+101.4° (c 1.0, $CHCl_3$); TLC in EtOAc; NMR (Me_2SO-d_6–$CDCl_3$) δ 0.5–1.0 (m, 2 H, CH_2), 1.17 (s, 6 H, CH_3), 1.50 (dd, J = 8 Hz, 6 Hz, 1 H, COCH), 6.6, 7.3 (v br s, each 1 H, NH). Anal. ($C_6H_{11}NO$) C, H, N. The racemic amide **11** melted at 175–177 °C (lit.[16] mp 177–177.5 °C).

Crystal Structure of (−)-Quinine Salt of (+)-2,2-Dimethylcyclopropanecarboxylic Acid (26). Suitable crystals of the (−)-quinine salt of **26** formed from a methanol–water mixture with space group symmetry of $P2_1$ and cell constants of a = 6.840 (1) Å, b = 18.238 (4) Å, c = 10.608 (2) Å, and β = 107.74 (1) Å for Z = 2 and a calculated density of 1.203 g/cm^3. Of the 1764 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1684 were observed ($I > 3\sigma(I)$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[57] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.044. A molecule of water was found cocrystallized in the asymmetric unit. No abnormally short intermolecular contacts were noted. The positions for the atoms in the vinyl group refined poorly; therefore, the geometry for this group differs from standard values. Three tables containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material.

Renal Dipeptidase Inhibition Assay. Assays were run in 1-mL reaction mixtures containing 50 mM MOPS pH 7.1 buffer, 5 μg of a solubilized renal dipeptidase preparation, and ≤0.1 mM inhibitor candidate. The enzyme preparation corresponds to the 50–75% ammonium sulfate fraction of Campbell[4,6] and had 0.174 unit specific activity. After 5 min of equilibration at 37 °C, glycyldehydrophenylalanine (K_m = 0.6 mM[6]) was added to give a concentration of 50 μM. The rate of hydrolysis of this substrate was computed from the decrease in absorption at 275 nm over a 10-min period following addition, during which time first-order kinetics was obeyed. Inhibitor activity, I_{50}, was computed from the relation $I_{50} = I(V/V_o - V)$, where V_o is the rate in the absence of inhibitor and V is the rate in the presence of concentration I of inhibitor. Since the substrate concentration in these assays was $\ll K_m$, I_{50} is equivalent to K_i for these inhibitors. Identical I_{50} values were found for substrates tested with thienamycin as substrate. The K_i values for most of the compounds in Tables I–III were determined only once and have an estimated accuracy of ±10%. Kim and Campbell[46] found that **113** showed reversible, competitive inhibition of pure porcine renal dipeptidase with a K_i of 0.67 ± 0.04 μM using glycyldehydrophenylalanine as substrate. Recently Campbell et al.[12] reported a K_i of 0.73 ± 0.02 μM for cilastatin (**176**) when tested against pure human renal dipeptidase with imipenem as substrate.

Acknowledgment. We are indebted to F. M. Kahan, H. Kropp, and J. G. Sundelof for discovering the activity of **59** and for the K_i measurements. We thank Drs. S. H. Pines and G. Love for supplies of **28**, Dr. G. Love and C. D'Annuzio for preparing **241**, Dr. R. W. Ratcliffe for synthesizing **239**, and Dr. C. Shunk and A. Matzuk for the preparation of intermediates. We are grateful to Dr. P. Gund for the Hansch analysis. We thank Dr. B. G. Christensen for his encouragement and Professors C. Walsh and E. T. Kaiser for helpful discussions. We also thank Carol D. Babish for her secretarial assistance.

Supplementary Material Available: Synthetic procedures for compounds **114**, **115**, **157**, **186**, **194**, **208**, **227**, and the following amides: ethyl 5-amino-5-oxopentanoate (for **80**), 5-methoxy-3-methylpentanamide (for **88**), and 2,2-difluorocyclopropanecarboxamide (for **128**). Tables of the atomic positional and thermal parameters, bond angles for the (−)-quinine salt of **26** (11 pages). Ordering information is given on any current masthead page.

(57) The following library of crystallographic programs was used: MULTAN 80, Main, P.; et al., University of York, York, England, 1980. ORTEP-II, Johnson, C. K., Oak Ridge National Laboratory, Oak Ridge, TN, 1970. SDP+V1.1, Okaya, Y.; et al., B. A. Frenz and Associates, College Station, TX, 1984.

