animals were placed individually on top of a square (13 cm  $\times$  13 cm) wire screen (no. 4 mesh), which was mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen within 1 min was determined. This measurement was performed 0.5, 1, 2, 3, and 4 h posttreatment to determine the approximate time of peak effect. Each compound was then retested at the estimated time of peak effect by using at least four doses with 12 mice at each dose. The HS  $ED_{50}$  was calculated according to the method of Litchfield and Wilcoxon.23

Inhibition of MES-Induced Seizures. Three groups of mice were administered a range of oral doses of each compound as a suspension in 5% acacia/water. The time to peak effect (TPE) was determined by challenging the mice with MES 0.5, 1, 2, 3, and 4 h posttreatment. Electroshock (40 mA, 0.1 s, ac) was administered through corneal electrodes, and the mice were ob-

(23) Litchfield, J. T., Jr.; Wilcoxon, F. J. Pharmacol. Exp. Ther. 1949, 96, 99.

served for clonic, tonic-flexor, and tonic-extensor convulsions. Each compound was then retested at the estimated time of peak effect by using at least four doses with 12 mice at each dose. The MES ED<sub>50</sub> for the prevention of tonic-extensor convulsions was calculated according to the method of Litchfield and Wilcoxon.23

Effects on Hexobarbital-Induced Sleeping Time. Groups of 10 fasted mice were treated orally with various doses of each compound in 5% acacia/water. At the previously determined time of peak effect, hexobarbital (100 mg/kg, ip) was administered to the mice. The hexobarbital was solubilized with stoichiometric quantities of sodium hydroxide, and the volumes of administration for all test compounds, acacia, and hexobarbital was 10 mL/kg. Sleeping time or the time of loss of righting reflex was determined to the nearest minute for each mouse.

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## Synthesis and Biological Activity of Unsaturated Carboacyclic Purine Nucleoside Analogues<sup>†</sup>

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Two new carboacyclic nucleoside analogues, 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]adenine (6) and 9-[4hydroxy-3-(hydroxymethyl)-2-butenyl]guanine (5), modeled on the unsaturated carbocyclic nucleoside analogue neplanocin A (2), have been synthesized and tested for antiviral activity against HSV-2 and, in the case of 6, for activity against influenza and in vitro inhibition of S-adenosylhomocysteine hydrolase. The synthesis was accomplished through the coupling of either adenine or the guanine precursor 2-amino-6-chloropurine (15) to the key intermediate 1-(benzyloxy)-2-[(benzyloxy)methyl]-4-chloro-2-butene (13). Debenzylation of the N-9 adenine adduct gave 6 directly, while the product of the debenzylation of the N-9 adduct of 15 when treated with sodium hydroxide gave the guanine analogue 5. The carboacyclic guanine analogue (5) exhibited significant antiviral activity against HSV-2 (VR = 1.5,  $MIC_{50} = 65.6 \,\mu g/mL$ ), a level of activity that is superior to that of ara-A but inferior to that of acyclovir. The adenine analogue 6 was active against HSV-2 only at a very high dose; it was devoid of antiviral activity against influenza type A2, and it lacked inhibitory activity against S-adenosylhomocysteine hydrolase.

Many carbocyclic nucleoside analogues, in which the furanose oxygen atom has been replaced by a carbon, have been shown to have significant antiviral activity.<sup>1</sup> These carbocyclic analogues consist of two basic types, those with a cyclopentane ring, represented by aristeromycin (1), and those with a cyclopentene ring, represented by neplanocin A (2). Both types of carbocyclic adenosine analogues



exhibit antiviral activity commensurate with their degree of inhibition of S-adenosylhomocysteine hydrolase (AdoHcy-ase) and the consequential inhibition of the maturation of viral RNA.<sup>2</sup> The synthesis of the guanosine analogue of 2 has been reported but with only limited accompanying biological activity data.<sup>3</sup>

Since the discovery of the potent and highly selective antiherpetic activity of acyclovir (3),<sup>4</sup> a guanine nucleoside analogue in which both the 2'- and the 3'-carbon atoms of the ribose sugar have been excised, many acyclic nucleoside analogues have been prepared and studied for antiviral activity.5 It was found that 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, 4), an analogue in which only the 2'-CHOH has been deleted from the natural nucleoside, had 10-100-fold higher potency against herpes viruses than does 3.6

