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# SYNTHESIS OF 9-[2,2-BIS(HYDROXYMETHYL)CYCLOPROP-1-YL]GUANINE AS A POTENTIAL ANTIVIRAL AGENT

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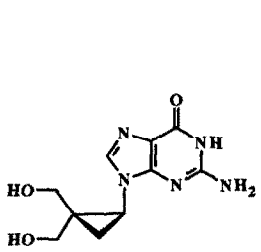
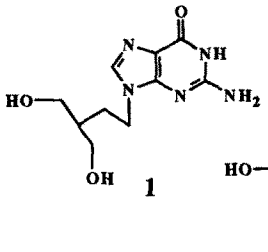
**Abstract:** The synthesis and antiviral activity of a cyclopropyl analogue of the antiviral agent penciclovir is reported.

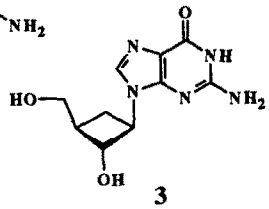
Acyclonucleosides have been extensively studied as antiviral agents.[1] Of these compounds penciclovir [BRL 39123, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine] **1** has emerged as a potent and selective anti-herpes-virus agent which is particularly active against herpes simplex types 1 and 2 (HSV-1 and HSV-2) and varicella zoster virus (VZV).[2-4] To help clarify the relationship of side chain conformation and flexibility to biological activity we have prepared the guanine derivative **2** in which rigidity is conferred upon the carbon skeleton of the penciclovir side chain by incorporation of a cyclopropane ring. This approach overlaps the area of carbocyclic nucleoside analogues which have also received considerable attention recently and very interestingly the isomeric compound SQ-32,829 **3**[5] has potent antiviral activity. Several other closely related structures have also been reported recently.[6-8]




**2**



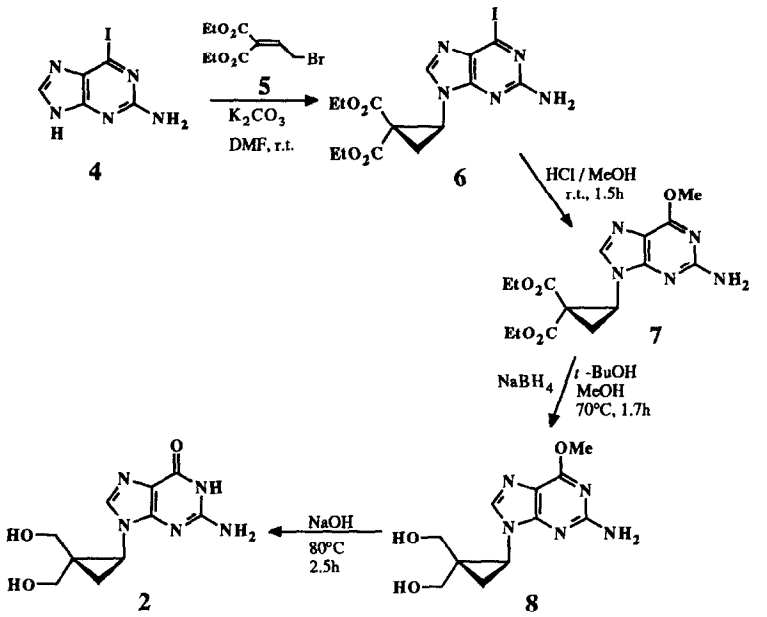

**1**




**3**

Compound **2** was prepared in three steps from the key intermediate **6**[9] obtained in 71% yield from the reaction of 2-amino-6-iodopurine **4** with diethyl 2-bromoethylidenemalonate **5**. Treatment of **6** with 1.7M methanolic hydrogen chloride gave the 2-amino-6-methoxypurine derivative **7** in 46% yield. Reduction of **7** using sodium borohydride afforded a 57% yield of the diol **8**. Hydrolysis of the 6-methoxy group of **8** in 2M sodium hydroxide solution afforded the guanine derivative **2**[10] in 81% yield.

The nucleoside analogue **2** was tested at concentrations up to 100μg $ml^{-1}$ for antiviral activity in cell cultures, but was found to be devoid of activity against HSV-1 (SC16 strain), HSV-2 (MS), VZV (Ellen) and CMV (cytomegalovirus) (AD169) in MRC-5 (human fibroblast) cells. In these tests no toxicity to the cell monolayers was observed. It is not currently known whether the lack of antiviral activity of **2** is due to lack of phosphorylation or inactivity of the triphosphate against the viral DNA polymerases. However, the decreased conformational flexibility as a consequence of introduction of the cyclopropyl ring into **2** appears to be unfavourable for interaction with at least one of the enzymes involved.



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**References and Notes**

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10. Analytical data for **2**: m.p. 190°C; $\lambda_{max}$ ($CH_3OH$) 256 (ε 12,045)nm; $\nu_{max}$ (KBr) 3400, 3210, 3125, 1695, 1610, 1535, 1485, and 1380cm$^{-1}$; $\delta_H$ [$(CD_3)_2SO$] 1.20 (2H, d, *J* 6Hz, $CH_2$), 3.06 (1H, d, *J* 10Hz, $CH_2O$), 3.20 (1H, t, *J* 6Hz, CH), 3.33 (1H, d, *J* 10Hz, $CH_2O$), 3.41 (1H, d, *J* 10Hz, $CH_2O$), 3.75 (1H, d, *J* 10Hz, $CH_2O$), 4.48 (1H, br s, $D_2O$ exchangeable, OH), 4.59 (1H, br s, $D_2O$ exchangeable, OH), 6.52 (2H, br s, $D_2O$ exchangeable, $NH_2$), 7.62 (1H, s, 8-H), 10.67 (1H, br s, $D_2O$ exchangeable, 3-H); $\delta_C$ [$(CD_3)_2SO$] 12.58 (3'-C), 29.92 (1'-C), 32.42 (2'C), 59.99 (4'-C/5'-C), 61.85 (4'-C/5'-C), 116.75, 138.41, 152.39, 153.81, 157.12; *m/z* ($NH_3$ c.i.) 252 ($MH^+$, 100%) (Found: C, 42.12; H, 5.69; N, 24.29%. $C_{10}H_{13}N_5O_3.2H_2O$ requires C, 41.81; H, 5.97; N, 24.38%).