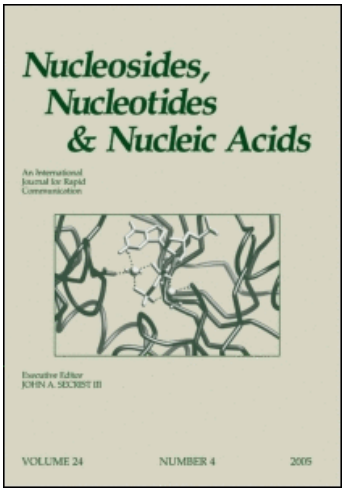

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Cyclohexenyl Nucleosides and Related Compounds

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CYCLOHEXENYL NUCLEOSIDES AND RELATED COMPOUNDS

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ABSTRACT: Cis and trans-1-(4-hydroxy-2-cyclohexenyl)- and 1-(2-hydroxy-5-cyclohexenyl)thymines were obtained by stereospecific routes. Oxidation of the 1,4-products afforded 1-(4-oxo-2-cyclohexenyl)thymine, the carbocyclic analog of a reportedly antiviral ketopyranosyl nucleoside. Exclusive 1,6-conjugate addition occurred with heterocyclic bases and methyl 1,3-cyclohexadiene-1-carboxylate. Reduction of the thymine adduct gave 1-(4-hydroxymethyl-3-cyclohexenyl)thymine. Michael-type addition provided a direct route to 3-oxocycloalkyl nucleosides, and lactone nucleosides resulted from addition of bases to α-methylene-γ-butyrolactone. Anti-HIV screening revealed no activity for the new compounds.

The broad spectrum antiviral activity of the naturally occurring nucleosides neplanocin A[1] and aristeromycin[2] stimulated interest in carbocyclic nucleoside analogs.[3] These compounds, in which the furanosyl oxygen is replaced by carbon, lack the N-glycoside link and are thus not susceptible to enzymatic cleavages that degrade their oxygenated counterparts.[4] Carbovir (1), a reverse transcriptase inhibitor, has emerged as a promising anti-HIV agent,[5] and the carbocyclic oxetanocin derivatives cyclobut-A and -G (2) are effective against a variety of pathogenic viruses.[6] The activity of 2 suggested ring-size as a variable in the construction of carbocyclic nucleoside analogs. Accordingly, we have investigated synthetic paths to 6-membered carbocycles.

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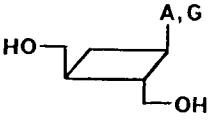

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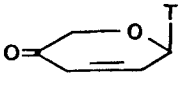
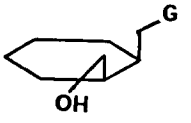


3

A number of pyranosyl nucleosides have been examined for antitumor and antiviral activity. Pedersen et al found no activity for either a series of 2',3'-unsaturated pyranosyl 5-aminouracils[7] or 3'-azidopyranosyl nucleosides,[8] and similar results were reported for other ketopyranosyl derivatives.[9] On the other hand, anti-HIV activity was attributed to a hexopyranosyl analog of AZT.[10] Additionally, ketopyranosyl compound 3 reportedly exhibits anti-HIV properties.[11] Although its mode of action was not described, it appeared probable that 3 functions as a Michael acceptor capable of alkylating nucleophilic biological groups.[12] The carbocyclic analog of 3 (9) which might function similarly was therefore of interest.

Six-membered cycloalkyl nucleosides have received limited attention. Early studies showed that 9-cyclohexyladenine exhibits antitumor activity,[13] and more recently it has been identified as a potent inhibitor of phosphatidylinositol 4-kinase.[14] Compound 4, another cyclohexyl-based nucleoside,



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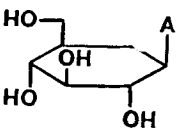