In an effort to develop more potent and selective antiviral agents, we attempted to combine in one molecule the

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unique structural elements of the neplanocin carbocyclic nucleoside series and DHPG. These efforts resulted in the syntheses of the unsaturated carboacyclic analogue 9-[4hydroxy-3-(hydroxymethyl)-2-butenyl]guanine (5) and its adenosine analogue 9-[4-hydroxy-3-(hydroxymethyl)-2butenyl]adenine (6). Other types of carboacyclic nucleoside analogues have been reported recently including 9-(2,3-dihydroxypropyl)adenine (7)<sup>2</sup> and the saturated carboacyclic DHPG analogue 8.<sup>7</sup> Both compounds show antiviral activity, but only the former is an inhibitor of AdoHcy-ase. The carboacyclic DHPG analogue 8 has antiherpetic activity of slightly lower potency than DHPG against herpes simplex 1 (HSV-1) in vitro and no activity against herpes simplex 2 (HSV-2) in vivo.<sup>7</sup>



A variety of carboacyclic guanosine analogues were patented in 1982, including the unsaturated carboacyclic analogue of acyclovir (9),<sup>8</sup> but no biological activity data was reported on the unsaturated analogues. In a patent released in late 1985, after most of this project had been completed, both the cis isomer of 9 and one of our target molecules, 5, were reported to have higher  $K_i$  values (7 and 25  $\mu$ M, respectively) for HSV-1 thymidine kinase and higher ID<sub>90</sub> values (10 and 25  $\mu$ M, respectively) against HSV-1 in Vero cells when compared to DHPG analogue 8 ( $K_i = 1.5 \mu$ M and ID<sub>90</sub> = 1  $\mu$ M).<sup>9</sup> More recently, an ID<sub>50</sub> of 3  $\mu$ M against HSV-1 C-42 plaque formation has been reported for compound 5 by the same group.<sup>10</sup>

### Chemistry

Synthesis of the target compounds was initiated from the known bis(benzyloxy) acetone  $(10)^{11}$  (Scheme I). Re-

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action of 10 with triethyl phosphonoacetate in a Horner-Emmons condensation gave the desired ethyl 4-(benzyloxy)-3-[(benzyloxy)methyl]-2-butenoate (11) in good yield as a viscous oil. Initial attempts at reduction of 11 resulted in complex mixtures of products, but it was found that LiAlH<sub>4</sub> which had been deactivated with 1 molar equiv of ethanol<sup>12</sup> cleanly reduced 11 to the allylic alcohol 12. In order to make this synthesis parallel to our previous work on the synthesis of neplanocin A (2),<sup>13</sup> we initially attempted to synthesize the tosylate of 12 to provide a good leaving group for direct displacement. In none of these reactions was the tosylate observed. The major product of the reaction of 12 with p-TsCl in triethylamine was found to be instead 1-(benzyloxy)-2[(benzyloxy)methyl]-4-chloro-2-butene (13), which was obtained in 23% yield. When the reaction was repeated in the presence of *p*-DMAP, as has been suggested for other primary allylic alcohols,<sup>14</sup> the yield of 13 was increased to 66%.

Direct coupling of adenine to 13 in  $Me_2SO$  with  $K_2CO_3$ as a basic catalyst gave a good yield of the desired N-9 alkylated adenine (14) (Scheme II). Attempted direct coupling of guanine to 13 under the same conditions resulted in a complex mixture of mono- and bisalkylated guanine products. It was therefore necessary to reach the desired guanine product indirectly. Coupling of 2amino-6-chloropurine (15) to 13 proceeded cleanly to give the N-9 alkylated adduct (16) as the major product.

The site of alkylation in 6 was proven unambiguously at the dibenzylated stage by coupled and selectively decoupled <sup>13</sup>C NMR studies. The fully coupled <sup>13</sup>C NMR spectrum of the N-9 alkylated adenine 14 clearly showed three bond coupling of the exocyclic methylene protons (corresponding to the H-1' proton in a nucleoside) to C-8, which appeared as a doublet of triplets (<sup>1</sup>J = 210 Hz and <sup>3</sup>J = 3.9 Hz). The coupling pattern of C-4, however, was not as clearly resolved. C-4 should show three bond coupling to H-8, to H-2, and to the two exocyclic methylene protons. In the fully coupled spectrum, C-4 appeared as a broad, unresolved peak. However, when the exocyclic methylene protons were selectively decoupled, using an irradiation of 0.01 W, C-4 was simplified to a clean doublet of doublets (residual <sup>3</sup>J = 14 and 6 Hz).

