Tetrahedron Letters,Vol.29,No.6,pp 701-704,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF 9-(3-HYDROXYPROPOXY)GUANINE, A NOVEL ANTIVIRAL ACYCLONUCLEOSIDE

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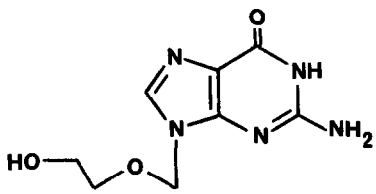
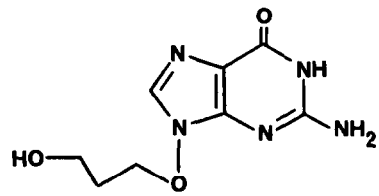
ABSTRACT: Synthetic approaches to 9-(3-hydroxypropoxy)guanine (2) involving the intermediacy of either a 1-alkoxyimidazole (7) or a 4-alkoxyaminopyrimidine (13) are described. This 9-alkoxyguanine (2) has potent and selective anti-herpesvirus activity and is the first reported member of a new series of antiviral acyclonucleosides.

As part of our studies on the synthesis and antiviral evaluation of novel acyclonucleosides,[1-5] we have prepared 9-(3-hydroxypropoxy)guanine (2), an isomer of 9-[(2-hydroxyethoxy)methyl]guanine (1, acyclovir)[6-8] in which the atom attached to N9 of guanine is oxygen.



1



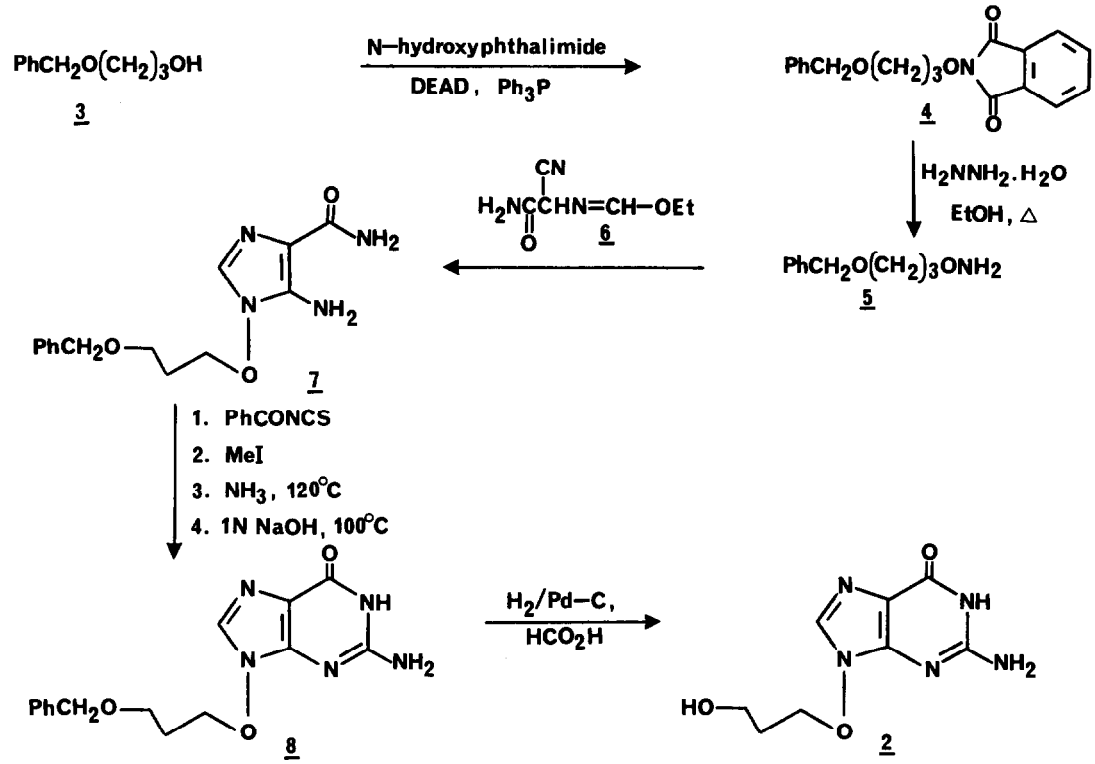
2

Our initial synthetic approach to 2 (Scheme 1) was based upon a published route to 9-hydroxyguanine via 5-amino-1-benzyloxy-4-carbamoylimidazole.[9]