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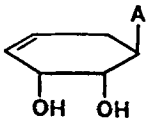
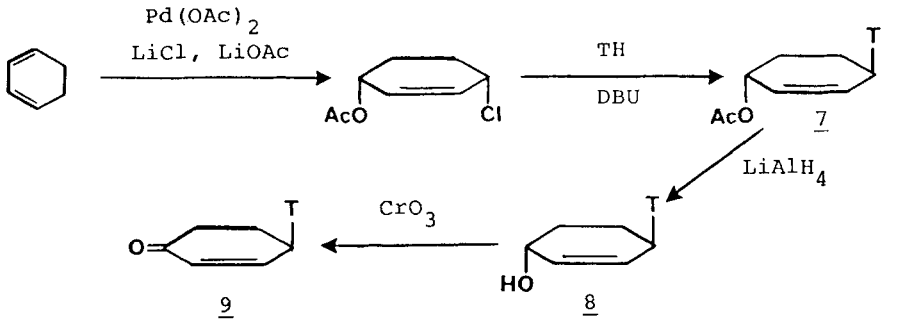


6

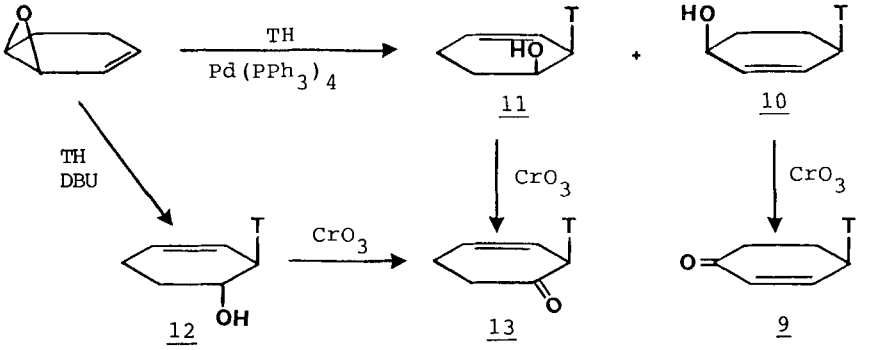
suppressed reactivation of latent HSV-1.[15] Carbocyclic 9-(ß-glucopyranosyl)adenine (5) has also been synthesized.[16] Recently, hydroxylated cyclohexyl- and cyclohexenyladenines e.g. 6 were prepared and found to be devoid of inhibitory activity against S-adenosylhomocysteine hydrolase.[17] The present work describes synthetic approaches to cyclohexenyl, 3-oxocycloalkyl and lactone nucleosides. The latter have been previously obtained by other routes.[18]

CHEMISTRY. 1-(4-Oxo-2-cyclohexenyl)thymine (9), the carbocyclic analog of 3, was prepared as shown in Scheme 1. As previously described, Pd-catalyzed 1,4-chloroacetoxylation of 1,3-cyclohexadiene gave cis-1-acetoxy-4-chloro-2-cyclohexene in excellent yield.[19] Under S_N2 conditions thyminyl anion displaced the allylic chloride to give the trans-4-acetoxy product 7. The crude product showed no evidence (NMR) of cis or rearranged products. Conversion to alcohol 8 by hydride reduction, followed by Jones oxidation completed the sequence (21% from

SCHEME 1



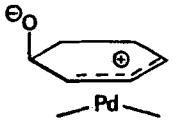
SCHEME 2



cyclohexadiene). The NMR of 9, particularly the deshielded ß-H (δ 6.98), confirmed the α,β-unsaturated ketone structure.

Addition of thymine to 3,4-epoxycyclohexene in the presence of tetrakis(triphenylphosphine)Pd(0) gave the expected cis-1-(4-hydroxy-2-cyclohexenyl)thymine (10), as well as substantial amounts (~20%) of an isomeric product (11) (Scheme 2). The identity of 10 was established by oxidation to 1-(4-oxo-2-cyclohexenyl)thymine (9), identical to that obtained from 8. Compound 11, on the other hand, was similarly oxidized to a different unsaturated, nonconjugated ketone (13). In accord with previous results, uncatalyzed nucleophilic ring-opening of the epoxide occurred with inversion of configuration and exclusive attack at the allylic position[20] giving trans-1-(2-hydroxy-5-cyclohexenyl)thymine (12). Oxidation of 12 afforded ketone 13, confirming the 1,2-substituent pattern of 11.