Notes

Synthesis and Antiviral Evaluation of Carbocyclic Analogues of 2-Amino-6-substituted-purine 3′-Deoxyribofuranosides

Y. Fulmer Shealy,* C. Allen O'Dell, and Gussie Arnett

Kettering-Meyer Laboratories, Southern Research Institute, Birmingham, Alabama 35255-5305. *Received July 1, 1986*

Carbocyclic analogues of 2-amino-6-substituted-purine 3′-deoxyribofuranosides were synthesized by beginning with (±)-(1α,3α,4β)-3-amino-4-hydroxycyclopentanemethanol and 2-amino-4,6-dichloropyrimidine. The route parallels the earlier syntheses of the corresponding ribofuranoside and 2′-deoxyribofuranoside analogues. The 2-amino-6-chloropurine, guanine, and 2,6-diaminopurine derivatives and the analogous 8-azapurines were prepared. The analogue (3′-CDG) of 3′-deoxyguanosine is active in vitro against a strain of type 1 herpes simplex virus (HSV-1) that induces thymidine kinase and is modestly active against a thymidine kinase inducing strain of type 2 HSV. 3′-CDG is not active against a strain of HSV-1 that lacks the thymidine kinase inducing capacity, whereas the carbocyclic analogue of 2-amino-6-chloropurine 3′-deoxyribofuranoside is active against that strain. The carbocyclic analogue of 2,6-diaminopurine 3′-deoxyribofuranoside displayed modest activity in vitro against influenza virus.

Previously, we described the synthesis of carbocyclic analogues of ribofuranosides[1,2] (**1** and **2**, R = OH) and of 2′-deoxyribofuranosides[3] (**1** and **2**, R = H) of 2-amino-6-substituted-purines. Lee and Vince[4] reported the synthesis of carbocyclic analogues of some arabinofuranosyl

(1) Shealy, Y. F.; Clayton, J. D. *J. Pharm. Sci.* **1973**, *62*, 1432–1434.
(2) Shealy, Y. F.; Clayton, J. D.; Arnett, G.; Shannon, W. M. *J. Med. Chem.* **1984**, *27*, 670–674.
(3) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1984**, *27*, 1416–1421.
(4) Lee, H.; Vince, R. *J. Pharm. Sci.* **1980**, *69*, 1019–1021.

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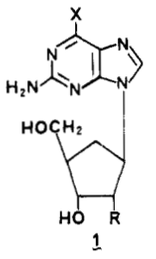
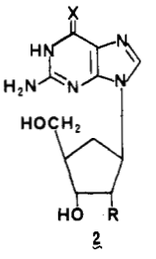


1

a: X = NH_2, R = OH
b: X = NH_2, R = H



2

a: R = OH
b: R = H

2-amino-6-substituted-purines. These investigations also included the preparation of some of the corresponding carbocyclic analogues of 2-amino-6-substituted-8-azapurine nucleosides.[1-4] Several of the *C*-ribofuranosides[5] have antiviral activity.[2] *C*-2,6-Diaminopurine ribofuranoside (**1a**, X = NH_2) is very active in vitro against vaccinia virus and against a strain (HF) of type 1 herpes simplex virus (HSV-1) that does not induce thymidine kinase,[2] and *C*-2,6-diaminopurine arabinofuranoside is also active against a strain of HSV-1.[4] All of the reported carbocyclic analogues of 2-amino-6-substituted-purine and 2-amino-6-substituted-8-azapurine 2′-deoxyribofuranosides are active against both HSV-1 and the type 2 herpes simplex virus (HSV-2).[3] Most of these compounds are highly active, and further studies have confirmed the activity of these compounds in vitro and have revealed activity in vivo by the carbocyclic analogues of 2′-deoxyguanosine (**2b**, X = O; (±)-2′-CDG) and 2,6-diaminopurine 2′-deoxyribofuranoside (**1b**, X = NH_2; (±)-*C*-2,6-DAP-2′-dR).[6] In this paper, we describe the synthesis and initial antiviral evaluation of carbocyclic analogues of 3′-deoxyribofuranosides of 2-amino-6-substituted-purines and -8-azapurines.

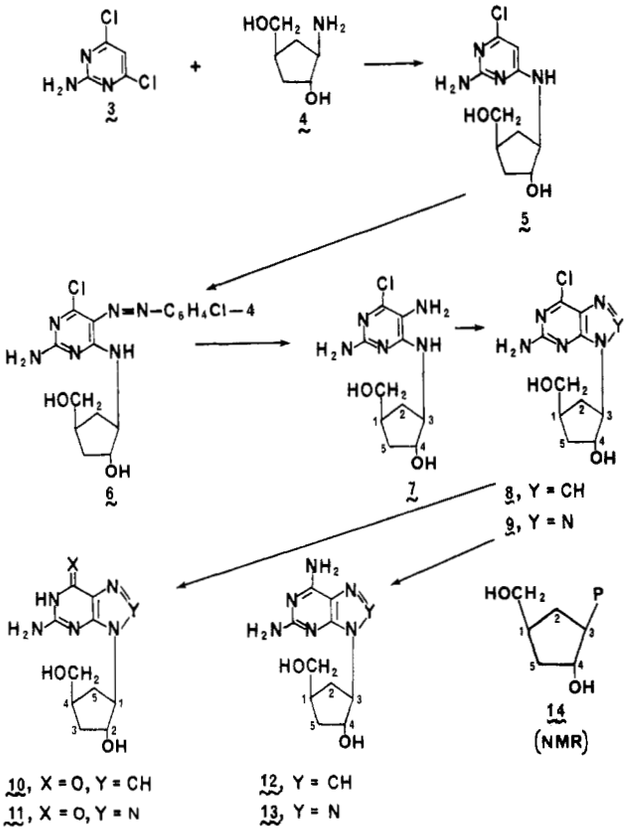
Chemistry. Carbocyclic analogues (**8–13**) of 2-amino-6-substituted-purine or 2-amino-6-substituted-8-azapurine 3′-deoxyribofuranosides were synthesized by the route outlined in Scheme I. This synthesis route parallels the routes to the corresponding analogues of ribofuranosides[1,2] or 2′-deoxyribofuranosides.[3] (Cyclopentylamino)pyrimidine **5** was obtained from a reaction of 2-amino-4,6-dichloropyrimidine (**3**) and (±)-(1α,3α,4β)-3-amino-4-hydroxycyclopentanemethanol (**4**). During one of the runs, a byproduct ($C_{14}H_{17}Cl_2N_7O_2$), consisting of two pyrimidine groups for each cyclopentyl group, was also isolated. The formation of a similar byproduct during the preparation of the similar pyrimidine precursor of the *C*-2′-deoxyribofuranosides was mentioned earlier.[3] The presence or absence of the byproduct of this reaction appears to be determined largely by the quality of the starting pyrimidine[7] **3**. Pyrimidine **5** was isolated in 59% yield when high-quality **3** (3 equiv) and **4** were allowed to react for 24 h in refluxing ethanol in the presence of triethylamine. The 5-(4-chlorophenylazo) intermediate **6** and the 5-aminopyrimidine precursor **7** were obtained in yields of 76% and 71%, respectively.

