The present structure is an intermolecular complex involving cytosine and a derivative of uracil. It appears to go against the rule of electronic complimentarity described above, since infrared studies of derivatives of these molecules have shown that there is no selective affinity for hydrogen bonding between uracil and cytosine derivatives.[8] Similarly, 1-methyl-5-fluorouracil forms a crystalline complex with 9-ethyladenine[3] but does not form one with cytosine derivatives.[39] However, it is important to note that the molecules involved in the present structure do not have side chains on their glycosidic nitrogen atoms. Instead, atom N(1) is protonated in both molecules and, of course, plays an important role in developing the hydrogen bonding system which stabilizes the entire crystal. Thus, it is likely that the electronic distributions in the pyrimidines are modified somewhat when they are substituted on the N(1) position so that their hydrogen-bonding properties are altered. Of course, in the present crystal structure, and that of the complex 1-methylcytosine–5-fluorouracil, the hydrogen bonding between the cytosine derivatives and 5-fluorouracil involves the atom N(1) of 5-fluorouracil. Such a mode of hydrogen bonding would be impossible if a substituent were present on this atom.

(39) A. Rich, unpublished observations.

Acknowledgments. We wish to thank Dr. S.-H. Kim for his assistance in pointing out the existence of the complex. This work was supported by grants from the National Institutes of Health, the U. S. Public Health Service, and the National Aeronautics and Space Agency.

Synthesis of Carbocyclic Analogs of Purine Ribonucleosides[1]

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Abstract: The racemic forms of the carbocyclic (cyclopentane) analogs of adenosine, inosine, 6-mercaptopurine ribonucleoside, and 6-(methylthio)purine ribonucleoside were synthesized from (±)-4β-amino-2α,3α-dihydroxy-1β-cyclopentanemethanol. This amine was synthesized by two routes from 2α,3α-diacetoxy-1β,4β-cyclopentanedicarboxylic acid *via* its anhydride and monoamide. The two routes differed in the order in which the amino group was introduced by a Hofmann reaction and the hydroxymethyl group, by metal hydride reduction of an ester or acid chloride group. The stereochemistry of the starting cyclopentane was fixed by the preparation of this compound from *exo-cis*-5-norbornene-2,3-diol, which was prepared by *cis*-dihydroxylation of norbornadiene. The structure of the norbornenediol was confirmed by chemical means and by nmr analysis.

It is now well established that alterations of either the furanose or the base moiety of naturally occurring purine and pyrimidine nucleosides may produce derivatives that exert interesting and powerful biological effects.[2] Replacement of the furanose oxygen atom of nucleosides with a methylene group would produce carbocyclic (cyclopentane) analogs in which the hydroxyl groups occupy the same positions, have the same *cis–trans* relationships, and may be expected to assume similar conformations.[4] The carbocyclic analogs have the potential, therefore, either to mimic or to antagonize the functions of the naturally occurring nucleosides and nucleotides. Unlike the nucleosides, the carbon–nitrogen bond joining the heterocyclic base to the cyclopentane ring should be comparable in stability to that of a simple alkyl derivative and should, therefore, be much less susceptible to enzymatic fission than the analogous bond of nucleosides. For these reasons we have synthesized the carbocyclic analogs (racemic forms) of the naturally occurring nucleosides adenosine and inosine and of two biologically active purine nucleosides. A preliminary account of our synthesis of the adenosine analog (C-Ado, **28**) has appeared;[3] subsequently, Kishi and coworkers[5] reported in a preliminary communication that X-ray analysis revealed the structure of a recently isolated antibiotic[6] to be an optically active form of C-Ado (**28**). Earlier, Murdock

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51 and by the C. F. Kettering Foundation.

(2) References to some of the large number of publications in this field may be found in the following reviews: J. A. Montgomery and H. J. Thomas, *Advan. Carbohydrate Chem.*, **17**, 301 (1962); J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966); S. S. Cohen, *ibid.*, **5**, 1 (1966); C. Heidelberger, *Ann. Rev. Pharmacol.*, **7**, 101 (1967); J. A. Montgomery, *Progr. Med. Chem.*, in press; *cf.* references cited in ref 3.

(3) Y. F. Shealy and J. D. Clayton, *J. Amer. Chem. Soc.*, **88**, 3885 (1966).

(4) The preferred conformations of simple substituted cyclopentanes are the puckered envelope and half-chair forms [K. S. Pitzer and W. E. Donath, *ibid.*, **81**, 3213 (1959); F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *ibid.*, **81**, 4915 (1959); M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, pp 72–78; E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965. In crystalline purine and pyrimidine nucleosides and nucleotides either C2′ or C3′ is displaced (either *endo* or *exo* to the base moiety) from the mean plane of the other four furanose-ring atoms by 0.5–0.6 Å; see the following publications and references cited therein: M. Sundaralingam, *J. Amer. Chem. Soc.*, **87**, 599 (1965); M. Sundaralingam and L. H. Jensen, *J. Mol. Biol.*, **13**, 930 (1965); A. E. V. Haschemeyer and A. Rich, *ibid.*, **27**, 369 (1967); P. Tollin, H. R. Wilson, and D. W. Young, *Nature*, **217**, 1148 (1968). There is evidence, however, of some difference in the stabilities of the preferred conformers of comparably substituted cyclopentanes and tetrahydrofurans [H. R. Buys, C. Altona, and E. Havinga, *Tetrahedron*, **24**, 3019 (1968)].

(5) T. Kishi, M. Muroi, T. Kusaka, M. Nishikawa, K. Kamiya, and K. Mizuno, *Chem. Commun.*, 852 (1967).

(6) T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi, and K. Mizuno, *J. Antibiot.* (Tokyo), **21**, 255 (1968).

and Angier[7] had reported the synthesis (by a different synthetic scheme) of the cyclopentane analog of a 2′-deoxynucleoside (thymidine), and (monohydroxycyclopentyl)purines have also been prepared.[8]

The complete synthetic route consists of three parts: synthesis of a cyclopentane with four functional groups in the desired geometric configurations (Chart I), conversion of the starting cyclopentane (**6**) to the required aminocyclopentane (**24**) (Chart II), and the preparation of C-Ado (**28**) and related purines from **24** (Chart III).

The rigid structure of the norbornene ring system offers a logical starting point for the synthesis of cyclopentanes of known geometric configuration. A prerequisite for ribose analogs is the presence of an *exo-cis*-dihydroxy moiety in a molecule such as *exo-cis*-5-norbornene-2,3-diol (**2**). Reaction of norbornadiene (**1**) with the *cis*-hydroxylating agents[9,10] potassium permanganate or osmium tetroxide should (in the absence of complications[11] peculiar to this diene) introduce *cis*-hydroxyl groups, and the rule of *exo* addition predicts that the *exo,exo*-diol should be predominately formed. Predominant *exo* addition to norbornenes is well established[12] and has also been described for addition reactions of norbornadienes.[16] Employment of permanganate or osmium tetroxide would be expected, therefore, to afford the desired norbornenediol (**2**) provided that reaction could be limited to one vinyl group, oxidation beyond the diol stage could be prevented, and rearrangement to tricyclic diols or to norbornene-2,7-diol could be avoided. Permanganate is preferable to osmium tetroxide for the dihydroxylation of sizeable quantities of an alkene, but its oxidizing action is not specific.[9] Although diol formation by permanganate is favored by high base concentration in aqueous solution (and ketol formation by low base concentration),[13] we assumed that the intermediate cyclic manganate (Mn^{V}) ester would be stabilized to hydrolysis and further oxidation in an anhydrous medium at low temperature; that further reactions,[13,17] which may result in ketol formation and carbon–carbon bond cleavage, would thereby be minimized; and that simultaneous introduction of base (to rapidly hydrolyze the cyclic Mn^{V} ester) and a reducing agent (to effect rapid reduction) at low temperature would quench oxidation.[19] Permanganate dihydroxylation of norbornadiene was, accordingly, carried out as follows: (1) the reaction was performed at −70° in dry acetone, (2) norbornadiene was employed in excess, and (3) aqueous base and a reducing agent were introduced simultaneously at −70°. This procedure afforded 25–28% yields (based on permanganate) of a diol; the same product was isolated in 21% yield from a hydroxylation of **1** with osmium tetroxide.

Although the structure of the diol may be logically assigned from the method of preparation, the modest yield obtained indicated that confirmation was desirable in order to eliminate the possibility that the isolated compound might have been a by-product. The melting point of the product differs from the melting points reported for *endo-cis*-5-norbornene-2,3-diol[20] (**8**), *exo,-exo*- and *exo-endo*-tricyclo[2.2.1.$0^{2,6}$]heptane-3,5-diols, and 5-norbornene-*exo*-2,*syn*-7-diol. The latter three compounds and *endo,endo*-tricyclo[2.2.1.$0^{2,6}$]heptane-3,5-diol (isolated as the dibenzoate) are products of Prévost, peracid, or lead tetraacetate oxidation of norbornadiene.[21,22] The melting points of the dibenzoates of the permanganate dihydroxylation product and of the *endo,endo*-tricyclic diol are similar, but nmr data (below) and a positive test on a tlc plate for a *vic*-diol clearly eliminated the latter compound from consideration. Chemical confirmation of the structure is summarized in Chart I. Reduction of the norbornenediol gave *exo-cis*-norbornane-2,3-diol[13,14] (**5**), identical with a specimen prepared by *cis* dihydroxylation of norbornene. Furthermore, the norbornenediol, its diacetate (**3**), and its reduction product (**5**) were shown to be different from the corresponding *endo-cis* isomers (**8, 9, 11**), prepared by the method of Newman and Addor,[20] by direct comparison of infrared and nmr spectra and melting points.