Assignment of the 1,2-substituent pattern of 11 and 12, as well as the 1,4-substituent pattern of 8 and 10, was substantiated by their COSY spectra. Strong coupling was observed between the easily recognized H_1, and H_2, in 11 and 12 while no coupling was seen for the corresponding H_1, and H_4, of the 1,4-substituted products 8 and 10. Formation of both cis-1,2 and cis-1,4 alcohols (10,11) in the Pd (0)-catalyzed reaction presumably arises from the common π-allyl intermediate 14. Exclusive cis-1,2-addition has been described in the adenine series,[17] as well as other examples of cis-1,4-addition.[17,21]



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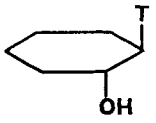

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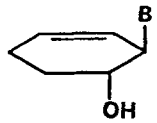
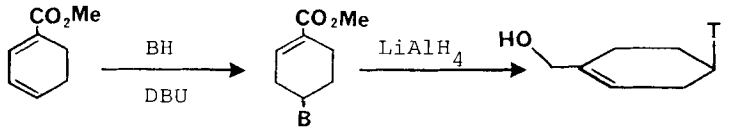


16 a. B = 9-adenyl
b. = 2-amino-6-chloro-9-purinyl
c. = 9-guanyl

Nucleophilic addition of bases to epoxide was further explored as a convenient, high-yield route to 6-membered carbocyclic nucleoside analogs. Cyclohexene oxide reacted well with thymine to produce 15, and 3,4-epoxycyclohexene afforded 16a,b with adenine and 2-amino-6-chloropurine. Hydrolysis of 16b gave the 9-guanyl derivative 16c.

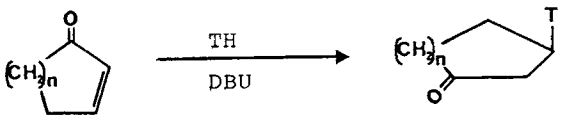
Conjugate addition of heterocyclic bases to methyl 1,3-cyclohexadiene-1-carboxylate was found to be an efficient route to 4-hydroxymethyl-3-cyclohexenyl nucleosides. With thymine, adenine and 2-amino-6-chloropurine only 1,6-addition was observed. The NMR of each adduct showed a single deshielded ß-proton (δ6.7-6.9) establishing the α,ß-unsaturated structures 17a-c. Lithium aluminum hydride reduction of 17a gave 1-(4-hydroxymethyl-3-cyclohexenyl)thymine.



17 a. B = 1-thyminyl
b. = 9-adenyl
c. = 2-amino-6-chloro-9-purinyl

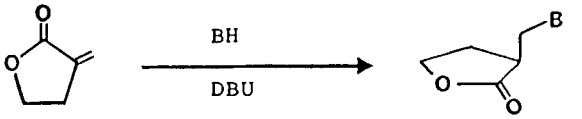
18

The efficacy of Michael-type addition for the preparation of nucleoside analogs has been noted previously.[22] Two additional examples of the reaction were examined. 3-Oxocycloalkyl adducts (19a-c) resulted from base-catalyzed addition of thymine to 2-cycloalkenones. Unfavorable equilibria with 2-cyclopentenone and



19 a. n=1
b. =2
c. =3

2-cyclohexenone, however, necessitated employment of 20-30 fold excess of the Michael acceptors to obtain satisfactory yields. (Excess ketone may be recovered by distillation or chromatography.) Although inefficient, the reaction provides a direct route to 3'-keto nucleosides. With α-methylene-γ- butyrolactone, on the other hand, excellent yields of lactones 20a-c were obtained. The 9-guanyl compound was prepared by hydrolysis of 20c.



