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SYNTHESIS OF 9-(HYDROXYALKYLAMINO)GUANINES, NOVEL ANTIVIRAL ACYCLONUCLEOSIDES

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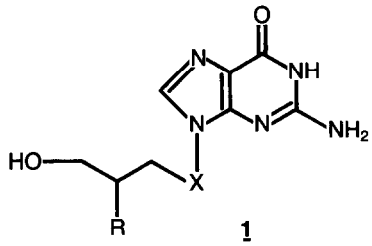
ABSTRACT: 9-Aminoguanine (3) has been prepared and used as an intermediate in syntheses of 9-(3-hydroxypropylamino)guanine (1d) and 9-[3-hydroxy-2-(hydroxymethyl)propylamino]guanine (1e), the first reported members of a new series of antiviral acyclonucleosides.

Certain 9-alkylated guanines such as acyclovir[1], ganciclovir[1] and 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123; 1a)[1,2] have potent and selective anti-herpesvirus activity. The synthesis and antiviral activity of



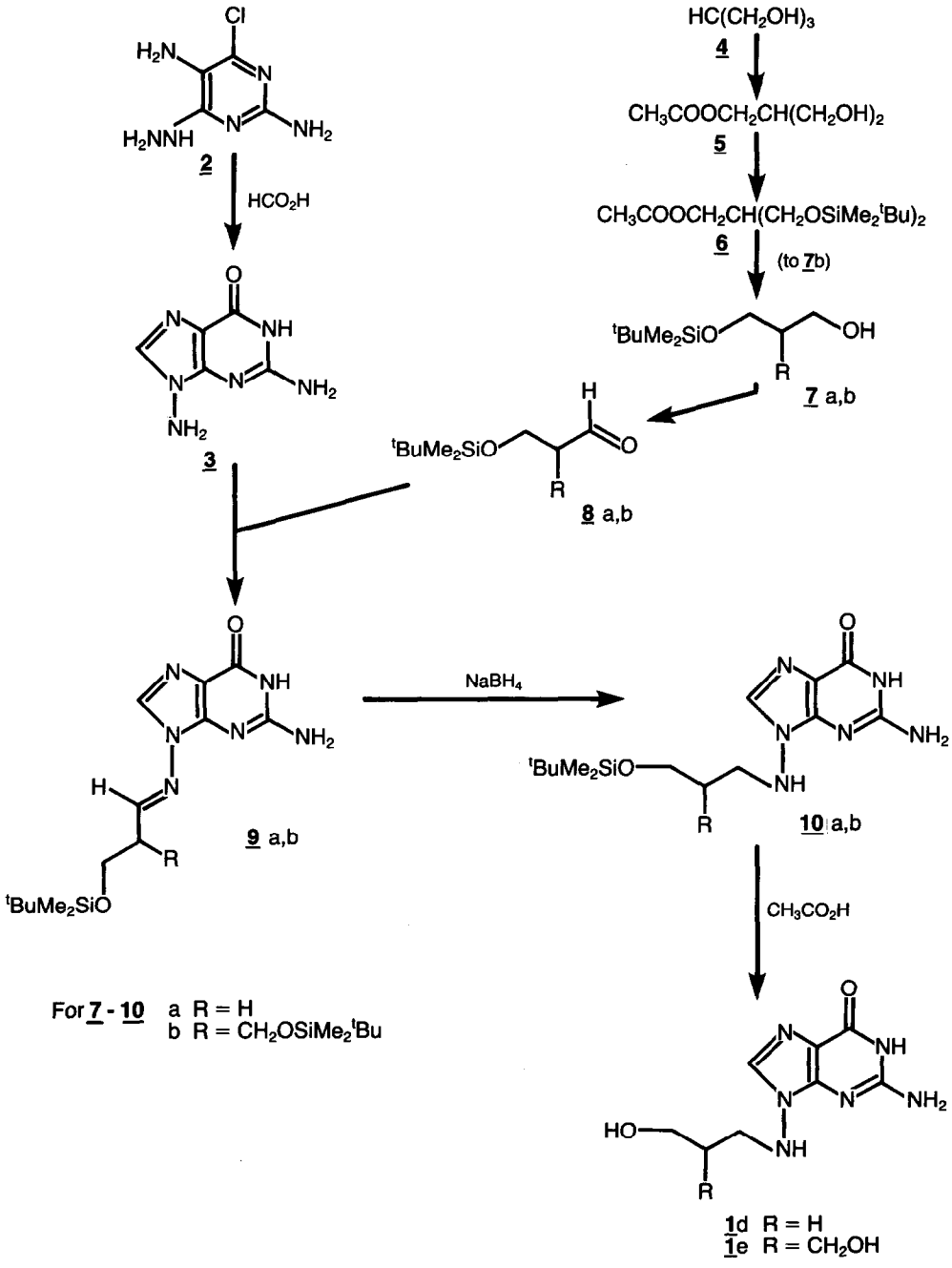
1

a X = CH_2, R = CH_2OH
b X = O , R = H
c X = O , R = CH_2OH
d X = NH , R = H
e X = NH , R = CH_2OH

novel 9-alkoxyguanines (eg 1b and 1c) have also been described recently.[3,4] In this communication we report the synthesis and anti-herpesvirus activity of two novel 9-alkylaminoguanines (1d and 1e).

Relatively few 9-aminopurine derivatives have been described although routes via pyrimidine[5,6] and imidazole[7,8] precursors as well as direct amination[9] have been reported. However, neither 9-aminoguanine (3) nor any derivative of it appear to have been prepared previously. We elected to use a pyrimidine precursor to synthesise 3, with subsequent imine formation and reduction, as the most convenient and convergent route to 9-alkylaminoguanines.