Nmr data obtained with the two norbornenediols (**2** and **8**), their diacetates (**3** and **9**), and the two norbornanediols (**5** and **11**) are entirely consistent with the *exo-cis*-diol structure assigned to the isolated potassium permanganate-dihydroxylation product.[23] Olefinic proton resonances are centered in the range δ 6.03–6.23 in the spectra of **2, 3, 8**, and **9**. In agreement with many observations[24] of deshielding of *exo* protons rel-

(7) K. C. Murdock and R. B. Angier, *J. Amer. Chem. Soc.*, **84**, 3758 (1962).

(8) H. J. Schaeffer and R. D. Weimar, Jr., *J. Org. Chem.*, **25**, 774 (1960); H. J. Schaeffer, D. D. Godse, and G. Liu, *J. Pharm. Sci.*, **53**, 1510 (1964).

(9) W. A. Waters, "Mechanisms of Oxidation of Organic Compounds," Methuen and Co., Ltd., London, 1964, pp 125–129.

(10) R. Stewart in "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter 1.

(11) For example, (a) S. Winstein and M. Shatavsky, *Chem. Ind.* (London), 56 (1956); (b) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963); (c) M. Green, *J. Chem. Soc.*, 541 (1965).

(12) For example, K. Alder and G. Stein, *Ann.*, **515**, 185 (1935); K. Alder and G. Stein, *ibid.*, **525**, 183 (1936); references cited in E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **84**, 2611 (1962); H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967); C. W. Jefford and W. Wojnarowski, *Tetrahedron Lett.*, 193 (1968); references 11a and 13–15. For an exception, see A. C. Oehlschlager and L. H. Zalkow, *Chem. Commun.*, 5 (1966).

(13) K. B. Wiberg and K. A. Saegebarth, *J. Amer. Chem. Soc.*, **79**, 2822 (1957).

(14) H. Kwart and W. G. Vosburgh, *ibid.*, **76**, 5400 (1954); S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

(15) K. C. Pande and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).

(16) For example, K. Alder, J. Mönch, and H. Wirtz, *Ann.*, **627**, 47 (1959); H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 5832 (1959); W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *ibid.*, **89**, 410 (1967); C. W. Bird, R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc.*, 410 (1963); J. Meinwald, S. S. Labana, L. L. Labana, and G. H. Wahl, Jr., *Tetrahedron Lett.*, 1789 (1965).

(17) Permanganate oxidation of norbornene has given principally 1,3-cyclopentanedicarboxaldehyde, assumed to result from further oxidation of the cyclic Mn^{V} ester, in neutral solution;[13] norcamphoric acid under slightly acidic conditions;[18] and *exo-cis*-norbornane-2,3-diol in basic solution[13] or in neutral solution.[14]

(18) S. F. Birch, W. J. Oldham, and E. A. Johnson, *J. Chem. Soc.*, 818 (1947).

(19) Mn^{V} can disproportionate[10] to Mn^{VII} and Mn^{IV}; Mn^{VII} (unreacted or from disproportionation of Mn^{V}) is reduced to MnO_2 by sulfite.

(20) M. S. Newman and R. W. Addor, *J. Amer. Chem. Soc.*, **77**, 3789 (1955).

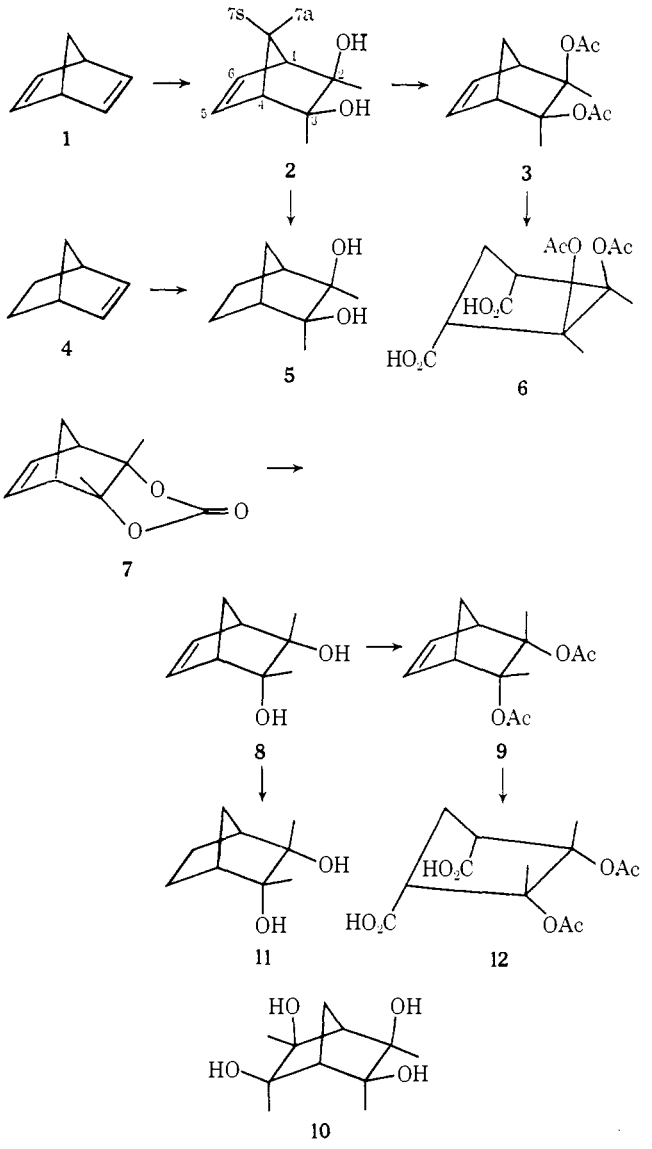
(21) J. P. Schaefer, *ibid.*, **82**, 4091 (1960); K. Alder, F. H. Flock, and H. Wirtz, *Chem. Ber.*, **91**, 609 (1958); A. Ferretti and G. Tesi, *J. Chem. Soc.*, 5203 (1965).

(22) Additional reasons for considering these potential products are: (1) permanganate could conceivably add 2,6 to **1** to give a cyclic Mn^{V} ester analogous to the tricycloheptane formed from **1** and methylphosphonous dichloride,[11c] and (2) even though *exo-cis* products are formed initially by oxymercuration and oxythallation of **1**, they are rather easily rearranged.[15]

(23) Detailed analyses of the nmr spectra of **2, 3, 8**, and **9** are part of a separate publication; M. Thorpe and W. C. Coburn, Jr., *J. Org. Chem.*, in press.

(24) (a) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962); (b) E. W. C. Wong and C. C. Lee, *ibid.*, **42**, 1245 (1964); (c) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964); (d) J. C. Davis, Jr., and T. V. Van Auken, *ibid.*, **87**, 3900 (1965); (e) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).

Chart I



ative to *endo* protons in norbornenes, the chemical shifts (ppm) of the *endo* protons of **2** (δ 3.69) and **3** (δ 4.73) are upfield relative to the *exo* protons of **8** (δ 4.14) and **9** (δ 5.22). A downfield shift of *exo*-proton signals relative to *endo* protons in substituted norbornanes has also been reported[24e,25] and was observed for **11** (δ 3.86) and **5** (δ 3.65). Proof of the structures of **2** and **3** was completed by spin-decoupling experiments which showed: (1) the stereospecific long-range coupling (W form) of the 7s protons (*syn* to the double bond) with the *endo* protons of **2** ($J_{7s,2} = J_{7s,3} = 1.7$ Hz) and **3** ($J_{7s,2} = J_{7s,3} = 1.8$ Hz) and the absence of coupling of the 7s protons with the *exo* protons of the *endo* isomers (**8**, **9**); (2) the absence of coupling of the bridgehead (1,4) protons with the *endo* protons of **2** and **3** and the presence of such coupling with the *exo* protons of **8** ($J_{1,2} = J_{3,4} = 3.7$ Hz) and **9** ($J_{1,2} = J_{3,4} = 4.0$ Hz). These determinations of spin–spin coupling are in agreement with previous studies of norbornenes.[24c-e] Also, the chemical shifts of the 7s protons of the *endo* isomers (**8**, **9**) are downfield from those of the 7a protons, whereas the positions of the 7s and 7a proton signals are reversed in the *exo* isomers (**2**, **3**).[23] There are recent precedents for this pattern of chemical shifts of the 7s and 7a protons of *exo*–*endo* isomer pairs.[24d-e,26]

Thus, the method of preparation, chemical evidence, and nmr data showed that **2** is the structure of the isolated diol. Small amounts of a norbornanetetraol, assumed from the method of preparation and nmr data to be **10**, were also isolated from some of the permanganate oxidations of **1**; basic permanganate oxidation of **1** has been reported,[27] since our work was performed,[3] to give a 15% yield of **10**. Oxidation of *exo-cis*-5-norbornene-2,3-diol diacetate (**3**) with sodium permanganate by the method[18] for norbornene afforded 2α,3α-diacetoxy-1β,4β-cyclopentanedicarboxylic acid[28a] (**6**), the starting cyclopentane with properly oriented functional groups; the *endo*-diacetate **9** was oxidized similarly to the analogous all-*cis* cyclopentane **12**.

