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AN IMPROVED SYNTHESIS OF THE ANTIVIRAL ACYCLONUCLEOSIDE 9-(4-HYDROXY-3-HYDROXYMETHYLBUT-1-YL)GUANINE

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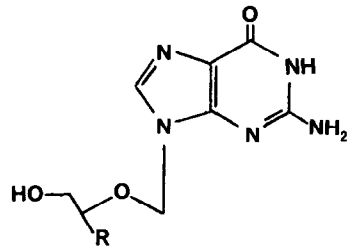
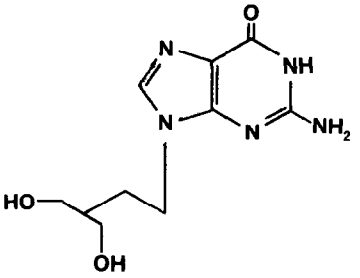
ABSTRACT: Alkylation of 2-amino-6-chloropurine with 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan (7) and subsequent acid hydrolysis provides an improved procedure for synthesis of the antiviral acyclonucleoside 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (3).

Since the discovery of the potent and selective anti-herpesvirus agent 9-(2-hydroxyethoxymethyl)guanine (1, acyclovir),[1-3] there have been intensive efforts by several groups directed at the preparation and evaluation of additional acyclic analogues of nucleosides. Of the compounds reported to date, the acyclonucleoside with the highest activity against herpesviruses is 9-(1,3-dihydroxy-2-propoxymethyl)guanine (2, DHPG).[4-6]

Some time ago we prepared 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (3), the carba-analogue of DHPG, and noted its antiviral properties.[7] An independent report of its anti-herpesvirus activity has also very recently been published.[8] We wish to describe here a short, novel synthesis of 3.

