animals were placed individually on top of a square (13 cm × 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 observed 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_{50} 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.

Acknowledgment. We thank Joseph Krushinski for initial preparation of **8**, Dr. Bob Rathbun for his interest and helpful discussions, and Patsy Abbett for typing the manuscript.

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Synthesis and Biological Activity of Unsaturated Carboacyclic Purine Nucleoside Analogues†

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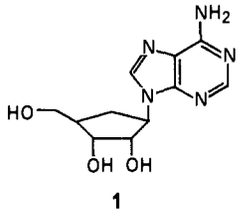
Two new carboacyclic nucleoside analogues, 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]adenine (**6**) and 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]guanine (**5**), modeled on the unsaturated carbocyclic nucleoside analogue neplanocin A (**2**), have been synthesized and tested for antiviral activity against 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 μg/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.[1] 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



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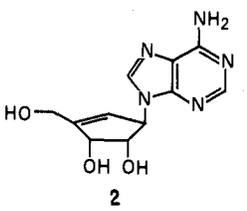

2

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.[2] The synthesis of the guanosine analogue of **2** has been reported but with only limited accompanying biological activity data.[3]

Since the discovery of the potent and highly selective antiherpetic activity of acyclovir (**3**),[4] 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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§ National Cancer Institute.

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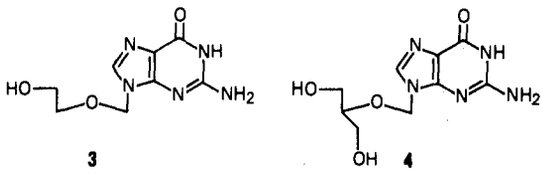
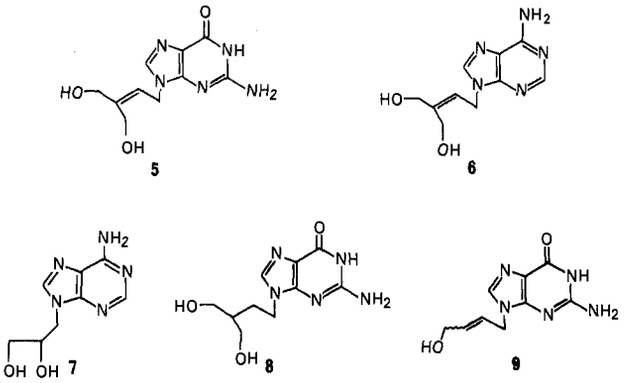


3 4

unique structural elements of the neplanocin carbocyclic nucleoside series and DHPG. These efforts resulted in the syntheses of the unsaturated carboacyclic analogue 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]guanine (**5**) and its adenosine analogue 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]adenine (**6**). Other types of carboacyclic nucleoside analogues have been reported recently including 9-(2,3-dihydroxypropyl)adenine (**7**)[2] and the saturated carboacyclic DHPG analogue **8**.[7] 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.[7]



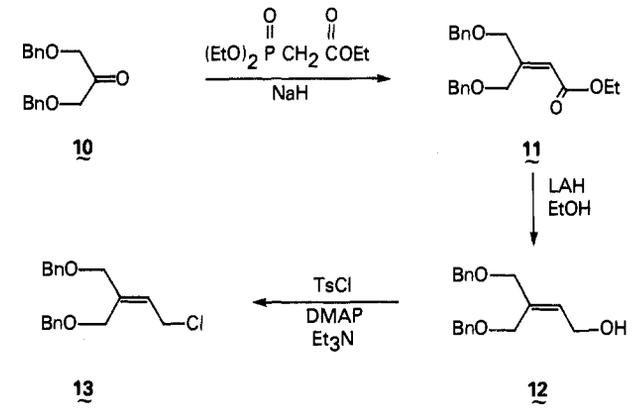
5 6 7 8 9

A variety of carboacyclic guanosine analogues were patented in 1982, including the unsaturated carboacyclic analogue of acyclovir (**9**),[8] 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 μM, respectively) for HSV-1 thymidine kinase and higher ID_{90} values (10 and 25 μM, respectively) against HSV-1 in Vero cells when compared to DHPG analogue **8** (K_i = 1.5 μM and ID_{90} = 1 μM).[9] More recently, an ID_{50} of 3 μM against HSV-1 C-42 plaque formation has been reported for compound **5** by the same group.[10]