The acid-catalyzed reaction of **7** with triethyl orthoformate in dimethylacetamide followed by treatment of the crude product successively with 50% acetic acid and with 10% ammonia in methanol at room temperature furnished the 2-amino-6-chloropurine **8** in 82% yield. Treatment of **8** with anhydrous ammonia at 90 °C afforded *C*-2,6-diaminopurine 3′-deoxyribofuranoside (*C*-2,6-DAP-3′-dR, **12**). *C*-3′-Deoxyguanosine (3′-CDG, **10**) could be obtained by treating the total crude product of the reaction of **7** and triethyl orthoformate with 88% formic acid and then with methanolic ammonia. *C*-2-Amino-6-chloro-8-azapurine 3′-deoxyribofuranoside (**9**) was obtained conventionally by treating **7** with sodium nitrite in aqueous acetic acid, and *C*-8-aza-3′-deoxyguanosine (**11**) and *C*-8-aza-2,6-DAP-3′-dR (**13**) were prepared by treating **9** with aqueous base or with anhydrous ammonia, respectively.

In the 300-MHz proton NMR spectra of purines **8**, **10**, and **12** in Me_2SO-d_6, the protons at positions 3 and 4 of structure **14** gave rise to overlapping multiplets at δ 4.33–4.43, and the methylene protons of the hydroxymethyl group produced multiplets at δ 3.36–3.39. Signals from the five protons at positions 1, 2 and 5 (structure **14**) appeared as three multiplets at δ 1.61–1.69 (two protons), 1.83–1.86 (one proton), and 2.20–2.22 (two protons). The latter signal was assigned to the proton at position 1 and one of the protons of the methylene groups (2 or 5). The spectrum of 8-azapurine **13** was similar except that (1) the chemical shifts (multiplets) of the protons at positions 3 and 4 were downfield and separated (δ 4.52 and 4.64) and (2) the multiplets produced by the proton at position 1 and one of the protons at position 2 were separated (δ 2.21 and 2.32).

Biological Evaluation. The *C*-3′-deoxyribofuranosides **8–13** were tested for antiviral activity against strains 377 and HF of HSV-1. Strain 377 induces thymidine kinase (TK^+) in host cells, whereas strain HF does not significantly induce this enzyme (TK^-). In all of these tests, *ara*-A was employed as a positive-control drug; and, in a few of the tests, acyclovir[8] was also a positive-control an-

Scheme I



(5) Read *C*- as "carbocyclic analogue of".
(6) Shannon, W. M.; Arnett, G.; O'Dell, C. A.; Shealy, Y. F. American Society for Virology, Annual Meeting—1985, Albuquerque, NM, July 21–25, 1985.
(7) Commercial, technical-grade **3** was used when considerable amounts of a dipyrimidinyl byproduct was obtained during the reaction of **3** and **4** or during the earlier work.[3] The byproduct was not observed when high-quality (>99%) commercial **3** was used.