3-Benzyloxypropoxyamine (5) was prepared in 73% overall yield by condensation of the monobenzyl ether of propane-1,3-diol (3) with N-hydroxyphthalimide,[10] followed by reaction with hydrazine hydrate. The alkoxyamine 5 was then reacted at room temperature with ethyl N-(carbamoylcyano)methylformimidate (6)[9] in methanol-ether to afford, after column chromatography on silica gel, the 1-alkoxyimidazole 7 in 15% yield: mp 139-141°C (from acetone-petroleum ether); λ_{max} (EtOH) 264 (ε 13,400)nm; δ_H [$(CD_3)_2SO$] 1.98 (2H, quintet, J 6.5Hz, $CH_2\underline{CH_2}CH_2$), 3.59 (2H, t, J 6.5Hz, $\underline{CH_2}OCH_2Ph$), 4.22 (2H, t, J 6.5Hz, CH_2ON), 4.49 (2H, s, CH_2Ph), 5.81 (2H, br.s, CNH_2), 6.71 (2H, br.s, $CONH_2$), 7.34 (6H, m, 2-H and C_6H_5). Found: C, 58.02; H, 6.31; N, 19.33%; M^+ 290.1378. $C_{14}H_{18}N_4O_3$ requires: C, 57.91; H, 6.26; N, 19.30%; M^+ 290.1379.

Using the same sequence of reactions as had been used previously to prepare 9-benzyloxyguanine[9], 7 was converted to 9-(3-benzyloxypropoxy)guanine (8) in 29% overall yield. Hydrogenolysis of 8 in 80% formic acid in the presence of 10% Pd on charcoal then provided the required 3-hydroxypropoxy derivative 2 in 89% yield: mp 275-276°C decomp (from water); λ_{max} (H_2O) 253 ε (13,600)nm; δ_H [$(CD_3)_2SO$] 1.80 (2H, quintet, J 6.6Hz and 6.0Hz

Scheme 1



$CH_2\underline{CH_2}CH_2$), 3.55 (2H, q, J 5.5Hz and 6.0Hz, $\underline{CH_2}OH$), 4.32 (2H, t, J 6.6Hz, CH_2ON), 4.57 (1H, t, J 5.5Hz, D_2O exchangeable OH), 6.57 (2H, br.s, D_2O exchangeable NH_2), 7.91 (1H, s, 8-H), 10.63 (1H, br.s, D_2O exchangeable NH). Found: C, 41.33; H, 5.20; N, 30.24%; M^+ 225.0874. $C_8H_{11}N_5O_3.0.4\ H_2O$ requires: C, 41.33; H, 5.13; N, 30.14%; M^+ 225.0862.

In antiviral tests carried out in Vero and MRC-5 cell cultures 9-(3-hydroxypropoxy)-guanine (2) had an IC_{50} (50% inhibitory concentration) for inhibition of the replication of herpes simplex virus types 1 and 2 $\approx 0.3\mu g/ml$ (cf. acyclovir $IC_{50} \approx 0.9\mu g/ml$) and against varicella zoster virus 2 had an $IC_{50} \approx 0.8\mu g/ml$ (cf. acyclovir $IC_{50} \approx 3.8\mu g/ml$). No effect upon uninfected cell monolayers was observed in the presence of concentrations of 2 up to $100\mu g/ml$.