Treatment of pyrimidine 2[10] with refluxing formic acid afforded 9-aminoguanine (3)[11] directly in 30-40% yield. Cyclisation to the purine structure rather than the isomeric pyrimidotriazine system was confirmed by the uv spectral data of 3 which had the characteristic profile of 9-substituted guanines. Attempted use of milder reagents such as diethoxymethyl acetate or triethyl orthoformate did not result in effective cyclisation.


Cl
H2N
N
H2NNH
NH2
2
HCO2H
O
NH
N
N
NH2
NH2
3
HC(CH2OH)3
4
CH3COOCH2CH(CH2OH)2
5
CH3COOCH2CH(CH2OSiMe2tBu)2
6
(to 7b)
tBuMe2SiO
OH
R
7 a,b
H
O
tBuMe2SiO
R
8 a,b
H
N
9 a,b
tBuMe2SiO
NaBH4
NH
10 a,b
CH3CO2H
HO
1d R = H
1e R = CH2OH
For 7 - 10 a R = H
b R = CH2OSiMe2tBu

Aldehyde 8a was obtained by pyridinium chlorochromate oxidation of alcohol 7a.[12] Synthesis of aldehyde 8b commenced from triol 4. Selective mono-protection of 4 was achieved with 1.5 equivalents of trimethyl orthoacetate and catalytic 4-toluenesulphonic acid in tetrahydrofuran, followed by acidic aqueous work-up. The monoacetate 5 was obtained in 69% yield. Silylation of 5 with t-butyldimethylsilyl chloride and imidazole in dimethylformamide afforded 6 (65% yield), which was deacetylated to 7b in quantitive yield with catalytic potassium carbonate in methanol. The alcohol 7b was oxidised to the aldehyde 8b with pyridinium chlorochromate in the presence of 4A molecular sieves.