Chemistry

Synthesis of the target compounds was initiated from the known bis(benzyloxy)acetone (**10**)[11] (Scheme I). Reaction 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 $LiAlH_4$ which had been deactivated with 1 molar equiv of ethanol[12] 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**),[13] 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,[14] the yield of **13** was increased to 66%.

Scheme I



10 11 12 13

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 2-amino-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 ^{13}C NMR studies. The fully coupled ^{13}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 (^1J = 210 Hz and ^3J = 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 ^3J = 14 and 6 Hz).

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

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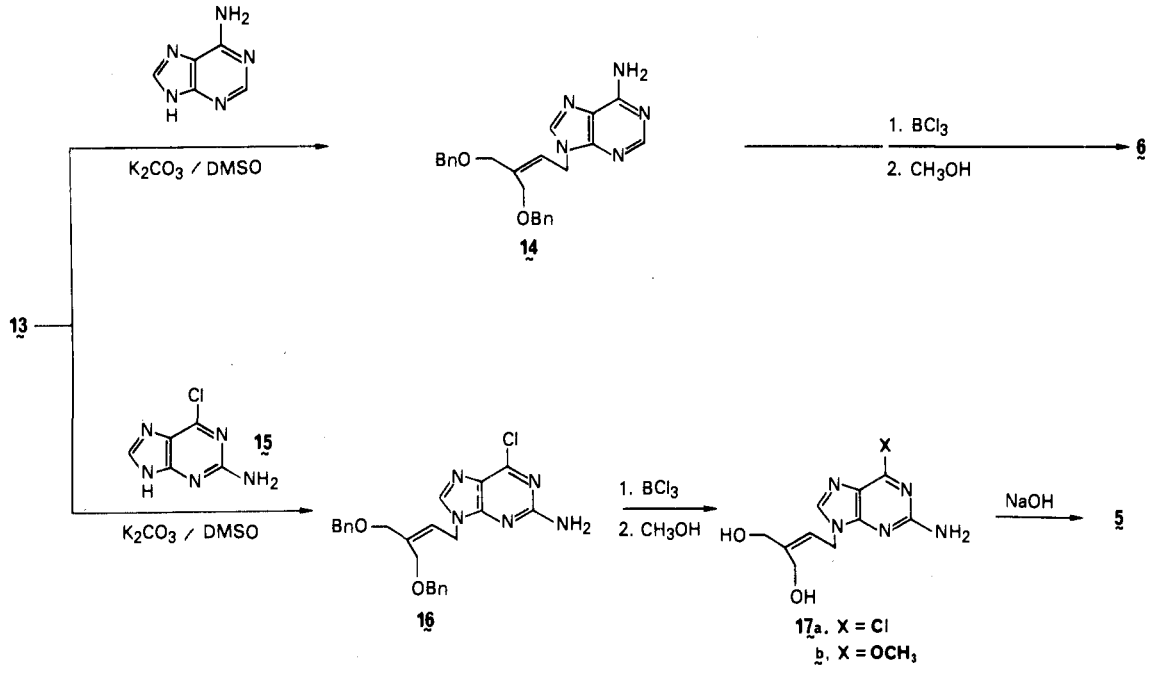
Scheme II



N-9 isomer **16** showed both C-8 and C-4 as doublets of triplets (C-8, ^1J = 211 Hz and ^3J = 4.0 Hz; C-4, ^3J = 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).[15]

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

Table I. Inhibition of HSV-2

compound	MIC_{50}[a]	VR[b]
3 (control)	4.3	5.1
5	65.6	1.5
6	939	0.6
ara-A (control)	26.8	1.2