A similar study of the major product of the 2-amino-6chloropurine coupling reaction confirmed that the product was the N-9 isomer. The fully coupled  $^{13}C$  NMR of the

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Scheme II



N-9 isomer 16 showed both C-8 and C-4 as doublets of triplets (C-8,  ${}^{1}J = 211$  Hz and  ${}^{3}J = 4.0$  Hz; C-4,  ${}^{3}J = 5.0$  and 2.5 Hz).

Deprotection of the benzylated coupling products 14 and 16 was accomplished by treatment with  $BCl_3$  in  $CH_2Cl_2$ followed by quenching of the reaction with methanol to give the desired 6 directly and to give a mixture of 17a and 17b from 16 (Scheme II). The methoxy group of 17b is the result of partial methanolysis of 17a during the workup of the reaction. Both 17a and 17b were converted, as a mixture, to the desired guanosine analogue 5 by treatment with hot concentrated NaOH solution.

#### **Biological** Activity

Because of the existing correlation between AdoHcy-ase inhibition and antiviral activity in the parent compound neplanocin and 7, 6 was tested for possible inhibitory activity against AdoHcy-ase. AdoHcy-ase inhibition was assessed by measuring S-adenosylhomocysteine (AdoHcy) levels in HT-29 cells treated with concentrations of 6 ranging from  $10^{-6}$  to  $10^{-4}$  M after a 24-h incubation period. However, neither changes in AdoHcy levels relative to controls nor cytotoxicity to the cells was observed with this analogue. Likewise, screening of 6 against the RNA virus, influenza type A2, resulted in no significant antiviral activity with a virus rating (VR) of only 0.3 as compared to the positive control ribavirin (VR = 2.8).<sup>15</sup>

In testing against HSV-2 in Vero cell monolayer culture, both 6 and 5 showed activity (Table I) with little or no cytotoxicity. As expected from previous results, 5, the guanosine analogue, gave the highest activity with a VR of 1.5, which was comparable to one positive control compound (ara-A, VR = 1.2) but significantly lower than the

compound	MIC <sub>50</sub> <sup>a</sup>	VR <sup>b</sup>	
3 (control)	4.3	5.1	
5	65.6	1.5	
6	939	0.6	
ara-A (control)	26.8	1.2	

<sup>a</sup> Minimum inhibitory concentration for 50% inhibition of virus-induced cytopathogenic effects (in micrograms/milliter). <sup>b</sup> Virus rating (ref 15).

other (acyclovir, VR = 5.1). The adenosine analogue **6** showed only moderate activity (VR = 0.6) at a very high dose.

Although these compounds were designed initially as extensions of the neplanocin A series, their spectrum of antiviral activity correlates better with the activities of acyclovir and DHPG. Failure of 6 to inhibit AdoHcy-ase, coupled with the inhibition of this enzyme by 7, argues in favor of the necessity of a 2'-hydroxyl function equivalent for effective interaction with the enzyme.

#### **Experimental Section**

All chemical reagents were commercially available and were purchased from either Aldrich Chemical Co. or Sigma Chemical Co. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton and <sup>13</sup>C NMR spectra were obtained on a Varian XL-200 instrument. Proton chemical shifts are expressed as  $\delta$  values with reference to Me<sub>4</sub>Si. For <sup>13</sup>C NMR, the peak positions were determined by reference to  $\text{CDCl}_3$  ( $\delta$  77.0) as an internal reference. Normal phase column chromatography was run on silica gel (EM Reagents, Kieselgel 60, 70-230 mesh) while reversed-phase column chromatography was run on bonded phase octadecyl (C18) from J. T. Baker Chemical Co. Preparative normal phase TLC was performed on Analtech taper plates (silica gel, Uniplate, 1500  $\mu$ m). Normal phase analytical TLC was performed on Analtech silica gel (GHLF, 250  $\mu$ m) and reversed-phase TLC used Analtech RPS-F  $(250 \ \mu m)$ . Elution was by the solvent or solvent gradient indicated in the experiment. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Positive fast atom bombardment (FAB) mass spectra were obtained on a VG 7070E mass spectrometer which was equipped with a FAB ion source. The sample was used either neat or as a matrix in glycerol and ionization was effected by a beam of xenon derived by neutralizing xenon ions accelerated through 8.6 kV. S-Adenosylhomocysteine hydrolase inhibition was measured as previously reported.<sup>16</sup>