20 a. B = 1-thyminyl
b. = 9-adenyl
c. = 2-amino-6-chloro-9-purinyl
d. = 9-guanyl

BIOLOGICAL RESULTS. Several of the compounds prepared in this work were evaluated in the in vitro NCI Anti-HIV Screening Program. Although some were cytotoxic (IC_{50} <0.20 mM: 9,16b,17b, c,19a-c,20c,d), none were active against HIV-I. The following compounds were screened: 8-12,15,16a-c,17a-c, 19a-c and 20a-d.

EXPERIMENTAL

General Methods. Melting points are uncorrected. NMR (^1H) spectra were obtained with a Bruker (IBM) 200 AC (200 MHz) instrument on DMSO-D_6 solutions with TMS as an internal standard.

UV spectra were recorded with a Carey 2300 spectrophotometer. Thin layer chromatography used silica gel plates (EK-F254) and column chromatography employed Merck silica gel (230-400 mesh). Preparative rotary chromatography was performed with a Chromatotron Model 7924 apparatus. Elemental analyses were done by Atlantic Microlab, Norcross, GA, USA.

trans-1-(4-Acetoxy-2-cyclohexenyl)thymine (7). A solution of cis-1-acetoxy-4-chloro-2-cyclohexene[19] (13.97g, 80.0 mmol), thymine (7.57g, 60 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 12.18g, 80.0 mmol) in dimethylformamide (100 mL) was stirred and heated (80-90°C) for 25 h. Volatile material was removed under reduced pressure (80°, 1 mm) and the crude product was suspended in aqueous ammonium chloride. The dark suspension was extracted with $CHCl_3$ (4x100-mL) and the extracts washed with 100 mL portions of 0.2 M HCl, H_2O, $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), charcoal decolorization, and removal of solvent in vacuo, 7 (5.47 g 35%) was obtained. Recrystallized from toluene, mp 238-240°C. NMR:δ 11.28 (s, 1, NH_2); 7.33 (s, 1, C(6)H); 5.91 (d, J=10 Hz, 1, C(3')H); 5.72 (d, J=10 Hz, 1, C(2')H); 5.39 (m,1,C(4')H); 5.11 (m,1,C(1')H); 2.04 (s,3,CH_3CO); 1.77 (s,3,CH_3); 1.2-1.7 (m, 4, C(5',6')H). Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.06; H, 6.10; N, 10.54.

trans-1-(4-Hydroxy-2-cyclohexenyl)thymine (8). Under N_2, a solution of 7 (2.00 g, 7.57 mmol) in THF (125 mL) was added dropwise to a stirred solution of lithium aluminum hydride (0.59 g, 15.5 mmol) in THF (30 mL). After stirring 0.5 h, water (1.12 mL, 62 mmol) was cautiously added, followed by glacial acetic acid (30 drops). The suspension was filtered, the residue rinsed with THF, and the combined filtrate was dried ($MgSO_4$) and evaporated to give 8 (1.28 g, 76%). Recrystallized from MeOH, mp 244-246°C. UV (MeOH) λ_{max} 272 nm. NMR: δ 11.27 (s, 1, NH); 7.25 (s, 1, C(6)H); 5.95 (d, J=10.3 Hz, 1, C(3')H); 5.50 (d, J=10.3 Hz, 1, C(2')H); 5.04 (m, 1, C(1')H); 4.98 (d, D_2O exch., 1, OH); 4.19 (m, 1, C(4')H); 1.76 (s, 3, CH_3); 1.4-1.9 (m, 4, C(5', 6')H). Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.35; H, 6.39; N, 12.60.