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

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 ^{13}C NMR spectra were obtained on a Varian XL-200 instrument. Proton chemical shifts are expressed as δ values with reference to Me_4Si. For ^{13}C NMR, the peak positions were determined by reference to $CDCl_3$ (δ 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 (C_{18}) from J. T. Baker Chemical Co. Preparative normal phase TLC was performed on Analtech taper plates (silica gel, Uniplate, 1500 μm). Normal phase analytical TLC was performed on Analtech silica gel (GHLF, 250 μm) and reversed-phase TLC used Analtech RPS-F (250 μm). 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.[16]

(15) 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). Sodium 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)]: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 4.17 (q, 2 H, J = 7.3 Hz, CH_2CH_3), 4.30 (s, 2 H, allyl CH_2), 4.52 (s, 2 H, allyl CH_2), 4.59 (s, 2 H, benzyl CH_2), 4.72 (s, 2 H, benzyl CH_2), 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^+, 19), 233 (MH - $PhCH_2OH$, 100). Anal. ($C_{21}H_{24}O_4$) 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 mL of 1 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 quenched 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 CH_2Cl_2 was obtained by preparative TLC: ^{1}H NMR ($CDCl_3$) 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_2), 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^+, 15), 181 (MH - $PhCH_2OH$, 100). Anal. ($C_{19}H_{22}O_3 \cdot {}^1/_{32}CH_2Cl_2$) C, H.

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 $NaHCO_3$, and the product was extracted into CH_2Cl_2. Chromatography (2% ethyl acetate in hexane) gave **13** (0.312 g, 66%): ^{1}H, NMR ($CDCl_3$) δ 4.08 (s, 2 H, allyloxy CH_2), 4.13 (s, 2 H, allyloxy CH_2), 4.17 (d, 2 H, J = 7.9 Hz, CH_2Cl), 4.50 (s, 2 H, benzyl CH_2), 4.52 (s, 2 H, benzyl CH_2), 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_2SO (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_2Cl_2, the solvent was evaporated, and the remaining oil was placed under high vacuum overnight to remove residual Me_2SO. Purification was accomplished by column chromatography (ethyl acetate to 10% ethanol in ethyl acetate), giving **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; ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 2 H, CH_2O), 4.21 (s, 2 H, CH_2O), 4.46 (s, 2 H, benzyl CH_2), 4.53 (s, 2 H, benzyl CH_2), 4.89 (d, 2 H, J = 6.9 Hz, CH_2N), 5.89 (t, 1 H, J = 6.9 Hz, =C*H*), 6.72 (s, 2 H, NH_2), 7.27 and 7.30 (10 H, phenyl protons), 7.75 (s, 1 H, H-2), 8.34 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) δ 40.5 (CH_2N), 65.9 (CH_2O), 71.9 (CH_2O), 72.4 and 72.8 (benzyl CH_2's), 119.4 (C-5, d, ^3J = 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, ^1J = 210 Hz, ^3J = 3.9 Hz), 149.8 (C-4, m), 152.7 (C-2, d, ^1J = 201 Hz), 155.7 (C-6, d, ^3J = 11.3 Hz). Anal. ($C_{24}H_{25}N_5O_2$) 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 ~1 g) were combined in 2 mL of Me_2SO. After stirring for 4 h at room temperature, the reaction mixture was quenched by the addition of water. Extraction of the products into CH_2Cl_2, 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; ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 2 H, CH_2O), 4.20 (s, 2 H, CH_2O), 4.48 (s, 2 H, benzyl CH_2), 4.54 (s, 2 H, benzyl CH_2), 4.78 (d, 2 H, J = 7.0 Hz, CH_2N), 5.29 (s, 2 H, NH_2), 5.84 (t, 1 H, J = 7.0 Hz, =C*H*), 7.29 and 7.32 (10 H, phenyl protons), 7.72 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) 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, ^1J = 211 Hz, ^3J = 4.0 Hz), 151.1 (C-6, s), 153.6 (C-4, dt, ^3J = 5.0 and 2.5 Hz), 159.1 (C-2, s). Anal. ($C_{24}H_{25}N_5O_3Cl$) C, H, N, Cl.