<sup>(15)</sup> The virus rating, as defined by Southern Research Institute, is a measurement of selective antiviral activity which takes into account the degree of inhibition of virus-induced cytopathogenic effects and the degree of cytotoxicity produced by the test compound, determined by a modification of the method of Erlich et al. (Ehrlich J.; Sloan, B. J.; Miller, F. A.; Machamer, H. E. Ann. N.Y. Acad. Sci. 1965, 130, 5). A VR of 1.0 or greater indicates definite activity, 0.5-0.9 indicates marginal to moderate activity, and less than 0.5 indicates no significant activity.

Antiviral studies were performed under contract by Southern Research Institute, Birmingham, AL, employing herpes simplex virus type 2 (HSV-2), strain MS, propagated in Vero cell monolayer culture or influenza virus type A2/Aichi/2/68 in MDCK cell culture. Inhibitory activity was measured as the degree of inhibition of virus-induced cytopathogenic effects.

Ethyl 4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-butenoate (11). Šodium hydride (0.287 g 80% dispersion in oil, 9.6 mmol) was suspended in 10 mL of dry toluene, and the suspension was cooled in an ice bath. After a slow addition of triethyl phosphonoacetate (2.15 g, 9.6 mmol), the reaction mixture was stirred at room temperature until the NaH had reacted. The resulting yellow solution was once again cooled and 1,3-bis(benzyloxy)acetone (10; 2.58 g, 9.6 mmol) was added as a solution in 3 mL of toluene. A viscous oil formed immediately, and after 45 min of stirring at room temperature, it was dissolved by the addition of a minimum amount of absolute ethanol. The reaction mixture was stirred at room temperature for a further 45 min and then quenched by the addition of water. The product was extracted into ethyl acetate, the solvent was evaporated, and the residual water was removed azeotropically by coevaporation with ethanol. Purification was achieved by column chromatography (0.6% ethyl acetate in petroleum ether) to give 11 (2.57 g, 7.6 mmol, 79%). An analytical sample was obtained by distillation in a Kugelrohr apparatus (bp 165 °C (~0.3 torr)]: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.28 (t,  $3 \text{ H}, J = 7.3 \text{ Hz}, \text{CH}_2\text{CH}_3), 4.17 (q, 2 \text{ H}, J = 7.3 \text{ Hz}, \text{CH}_2\text{CH}_3),$ 4.30 (s, 2 H, allyl CH<sub>2</sub>), 4.52 (s, 2 H, allyl CH<sub>2</sub>), 4.59 (s, 2 H, benzyl CH<sub>2</sub>), 4.72 (s, 2 H, benzyl CH<sub>2</sub>), 6.16 (s, 1 H, vinyl H), 7.32 and 7.36 (2 br s, 10 H, aromatic protons); FAB mass spectrum (neat), m/z (relatively intensity) 341 (MH<sup>+</sup>, 19), 233 (MH – PhCH<sub>2</sub>OH, 100). Anal. (C<sub>21</sub>H<sub>24</sub>O<sub>4</sub>) C, H.