1-(4-Oxo-2-cyclohexenyl)thymine (9). A stirred solution of 8 (0.301 g, 1.35 mmol) in acetone (150 mL) was cooled to 0°C and treated with Jones Reagent (ca. 50 drops) until a permanent yellow-orange color was obtained. Isopropyl alcohol (1 mL) was added, followed by solid $NaHCO_3$ (1.50 g). After 0.5 h the

suspension was filtered through a plug of silica gel (5 g) and washed with additional acetone. Removal of the solvent under reduced pressure gave 9 (0.261 g, 88%). Recrystallized from MeOH-EtOAc, mp 251-253°C. UV (MeOH) λ_{max} 269 nm. NMR: δ 11.35 (s, 1, NH); 7.45 (s, 1, C(6)H); 6.99 (d, J=10.2 Hz, 1, C(2')H); 6.05 (d, J=10.2 Hz, 1, C(3')H); 5.40 (m, 1, C(1')H); 1.77 (s, 3, CH_3); 1.6-2.6 (m, 4, C(5',6')H). Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.08; H, 5.52; N, 12.76.

cis-1-(4-Hydroxy-2-cyclohexenyl)thymine (10) and cis-1-(2-hydroxy-5-cyclohexenyl)thymine (11). Thymine (4.48 g, 35.5 mmol) and anhydrous dimethylsulfoxide (40 mL) were placed in a 3-neck 250 mL flask (wrapped with aluminum foil to exclude light) and tetrakis(triphenylphosphine)Pd (0.391 g, 3.38 mmol) was added under a N_2 atmosphere. After stirring 5 min at room temperature the mixture was cooled to 0°C and a solution of 3,4-epoxycyclohexene[23] (3.10 g, 32.2 mmol) in THF (35 mL) was added dropwise over 20 min. The mixture was allowed to warm slowly to room temperature (overnight) and volatile material including DMSO was removed in vacuo giving a light yellow solid. TLC ($CHCl_3$-MeOH, 8:2) showed, in addition to unreacted thymine, two organic products, ca.5:1. The crude product was suspended in aqueous NH_4Cl (half saturated, 100 mL) and continuously extracted with $CHCl_3$ for 2 days. The resulting extract was free of thymine. After drying and removal of the solvent crude product (7.16 g, 89%) was obtained. A 500 mg sample was separated by rotary chromatography. Elution with 2% MeOH in $CHCl_3$ gave the pure minor product 11 (62 mg); elution with 4% MeOH in $CHCl_3$ gave pure 10 (209 mg). Mixtures of 10 and 11 were also collected.

Compound 10. Recrystallized from MeOH-EtOAc, mp 227-229°C. UV (MeOH) λ_{max} 271 nm. NMR: δ 11.27 (s, 1, NH); 7.32 (s, 1, C(6)H); 6.07 (dm, J=10 Hz, 1, C(3')H); 5.60 (dd, J=10, 2 Hz, 1, C(2')H); 4.92 (m, 1, C(1')H); 4.89 (m, D_2O exch., 1, OH); 3.99 (m, 1, C(4')H); 1.78 (s, 3, CH_3); 1.6-1.8 (m, 4, C(5', 6')H). The COSY spectrum showed no coupling between C(1')H and C(4')H. Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.35; H, 6.37; N, 12.52.

Oxidation of 10 with CrO_3 (see 9 above) gave 9 (85%) identical to that obtained from 8.

Compound 11. Recrystallized from MeOH-EtOAc, mp 205-207°C. UV (MeOH) λ_{max} 269 nm. NMR: δ 11.19 (s, 1, NH); 7.12 (s, 1, C(6)H); 6.01 (m, 1, C(5')H); 5.40 (d, J=10.1 Hz, C(6')H); 5.40 (s, D_2O exch., 1, OH); 5.02 (m, 1, C(1')H); 3.93 (m, 1, C(2')H);

1.75 (s, 3, CH_3); 1.6-2.2 (m, 4, C(3',4')H). Coupling was observed in the COSY spectrum between C(1')H and C(2')H. Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.42; H, 6.39; N, 12.56.