Table I. Antiviral Evaluation of *C*-3′-Deoxyribofuranosides[a]

virus[c]	carbocyclic analogue[b] compound	VR[d]	MIC_{50},[e] μg/mL	positive-control drug compound	VR	MIC_{50}, μg/mL	VR/(VR of pos control)[f]
HSV-1, 377	(±)-2-NH_2-6-Cl-pur-3′-dR (**8**)	0.1		*ara*-A	2.0	15	
HSV-1, HF	**8**	1.5	190	*ara*-A	2.4	6	0.63
				acyclovir	0		
influenza, A_0/PR/8/34	**8**	0.5	>284	RV[g]	2.6	54	0.19
HSV-1, 377	(±)-3′-CDG (**10**)	2.6	67	*ara*-A	2.0	15	1.3
		3.1	26	*ara*-A	2.1	18	1.5
		1.9	170	acyclovir	5.7	3	0.33
				ara-A	2.0	34	0.95
HSV-1, HF	**10**	0		*ara*-A	2.4	85	
				acyclovir	0		
HSV-2, MS	**10**	1.3	260	*ara*-A	0.9	56	1.44
influenza, A_0/PR/8/34	(±)-C-8-aza-2,6-DAP-3′-dR (**13**)	1.3	200	RV[g]	2.9	14	0.45

[a] The antiviral activity of each compound is expressed as a virus rating (VR), and the potency is given as a minimum inhibitory concentration (MIC_{50}). The VR is a weighted measurement of antiviral activity that takes into account both the degree of inhibition of virus-induced cytopathogenic effects and the degree of cytotoxicity produced by the test compound. [b] Compounds **8**, **9**, and **11–13** were not active in tests against strain 377 of HSV-1, and **9–13** were not active against strain HF. Compounds **8**, **10**, **12**, and **13** were tested against type A_0/PR/8/34 of influenza virus; **10** and **12** were not active. [c] Host cells for these tests were as follows: strain 377 of HSV-1 and strain MS of HSV-2, monolayers of Vero cells; strain HF of HSV-1, monolayers of H.Ep.-2 cells; type A_0/PR/8/34 of influenza virus, Madin-Darby canine kidney cells. [d] A virus rating (VR) equal to or greater than 1.0 indicates definite and significant antiviral activity, a VR of 0.5–0.9 indicates marginal to moderate antiviral activity, and a VR less than 0.5 usually indicates no significant antiviral activity. [e] MIC_{50} is the concentration of the tested compound required to inhibit cytopathogenic effects by 50%. [f] Ratio of the VR of the *C*-3′-deoxyribofuranoside to the VR of the positive-control drug in the same experiment. [g] RV = ribavirin.

tiviral agent. In the tests of **8–13** against strain 377 replicating in Vero cells, only 3′-CDG (**10**) was active. The results, summarized in Table I, of three separate experiments with 3′-CDG indicate that the activity of this compound is equal to, or greater than, the activity of *ara*-A; i.e., the ratios of the virus ratings (VR) of 3′-CDG to the VR of *ara*-A were 0.95–1.5. 3′-CDG was less active than acyclovir (VR/VR = 0.33). In a test against HSV-2, strain MS, 3′-CDG was at least as active as *ara*-A (VR/VR = 1.44). However, 3′-CDG was less potent (MIC_{50}) than *ara*-A against either HSV-1 or HSV-2. In tests of **8–13** against strain HF, only *C*-2-amino-6-chloropurine 3′-deoxyribofuranoside (**8**) was active. It was less active then *ara*-A (VR/VR = 0.63); acyclovir, as expected, was not active in this test. Analogues **8**, **10**, **12**, and **13** were also tested against human influenza virus, strain A_0/PR/8/34. These tests (Table I) indicate that the 2-amino-6-chloropurine **8** has borderline activity and that the 2,6-diamino-8-azapurine **13** has modest activity (VR = 1.3, VR/(VR of ribavirin) = 0.45). Antiviral activity by these carbocyclic analogues of 3′-deoxyribofuranosides is significant because of the absence of activity among other carbocyclic analogues of this type. Previously, antiviral activity was not observed among *C*-3′-deoxyuridines[9] or *C*-3′-deoxycytidines.[10]

Compounds **8–13** were tested for inhibition of the proliferation of mouse leukemia L1210 cells in culture. The 2-amino-6-chloro-8-azapurine derivative **9** was the most cytotoxic compound of the group, the IC_{50} being 10–15 μg/mL. Among the remaining compounds (tested at concentrations of 25, 50, and 100 μg/mL), *C*-8-aza-3′-deoxyguanosine (**11**) was mildly cytotoxic with a value of IC_{50} of about 50 μg/mL; values of IC_{50} for **8**, **10**, **12**, and **13** were greater than 50 μg/mL. Compounds **8** and **10–13** were also tested (at concentrations of 10, 25, and 50 μg/mL) against cultured human epidermoid carcinoma (H. Ep.-2) cells for inhibition of colony formation. None were significantly active; colony formation was 80–100% of control values.

Experimental Section[11]