Deprotection of Dibenzylated Acyclic Nucleoside Analogues. The benzylated nucleoside analogue (~0.15 mmol) was dissolved in 3 mL of CH_2Cl_2 and cooled to −78 °C. An 1 M boron trichloride solution in CH_2Cl_2 (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 and 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; ^{1}H NMR (D_2O) δ 3.49 (s, 2 H, CH_2O), 3.67 (s, 2 H, CH_2O), 4.40 (d, 2 H, J = 7.4 Hz, CH_2N), 5.16 (t, 1 H, J = 7.4 Hz, =C*H*), 7.67 (s, 1 H, H-8), 7.74 (s, 1 H, H-2); FAB mass spectrum (glycerol), m/z (relative intensity) 236 (MH^+, 100), 136 (b + 2 H, 62). Anal. ($C_{10}H_{13}N_5O_2 \cdot HCl$) 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_2O. The reaction mixture was heated at 80 °C for 2 h until reversed-phase TLC (20% CH_3OH in H_2O) 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_2O to 20% CH_3OH in H_2O) 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_3CN: mp 240–250 °C dec; ^1H NMR (D_2O) δ 4.11 (s, 2 H, CH_2O), 4.27 (s, 2 H, CH_2O), 4.40 (br m, 2 H, CH_2N), 5.73 (t, 1 H, J = 8 Hz, =C*H*), 7.73 (s, 1 H, H-8); FAB mass spectrum (glycerol), m/z (relative intensity) 252 (MH^+, 79), 152 (b + 2 H, 45). Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

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Registry No. 5, 99776-28-0; 6·HCl, 107053-43-0; 10, 77356-14-0; 11, 107053-40-7; 12, 107053-41-8; 13, 99776-39-3; 14, 107053-42-9; 15, 10310-21-1; 16, 99796-40-4; 17a, 107053-44-1; 17b, 107053-45-2; triethyl phosphonoacetate, 867-13-0; adenine, 73-24-5.

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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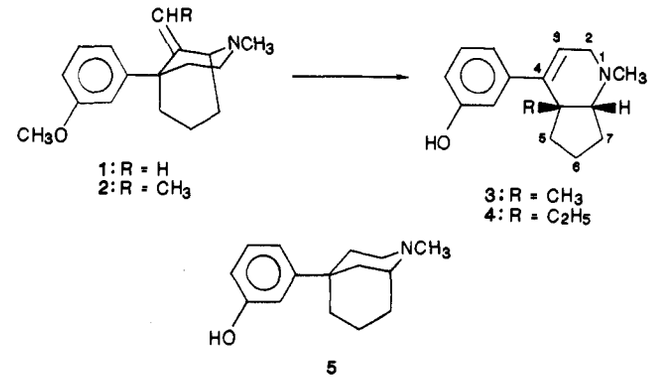
9-Methylene- and 9-ethylidene-5-(*m*-methoxyphenyl)-2-methylmorphans (1, 2) and refluxing 48% HBr have given rearrangement products 3 and 4, respectively. The structure of 4 [4a-ethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-1-pyrindine] was determined by X-ray crystallography and that of 3 [1,4a-dimethyl-2,4a,5,6,7,7a-hexahydro-4-(3-hydroxyphenyl)-1-methyl-1*H*-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 μ opioid receptor.

5-(*m*-Hydroxyphenyl)-2-methylmorphan[1,2] (5) (a flexible molecule compared with morphine) and its optical isomers[3] 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[3–5] but binds weakly to μ receptors.[4] Addition of a 9-methyl substituent to 5 virtually abolishes antinociceptive activity and induces properties of antagonism to the molecule.[4] 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.[6–10] Attempts to bridge the phenyl and cyclohexane rings of 9-methylene- and 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)-9-methylene-2-methylmorphan (1)[4] 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.[11]

Scheme I



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

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