Oxidation of 11 with CrO_3 (see 9 above) gave ketone 13 (69%).

trans-1-(2-Hydroxy-5-cyclohexenyl)thymine (12). A stirred solution of thymine (0.252 g, 2.00 mmol), 3,4-epoxycyclohexene[23] (0.240 g, 2.50 mmol), DBU (0.310 g, 2.04 mmol) and DMF (5 mL) was heated at 90-100°C for 6 h. After removal of the solvent (100°C, 1 mm) the crude product was suspended in aqueous NH_4Cl and extracted continuously with $CHCl_3$ for 2 days. The extract was dried ($MgSO_4$), the solvent evaporated and the product recrystallized from water to give 12 (0.143 g, 32%), mp 238-240°C. NMR: δ 11.17 (s, 1, NH); 7.28 (s, 1, C(6)H); 5.86 (dm, 1, C(5')H); 5.36 (d, J=9.8 Hz, 1, C(6')H); 5.09 (d, D_2O exch., 1, OH); 4.86 (m, 1, C(1')H); 2.16 (m, 2, C(4')H); 1.77 (s, 3, CH_3); 1.6-1.8 (m, 2, C(3')H). Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.32; H, 6.32; N, 12.57.

1-(2-Oxo-5-cyclohexenyl)thymine (13). Prepared from 12 as described for 9 (77%). Recrystallized from MeOH-EtOAc, mp 211-213°C. NMR: δ 11.34 (s, 1, NH); 7.16 (s, 1, C(6)H); 6.12 (m, 1, C(5')H); 5.67 (overlapping m's, 2, C(1',6')H); 2.4-2.8 (m, 4, C(3',4')H; 1.75 (s, 3, CH_3). Anal Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.89; H, 5.53; N, 12.67.

trans-1-(2-Hydroxycyclohexyl)thymine (15). Prepared from thymine and cyclohexene oxide as described for 12 (68%). Recrystallized from water, mp 289-292°C. NMR: δ 11.10 (s, 1, NH); 7.58 (s, 1, C(6)H); 4.85 (d, D_2O exch., 1, OH); 4.11 (m, 1, C(2')H); 3.66 (m, 1, C(1')H); 1.78 (s, 3, CH_3); 1.3-1.9 (m, s, 8, C(3', 4', 5', 6')H). Anal. Calcd. for $C_{11}H_{16}N_2O_3 \cdot 1/5H_2O$: C, 57.98; H, 7.25; N, 12.29. Found: C, 58.07; H, 7.14; N, 12.28.

trans-9-(2-Hydroxy-5-cyclohexenyl)adenine (16a). Prepared from adenine as described for 12 (72%), mp 278-280°C. UV (MeOH) λ_{max} 261 nm. NMR: δ 8.15, 8.10 (s's, 2, C(2, 8)H); 7.23 (s, 2, NH_2); 5.94 (m, 1, C(5')H); 5.61 (d, J=9.5 Hz, 1, C(6')H); 5.18 (d, D_2O exch., 1, OH); 4.94 (m, 1, C(1')H); 4.16 (m, 1, C(2')H); 2.30 (m, 2, C(4')H); 1.96, 1.75 (m's, 2, C(3')H). Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.17; H, 5.67; N, 30.22.

trans-2-Amino-6-chloro-9-(2-hydroxy-5-cyclohexenyl)purine (16b). Prepared from 2-amino-6-chloropurine as describe for 12 (76%), mp dec. >222°C. NMR: δ 8.10 (s, 1, C(8)H); 6.85 (s, 2,

NH_2); 5.92 (m, 1, C(5')H); 5.52 (d, J=9.8 Hz, 1, C(6')H); 5.15 (s, D_2O exch., 1, OH); 4.81 (m, 1, C(1')H); 4.07 (m, 1, C(2')H); 2.24 (m, 2, C(4')H); 1.93, 1.67 (m's, 2, C(3')H). Anal. Calcd. for $C_{11}H_{12}ClN_5O$: C, 49.73; H, 4.55; Cl, 13.34; N, 26.36. Found: C, 49.73; H, 4.61; Cl, 13.27; N, 26.30.