General Methods. Decomposition and melting temperatures (mp) were determined in capillary tubes heated in a Mel-Temp apparatus. Ultraviolet spectra (UV) were recorded with a Cary Model 17 spectrophotometer, and absorption maxima are reported in nanometers; sh = shoulder. Solutions for ultraviolet spectral determinations were prepared by diluting a 5-mL aliquot of a water or ethanol solution to 50 mL with 0.1 N hydrochloric acid, phosphate buffer (pH 7), or 0.1 N sodium hydroxide. Absorption maxima of these solutions are reported as being determined at pH 1, 7, or 13, respectively. Infrared spectra (IR) were recorded with a Nicolet MX-10 Fourier-transform spectrometer from samples in pressed potassium bromide disks. Only prominent bands are listed; vs = very strong, s = strong, m = medium, br = broad. Mass spectral data (MS) were taken from low-resolution electron-impact (EI) or fast-atom-bombardment (FAB) spectra determined at 70 eV with a Varian/MAT 311A spectrometer. The peaks listed are those arising from the molecular ion (M), those attributable to the loss of certain fragments (M minus a fragment), and some other prominent peaks. Fragments containing the complete purine or pyrimidine moiety may be designated P plus an atom or group. Proton NMR spectra were recorded at 300.64 MHz with a Nicolet 300 NB NMR spectrometer. Tetramethylsilane was the internal standard; m = multiplet, s = singlet, d = doublet, t = triplet. The apparent multiplicity of the signals, the number of protons, and the assigned position of the protons (structure **14**) are listed parenthetically with the chemical shifts. Thin-layer chromatography (TLC) was performed on plates of silica gel (silica gel GF), and developed plates were examined by UV light (254 nm);[12] the amount of a compound applied and the

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(9) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1983**, *26*, 156–161.
(10) Shealy, Y. F.; O'Dell, C. A.; Arnett, G.; Shannon, W. M.; Thorpe, M. C.; Riordan, J. M.; Coburn, W. C., Jr. *J. Med. Chem.* **1986**, *29*, 1720–1725.

(11) In accordance with *Chemical Abstracts* nomenclature, compounds **4–9**, **12**, and **13** are named as cyclopentanemethanols, and substituents on the cyclopentane ring are designated 1α,3α,4β. Because compounds **10** and **11** have an oxo substituent on the heterocyclic ring, they are named as a cyclopentylpurine and a cyclopentyl-1,2,3-triazolo[4,5-*d*]pyrimidine; therefore, substituents on the cyclopentane ring are designated 1α,2β,4α. The numbering system for NMR assignments is shown with structure **14**.

developing solvent are stated parenthetically in the procedures below.

(±)-(1α,3α,4β)-3-[(2-Amino-6-chloro-4-pyrimidinyl)amino]-4-hydroxycyclopentanemethanol (5). A mixture of 2-amino-4,6-dichloropyrimidine[7] (13.5 g, 82.3 mmol, >99% pure), 3.60 g (27.4 mmol) of (±)-(1α,3α,4β)-3-amino-4-hydroxycyclopentanemethanol[13,14] (4), 10.4 mL of triethylamine, and 360 mL of ethanol was boiled under reflux for 24 h and then placed in a freezer (−20 °C). Unreacted 4 (9.8 g) was separated from the cold mixture by filtration, and the filtrate (including ethanol washings) was concentrated under reduced pressure to a partially solid residue. The residue was slurried with 9:1 chloroform–methanol (45 mL), and a tan solid was collected from the chilled (−20 °C) mixture, washed with the same cold solvent, and dried in vacuo at room temperature: yield, 4.17 g (59%);[15] mp 155–157 °C. This material was suitable for the next step. Another specimen of **5** (600 mg, mp 158–160 °C) was recrystallized from acetonitrile–ethanol (6:1): weight, 560 mg (93% recovery); mp 158–161 °C; TLC (40 μg, 5:1 chloroform–methanol), 1 spot; UV λ_{max} 213 nm (ε 18 400), 238 (11 700), 273 (8800), 305 (sh) at pH 1; 212 nm (ε 24 700), 239 (10 300), 287 (9500) at pH 7; 238 nm (ε 10 400), 286 (9400) at pH 13; MS (FAB), *m/e* 259 (M + H), 171 (PNH + C_2H_4), 145 (PNH + 2H); IR 3310 (br), 3155 (br), 2880, 1655, 1580 (vs), 1475 (s), 1365 (m), 1160 (m), 1035 (m), 975 (m), 795 (m) cm^{-1}. Anal. ($C_{10}H_{15}ClN_4O_2 \cdot {}^1/_4CH_3CN$) C, H, N.

(±)-(1α,3α,4β)-3-[(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]-4-hydroxycyclopentanemethanol (7) via 6. A solution of 4-chlorobenzenediazonium chloride was prepared at 0 °C from 10.57 g (82.9 mmol) of 4-chloroaniline, 78 mL of water, 23 mL of 12 N hydrochloric acid, and 6.31 g (91 mmol) of sodium nitrite dissolved in 78 mL of water. The cold diazonium salt solution was added dropwise during 0.5 h to a solution (stirred at room temperature) of 19.4 g (75 mmol) of **5**, 150 g of sodium acetate trihydrate, 375 mL of acetic acid, and 375 mL of water. The mixture was stirred at room temperature overnight, and the yellow precipitate (which began to form after about 1 h) was collected by filtration, washed well with water, and dried in vacuo: yield of yellow solid (**6**), 22.6 g (76%); mp 230–233 °C dec (inserted at 150 °C, 3 deg/min); TLC, 1 spot (120 μg, 5:1 chloroform–methanol).