Two routes, outlined in Chart II, were developed for the synthesis of (±)-4β-amino-2α,3α-dihydroxy-1β-cyclopentanemethanol (**24**) from the starting cyclopentane (**6**). Crystalline 2α,3α-diacetoxycyclopentane-1β,4β-dicarboxylic anhydride (**13**) was obtained in good yield by treating **6** with ethoxyacetylene. The anhydride (**13**) is very sensitive to moisture and appears to be considerably more reactive than norcamphoric anhydride, but treatment of **13** with ammonia under anhydrous conditions gave (±)-2α,3α-diacetoxy-4β-carbamoyl-1β-cyclopentanecarboxylic acid (**14**) in yields of 75–85%. (At this point it should be noted that opening of the anhydride ring of **13** produces an enantiomeric pair and that all cyclopentyl derivatives beyond **13** were obtained in the racemic form.)[28b] Reaction of **6** with acetic or trifluoroacetic anhydride usually gave a syrupy anhydride product that could be used to prepare the amide acid **14**, but there was some evidence, particularly with acetic anhydride, of mixed anhydride or polymeric anhydride in the product since small amounts of the dicarboxamide of **6** were sometimes isolated. Generally, ethoxyacetylene gave superior results. One route to **24** consists of the conversion of **14** to the acid chloride **15** with thionyl chloride in DMF, reduction of **15** with sodium borohydride to (±)-2α,3α-diacetoxy-4β-(hydroxymethyl)-1β-cyclopentanecarboxamide (**18**), a Hofmann hypobromite reaction of **18** followed by acetylation (to facilitate isolation), and either alkaline saponification of the syrupy tetraacetyl derivative **23** to (±)-4β-acetamido-2α,3α-dihydroxy-1β-cyclopentanemethanol (**22**) or acidic hydrolysis to **24**. Inclusion of an acetylation step after the reduction of **15** gave the pure triacetyl derivative **19**, but the yield was not improved by including this step. In this route the hydroxymethyl group is introduced prior to the amino group; in the second route the amino group is introduced first. The second route has generally been used for large-scale work and consists of the following steps: a Hofmann hypobromite reaction of **14** followed by esterification of the carboxyl function (**17**) and acety-

(25) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963).

(26) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968).

(27) H. Z. Sable and H. Katchian, *Carbohyd. Res.*, **5**, 109 (1967).

(28) (a) The convention used to designate substituent orientation in steroids and carbohydrate anomers was adopted for the tetrasubstituted cyclopentanes. Substituents written below the plane of the cyclopentane ring are designated α; those above, β. The intermediate cyclopentanes (**13–24**, **26**) are written in such a way that the purine ring in the purine derivatives will be β. Structures **6** and **12** are named in this way but are written "upside down" to show their derivation from the norbornenes. (b) Structures **14–24** and **26–33** depict only one enantiomer of the racemic form actually obtained.

Chart II[28b]

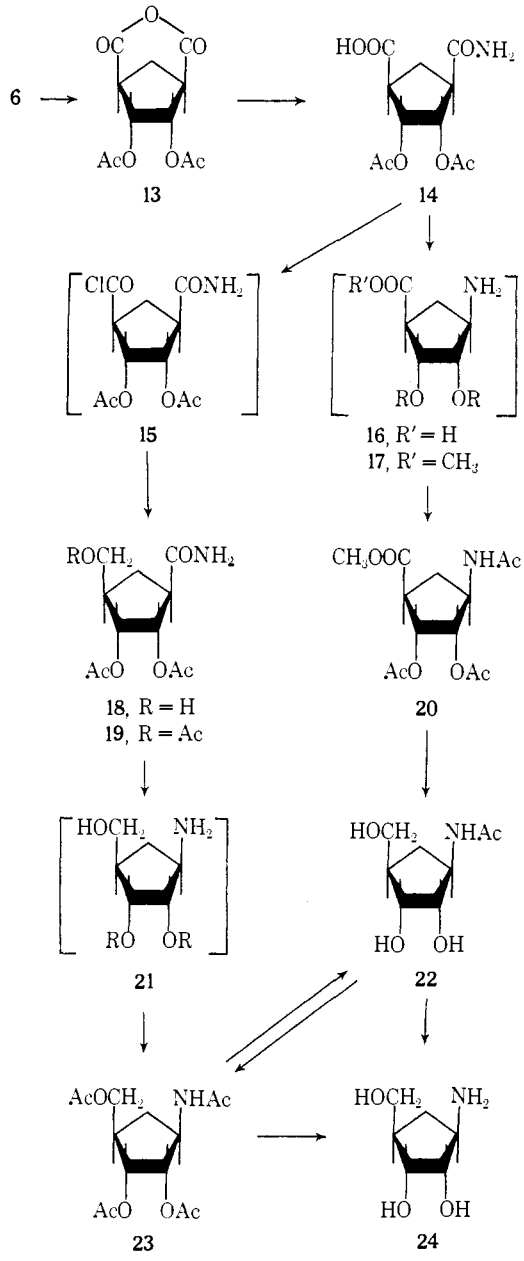
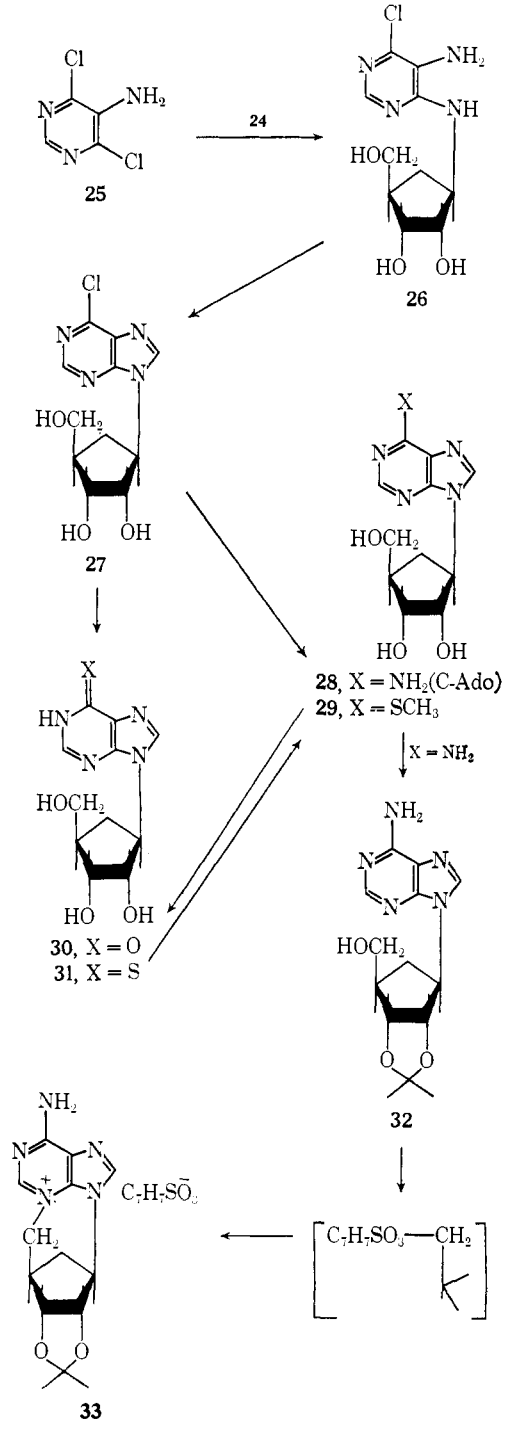


Chart III[28b]



lation of the amino and hydroxyl groups to methyl (±)-4β-acetamido-2α,3α-diacetoxy-1β-cyclopentanecarboxylate (**20**), reduction of the methyl ester function with lithium borohydride, and acetylation of the resulting acetamide (**22**) to **23** or direct acidic hydrolysis of **22** to **24**. Compound **20** was originally[3] isolated, without first purifying **16** and **17**, by chromatography on silica gel, but in later preparations this time-consuming method was obviated by ion-exchange chromatography of the product from the Hofmann reaction. Complete acetylation after the amino and hydroxymethyl groups had been introduced was initially[3] included in both routes because the tetraacetyl derivative (**23**) is extractable with organic solvents; subsequently, improved isolation techniques gave the crystalline acetamide (**22**) directly from **20** in 84% yield. Specimens of **23** and of **22** obtained from the two routes were shown to be identical. The desired amine (**24**), obtained by acidic hydrolysis of either **22** or **23**, was a colorless syrup that retained solvents tenaciously and was generally used without purification in the next step in the synthesis of purines; however, an analytically pure specimen was obtained by short-path vaporization.

The remainder of the synthesis of C-Ado (**28**) and related purines (Chart III) is based on the known[29] three-step sequence that begins with the reaction of an alkylamine with 5-amino-4,6-dichloropyrimidine (**25**). The 6-chloropurine derivative (**27**) was obtained as a hygroscopic hydrochloride and was used as such as an intermediate. C-Ado was prepared from **27** and ammonia and was purified by ion-exchange chromatography. Compounds **29–31** are the racemic forms[28b]

(29) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **79**, 5238 (1957).

of the analogs of 6-(methylthio)purine ribonucleoside, inosine, and 6-mercaptopurine ribonucleoside, respectively. The inosine analog (**30**) was prepared by hydrolysis of the 6-chloropurine (**27**) and by nitrosation of C-Ado; the purine-6-thione (**31**) and the 6-(methylthio)purine (**29**) derivatives were prepared by conventional methods.