trans-9-(2-Hydroxy-5-cyclohexenyl)guanine (16c). Compound 16b (0.563 g, 212 mmol) was refluxed with 2M HCl (10 mL) for 1h. The solution was cooled, neutralized with solid $NaHCO_3$ and the precipitated product 16c was collected (0.179 g, 30%). Recrystallized from H_2O, mp dec. >320°C. UV (MeOH) λ_{max} 254, 280 sh nm. NMR: δ 10.58 (s, 1, NH); 7.63 (s, 1, C(8)H); 6.40 (s, 2, NH_2); 5.87 (m, 1, C(5')H); 5.45 (d, J=10.0 Hz, 1, C(6')H); 5.51 (d, D_2O exch., 1, OH); 4.69 (m, 1, C(1')H); 3.99 (m, 1, C(2')H); 2.20 (m, 2, C(4')H); 1.88, 1.63 (m's, 2, C(3')H). Anal. Calcd. for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.35; H, 5.31; N, 28.27.

1-(4-Methoxycarbonyl-3-cyclohexenyl)thymine 17a. A mixture of thymine (0.586 g, 4.65 mmol), methyl 1,3-cyclohexadiene-1-carboxylate[24] (12.06 g, 14.9 mmol), DBU (0.175 g, 1.15 mmol) and anhydrous DMF (5 mL) was stirred and heated (70-75°C) for 2 days. After addition of acetic acid (5 drops), volatile material was removed in vacuo and the residue was suspended in aq. NH_4Cl and extracted with 3x20-mL portions of CH_2Cl_2. The dried ($MgSO_4$) extracts were evaporated to give crude product (1.08 g, 88%). Recrystallized from EtOAc, mp 238-240°C. NMR: δ 11.25 (s, 1, NH_2); 7.57 (s, 1, C(6)H); 6.89 (m, 1, C(3')H); 4.47 (m, 1, C(1')H); 3.68 (s, 3, OCH_3); 2.47 (m, 4, C(2',5')H); 1.77 (s, 3, CH_3); 1.7-1.9 (m, 2, C(6')H). Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.95; H, 6.04; N, 10.59.

9-(4-Methoxycarbonyl-3-cyclohexenyl)adenine 17b. Prepared from adenine as described for 17a (63%), mp 216-217°C. Anal. Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 56.10; H, 5.52, N, 25.62.

2-Amino-6-chloro-9-(4-methoxycarbonyl-3-cyclohexenyl)purine 17c. Prepared form 2-amino-6-chlorpurine as describe for 17a (78%), mp 205-206°C. Anal. Calcd. for $C_{13}H_{14}ClN_5O_2$: C, 50.74; H, 4.59; Cl, 11.52; N, 22.76. Found: C, 50.79; H, 4.56; Cl, 11.51; N, 22.71.

1-(4-Hydroxymethyl-3-cyclohexenyl)thymine 18. Under N_2, a solution of 17a (0.232 g, 0.878 mmol) in anhydrous THF (40 mL) was added to lithium aluminum hydride (0.098 g, 2.56 mmol) suspended in THF (10 mL). Water (0.185 mL, 10.3 mmol) was added dropwise, followed by glacial acetic acid (5 drops). The mixture

was filtered and the residue washed thoroughly with THF (ca. 100 mL). Removal of the solvent gave 18 (0.203, 97%). Recrystallized from toluene, mp 208-210°C. NMR: δ 11.20 (s, 1, NH); 7.57 (s, 1, C(6)H); 5.57 (m, 1, C(3')H); 4.75 (s, D_2O exch., OH); 4.46 (m, 1, C(1')H); 3.83 (s, 2, CH_2); 1.77 (s, 3, CH_3); 1.7-2.2 (m's, 6, C(2',5',6')H). Anal. Calcd for $C_{12}H_{16}N_2O_3$; C, 61.00; H, 6.83; N, 11.86. Found: C, 60.78; H, 6.88; N, 11.79.

General method for 19a-c. Compounds 19a-c were prepared by heating (65-75°C) a mixture of base (10.0 mmol), 2-cycloalkenone (40-300 mmol), DBU (1.0 mmol) and DMF (30 mL) for 2-4 days. After addition of acetic acid (12 drops), volatile material was removed under reduced pressure and the residue chromatographed over silica gel. Products eluted with EtOAc-Pet. ether (30-60°) (1:1) and were recrystallized from toluene.