A mixture of 5.50 g (13.8 mmol) of **6**, 120 mL of ethanol, 120 mL of water, and 12 mL of acetic acid under an atmosphere of nitrogen was stirred vigorously and heated to 70 °C. Zinc dust (11.3 g) was added in small portions during 45 min to the stirring mixture, and heating of the vigorously stirred mixture at 70 °C was continued for 1.5 h. The mixture was filtered under a current of nitrogen, the solid residue was washed well with ethanol, the filtrate and washings were combined, and the solution was concentrated to about one-fourth of the original volume of the filtrate. The aqueous mixture was extracted with ether (3 × 25 mL) to remove 4-chloroaniline, the pH was raised to 5.9 by adding 2 N sodium hydroxide, and the red-brown precipitate was collected by filtration, washed well with cold water, and dried in vacuo at 78 °C: yield, 2.69 g (71%); mp 170–175 °C; TLC, a major spot + 2 weak impurity spots (80 μg, 3:1 chloroform–methanol). This material was suitable for the preparation of **8** or **9**. A small portion of the crude material was recrystallized from methanol. Yellow crystals (**7**) were dried in vacuo at 78 °C: mp 180–185 °C dec (inserted at 125 °C, 3 deg/min); UV λ_{max} 298 nm (ε 8200) and 238 (15 800) at pH 1; 304 nm (ε 9000) and 240 (sh) at pH 7 and 13; MS (EI, direct-probe temperature 20 °C), *m/e* 273 (M), 254, 224 (M–H_2O–CH_2OH), 198, 196, 186 (PNH + C_2H_4), 172 (PNH + CH_2), 170, 159 (PNH + H), 134, 108. Anal. ($C_{10}H_{16}ClN_5O_2 \cdot {}^1/_4CH_3OH$) C, H, N.

(±)-(1α,3α,4β)-3-(2-Amino-6-chloro-9*H*-purin-9-yl)-4-hydroxycyclopentanemethanol (8). Freshly distilled triethyl orthoformate (5.2 mL) and 12 N hydrochloric acid (0.25 mL) were added to a cold (0 °C) solution of 680 mg (2.48 mmol) of **7** in 5.2 mL of dimethylacetamide. The mixture was stirred overnight in a stoppered flask at room temperature and then concentrated in vacuo (oil pump) to a red gummy residue. After several portions of water had been added to and evaporated from the residue, it was dissolved in 50% acetic acid (20 mL), and the solution was stirred for 4 h at room temperature and then concentrated in vacuo to a gummy residue. Several portions of methanol were added to and evaporated from the residue, and a solution of the residue in ammonia–methanol (10% NH_3) was stirred at room temperature for 4 h, during which time a yellow precipitate formed. The precipitate was filtered from the chilled (−20 °C) mixture, washed with cold methanol, and dried in vacuo at 78 °C: yield, 580 mg (82%); mp 214–217 °C dec (inserted at 120 °C, 3 deg/min); UV λ_{max} 313 nm (ε 7200), 242 (5400), 221 (25 500) at pH 1; 307 nm (ε 7700), 246 (4900), 223 (27 500) at pH 7; 308 nm (ε 7700), 245 (4900), 223 (26 800) at pH 13; MS (EI, direct-probe temperature 180 °C), *m/e* 283 (M), 266 (M − OH), 252 (M − CH_2OH), 224, 196 (P + C_2H_4), 170 (P + 2H), 134; ^1H NMR (Me_2SO-d_6) δ 1.69 (m, 2 H, 2 and 5), 1.86 (m, 1 H, 2 or 5), 2.22 (m, 2 H, 1 and 2 or 5), 3.39 (t, 2 H, CH_2OH), 4.43 (m, 2 H, 3 and 4), 4.63 (t, 1 H, CH_2OH), 5.15 (d, 1 H, sec OH), 6.85 (s, NH_2), 8.24 (s, 1 H, 8-pur). Anal. ($C_{11}H_{14}ClN_5O_2$) C, H, N.

(±)-(1α,3α,4β)-3-(5-Amino-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxycyclopentanemethanol (9). A solution of 294 mg (4.26 mmol) of solution nitrite in 7 mL of water was added dropwise to a cold (0 °C), stirred solution of 1.00 g (3.66 mmol) of **7** in 10 mL of water and 3.4 mL of acetic acid. The mixture was stirred at 0 °C for 1 h, and the precipitated product was separated by filtration, washed several times with cold water, and dried in vacuo at room temperature: yield, 702 mg (67%); mp 156–158 °C. Portions of this material were used to prepare **11** and **13**. A 200-mg specimen was recrystallized from ethanol–ethyl acetate (1:1); because the chloro substituent is easily replaced, dissolution of **9** was effected at 40–45 °C. After the solution had been filtered and chilled (−20 °C), crystalline **9** was separated by filtration, washed with cold ethanol, and dried in vacuo at 78 °C: weight, 104 mg; mp 175–178 °C dec (inserted at 120 °C, 3 deg/min); TLC, 1 spot (80 μg, 3:1 chloroform–methanol); UV λ_{max} 316 nm (ε 7600), 245 (sh), 226 (23 200) at pH 1; 316 nm (ε 7600), 245 (sh), 225 (23 300) at pH 7 (unstable at pH 13); MS (FAB), *m/e* 285 (M + H), 171 (P + 2 H); IR (strong and medium bands) 3330, 3215, 1635, 1615, 1565, 1510, 1050, 1010 cm^{-1}. Anal. ($C_{10}H_{13}ClN_6O_2 \cdot {}^1/_2H_2O$) C, H, N.