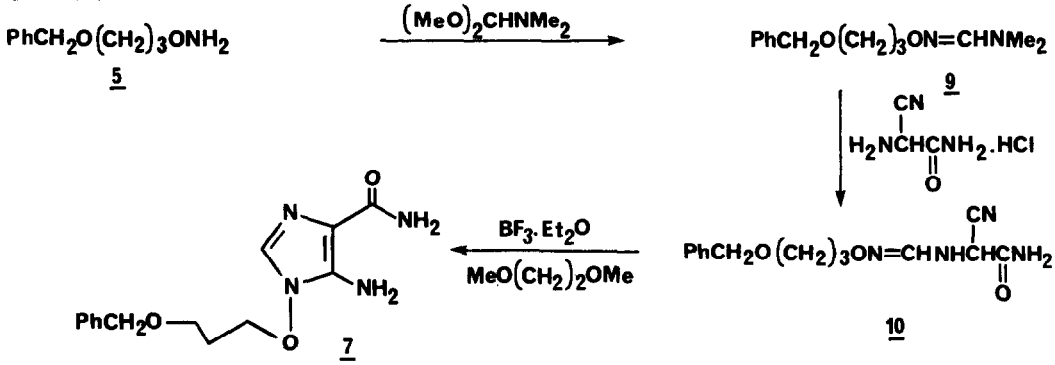
These interesting biological properties prompted us to investigate more efficient procedures for synthesis of 2 (Scheme 2). Brief reaction of the protected alkoxyamine 5 with N,N-dimethylformamide dimethyl acetal at room temperature afforded the dimethylformamidine 9, which was isolated as an oil in 92% yield: δ_H ($CDCl_3$) 1.95 (2H, m, $CH_2\underline{CH_2}CH_2$), 2.76 (6H, s, 2 x CH_3), 3.57 (2H, t, J 6.5Hz, $\underline{CH_2}OCH_2Ph$), 3.95 (2H, t, J 6.5Hz, CH_2ON), 4.51 (2H, s, CH_2Ph), 7.30 (5H, m, C_6H_5), 7.61 (1H, s, CH). Found: M^+ 236.1527. $C_{13}H_{20}N_2O_2$ requires: M^+ 236.1524. Reaction of 9 with aminocyanoacetamide hydrochloride in methanol at room temperature gave the amidine 10 as a mixture of geometric isomers, isolated as an

unstable oil in 70% yield: δ_H [$(CD_3)_2SO$] 1.86 (2H, m, $CH_2\underline{CH_2}CH_2$), 3.53 (2H, m, $\underline{CH_2}OCH_2Ph$), 3.85 and 3.94 (2H, 2t, J 6.5Hz, CH_2ON), 4.46 (2H, s, CH_2Ph), 5.06 and 5.23 (1H, 2d, J 8Hz, CHCN), 6.76 (1H, d, J 10.5Hz, =CH), 6.95 (1H, dd, J 10.5Hz and 8Hz, D_2O exchangeable NH), 7.2-7.4 (5H, m, C_6H_5), 7.95 (2H, s, D_2O exchangeable NH_2). Found: M^+ 290.1369.$C_{14}H_{18}N_4O_3$ requires: M^+ 290.1376. Attempted cyclisation of 10 using either mineral or organic acids gave complex mixtures of products and low yields of the 1-alkoxyimidazole 7. However, in the presence of the Lewis acid boron trifluoride etherate, in 1,2-dimethoxyethane at 60-80°C 10 cyclised cleanly to afford 7 in 63% yield.

Thus, using these adaptations we were able to increase the overall yield for conversion of 5 ->7 from 15% to 40%. However, there still remained the problem of conversion of 7 to the guanine 8, which we had never achieved in greater than 30% overall yield.