1-(3-Oxocyclopentyl)thymine 19a. 28%. mp 160-161°C. NMR: δ 10.90 (s, 1, NH); 7.30 (s, 1, C(6)H); 5.57 (m, 1, C(1')H); 2.48-2.03 (m's, 6, C(2',4',5')H); 1.76 (s, 3, CH_3). Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.92; H, 5.80; N, 13.34.

1-(3-Oxocyclohexyl)thymine 19b. 33%. mp 193-194°C. NMR: δ 10.87 (s, 1, NH); 7.28 (s, 1, C(6')H); 5.00 (m, 1, C(1')H); 2.50, 2.32 (m's, 4, C(2',4')H); 1.92, 1.57 (m's, 4, C(5',6')H); 1.76 (s, 1, CH_3). Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45, H, 6.35; N, 12.60. Found: 59.57; H, 6.40; N, 12.58.

1-(3-Oxocycloheptyl)thymine 19c. 68%. mp 202-204°C. NMR: δ 11.23 (s, 1, NH); 7.59 (s, 1, C(6)H); 4.59 (m, 1, C(1')H); 2.47-2.39 (m, 4, C(2',4')H); 1.88-1.40 (m) and 1.77 (s) (9, C(5',6',7')H, CH_3). Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.93; H, 6.84; N, 11.81.

General method for 20a-c. Compounds 20a-c were prepared by refluxing thymine (10.0 mmol), α-methylene-γ-butyrolactone (15.0 mmol), DBU (1.0 mmol) and acetonitrile (100 mL) for 4 h. After addition of acetic acid (10 drops) the reaction mixtures were crystallized at -20°C. Products were recrystallized from EtOH.

1-[(2-Oxotetrahydro-3-furanyl)methyl]thymine 20a. 71%. mp 198-199°C. NMR: Assignments made with aid of COSY spectrum. δ 11.31 (s, 1, NH); 7.51 (s,1,C(6)H); 4.32, 4.18 (m's, 2,OCH_2); 3.96, 3.76 (m's, 2, CH_2T); 3.15 (m, 1, COCH); 2.32, 2.10 (m,2,CH_2CH_2); 1.75 (s, 3, CH_3). Anal. Calcd for $C_{10}H_{12}N_2O_4$; C, 53.57; H, 5.39; N, 12.49. Found: C, 53.64; H, 5.44; N, 12.45.

9-[(2-Oxotetrahydro-3-furanyl)methyl]adenine 20b. 96% mp 242-243°C. UV (MeOH) λ_{max} 261 nm. Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.48; H, 4.77; N, 29.93.

2-Amino-6-chloro-9-[(2-oxotetrahydro-3-furanyl)methyl]purine 20c. 78%. mp 226-228°C. UV (MeOH), λ_{max} 254, 281 sh nm. Anal. Calcd. for $C_{10}H_{10}ClN_5O_2$: C, 44.87; H, 3.77; Cl, 13.24; N, 26.16. Found: C, 44.93; H, 3.79; Cl, 13.32; N, 26.10.

9-[(2-Oxotetrahydro-3-furanyl)methyl]guanine 20d. A solution of 20c (0.268 g, 1.00 mmol) in 2M HCl (5 mL) was refluxed 1.5 h, cooled and neutralized with solid $NaHCO_3$. After standing in the refrigerator, crystallized product was collected and washed with cold water (0.189 g, 80%). Recrystallized from MeOH-H_2O, mp dec > 250°C. NMR: δ 10.64 (s, 1, NH); 7.64 (s, 1, C(8)H); 6.52 (s, 2, NH_2); 4.3-4.1 (m's, 4, OCH_2, CH_2G); 3.19 (m, 1, COCH), 2.2-2.0 (m's, 2, CH_2CH_2). Anal. Calcd. for $C_{10}H_{11}N_5O_3$ - 3/4 H_2O: C, 45.71; H, 4.80; N, 26.45. Found: C, 45.69; H, 4.81; N, 26.58.

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