(±)-2-Amino-1,9-dihydro-9-[(1α,2β,4α)-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-6*H*-purin-6-one (10). A solution of 310 mg (1.13 mmol) of **7**, 2.5 mL of triethyl orthoformate, 2.5 mL of dimethylacetamide, and 0.12 mL of 12 N hydrochloric acid was prepared, as described above for the preparation of **8**, and stirred at room temperature overnight. The reaction mixture was concentrated in vacuo (oil pump, 45 °C) to a red, gummy residue. A solution of the crude product (**8** and its derivatives) in 88% formic acid (15 mL) was boiled under reflux overnight and then concentrated in vacuo (oil pump, 30 °C) to a gummy residue. Several portions of methanol were evaporated from the residue, and a solution of the residue in ammonia–methanol (10% NH_3) was stirred at room temperature for 4 h. The mixture, containing a precipitate, was placed in a refrigerator and then filtered, and the solid was washed with cold methanol and dried in vacuo at 78 °C: weight, 98 mg; mp 280–285 °C dec (darkening above 265 °C). The residue obtained by concentrating the filtrate was triturated with ethanol (3 mL), the mixture was stored in a refrigerator, and the solid was collected by filtration, washed with cold ethanol, and dried in vacuo at 78 °C: weight, 46 mg; mp 275–280 °C dec. The two portions were combined and recrystallized from water, and the crystalline product was dried in vacuo at 78 °C: yield, 86 mg (29% from **7**); mp 291–294 °C dec (inserted at 100 °C, 3 deg/min, darkening above 285 °C); TLC, 1 spot (40 or 120 μg, 5:2:3 butanol–acetic acid–water); UV λ_{max} 279 nm (ε 8000) and 255 (12 000) at pH 1; 268 nm (sh, ε 9600) and 253 (13 000) at pH 7; 268 nm (ε 10 900) and 257–262 (sh, 10 300) at pH 13; ^1H NMR (Me_2SO-d_6) δ 1.61 (m, 2 H, 2), 1.83 (m, 1 H, 5), 2.20 (m, 2 H, 1 and 5), 3.36 (t, CH_2OH), 3.34 (s, H_2O), 4.33 (m, 2 H, 3 and 4), 4.60 (t, 1 H, CH_2OH), 5.13 (d, 1 H, sec OH), 6.85 (s, NH_2), 7.76

(12) Analytical TLC was performed with plates of silica gel GF. [Precoated thin-layer chromatography plates (fluorescent), 250 μm in thickness, were purchased from Analtech Inc., Blue Hen Industrial Park, Newark, DE 19711.]
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(15) The filtrate contained additional **5**.

(s, 8-Pur). Anal. ($C_{11}H_{15}N_5O_3 \cdot 1^1/_4H_2O$) C, H, N.

(±)-5-Amino-3,6-dihydro-3-[(1α,2β,4α)-2-hydroxy-4-(hydroxymethyl)cyclopentyl]-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (11). A mixture of 150 mg (0.53 mmol) of **9** and 5 mL of 0.25 N aqueous sodium hydroxide was boiled under reflux for 3 h. The mixture was treated with activated charcoal and filtered, and the colorless filtrate was acidified to pH 3 with 1 N HCl. A crystalline precipitate was collected by filtration, washed thoroughly with cold water, and dried in vacuo at 78 °C: yield, 97 mg (69%); mp 278–280 °C dec (inserted at 120 °C, 3 deg/min); UV λ_{max} 270 nm (sh, ε 8200) and 253 (11 600) at pH 1; 270 nm (ε 8400) and 253 (11 000) at pH 7; 278 nm (ε 10 800) and 255 (sh) at pH 13; IR (strong and medium bands) 3360, 3320, 3245, 3200, 1710, 1700, 1645, 1590, 1575, 1535, 1375, 1185, 1040, 1015, 780 cm^{-1}. Anal. ($C_{10}H_{14}N_6O_3$) C, H, N.