The *cis–trans* relationships of the substituents on the cyclopentane ring of **28–31** derive from the established geometrical configuration of the starting cyclopentane (**6**) and the two synthetic routes. The Hofmann hypobromite reaction proceeds with retention of configuration;[30] in fact, Archer[31] has pointed out that the first demonstration of retention of configuration in the Hofmann reaction came from the work of Noyes[32] with 3-carbamoylcyclopentanecarboxylic acids (camphoramidic acids) similar to **14**. Other reactions were performed under mild conditions in order to assure preservation of the configurations of the four substituents. The preparation in high yield of an O-isopropylidene derivative (**32**) of C-Ado showed that the secondary hydroxyl groups were still *cis*, and the formation of a cyclopentane cyclonucleoside analog (**33**) *via* the covalent tosylate confirmed the *cis* arrangement of the hydroxymethyl group and the purine ring. These reactions had been used to confirm the stereochemical relationships of the four groups in adenosine.[33]

Biochemical studies[34] of C-Ado have shown that it is highly cytotoxic (ED_{50} 0.7 μM) to H.Ep.-2 cells in culture and that it is a substrate for adenosine kinase and adenosine deaminase. Daily treatment of mouse lymphoid leukemia L1210 (QD 1–9) or of rat intramuscular Walker carcinosarcoma 256 (QD 3–6) with C-Ado showed that it was toxic at doses of 50 mg/kg/day, and above, and nontoxic and inactive at 25 mg/kg/day.[35] Compounds **29–31** are not cytotoxic to H.Ep.-2 cells in culture,[34b] and initial tests of the inosine analog **30** and the purine-6-thione derivative **31** have not revealed activity *vs.* L1210.

Experimental Section

Spectral data were determined with the following spectrometers: ir, Perkin-Elmer Model 521; uv, Cary Model 14; nmr, Varian A60A equipped with a Model V-6058A spin decoupler; mass spectra, Hitachi-Perkin-Elmer RMU-7 double focusing. Unless otherwise stated, ir data are from spectra recorded from samples in KBr disks. Uv data are from solutions prepared by diluting a 5-ml aliquot of an H_2O or ethanol solution of the compound to 50 ml with 0.1 *N* HCl, phosphate buffer (pH 7), or 0.1 *N* NaOH. For ir and uv, sh = shoulder. Unless otherwise stated, $CDCl_3$ solutions with tetramethylsilane (TMS) as internal reference were used to determine nmr data; chemical shifts (δ) are in parts per million (ppm) downfield from TMS and coupling constants are in hertz (Hz). The designated multiplicities (s = singlet, d = doublet, t = triplet, m = multiplet) are descriptive of the appearance of the resonance signals and are not necessarily true multiplicities. Unless otherwise stated, melting points were determined on a Kofler Heizbank apparatus (gradiently heated bar); melting points determined in a capillary in a Mel-Temp apparatus are labeled "MT." Thin layer chromatography (tlc) was performed on silica gel, and the developing solvent and method of detection are specified at the appropriate places in the procedures.

exo-cis-**5-Norbornene-2,3-diol (2). Permanganate Method.** A solution, protected from moisture, of 25 ml (23.5 g, 254 mmol) of redistilled norbornadiene in 220 ml of reagent acetone was chilled to −72° with an acetone–Dry Ice bath, and to the vigorously stirred solution was added, over a 10-min period, 15.8 g (100 mmol) of finely powdered potassium permanganate. The addition rate was such that the temperature of the mixture was maintained between −64 and −70°. The reaction mixture was stirred for 1 hr at −65 to −72°, and then a solution, precooled to 0°, of 4 g (100 mmol) of sodium hydroxide and 13 g (103 mmol) of sodium sulfite in 70 ml of water was added in portions over a 5-min period. The temperature was maintained at −60 to −70° during the basic sulfite addition and for an additional 10 min before the cooling bath was removed, and the thick brown-black mixture was allowed to warm slowly to room temperature over a 2-hr period. Vigorous stirring was employed throughout these operations. The solid phase was allowed to settle, the supernatant was decanted, the solid phase was washed three times in the flask by vigorous stirring with 100-ml portions of 90% acetone–water and by decanting each portion, and the combined decantates were concentrated *in vacuo* at 35° until the acetone had been removed. The red aqueous residue was saturated with NaCl and extracted with $CHCl_3$ (four 50-ml portions). The total chloroform extract was dried (Na_2SO_4) and evaporated *in vacuo* at 35°. Further evacuation (oil pump) and seeding of the residual brown oil produced 6.8 g of crude solid product, which was stirred overnight with 20 ml of cyclohexane containing a few drops of chloroform. The tan solid was removed by filtration, washed with cyclohexane, and combined with small second and third crops obtained by concentrating the combined filtrate and washings. The product remaining after drying (56°, 1 mm), the combined portions for 1 hr, amounted to 3.5 g (28% based on permanganate, mp 114–116° with sublimation), was homogeneous by tlc (95:5 $CHCl_3$–CH_3OH, detection by basic permanganate spray), and was satisfactory for further synthetic work. Specimens for analysis and nmr were purified further by recrystallization from cyclohexane or by sublimation: mp 118°; positive periodate–Schiff's test for a *vic*-diol on a thin-layer chromatogram (5:3:2 butanol–H_2O–acetic acid or 95:5 $CHCl_3$–CH_3OH); nmr δ 1.62 (m, H_{7s}), 1.88 (m, H_{7a}), 2.69 (m, H_1H_4), 3.41 (m, OH), 3.69 (m, H_2H_3), 6.03 (t, H_5H_6); infrared bands (cm^{-1}): 3410, 3250 (OH); 3055 (olefinic CH); 2985, 2975, 2960, 2950 sh, 2875 (aliphatic CH); 1570 (C=C).[36]

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.81; H, 8.18.

Specimens of **2** obtained by the permanganate procedure were identical (melting point, mixture melting point, ir, and tlc) with a specimen obtained by reaction of **1** with osmium tetroxide; the ir spectrum and melting point of **2** were different from those of the *endo*-diol **8**.

Preparation of **2** by the permanganate method was first performed by a similar procedure except that a solution, precooled in a Dry Ice–acetone bath, of potassium permanganate in acetone was added to an acetone solution of **1**. When this procedure was used, the formation of a brown precipitate could be observed within a few minutes. After 15 min of vigorous stirring, an aqueous solution of NaOH and Na_2SO_3 (3 mol of each/mol of $KMnO_4$) was added and stirring continued for 15 min. During the basic sulfite treatment the heavy brown precipitate became black. In order to reduce the volume of the reaction mixture for large-scale preparations, solid permanganate was added, as described above, and this procedure applied on a 120-fold scale has afforded a similar yield (415 g) of **2** after recrystallization from cyclohexane (7 ml/g).

A small amount of a tetraol, presumably **10**, was isolated from an experiment in which permanganate was added in acetone solution and the reaction mixture processed by substituting continuous liquid–liquid extraction with ethyl acetate for the chloroform extraction described above. The residue from evaporation of the ethyl acetate was chromatographed in $CHCl_3$–CH_3OH (95:5) on silica gel and gave **2** (25%). The aqueous layer from the ethyl acetate extraction was combined with an aqueous solution obtained by stirring the manganese dioxide residue with water for 1.5 days. This aqueous mixture was extracted continuously with ethyl acetate. Recrystallization (1:1 ethanol–hexane) of the residue from the ethyl acetate extract gave a white solid: mp 196° (lit.[27] 196.5–

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197°); nmr δ 1.47 (broad s, H_7), 1.85 (t, H_1H_4), 3.43 (s, $H_2H_3H_4H_5$), *ca.* 4.4 (s, OH).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.49; H, 7.64

Osmium Tetroxide Method. A solution of 1.0 g (3.94 mmol) of osmium tetroxide in 50 ml of ether was added dropwise during 15 min to a stirred solution of 724 mg (7.9 mmol) of redistilled **1** in 25 ml of ether. The reaction mixture, which became black, was protected from light, stirred at 20° for 48 hr, sparged with H_2S for 30 min, allowed to stand at room temperature for 1 hr, and then filtered. The solid residue was washed with hot ethyl acetate and hot methanol. Concentration of the combined filtrate and washings *in vacuo* left a mixture of solid and syrup that afforded 107 mg (21%) of white crystalline solid after trituration with cyclohexane. Sublimation (60°, 0.1 mm) gave pure **2**, melting at 118°, in excellent recovery.

***exo-cis*-Norbornane-2,3-diol (5). From 2.** A solution of 504 mg of **2**, 70 ml of CH_3OH, and 4 ml of H_2O was treated with H_2 on a 5% Pd–C catalyst at approximately atmospheric pressure. The catalyst was removed by filtration and washed twice with CH_3OH. Evaporation of the solvents from the filtrate and washings left a residue that was dried further by adding and evaporating ethanol. Dissolution of the residue in ethyl acetate–hexane (1:5) and chilling the mixture on Dry Ice, after some of the product had precipitated, yielded 464 mg (91%) of white crystals, mp 139–140°. The ir spectrum was identical with that of a specimen of **5** from **4** and different from that of *endo-cis*-norbornane-2,3-diol (**11**); a mixture melting point of specimens from **4** and **2** was 140°.