4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-buten-1-ol (12). To a cold solution of 11 (1.19 g, 3.3 mmol) in 7.5 mL of THF was added 2 mL of a previously deactivated solution of  $LiAlH_4$  (0.46 mL of ethanol was added to  $8 \text{ mL of } 1 \text{ M LiAlH}_4$  in THF). The reaction mixture was stirred at room temperature for 2 h, whereupon TLC (6% ethyl acetate in hexane) still showed starting material. A further 1.2 mL of the stock solution of  $LiAlH_4$  was added to the cooled reaction mixture. After another 30 min at room temperature, the starting material had reacted completely. The reaction mixture was guenched by the addition of methanol and then water. The resulting suspension was filtered and the solid washed thoroughly with ethyl acetate. Evaporation of the solvent gave an oil, which was purified by column chromatography (5-20% ethyl acetate in hexane) to give 12 (0.64 g, 68%). A pure sample containing a small amount of residual CH2Cl2 was obtained by preparative TLC: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.03 (s, 2 H, allyloxy  $CH_2$ ), 4.09 (s, 2 H, allyloxy  $CH_2$ ), 4.19 (d, 2 H, J = 6.7 Hz,  $CH_2OH$ ), 4.49 (s, 4 H, 2 benzyl CH<sub>2</sub>), 5.93 (t, 1 H, J = 6.7 Hz, vinyl H), 7.35 (s, 10 H, aromatic protons); FAB mass spectrum (neat), m/z(relative intensity) 299 (MH<sup>+</sup>, 15), 181 (MH - PhCH<sub>2</sub>OH, 100). Anal.  $(C_{19}H_{22}O_3, 1/_{32}CH_2Cl_2) C$ , H. 1-(Benzyloxy)-2-[(benzyloxy)methyl]-4-chloro-2-butene

1-(Benzyloxy)-2-[(benzyloxy)methyl]-4-chloro-2-butene (13). To a solution of 12 (0.443 g, 1.49 mmol) in 3.5 mL of  $CH_2Cl_2$ were added DMAP [4-(dimethylamino)pyridine (0.11 g, 0.9 mmol)], *p*-toluenesulfonyl chloride (0.346 g, 1.8 mmol), and triethylamine (0.26 mL) in sequence. After 40 min of stirring at room temperature, the reaction mixture was quenched by extraction with dilute NaHCO<sub>3</sub>, and the product was extracted into  $CH_2Cl_2$ . Chromatography (2% ethyl acetate in hexane) gave 13 (0.312 g, 66%): <sup>1</sup>H, NMR (CDCl<sub>3</sub>)  $\delta$  4.08 (s, 2 H, allyloxy CH<sub>2</sub>), 4.13 (s, 2 H, allyloxy CH<sub>2</sub>), 4.17 (d, 2 H, J = 7.9 Hz, CH<sub>2</sub>Cl), 4.50 (s, 2 H, benzyl CH<sub>2</sub>), 4.52 (s, 2 H, benzyl CH<sub>2</sub>), 5.94 (t, 1 H, J = 7.9 Hz, vinyl H), 7.33 (s, 10 H, aromatic protons).

9-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-2-butenyl]adenine (14). Adenine (0.086 g, 0.639 mmol), 13 (0.100 g, 0.318 mmol), and an excess of  $K_2CO_3$  (~1 g) were combined in Me<sub>2</sub>SO (1.5 mL). The reaction mixture was stirred at room temperature and followed by TLC (40% ethyl acetate in hexane). After 4 h, no starting material remained and the reaction mixture was quenched by pouring it into water. The products were extracted into CH<sub>2</sub>Cl<sub>2</sub>,

the solvent was evaporated, and the remaining oil was placed under high vacuum overnight to remove residual Me<sub>2</sub>SO. Purification was accomplished by column chromatography (ethyl acetate to 10% ethanol in ethyl acetate), giving  $\overline{14}$  as the first UV-absorbing product from the column as a colorless oil. Addition of ethanol to this oil produced crystals of analytical purity (0.067 g, 51%): mp 106-107.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.03 (s, 2 H, CH<sub>2</sub>O), 4.21 (s, 2 H, CH<sub>2</sub>O), 4.46 (s, 2 H, benzyl CH<sub>2</sub>), 4.53 (s, 2 H, benzyl CH<sub>2</sub>), 4.89 (d, 2 H, J = 6.9 Hz, CH<sub>2</sub>N), 5.89 (t, 1 H, J = 6.9 Hz, =CH), 6.72 (s, 2 H, NH<sub>2</sub>), 7.27 and 7.30 (10 H, phenyl protons), 7.75 (s, 1 H, H-2), 8.34 (s, 1 H, H-8); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  40.5 (CH<sub>2</sub>N), 65.9 (CH<sub>2</sub>O), 71.9 (CH<sub>2</sub>O), 72.4 and 72.8 (benzyl  $CH_2$ 's), 119.4 (C-5, d,  ${}^{3}J = 8.0$  Hz), 124.1 (=CH), 127.5-128.3, 137.6, and 137.8 (phenyl carbons), 138.8 (>C=), 139.9 (C-8, dt,  ${}^{1}J = 210 \text{ Hz}, {}^{3}J = 3.9 \text{ Hz}), 149.8 (C-4, m), 152.7 (C-2, d, {}^{1}J = 201$ Hz), 155.7 (C-6, d,  ${}^{3}J$  = 11.3 Hz). Anal. (C<sub>24</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>) C, H, N.