(±)-(1α,3α,4β)-3-(2,6-Diamino-9*H*-purin-9-yl)-4-hydroxycyclopentanemethanol (12). A solution of 150 mg (0.53 mmol) of **8** in 15 mL of anhydrous ammonia was heated for 18 h at 90 °C in a stainless steel bomb having a glass liner. The bomb was chilled and opened, ammonia was allowed to evaporate, and the residue was concentrated further with a stream of nitrogen and dissolved in methanol. The solution was filtered and stored at −20 °C, and a white crystalline precipitate was collected by filtration, washed with cold methanol, and dried in vacuo at 78 °C: yield, 74 mg (53%); mp 125–130 °C, resolidified, remelted at 202–204 °C (inserted at 115 °C, 3 deg/min); UV λ_{max} 292 nm (ε 9900), 254 (9700), 219 (22 000) at pH 1; 280 nm (ε 10 400), 256 (8400), 250 (sh), 216 (28 600) at pH 7; 280 nm (ε 10 500), 256 (8400), 250 (sh) at pH 13; MS (FAB), *m/e* 265 (M + H), 151 (P + 2H); ^{1}H NMR (Me_2SO-d_6) δ 1.65 (m, 2 H, 2 and 5), 1.83 (m, 1 H, 5), 2.22 (m, 2 H, 1 and 2), 3.34 (s, H_2O), 3.37 (m, 2 H, CH_2OH), 4.35 (m, 2 H, 3 and 4), 4.61 (m, 1 H, CH_2OH), 5.32 (m, 1 H, sec OH), 5.75 (s, NH_2), 7.76 (s, 8-Pur). A specimen was dried at 100 °C for analysis. Anal. ($C_{11}H_{16}N_8O_2 \cdot {}^1/_2H_2O$) C, H, N.

(±)-(1α,3α,4β)-3-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxycyclopentanemethanol (13). A solution of 150 mg (0.527 mmol) of **9** in 20 mL of anhydrous ammonia was heated for 18 h at 60 °C in a stainless steel bomb containing a glass liner. The bomb was chilled and opened, and ammonia was evaporated with a current of nitrogen. The residual solid was dissolved in hot water (6 mL), the hot solution was filtered, and the filtrate was cooled and placed in a refrigerator. The crystalline precipitate was separated by filtration, washed with cold water, and dried in vacuo at 78 °C: yield, 108 mg (77%); mp 220–224 °C dec (inserted at 120 °C, 3 deg/min); UV λ_{max} 285 nm (ε 7500), 254 (9400), 213 (25 100) at pH 1; 287 nm (ε 10 300), 259 (5700), 223 (25 300) at pH 7; 286 nm (ε 10 300), 258 (5600), 222 (25 100) at pH 13; MS (FAB), *m/e* 266 (M + H), 152 (P + H); ^{1}H NMR (Me_2SO-d_6) δ 1.70 (m, 1 H, 2), 1.85 (m, 2 H, 5), 2.21 (m, 1 H, 1), 2.32 (m, 1 H, 2), 3.40 (t, CH_2OH), 4.52 (m, 1 H, 4), 4.64 (m, 1 H, 3), 4.62 (m, 1 H, CH_2OH), 5.21 (d, 1 H, sec OH), 6.34 (s, NH_2). Anal. ($C_{10}H_{15}N_7O_2$) C, H, N.

Antiviral Evaluations in Vitro. Compounds **8**–**13** were tested for their ability to inhibit the cytopathogenic effects produced by strain 377 (TK$^+$) of HSV-1 or strain MS (TK$^+$) of HSV-2 replicating in monolayers of Vero cells, strain HF (TK$^-$) of HSV-1 in monolayers of H.Ep.-2 cells, or strain A_0/PR/8/34 of influenza virus in monolayers of Madin-Darby canine kidney cells. These tests were performed by methods and procedures described previously for the evaluation of compounds for antiviral activity in vitro.[10] The general assay method was described by Ehrlich et al.,[16] but some modifications were incorporated.

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Resolution of (±)-2-Tetradecyloxiranecarboxylic Acid. Absolute Configuration and Chiral Synthesis of the Hypoglycemic *R* Enantiomer and Biological Activity of Enantiomers

Winston Ho,* Okan Tarhan,† Timothy C. Kiorpes, Gene F. Tutwiler, and Richard J. Mohrbacher

Departments of Chemical Research and Biological Research, McNeil Pharmaceutical, Spring House, Pennsylvania 19477.
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The resolution of the hypoglycemic agent (±)-2-tetradecyloxiranecarboxylic acid (**3**) as its *d*- and *l*-ephedrine salts is presented. The active enantiomer (*R*)-(+)-**3** was also synthesized by the Sharpless chiral epoxidation procedure and its methyl ester (*R*)-(+)-**4** was shown to be identical with the corresponding ester from the resolved acid. Single-crystal X-ray structure analysis of the diastereomeric salt of (+)-**3** and (−)-ephedrine allowed assignment of (+)-**3** as the *R* configuration. The effects on fatty acid oxidation and glucose tolerance of the racemic and enantiomeric forms of **3**, **4**, and the CoA ester of **3** are presented. A postulated mechanism of action for the active enantiomer as an enantioselective, active-site-directed, irreversible inhibitor of carnitine palmitoyl transferase is suggested.

Racemic methyl 2-tetradecyloxiranecarboxylate (**4**) (methyl palmoxirate) is a potent inhibitor of fatty acid oxidation in vitro and an orally active hypoglycemic agent in rats, dogs, monkeys,[1–3] and humans.[4] In order to study the biological activity of **4** and its precursor, **3**, more thoroughly, we have obtained the two enantiomers of 2-tetradecyloxiranecarboxylic acid (**3**) by classical resolution. We have determined the absolute configuration of the bioactive enantiomer (+)-**3** by X-ray crystallography and

† Visiting Professor from Middle East Technical University, Ankara, Turkey.

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