From 4. Treatment of an acetone solution of **4** with an acetone solution of potassium permanganate by a procedure similar to that used for the dihydroxylation of **1** gave **5**: mp 140° (lit.[13,14] 139.5–140.5°, 140.2–140.6°, 139–140°); nmr δ 0.8–2.0 (m, $H_5H_6H_7$), 2.13 (m, H_1H_4), 3.51 (m, OH), 3.65 (m, H_2H_3).

***endo-cis*-Norbornene-2,3-diol (8)** was prepared from the adduct (**7**, mp 114°, lit.[20] 114.4–115°) of cyclopentadiene and vinylene carbonate as described by Newman and Addor:[20] mp 178° subl. (lit. 176–179° dec); nmr δ 1.20 (m, H_{7a}), 1.49 (m, H_{7s}), 2.78 (m, OH), 2.99 (m, H_1H_4), 4.14 (m, H_2H_3), 6.23 (t, H_5H_6); infrared bands (cm^{-1}): 3440, 3390, 3200 (OH); 3075, 3060 (olefinic CH); 2995, 2980, 2960, 2945, 2935, 2915, 2900, 2890, 2870 (aliphatic CH); 1568 (C=C).

***endo-cis*-Norbornane-2,3-diol (11)** was prepared from **8** by the procedure used to reduce the *exo-cis*-diol (**2**) and was purified by sublimation (70°, 0.25 mm): mp 213° (lit.[20] 210.6–212.4°); nmr δ 0.8–2.0 (m, $H_5H_6H_7$), 2.32 (m, H_1H_4), 3.17 (broad s, OH), 3.86 (m, H_2H_3).

***exo-cis*-5-Norbornene-2,3-diol Diacetate (3) and Dibenzoate.** To a solution of 161 g of *exo-cis*-5-norbornene-2,3-diol (**2**) in 1.5 l. of dry pyridine at −70° was added, in one portion, 600 ml of acetic anhydride. The solution was kept at room temperature for 36 hr and then poured into 3 l. of cracked ice. After 1 hr, the mixture was extracted with three 600-ml portions of dichloromethane, and the total dichloromethane extract was washed successively with cold 2 *N* HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Concentration of the dried (Na_2SO_4) solution *in vacuo* yielded 258 g (96%) of crystalline **3**: mp 41–43° (MT); nmr δ 1.72 (m, H_{7s}), 2.03 (m, H_{7a}), 2.05 (s, CH_3CO), 2.82 (m, H_1H_4), 4.73 (d, H_2H_3), 6.16 (t, H_5H_6). The ir spectrum (film, cm^{-1}) was different from that of the *endo-cis* isomer (**9**): 3065 (olefinic CH); 2985, 2950, 2870 (aliphatic CH); 1740 (ester C=O).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.01; H, 6.77.

exo-cis-5-Norbornene-2,3-diol dibenzoate was prepared similarly except that a CH_2Cl_2 solution of benzoyl chloride was added to the pyridine solution of **2** at 10–20°, the reaction was maintained at 20–25° for 6 hr, and $CHCl_3$ was substituted for CH_2Cl_2 for the extraction. The recrystallized (1:4 benzene–hexane) dibenzoate melted at 118–118.5° (MT) [different than reported[21] melting point of dibenzoates of *exo-syn*-5-norbornene-2,7-diol (93–94°) and the *exo-exo* (110.5–111.5°) and *exo-endo* (87.5–88°) isomers of tricyclo[2.2.1.$0^{2,6}$]-3,5-diol, melting point of *endo-endo* tricyclic isomer 116.5–117°].

Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.42; H, 5.43. Found: C, 75.59; H, 5.52.

***endo-cis*-5-Norbornene-2,3-diol diacetate (9)** was obtained in 94% yield by the procedure used for **3** except that the product was extracted with $CHCl_3$ and triturated with hexane: mp 53.5–54.5°; nmr δ 1.36 (m, H_{7a}), 1.58 (m, H_{7s}), 1.98 (s, CH_3CO), 3.12 (m, H_1H_4), 5.22 (m, H_2H_3), 6.20 (t, H_5H_6); infrared bands (cm^{-1}): 3070 (olefinic CH); 3000, 2980, 2970, 2955, 2930, 2880 (aliphatic CH); 1740 (ester C=O); 1570 (C=C).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.98; H, 6.79.

2α,3α-Diacetoxy-1β,4β-cyclopentanedicarboxylic Acid[28a] (6). A solution of 66.6 g (0.34 mol) of sodium permanganate trihydrate in 500 ml of H_2O was added dropwise during 1.5 hr to a vigorously stirred mixture, into which was bubbled CO_2, of 23.3 g (0.11 mol) of **3** in 580 ml of 2,2,4-trimethylpentane and 730 ml of water. The temperature of the mixture was maintained at 10–15° and vigorous CO_2 sparging was continued throughout the permanganate addition. Immediately after the addition was complete, the purple suspension was sparged with SO_2 (at about 20°) until the mixture became colorless. The resulting mixture was concentrated *in vacuo* to *ca.* 400 ml, filtered to remove small amounts of tarry material, cooled in an ice bath, and acidified with 30 ml of 12 *N* HCl. After the precipitate had been collected by filtration, washed with 30 ml of cold water, and dried (P_2O_5), it amounted to 22.5 g (74%), mp 169°. An additional 3.3 g (11%) of **6**, mp 166–171°, was obtained in three crops by saturating the combined filtrate and washing with NaCl, extracting the aqueous solution with three 80-ml portions of ether, evaporating the dried ether extracts, and crystallizing the residual yellow syrup from ethyl acetate. For analysis, the product was recrystallized from ethyl acetate–hexane (1:3): mp 169–171°; infrared bands (cm^{-1}): 3500–3340, 2780, 2720–2560 (OH); 3100–2880 (OH, CH); 1765, 1715 (C=O); 1270, 1240, 1210 (C—O).

Anal. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15. Found: C, 48.25; H, 5.19.

2β,3β-Diacetoxy-1β,4β-cyclopentanedicarboxylic Acid[28a] (12). The *endo-cis*-diol diacetate (**9**) was oxidized by the procedure used for the oxidation of **3**. The all-*cis* derivative (**12**) was obtained in 70% yield: mp 180°; infrared bands (cm^{-1}): 3400, 3170, 3130, 2780–2560 (OH); 2940 (CH); 1750, 1735, 1720, 1695 (C=O); 1280, 1260, 1235, 1215 (C—O).

Anal. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15. Found: C, 48.14; H, 5.28.

2α,3α-Diacetoxy-1β,4β-cyclopentanedicarboxylic Acid Anhydride (13). Ethoxyacetylene (34.5 ml) was added in one portion to a stirred suspension of 87 g of **6** in 500 ml of dry dichloromethane. The mixture was stirred at room temperature for 24 hr, external cooling being necessary in the first hour. The reaction solution was concentrated to dryness *in vacuo*, and the residue pulverized with 50 ml of dry tetrahydrofuran, separated by filtration, washed with dry tetrahydrofuran (two 50-ml portions), and dried *in vacuo* at room temperature: yield, 70 g (86%), mp 162°. An additional 4.1 g (5%) of anhydride, mp 162°, was recovered from the filtrate and washings. An analytical sample was prepared by sublimation (120°, 0.2 mm): mp 163–164°; ir (cm^{-1}) 1820, 1780, 1745 (C=O).

Anal. Calcd for $C_{11}H_{12}O_7$: C, 51.57; H, 4.73; O, 43.70. Found: C, 51.44; H, 4.78; O, 43.74.

(±)-2α,3α-Diacetoxy-4β-carbamoyl-1β-cyclopentanecarboxylic Acid (14). A forceful stream of dry ammonia gas was blown over the surface of a vigorously stirred, chilled (5°) solution of 70 g of **13** in 1.2 l. of dry tetrahydrofuran for 25 min (or until precipitation was complete). Volatile materials were removed *in vacuo*, and the white powdery residue was dissolved in 350 ml of water. After the solution had been filtered from a small amount of insoluble material, the filtrate was chilled (0°), acidified (pH 2) with 23 ml of 12 *N* HCl, then stored at 2° for 16 hr. The white crystalline product was collected by filtration, washed with cold water, and combined with a second crop obtained by concentrating the combined filtrate and washing *in vacuo* to 100 ml. The combined crops, both with mp 183°, amounted to 61 g (82%) after drying (P_2O_5) *in vacuo* at 50°. Compound **14** may be recrystallized from ethyl acetate–hexane or from ethanol–ethyl acetate. A small sample recrystallized from the latter solvent pair melted at 166°, resolidified, and remelted at 182–183°; the two forms are identical and homogeneous by tlc (silica gel, CH_3OH, detection by basic permanganate spray or cellulose, 86:14 butanol–H_2O, detection by brom cresol green); ir (cm^{-1}) 1745 (ester C=O), 1705 (carboxyl C=O), 1660 (amide I), 1600 (amide II).

Anal. Calcd for $C_{11}H_{15}NO_7$: C, 48.35; H, 5.54; N, 5.13. Found: C, 48.22; H, 5.50; N, 5.19.