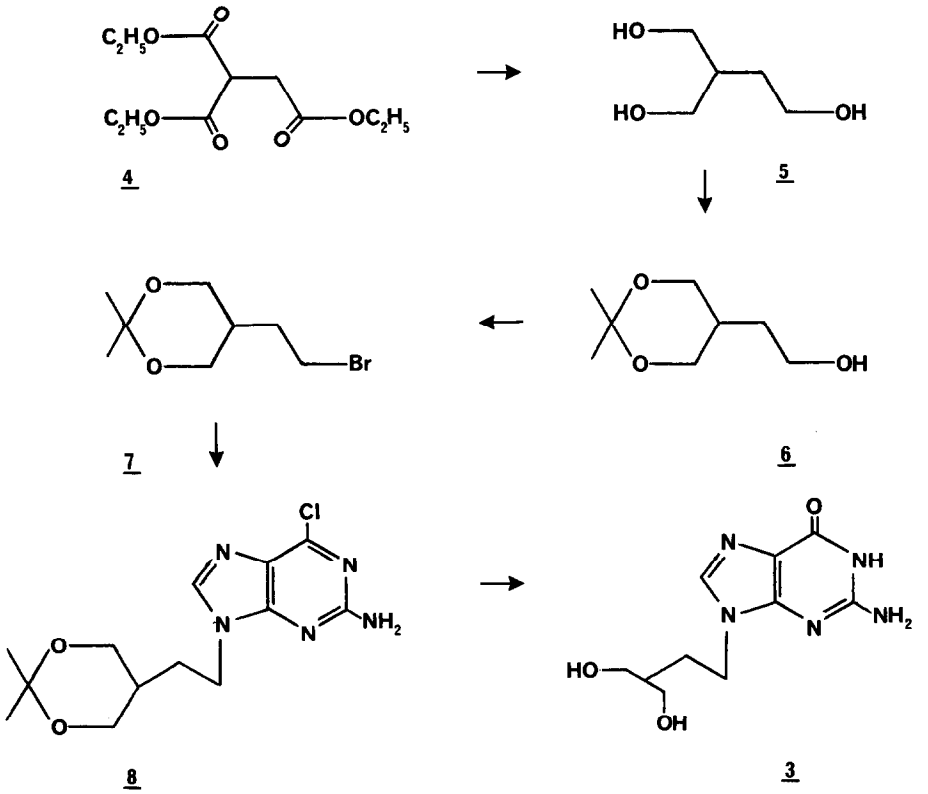


1 R = H
2 R = CH_2OH



3

The triester 4 was reduced to the triol 5 with sodium borohydride/ methanol in refluxing t-butanol.[9] We found that this borohydride system was much more selective than lithium aluminium hydride and gave a quantitative yield of 5. The 1,3-diol moiety of 5 was protected selectively by reaction with 2,2-dimethoxypropane and catalytic p-toluenesulphonic acid to give the acetonide 6 (47% after column chromatography on silica gel). The preference for 6- rather than 7-membered ring acetonide formation, although adequate, was not strongly predominating. Reaction of 6 with triphenylphosphine and carbon tetrabromide in N,N-dimethylformamide gave the bromide 7, which was obtained essentially pure in 87% yield after partitioning of the reaction mixture between hexane and aqueous sodium bicarbonate. The bromide 7 has a melting point just below room temperature (ca. 18°C) and could be stored without decomposition at -20°C.



Alkylation of 2-amino-6-chloropurine with 7 in N,N-dimethylformamide with potassium carbonate at room temperature gave almost exclusively the desired 9-isomer 8, with the 7-isomer barely detectable. After column chromatography on silica gel 8 was obtained in 70% yield: mp 125-126°C; λ_{max} (MeOH) 223, 247 and 310nm; δ_H [$(CD_3)_2SO$] 1.26 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.45-1.85 (3H, m, $\underline{CHCH_2}CH_2N$), 3.51 (2H, dd, J 7Hz and 11Hz, 2 x H_{ax}), 3.78 (2H, dd, J 4Hz and 11Hz, 2 x H_{eq}), 4.05 (2H, t, J 7Hz, CH_2N), 6.89 (2H, s, D_2O exchangeable, 2-NH_2), and 8.38 (1H, s, 8-H).

Acid hydrolysis of 8 (2M hydrochloric acid, reflux, 75min) converted the 6-chloro to the 6-oxo function and removed the acetonide protecting group. After neutralisation and crystallisation, 3 was obtained in 72% yield: mp 275-277°C; λ_{max} (H_2O) 253 and 270 (sh) nm; δ_H [$(CD_3)_2SO$] 1.45 (1H, m, CH), 1.72 (2H, q, J 7.1Hz, CH_2), 3.39 (4H, m, 2 x CH_2O), 4.00 (2H, t, J 7.4Hz, CH_2N), 4.40 (2H, t, J 5.2Hz, D_2O exchangeable, 2 x OH), 6.42 (2H, s, D_2O exchangeable, 2-NH_2), 7.67 (1H, s, 8-H), and 10.52 (1H, s, D_2O exchangeable, 1-H); M^+ observed 253.1176, M^+ theoretical 253.1175.

This route is considerably shorter and more convenient than both the 8-stage synthesis of 3 reported some years ago[10] and the recently reported variation of it,[8] which includes a step of 8% yield. Furthermore, the m.p. that we and the Syntex workers[8] obtained for 3 is about 100°C higher than the m.p. quoted in the original publication and in the Ph.D. thesis[11] referenced as the data source. On repetition of the synthetic procedure under the experimental conditions described by Grose,[11] we obtained a product, m.p. 170-175°C,[12] which was a mixture containing 3 and substantial quantities of its O-benzylated derivatives.

Analytical and spectroscopic data for all compounds reported in this communication were consistent with the structures given. Studies of the biological activity of 3 against members of the herpesvirus family will be described elsewhere.

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12. The melting point for 3 quoted by Grose[11] is 176-178°C and he states that "a satisfactory microanalysis could not be obtained".

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