ 2.81 (s, 1H, OH, D_2O exchangeable), 3.51 (d, 2H, OCH_2C), 2,83 (d, 2H, CH_2N), 3.97 (m, 1H, CH), 4.52 (s, 2H, $ArCH_2O$), 7.30 (m, 5H, C_6H_5), 7.68 (m, 4H, C_6H_4). The key intermediate, the chloromethyl ether (5), was synthesized in almost quantitative yield by treatment of 4 with paraformaldehyde and dry HCl in 1,2-dichloroethane at 0-5° for 2 hr. and after drying with $CaCl_2$ to remove the water formed, the reaction was continued for another 2 hr. Chloride (5) was used for the next step without further purification: NMR ($CDCl_3$) δ 3.62 (d, 2H, OCH_2C), 3.87 (d, 2H, CH_2N), 4.28 (m, 1H, CH), 4.56 (s, 2H, $ArCH_2O$), 5.46 (s, 2H, OCH_2Cl), 7.26 (m, 5H, C_6H_5), 7.72 (m, 4H, C_6H_4).

Alkylation of tris(trimethylsilyl)guanine (6) with (5) in the presence of triethylamine in toluene gave a mixture of the protected guanine acyclic nucleoside 7a and its isomer 7b in 80% yield. The ratio of the two isomers could be varied depending on the reaction conditions used. For example, the ratio (by comparing the integration of NMR spectra of the mixture) of 7a over 7b was 3:2 when the reaction mixture was refluxed for 48hr. However, when the reaction mixture was stirred first at room temperature for 24 hr. and then refluxed for another 24 hr. it yielded a mixture of 7a and 7b in a ratio of 4:1. The two isomers, 7a and 7b, were separated by crystallizing from DMSO (7a was more soluble), and purified by silica gel column chromatography ($CHCl_3$-EtOH, 2:1): 7a, mp 226-228°C; NMR (DMSO-d_6) δ 2.50-3.68 (m, 4H, H-3' and H-5'), 4.12 (m, 1H, H-4'), 4.50 (s, 2H, $ArCH_2O$), 5.30 (q, 2H, H-1'), 6.24 (s, 2H, NH_2, D_2O exchangeable), 7.31 (m, 5H, C_6H_5), 7.57 (s, 1H, H-8), 7.65-7.74 (m, 4H, C_6H_4), 10.14 (s, 1H, NH-1, D_2O exchangeable); Ib, mp 275-277°, NMR (DMSO-d_6) δ 3.49-3.68 (m, 4H, H-3' and H-5'), 4.21 (m, 1H, H-4'), 4.51 (s, 2H, $ArCH_2O$), 5.50 (q, 2H, NCH_2O), 5.93 (s, 2H, NH_2, D_2O exchangeable), 7.31 (m, 5H, C_6H_5), 7.65-7.75 (m, 4H, C_6H_4), 7.87 (s, 1H, H-8), 10.40 (s, 1H, NH-1, D_2O exchangeable). The phthaloyl protective groups of 7a and 7b were removed with hydrazine in EtOH to yield 8a (65%): mp 100-102°C; NMR (DMSO-d_6) δ 2.51 (d, 2H, H-3'), 3.45 (d, 2H, H-5'), 3.70 (m, 1H, H-4'), 4.10 (s, 2H, NH_2-3', D_2O exchangeable), 4.40 (s, 2H, $ArCH_2O$), 5.38 (q, 2H, H-1'), 6.50 (s, 2H, NH_2-2), 7.18 (m, 5H, C_6H_5), 7.74 (s, 1H, H-8), and, 8b (60%): 180°C (dec); NMR (DMSO-d_6) δ 2.70 (d, 2H, H-3'), 3.41 (d, 2H, H-5'), 3.80 (m, 1H, H-4'), 4.30 (s, 2H, NH_2-3', D_2O exchangeable), 4.40 (s, 2H, $ArCH_2O$), 5.62 (q, 2H, H-1'), 6.42 (s, 2H, NH_2-2, D_2O exchangeable), 7.30 (m, 5H, C_6H_5), 8.10 (s, 1H, H-8).

Debenzylation of 7a and 7b were unusually difficult. However, the final products 1a and 1b were obtained by debenzylation of 7a and 7b, respectively, through hydrogenation in methanol using $PdCl_2$ as a catalyst. The debenzylation of 7b was more difficult than that of 7a with 7b requiring 3 days to complete the reaction (followed by NMR). After removal of the catalyst and the solvent, the final products were obtained as hydrocholoride salts. The products were recrystallized from EtOH-H_2O: 1a.HCl (65%); mp 158-160°C; NMR δ 2.84-3.49 (m, 4H, H-3' and H-5'), 3.89 (m, 1H, H-4'), 5.05 (s, 1H, OH, D_2O exchangeable), 5.45 (q, 2H, H-1'), 6.74 (s, 2H, NH_2-2, D_2O exchangeable), 7.86 (s, 1H, H-8), 8.05 (s, 3H, NH_3-3', D_2O exchangeable), 10.89 (s, 1H, NH-1, D_2O exchangeable); 1b.HCl (52%), mp 208-210°C (dec); NMR

(DMSO-d_6) δ 2.84-3.49 (m, 4H, H-3' and H-5'), 3.88 (m, 1H, H-4'), 5.10 (s, 1H, OH, D_2O exchangeable), 8.12 (s, 1H, H-8), 8.15 (s, 3H, NH_3-3', D_2O exchangeable). The free base 1a and 1b were obtained by adjusting the aqueous solution of 1a.HCl and 1b.HCl with 2N NaOH to pH 8.8, and then recrystallized from water: 1a:mp 148-150°C; UV (H_2O), λ271 nm (sh); λmax 253 nm; λmin 221 nm; NMR (DMSO-d_6) δ 2.45 (d, 2H, H-3'), 3.35 (d, 2H, H-5'), 3.53 (m, 1H, H-4'), 4.10 (s, 3H, OH and NH_2-3', D_2O exchangeable), 5.35 (q, 2H, H-1'), 6.51 (s, 2H, NH_2-2, D_2O exchangeable), 7.74 (s, 1H, H-8); 1b:mp 160-162°C, UV (H_2O) λ max 285 nm, λmin 261 nm, λ242 nm (sh), NMR (DMSO-d_6) δ 2.60 (d, 2H, H-3'), 3.34 (d, 2H, H-5'), 3.60 (m, 1H, H-4'), 4.25 (s, 3H, OH and NH_2-3', D_2O exchangeable), 5.60 (q, 2H, H-1'), 6.41 (s, 2H, NH_2-2, D_2O exchangeable), 8.02 (s, 1H, H-8).



The structural assignments of the isomers 1a and 1b were made on the basis of the comparison of their spectroscopic and chemical properties with those of the similar known compounds.[5,10,11] The UV spectra of 1a and 1b were similar to those observed for 9-methyl and 7-methylguanine[10] respectively. The NMR chemical shift of H-8 of 1b (8.02 δ) was more downfield than that of 1a (7.74 δ) and the same phenomenon was also observed for the similar compounds of N^2-acetyl-9-[[1,3-bis(benzyloxy)-2-propoxyl]methyl]guanine and N^2-acetyl-7-[[1,3-bis(benzyloxy)-2-propoxy]methyl]guanine[5]. The relative stability of 1a and 1b to acid catalyzed hydrolysis was compatible to those of guanosine and its 7-isomer[11].

All new compounds gave satisfactory elemental anaylsis for carbon, hydrogen and nitrogen. The biological and biochemical studies of 1a and its (R) and (S) optical isomers are underway, and the results will be reported elsewhere.

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