After removal of **14** from some preparations in which the total crude anhydride from the preceding step was used **2α,3α-diacetoxy-1β,4β-cyclopentanedicarboxamide** was isolated and recrystallized from H_2O: mp 230° dec; ir (cm^{-1}) 1735 and 1720 (ester C=O), 1665 (amide I), 1615 and 1600 (amide II).

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.92; N, 10.29. Found: C, 48.46; H, 5.45; N, 9.99.

(±)-2α,3α-Diacetoxy-4β-(hydroxymethyl)-1β-cyclopentanecarboxamide (18). To a solution of 1.092 g (4.0 mmol) of dry **14** in 30 ml of dry, redistilled dimethylformamide was added, in one portion and with stirring, 0.5 ml (6.9 mmol) of thionyl chloride. The resulting solution was kept at 0° for 15 min, at room temperature for 3 hr, and at 60° for 1 hr. (This reaction and the subsequent reduction were protected from atmospheric moisture.) The brown solution was evaporated to dryness at 35° *in vacuo*, and dry tetrahydrofuran was added and evaporated *in vacuo* to facilitate removal of volatile material. The crude, solid acid chloride (**15**) was dissolved in 40 ml of dry, redistilled bis(2-methoxyethyl) ether, the solution chilled in an ice bath, sodium borohydride (500 mg, 98% pure) added in one portion, and the mixture stirred at room temperature for 18 hr. To the mixture at 0° was cautiously added 20 ml of water and then 10 ml of 2 *N* HCl. The clear brown solution was kept at 0–5° for a few minutes, neutralized to pH 7.2 with 6 *N* NaOH, and evaporated *in vacuo* at 30–35°. Ethanol was added to the residue and then evaporated to effect further drying. The residue was leached with hot $CHCl_3$ (three 30-ml portions), and the total $CHCl_3$ extract was filtered and freed of solvent *in vacuo* at 30°. The syrupy residue (1.019 g) was chromatographed on a column of silica gel. Development of the column with 96:4 $CHCl_3$–CH_3OH revealed the product as an opaque band moving down the translucent column. Evaporation of solvent from effluent fractions containing material from the opaque band yielded 440 mg (43%) of **18**: mp 97–99° (MT); one spot on tlc (9:1 $CHCl_3$–CH_3OH, basic permanganate spray); ir (cm^{-1}) 1740 and 1720 (ester C=O), 1675 (amide I), 1620 (amide II).

Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.93; H, 6.59; N, 5.31.

(±)-4β-(Acetoxymethyl)-2α,3α-diacetoxy-1β-cyclopentanecarboxamide (19). The procedure described for **18** was repeated except that formation of the acid chloride was performed at room temperature for 3 days. The crude syrup (1.01 g) from the borohydride reduction was treated with 5 ml of acetic anhydride in 15 ml of dry pyridine at room temperature for 20 hr. Crushed ice (10 ml) was added to the dark residue remaining after evaporation of volatile material *in vacuo* at room temperature, and the mixture was extracted, after 1 hr at room temperature, with several portions of chloroform. The total chloroform extract (100 ml) was washed successively with 10-ml portions of 2 *N* HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Evaporation of the dried (Na_2SO_4) chloroform layer left 892 mg of red syrup that was chromatographed on silica gel by the procedure described for the purification of **18** except that the developing solvent was 99:1 $CHCl_3$–CH_3OH. The yield of **19** was 44%: mp 86–89°; one spot on tlc (9:1 ethyl acetate–CH_3OH, basic permanganate spray); saponification equivalent 102 (calcd 100.4); ir (cm^{-1}, film) 1740 (ester C=O), 1670 (amide I), 1610 (amide II).

Anal. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.35; N, 4.65. Found: C, 52.05; H, 6.58; N, 4.82.

Methyl (±)-4β-Acetamido-2α,3α-diacetoxy-1β-cyclopentanecarboxylate (20). To a solution of 12.1 ml (0.236 mol) of bromine in 2 l. of 1.0 *N* NaOH was immediately added a prechilled (5°) solution of 54.6 g (0.2 mol) of **14** in 300 ml of 0.67 *N* NaOH. The resulting solution was successively maintained at 0–4° for 1 hr, warmed to 20° during 1 hr, heated at 70° for 1 hr, cooled to 0°, acidified with 12 *N* HCl, and passed through a column of 900 g (dry weight) of cation-exchange resin (Amberlite CG-120, H^+ form). The column was washed with 6 l. of water and the eluate discarded. Next, the column was eluted with 6 l. of 2 *N* HCl, and this eluate was concentrated *in vacuo* at 35–40° to a residue consisting of basic organic material and NaCl. A single organic spot, presumably (±)-4β-amino-2α,3α-dihydroxy-1β-cyclopentanecarboxylic acid (**16**, R = H) hydrochloride, was revealed by tlc (5:3:2 butanol–H_2O–acetic acid, periodate–Schiff's, and ninhydrin detection) of the residue.

After the residue had been dried further by adding and evaporating several portions of CH_3OH, it was suspended in 2 l. of dry CH_3OH, and dry HCl was bubbled into the mixture for 1 hr with stirring and with spontaneous heating and for an additional hour with external cooling (ice bath). The mixture was stirred overnight at room temperature, sparged with dry N_2, and concentrated *in vacuo*. The residue, containing **17** (presumably R = H), was then mixed with 1.5 l. of pyridine, and to the chilled (Dry Ice–acetone bath), thoroughly shaken suspension was added 500 ml of acetic anhydride. The acetylation mixture was stirred at room temperature for 17 hr, the volume was reduced *in vacuo* to a mixture of thin syrup and sodium chloride, crushed ice (1.2 l.) was added with stirring to the mixture, and the product was extracted with $CHCl_3$ (three 400-ml portions). The total $CHCl_3$ extract was washed with successive portions of ice-cold 3 *N* HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Removal of the solvent *in vacuo* from the dried (Na_2SO_4) $CHCl_3$ layer left a syrup that crystallized: yield, 33.5 g (56% from **14**); mp 110–116°. Recrystallization from $CHCl_3$–hexane (1:9) afforded pure colorless crystals: mp 116°; ir (cm^{-1}) 1750 sh, 1740 sh, 1735 (ester C=O), 1655 (amide I), 1540 (amide II).

Anal. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.35; N, 4.65. Found: C, 51.70; H, 6.21; N, 4.74.

(±)-4β-Acetamido-2α,3α-diacetoxy-1β-cyclopentanemethyl Acetate (23). A. From 18. A cold (0°) solution of 232 mg of **18** in 10 ml of water was added to a cold (0°) solution of 0.056 ml of bromine, 18 ml of 1.0 *N* NaOH, and 20 ml of H_2O. The colorless solution was stirred at 0° for 1 hr, warmed to 20° during 20 min, and finally kept at 70° for 55 min. The cooled yellow solution was neutralized (pH 6.8) with 2 *N* HCl and evaporated to dryness *in vacuo*. After ethanol and toluene had been added to and evaporated from the residue to remove traces of water, a suspension of the residue in 15 ml of dry pyridine was stirred at room temperature for 1 hr to ensure dissolution of **21** (presumably R = H), cooled to 0°, and acetylated with 4 ml of acetic anhydride at room temperature for 16 hr. The mixture was cooled, diluted with 4 ml of CH_3OH, stirred at room temperature for 1 hr, and concentrated *in vacuo* to remove volatile components. A 10-ml H_2O solution of the residue was extracted with three 30-ml portions of $CHCl_3$, and the $CHCl_3$ solution was washed successively with 2 *N* HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Evaporation of the dried (Na_2SO_4) $CHCl_3$ layer *in vacuo* left 216 mg of dark syrup that was chromatographed on silica gel. Development of the column with 98:2 $CHCl_3$–CH_3OH by the method outlined for **18** afforded 175 mg (62%) of **23**. A specimen for analysis was prepared by filtering an ethanol solution of **23**, evaporating the solvent, and drying the residual syrup at 35° (0.5 mm) for 6 hr; ir (3400–1000 cm^{-1}, film) 3360, 3280, 3070, 2950, 2890, 1740, 1670 sh, 1655, 1540, 1430, 1370, 1230, 1140, 1120, 1070, 1040.

Anal. Calcd for $C_{14}H_{21}NO_7$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.07; H, 6.44; N, 4.51.

B. From 20. Reduction of 4.07 g of **20** with lithium borohydride was performed by the method described below for the preparation of **22** from **20** except that hydrochloric acid, instead of an ion-exchange resin, was used to decompose borate esters. After the reduction mixture had been cautiously diluted with H_2O (200 ml) and then with 31 ml of 6 *N* HCl, the resulting solution was stirred at room temperature for 12 hr, concentrated to half its volume *in vacuo*, neutralized with 6 *N* NaOH, and concentrated to dryness *in vacuo*. Further drying of the residue was effected by repeated evaporations of portions of methanol and benzene. An acetylation mixture (consisting of the residue, 100 ml of dry pyridine, and 100 ml of acetic anhydride) was prepared and processed by the procedure described for **20**. Removal of the last traces of solvent from the syrupy tetraacetyl derivative (**23**) is difficult. Vpc analysis of the crude syrup (3.39 g, 80% yield) indicated it to be 90% pure **23**: tlc (95:5 $CHCl_3$–CH_3OH, permanganate detection) showed one spot. The ir spectrum of a specimen collected by vpc for analysis (found: C, 53.29; H, 6.91; N, 4.40) was identical with that of **23** prepared from **18**.