2-Amino-9-[4-(benzyloxy)-3-[(benzyloxy)methyl]-2-butenyl]-6-chloropurine (16). In a procedure similar to that described for the synthesis of 14, 2-amino-6-chloropurine (0.225 g, 1.330 mmol), 13 (0.210 g, 0.664 mmol), and  $K_2CO_3 \sim 1$  g) were combined in 2 mL of Me<sub>2</sub>SO. After stirring for 4 h at room temperature, the reaction mixture was quenched by the addition of water. Extraction of the products into CH<sub>2</sub>Cl<sub>2</sub>, followed by the evaporation of the solvents, produced a solid residue. Chromatography (40% ethyl acetate in hexane) gave 16, the first major eluent from the column, as colorless crystals (0.160 g, 54%), upon evaporation of the solvent. The solid was recrystallized from ethyl acetate: mp 103.5–104.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.03 (s, 2 H, CH<sub>2</sub>O), 4.20 (s, 2 H, CH<sub>2</sub>O), 4.48 (s, 2 H, benzyl CH<sub>2</sub>), 4.54 (s, 2 H, benzyl CH<sub>2</sub>), 4.78 (d, 2 H, J = 7.0 Hz, CH<sub>2</sub>N), 5.29 (s, 2 H, NH<sub>2</sub>), 5.84 (t, 1 H, J = 7.0 Hz, =-CH), 7.29 and 7.32 (10 H, phenyl protons), 7.72 (s, 1 H, H-8); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 40.6  $(CH_2N)$ , 66.0  $(CH_2O)$ , 71.9  $(CH_2O)$ , 72.5 and 72.9  $(benzyl CH_2's)$ , 123.6 (=CH) 125.1  $(C-5, d, {}^3J = 11.5 Hz)$ , 127.6–128.4, 137.6, and 137.8 (phenyl carbons), 139.0 (>C=), 141.9 (C-8, dt, <sup>1</sup>J = 211 Hz,  ${}^{3}J = 4.0$  Hz), 151.1 (C-6, s), 153.6 (C-4, dt,  ${}^{3}J = 5.0$  and 2.5 Hz), 159.1 (C-2, s). Anal. (C<sub>24</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>Cl) C, H, N, Cl.

Deprotection of Dibenzylated Acyclic Nucleoside Analogues. The benzylated nucleoside analogue ( $\sim 0.15$  mmol) was dissolved in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> and cooled to -78 °C. An 1 M boron trichloride solution in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL, 1.5 mmol) was added, and the reaction mixture was stirred at -78 °C for 1.5 h and then slowly warmed to 0 °C. After a total time of 2 h, the reaction mixture was cooled again to -78 °C cand quenched by the addition of methanol. The solvents were evaporated, and methanol was added and evaporated several times to remove the boron as trimethylborate. The products were treated as described individually below.

9-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]adenine (6). The oil that resulted from the deprotection was dissolved in a minimum amount of methanol, whereupon analytically pure crystals of the HCl salt formed (80%): mp 201-202 °C; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  3.49 (s, 2 H, CH<sub>2</sub>O), 3.67 (s, 2 H, CH<sub>2</sub>O), 4.40 (d, 2 H, J = 7.4 Hz, CH<sub>2</sub>N), 5.16 (t, 1 H, J = 7.4 Hz, =CH), 7.67 (s, 1 H, H-8), 7.74 (s, 1 H, H-2); FAB mass spectrum (glycerol), m/z (relative intensity) 236 (MH<sup>+</sup>, 100), 136 (b + 2 H, 62). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>·HCl) C, H, N.

Mixture of 2-Amino-6-chloro-9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]purine (17a) and 2-Amino-9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]-6-methoxypurine (17b). Deprotection of 16 resulted in a mixture of 17a and 17b due to partial methanolysis of 17a during the workup. The mixture was used directly without further purification.