Condensation of the aldehydes 8a and 8b with 9-aminoguanine in dimethyl sulphoxide-acetic acid (10:1 or 20:1, 50°C) afforded the imines 9a and 9b, both in 30% yield. The ^1H nmr spectra of 9a and 9b showed that the 9-NH_2 and not the 2-NH_2 group had reacted and that a single stereoisomer of the imine was obtained. Irradiation of the 8-H resonance of the purine resulted in a positive nOe at the imine proton, further confirming the site of reaction and indicating that the compounds had E-anti stereochemistry (as shown). Reduction of the imines was carried out with sodium borohydride in methanolic or ethanolic tetrahydrofuran and afforded the alkylaminoguanines 10a and 10b in good yields (79% and 87% respectively). Deprotection with 80% acetic acid at 70°C followed by reverse-phase column chromatography gave the 9-(3-hydroxyalkylamino)guanines 1d (77% yield)[13] and 1e (66% yield).[14]

In antiviral tests carried out in MRC-5 cells the IC_{50}'s (50% inhibitory concentration) for inhibition of the replication of herpes simplex virus types 1 and 2 and of varicella zoster virus were 3.7, 13 and 63 μg/ml for 1d and 11, 2.4 and 18 μg/ml for 1e (cf. 1.4, 0.6 and 3.8 μg/ml for acyclovir). 9-Aminoguanine (3) had no antiviral activity and, at concentrations up to 100μg/ml, none of the compounds showed effects upon uninfected cell monolayers. The 9-(hydroxyalkylamino)guanines 1d and 1e are thus selective anti-herpesvirus agents, although less potent than analogous 9-alkyl[1,2] and 9-alkoxyguanines.[3,4]

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11. Compound 3: mp >320 °C; λmax (1M HCl) 253 (ε 10,200) and 277 (7,120)nm, (1M NaOH) 265 (ε 9,870)nm; δ_H [$(CD_3)_2SO$] 5.75 (2H, s, D_2O exchangeable, 9-NH_2), 6.44 (2H, s, D_2O exchangeable, 2-NH_2), 7.56 (1H, s, 8-H), and 10.53 (1H, s, D_2O exchangeable, 1-H). Found: C, 34.86; H, 3.83; N, 48.72%; M^+ 166.0588. $C_5H_6N_6O.0.4H_2O$ requires C, 34.65; H, 3.95; N, 48.48%; M 166.0599.
12. P.G. McDougal, J.G. Rico, Y.-I. Oh, and B.D. Condon, J. Org. Chem., 51, 3388 (1986).
13. Compound 1d: mp 281-283°C (with decomp); λmax 253 (ε 12,800) and 269 (sh. 9,660)nm; δ_H [$(CD_3)_2SO$] 1.50 (2H, quintet, J 6.7Hz, CCH_2C), 3.10 (2H, q, J 6.4Hz, CH_2N), 3.46 (2H, q, J 5.9Hz, CH_2O), 4.42 (1H, t, J 5.1 Hz, D_2O exchangeable, OH), 6.40 (1H, t, J 5.0Hz, D_2O exchangeable, 9-NH), 6.44 (2H, s, D_2O exchangeable, 2-NH_2), 7.57 (1H, s, 8-H), and 10.53 (1H, s, D_2O exchangeable, 1-H). Found: C, 42.67; H, 5.32; N, 37.54%; M^+ 224.1029. $C_8H_{12}N_6O_2$ requires C, 42.85; H, 5.39; N, 37.48%; M 224.1018.
14. Compound 1e: mp 252-255°C; λmax 253 (ε 12,700) and 270 (sh. 9,480)nm; δ_H [$(CD_3)_2SO$] 1.57 (1H, m, CH), 3.05 (2H, t, J 5.8Hz, CH_2N), 3.45 (4H, t, J 5.3Hz, 2 x CH_2O), 4.38(2H, t, J 5.2Hz, D_2O exchangeable, 2 x OH), 6.35 (1H, t, J 5.1Hz, D_2O exchangeable, 9-NH), 6.43 (2H, s, D_2O exchangeable, 2-NH_2), 7.58 (1H, s, 8-H), and 10.53 (1H, s, D_2O exchangeable, 1-H). Found: C, 41.54; H, 5.72; N, 32.48%; M^+ 254.1124. $C_9H_{14}N_6O_3.0.3H_2O$ requires C, 41.63; H, 5.67; N, 32.37%; M 254.1123.

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