(±)-4β-Acetamido-2α,3α-dihydroxy-1β-cyclopentanemethanol (22). A. From 20. A solution of 1.0 g of **20** in 30 ml of dry, redistilled tetrahydrofuran was added to a stirred mixture of 590 mg of lithium borohydride and 100 ml of tetrahydrofuran at 40°. The borohydride mixture had been refluxed for an hour prior to the addition and allowed to cool to 40°. (Iodometric titration of an aliquot of the supernatant indicated that 280 mg (12.2 mmol) of lithium borohydride was in solution.) The reaction mixture was heated under reflux for 3 hr, cooled in an ice bath, and treated cautiously with 100 ml of ice water. A cation-exchange resin (Amberlite CG-120, H^+ form) was added in small portions until 12 g had been added, the mixture was stirred at 20° for 4 hr and filtered, the resin was washed with water (five 30-ml portions), and the aqueous solution (filtrate and washings) was concentrated *in vacuo* at 40° to a turbid syrup. The syrup was dissolved in 50 ml of CH_3OH, the solvent was evaporated under reduced pressure at 50°, and this CH_3OH treatment was repeated four times. This treatment was assumed to aid in the removal of boron as methyl borate, and it caused a change in the appearance of the residue. The residual syrup was dissolved in 100 ml of water, the solution treated with 8 g of an anion-exchange resin (Amberlite CG-400, OH^- form), and a final colorless syrup was recovered by a procedure similar to that used following treatment with the cation-exchange resin. Trituration of the

syrup with a mixture (1:5:1) of ethanol, ethyl acetate, and hexane effected crystallization and yielded, after an ethyl acetate–hexane (1:1) washing and drying at 56°, 528 mg (84%) of **22**: mp 115–117°; ir (cm^{-1}) 1635 (amide I), 1545 (amide II). Compound **22** can be recrystallized from an ethanol–ethyl acetate–benzene mixture. In a subsequent experiment, treatment with the anion-exchange resin was omitted; the yield was 74%.

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.79; H, 7.99; N, 7.40. Found: C, 50.68; H, 7.93; N, 7.46.

B. From 18 *via* 23. A solution of 408 mg of **23** (from **18**) in 15 ml of dry CH_3OH was added to a solution prepared from *ca.* 120 mg of sodium and 15 ml of dry CH_3OH. The mixture was stirred at room temperature for 18 hr and deionized by addition of a cation-exchange resin (Rexyn RG-50, H^+ form). The filtrate, plus H_2O washings from the resin, was concentrated to a syrup *in vacuo*. Addition and evaporation (under reduced pressure) of several portions of ethanol left a syrup that was dissolved in a mixture of 3 ml of ethanol and 10 ml of ethyl acetate. Dilution of the hot solution with hexane (10 ml) and chilling gave a solid which was washed with ethanol–hexane (1:5) and dried (P_2O_5) *in vacuo* at 56°: yield 161 mg (66%); mp 114–116° (MT). The ir spectrum and tlc in two solvents (3:1 $CHCl_3$–CH_3OH and 4:1 ethanol–15 *N* aqueous NH_3, detection by basic permanganate) were identical with those of a specimen obtained from **20**.

(±)-4β-Amino-2α,3α-dihydroxy-1β-cyclopentanemethanol (24). From 23. Initial experiments indicated that it was expedient to perform the deacetylation in two stages without isolating intermediate products. A solution of 15 g of **23** (90% pure by vpc), 110 ml of ethanol, and 60 ml of 6 *N* HCl was kept at room temperature for 18 hr. After the volatile materials had been removed *in vacuo*, the residual syrup was refluxed in 600 ml of 6 *N* HCl for 4.5 hr. The solution was treated with activated carbon and then evaporated *in vacuo*, several portions of water were evaporated *in vacuo* from the residual syrup, and a water (200 ml) solution of the syrup was stirred with an anion-exchange resin (Amberlite CG-400, OH^- form) until free of chloride ion. Removal of the resin, concentration of the filtrate at 0.5 mm, and evaporation of several portions of ethanol from the residue left 6.0 g (95%) of a faintly yellow syrup. The very viscous syrup is difficult to free completely from solvents, but it is suitable for use as an intermediate. Short-path, high-vacuum vaporization of a small specimen yielded an analytical sample as a thick, colorless syrup; ir (3500–1000 cm^{-1}, film) 3500–3000, 2910, 2860, *ca.* 2700 sh, 1590 (NH_2), 1445, 1380, 1330, 1220, 1105, 1040.

Anal. Calcd for $C_6H_{13}NO_3$: C, 48.96; H, 8.90; N, 9.52. Found: C, 48.72; H, 8.91; N, 9.37.

From 22. A solution of 16.2 g of **22** in 200 ml of 6 *N* HCl was refluxed for 4 hr, cooled, stirred with activated carbon for 5 hr at room temperature, and concentrated *in vacuo* to a syrup after removal of the carbon. A solution of the syrup in 120 ml of H_2O was passed through a column of 72 g of a cation-exchange resin (300 mequiv of Rexyn RG-50, H^+ form). The column was washed with 500 ml of H_2O to remove Cl^- and any neutral or acidic impurities, the H_2O effluents were discarded, and **24** was then eluted from the column with 500 ml of 2 *N* aqueous NH_3. Evaporation of the solvent *in vacuo* from the eluate followed by evaporation of several portions of ethanol *in vacuo* left 13.2 g of a yellow syrup that was homogeneous according to tlc (5:3:2 butanol–H_2O–acetic acid and 4:1 ethanol–aqueous NH_3, detection by ninhydrin and basic permanganate or periodate–Schiff's reagents). In an alternative procedure an aqueous solution of the initial residual syrup was treated with an anion-exchange resin (Amberlite CG-400, OH^- form) to remove Cl^- and usually gave a pale yellow or colorless syrup. The crude syrup (identified as **24** by ir and tlc) from either resin treatment was generally used without further purification.

(±)-4β-(5-Amino-6-chloro-4-pyrimidinylamino)-2α,3α-dihydroxy-1β-cyclopentanemethanol (26). A solution containing 7.9 g of syrupy **24**, 25 g of 5-amino-4,6-dichloropyrimidine (**25**), 14.4 ml of triethylamine, and 700 ml of dry 1-butanol was heated under reflux for 51 hr. After volatile material had been removed *in vacuo*, the residue was partitioned between 400 ml of H_2O and 200 ml of $CHCl_3$. The H_2O layer was extracted with additional $CHCl_3$ (three 50-ml portions) and then passed through a column of cation-exchange resin (320 mequiv of Amberlite CG-120, H^+ form). (Unreacted **25** may be recovered from the $CHCl_3$ layers.) The column was washed with water (250 ml) and the aqueous effluents discarded. The column was chilled with an ice-water jacket and eluted with 400 ml of cold 1.7 *N* aqueous NH_3. The effluent was concentrated to dryness *in vacuo;* several portions of ethanol were evaporated from the syrupy residue; and an ethanol solution of the residue was diluted with ethyl acetate and petroleum ether and was chilled. The brownish crystalline precipitate was separated by filtration, washed with ethyl acetate, and dried *in vacuo* (P_2O_5) at 60°: yield 10.21 g (69%); mp 179–184° (MT). For analysis, a small sample was recrystallized from ethanol–ethyl acetate–hexane; mp 182–184° (MT). Subsequently, **26** with mp 204–205° was obtained from ethanol or ethanol–ethyl acetate, and a specimen of the lower melting form was observed to melt at 182–184°, resolidify, and remelt at 204–205°; uv λ_{max} in mμ ($\epsilon \times 10^{-3}$): 307 (13.2), 285 (sh), 220 (sh), 207 (12.5) in 0.1 *N* HCl; 293 (9.6), 263 (8.9), 207 (19.6) at pH 7; 292 (9.3), 263 (8.8) in 0.1 *N* NaOH.

Anal. Calcd for $C_{10}H_{15}ClN_4O_3$: C, 43.72; H, 5.51; Cl, 12.90; N, 20.40. Found: C, 43.99; H, 5.36; Cl, 12.9; N, 20.34.