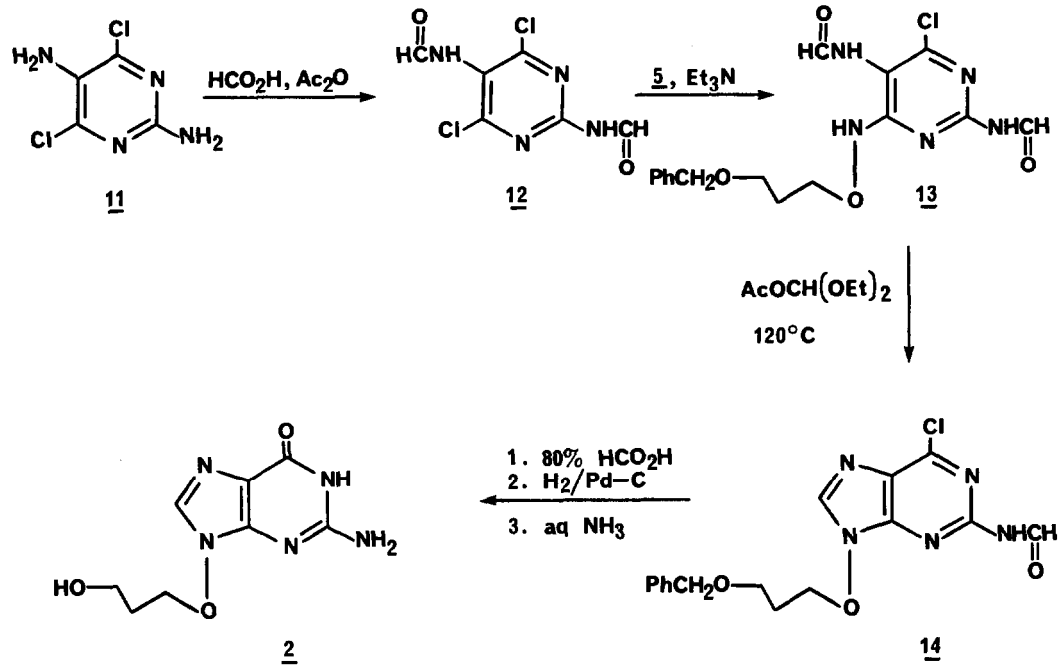
For this reason we also explored an alternative synthesis of 2 via pyrimidine intermediates (Scheme 3). Although displacement of chloride from 2,5-diamino-4,6-dichloropyrimidine (11)[11] with the alkoxyamine 5 did not occur readily, 11 was converted in 70% yield to its di-N-formyl derivative 12, which in the presence of triethylamine reacted in refluxing dioxane with 5 to afford, after column chromatography on silica gel, the alkoxyaminopyrimidine 13 in 51% yield: δ_H [$(CD_3)_2SO$] 1.88 (2H, quintet, J 6.3Hz, $CH_2\underline{CH_2}CH_2$), 3.57 (2H, t, J 6.3Hz, $\underline{CH_2}OCH_2Ph$), 3.95 (2H, t, J 6.3Hz, CH_2ON), 4.47 (2H, s, CH_2Ph), 7.32 (5H, m, C_6H_5), 8.14 (1H, s, HCON), 9.26 (1H, s, HCON), 9.42 (1H, br.s, D_2O exchangeable, $N\underline{H}OCH_2$), 10.83 (2H, br.s, 2 x HCON$\underline{H}$). Found: M^+ 379.1026.$C_{16}H_{18}N_5O_4Cl$

Scheme 2



requires: M^+ 379.1047. Closure of the imidazole ring by heating at 120°C with diethoxymethyl acetate,[12] followed by treatment with ammonia in methanol, then gave the 6-chloropurine derivative 14, isolated in 95% yield after column chromatography on silica gel: δ_H ($CDCl_3$) 2.15 (2H, quintet, J 6Hz, $CH_2\underline{CH_2}CH_2$), 3.75 (2H, t, J 6Hz, $\underline{CH_2}OCH_2Ph$), 4.55 (4H, m, CH_2ON, CH_2Ph), 7.40 (5H, m, C_6H_5), 8.10 (1H, s, 8-H), 8.40 (1H, d, J 10Hz, D_2O exchangeable, HCON$\underline{H}$), 9.60 (1H, d, J 10Hz, H$\underline{C}$ONH). Found: M^+ 361.0942. $C_{16}H_{16}N_5O_3Cl$ requires: M^+ 361.0942. Hydrolysis of the 6-chloro group of 14 in 80% formic acid at 100°C, followed by hydrogenolysis of the O-benzyl protecting group in the presence of 10% Pd on charcoal and removal of the N2-formyl group with aqueous ammonia at 100°C, then afforded the guanine derivative 2 in 39% overall yield.

Scheme 3



This route (Scheme 3) is shorter and more efficient than the route via imidazole intermediates (Schemes 1 and 2) and has been used in syntheses of additional antiviral N9-alkoxyguanines, which will be reported in subsequent publications.

ACKNOWLEDGEMENTS: We thank Mr. M.R. Boyd and his colleagues for the antiviral data and Dr. M. Cole for his interest in, and encouragement for these studies.

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(Received in UK 27 November 1987)