9-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]guanine (5). The mixture obtained from the deprotection of 0.21 mmol of 17 was dissolved in a solution of NaOH (0.56 g, 14 mmol) in 6 mL of H<sub>2</sub>O. The reaction mixture was heated at 80 °C for 2 h until reversed-phase TLC (20% CH<sub>3</sub>OH in H<sub>2</sub>O) indicated disappearance of the two starting materials ( $R_f$  0.4 and 0.5) and appearance of the product at  $R_f$  0.7. Neutralization of the reaction with 1 equiv of acetic acid gave a cloudy solution, which was dried by lyophilization to give an off-white powder. Purification was accomplished by reversed-phase column chromatography (H<sub>2</sub>O to 20% CH<sub>3</sub>OH in H<sub>2</sub>O) followed by lyophilization of the solvent to produce a white powder. An analytically pure sample of 5 (24 mg, 45% from 17) was obtained by precipitation from water by

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the addition of CH<sub>3</sub>CN: mp 240–250 °C dec; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  4.11 (s, 2 H, CH<sub>2</sub>O), 4.27 (s, 2 H, CH<sub>2</sub>O), 4.40 (br m, 2 H, CH<sub>2</sub>N), 5.73 (t, 1 H, J = 8 Hz, —CH), 7.73 (s, 1 H, H-8); FAB mass spectrum (glycerol), m/z (relative intensity) 252 (MH<sup>+</sup>, 79), 152 (b + 2 H, 45). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub>) C, H, N.

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# Hexahydro-1*H*-1-pyrindines from Acid Rearrangement of 9-Alkylidene-5-(*m*-methoxyphenyl)-2-methylmorphans. A New Structural Type of Narcotic Antagonists

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9-Methylene- and 9-ethylidene-5-(*m*-methoxyphenyl)-2-methylmorphans (1, 2) and refluxing 48% HBr have given rearrangement products 3 and 4, respectively. The structure of 4 [4a-ethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1H-1-pyrindine] was determined by X-ray crystallography and that of 3 [1,4a-dimethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1H-pyrindine] follows from analogy and NMR data. Compounds 3 and 4 are opioid antagonists of about the potency of nalorphine in the tail-flick vs. morphine assay and precipitate a complete abstinence syndrome in morphine-dependent monkeys. Both are nearly devoid of antinociceptive activity and they have about 0.025 times the affinity of nalorphine for the  $\mu$  opioid receptor.

 $5-(m-Hydroxyphenyl)-2-methylmorphan^{1,2}$  (5) (a flexible molecule compared with morphine) and its optical isomers<sup>3</sup> have strong antinociceptive properties. The (-)-isomer will not substitute for morphine in dependent monkeys and in fact, like nalorphine and related antagonists, precipitates a strong withdrawal syndrome<sup>3-5</sup> but binds weakly to  $\mu$ receptors.<sup>4</sup> Addition of a 9-methyl substituent to 5 virtually abolishes antinociceptive activity and induces properties of antagonism to the molecule.<sup>4</sup> It seemed of interest to "freeze" the (equatorial) phenyl substituent of 5 to the cyclohexane ring in order to provide a more rigid structure. Synthesis and biological study of several derivatives of 5, in which the *m*-hydroxyphenyl substituent is conformationally restricted by oxide bridging to the morphan moiety, have been described.<sup>6-10</sup> Attempts to bridge the phenyl and cyclohexane rings of 9-methyleneand 9-ethylidene-5-(m-methoxyphenyl)-2-methylmorphans (1, 2) gave rearrangement products 3 and 4. The constitution and some biological properties of 3 and 4 are described herein.

**Chemistry.** On treatment of 5-(m-methoxyphenyl)-9methylene-2-methylmorphan (1)<sup>4</sup> with boiling 48% HBr, contraction of the cyclohexane ring occurred, giving the hexahydro-1*H*-pyrindine (3) instead of the desired fusion of the 9-methylene carbon to the benzene ring (Scheme I). The same type of rearrangement occurred with the 9-ethylidene homologue (2), giving 4, despite the presumed hyperconjugative-inductive effect of the ethylidene group of 2.<sup>11</sup>



The structure of 4 was determined by X-ray crystallography of the hydrobromide salt. NMR and mass

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