(±)-4β-(6-Chloro-9H-purin-9-yl)-2α,3α-dihydroxy-1β-cyclopentanemethanol (27) Hydrochloride. A mixture of 7.73 g of **26**, 180 ml of triethyl orthoformate, and 2.46 ml of 12 *N* HCl was stirred in a closed system at room temperature for 24 hr. The solution was concentrated *in vacuo* at 30° to a brown syrup, several portions of toluene were similarly evaporated from the residue, and a solution (protected from atmospheric H_2O) of the residual syrup in 175 ml of $CHCl_3$ and 70 ml of ether was cooled in an ice bath while dry HCl was passed in for 0.5 hr. The suspension was stirred for an additional 0.5 hr in the ice bath, sparged with dry N_2, and filtered under dry N_2. The hygroscopic solid (10.7 g) was washed twice with dry ether, dried *in vacuo* at room temperature, and used without further purification for the preparation of 6-substituted purines. No attempt was made to determine whether the 2α,3α-O-ethoxymethylidene derivative was present.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]adenine[37] **(28).** A solution of 5.08 g of crude **27** hydrochloride in 150 ml of liquid NH_3 was heated in a stainless steel bomb at 60° for 20 hr. The residue obtained after removal of the ammonia was dissolved in and kept in warm (45°) 0.4 *N* HCl for 0.5 hr. The cooled solution was passed through a column of cation-exchange resin (200 mequiv of Amberlite CG-120, H^+ form), the column was washed with water, and then the product was eluted with 2.5 *N* aqueous NH_3 (250 ml). Evaporation of the basic eluate and recrystallization of the residue from ethanol–water gave 1.82 g (59% yield from **26**) of **28** (mp 237–240°). A second recrystallization from H_2O with charcoal treatment gave the analytical material (dried at 78° for 2 hr, 80% recovery): mp 241–243° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 258 (14.5) and 212 (20.6) in 0.1 *N* HCl, 260 (14.8) at pH 7, 260 (15.0) in 0.1 *N* NaOH; nmr (DMSO-d_6) δ 1.5–2.6 (m, CH_2, $CHCH_2OH$), 3.53 (m, CH_2OH), 3.90 (m, *CH*), 4.2–5.0 (m, *CH*, *OH*) 7.13 (broad s, NH_2), 8.16 and 8.20 (s, purine-ring protons); mass spectrum (70 eV, direct-probe inlet temp 360°, chamber temperature *ca.* 200°) *m/e* above 80 (relative intensity ≥2.4) 265 (4.0), 248 (9.7), 234 (2.8), 218 (2.4), 206 (2.4), 191 (2.8), 190 (4.8), 178 (4.0), 163 (5.2), 162 (23.0), 148 (4.0), 137 (8.9), 136 (100), 135 (48.8), 119 (6.9), 109 (4.0), 108 (18.2), 105 (2.5), 95 (3.2), 94 (3.6), 82 (4.0), 81 (9.7).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.79; H, 5.70; N, 26.40. Found: C, 49.37; H, 5.75; N, 26.10.

The hydrochloride of **28** was obtained from and recrystallized from a mixture of aqueous HCl, ethanol, and ether: mp 218–221° dec (MT); one spot on tlc (5:3:2 butanol–H_2O–acetic acid and 4:1 ethanol–15 *N* NH_3, detection by basic permanganate and periodate–Schiff's reagent).

Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot HCl$: C, 43.79; H, 5.35; Cl, 11.74; N, 23.21. Found: C, 43.89; H, 5.35; Cl, 11.6; N, 22.99.

O-Isopropylidene Derivative (32) of 28. A mixture of 500 mg of **28**, 5.6 g of *p*-toluenesulfonic acid (prepared by heating the monohydrate *in vacuo* at 80° for 12 hr), and 200 ml of dry acetone was stirred for 3 hr. The solution was poured into cold aqueous $NaHCO_3$, the resulting mixture was evaporated to dryness *in vacuo* at room temperature, and the residue was leached with four 60-ml portions of hot $CHCl_3$. Evaporation of the dried (Na_2SO_4) $CHCl_3$ extracts *in vacuo* left 510 mg (89%) of white solid. Recrystallization from ethanol–hexane gave pure **32**: mp 216°; uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 259 (14.7) in 0.1 *N* HCl, 262 (14.8) at pH 7, 261 (14.9) in 0.1 *N* NaOH; nmr δ 1.33 and 1.59 (s, $C(CH_3)_2$), 2.3–2.7 (m, CH_2, $CHCH_2OH$), *ca.* 3.3 (OH), 3.83 (m, CH_2OH), 4.5–5.2 (m, 3 *CH*), 5.66 (broad s, NH_2), 7.83 and 8.34 (s, purine-ring protons).

(37) Previously,[3,34] DL was incorporated into the name of the adenine derivative (**28**) so that the nomenclature would be analogous to that of the 9-β-D-ribofuranosylpurines; here, (±) is substituted for DL in order to avoid confusion that may arise from the conventional use of D and L to designate configuration at a single asymmetric center.

Anal. Calcd for $C_{14}H_{19}N_5O_8$: C, 55.07; H, 6.27; N, 22.94. Found: C, 55.28; H, 6.59; N, 22.88.

Cyclonucleoside Analog (33). A solution of 336 mg of **32**, 5 ml of dry pyridine, and 231 mg of *p*-toluenesulfonyl chloride was prepared at 0° and stirred at room temperature for 22 hr. The mixture, containing a precipitate, was cooled to 0°, diluted with 1 ml of H_2O and with 15 ml of saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$ (four 15-ml portions) and with benzene (two 20-ml portions). The organic extracts were combined, filtered, dried (Na_2SO_4), and concentrated to a solid residue (228 mg, 45%). The residue, presumably the *p*-toluenesulfonate of **32**, was heated in 15 ml of refluxing dioxane for 1 hr to effect cyclization. The white solid that was filtered from the cooled mixture and dried at 70° *in vacuo* weighed 157 mg (31%); mp 328–330° dec (MT). Recrystallization from acetonitrile (50 ml) and water (1 ml) and similar drying gave 57 mg of **33**: mp 352–354° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 272 (14.9) in 0.1 *N* HCl and at pH 7, 272 (9.2) in 0.1 *N* NaOH.

Anal. Calcd for $[C_{14}H_{18}N_5O_2]^+[C_7H_7SO_3]^-$: C, 54.89; H, 5.48; N, 15.24; S, 6.98. Found: C, 55.08; H, 5.46; N, 15.25; S, 7.0.

Additional **33** was isolated by evaporating the aqueous $NaHCO_3$ layer to dryness and leaching the residue with hot acetonitrile. The residue remaining after evaporation of acetonitrile was heated in refluxing dioxane for 1 hr. Filtration gave 65 mg of solid, mp 330–335° dec (MT), identified as crude **33** by its ir and uv spectra.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]hypoxanthine (30). A solution of 3.45 g of **27** hydrochloride in 100 ml of 1 *N* HCl was heated under reflux for 3.5 hr, cooled, and concentrated *in vacuo* to a syrup from which several portions of H_2O were evaporated. A solution of the residue in 100 ml of H_2O was stirred with 20 g of the carbonate form of a basic resin (Dowex 1-8X, CO_3^{2-}). Since the solution was still acidic, portions of the basic resin (OH^- form) were added until the pH was 5–6. The filtrate (plus washings) from the resin was treated with activated carbon and concentrated *in vacuo* to a white solid, which was triturated with ethanol. The product was filtered from the cold mixture, washed with ethanol, and dried (P_2O_5) *in vacuo* at 60°: yield 1.64 g (57%); mp 222–225° dec (MT). Recrystallization from water–ethanol gave pure **30**: mp 225–227° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 250 (11.4) in 0.1 *N* HCl, 249 (12.1) at pH 7, 254 (13.0) in 0.1 *N* NaOH; ir (cm^{-1}) 1695 (C=O).

Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.30; H, 5.36; N, 20.93.

Compound **30** was also prepared by treating the adenine derivative **28** with sodium nitrite and acetic acid and was isolated by elution from a basic resin column with 25% aqueous acetic acid.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]-9H-purine-6(1H)-thione (31). A mixture of 1.0 g of **27** hydrochloride, 304 mg of thiourea, and 20 ml of 1-propanol was heated under reflux for 2 hr. Chilling and filtering the mixture afforded 650 mg (65%) of tan solid, mp 225–228° dec (MT), that analyzed as a hydrochloride.

Anal. Calcd for $C_{11}H_{14}N_4O_3S \cdot HCl$: C, 41.44; H, 4.74; Cl, 11.13; N, 17.57; S, 10.06. Found: C, 41.61; H, 4.79; Cl, 10.8; N, 17.55; S, 9.6.

A solution of 374 mg of the hydrochloride in water (7 ml) was adjusted to pH 5 with base, the cream-colored precipitate (239 mg in two crops) was washed with H_2O, recrystallized from H_2O, and dried at 110° *in vacuo:* mp 265–267° dec (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 323 (22.0) and 224 (9.6) in 0.1 *N* HCl, 321 (23.0) and 225 (10.4) at pH 7, 311 (23.0) and 232 (14.3) in 0.1 *N* NaOH.

Anal. Calcd for $C_{11}H_{14}N_4O_3S \cdot 0.25H_2O$: C, 46.06; H, 5.09; N, 19.53; S, 11.19. Found: C, 46.27; H, 5.14; N, 19.49; S, 10.77.

(±)-9-[β-(2α,3α-Dihydroxy-4β-(hydroxymethyl)cyclopentyl)]-6-(methylthio)purine (29). A mixture of 160 mg of **31** hydrochloride, 1.0 ml of 1.0 *N* NaOH, 1.0 ml of H_2O, and 0.2 ml of methyl iodide was stirred at room temperature for 4 hr and then evaporated *in vacuo* to dryness. The residue was dissolved in hot ethanol, the mixture cooled, and 20 mg of sodium halides removed by filtration. The filtrate was evaporated to a syrup, and the remaining sodium iodide and trace impurities were removed by column chromatography on silica gel (elution with 95:5 $CHCl_3$–CH_3OH). The product-containing fraction was evaporated to a foam that was induced to solidify by adding and evaporating ethyl acetate: yield of white product, 91 mg (61%); mp 172–175° (MT); uv λ_{max} in mμ ($\epsilon \times 10^{-3}$) 303 (sh), 295 (17.1), 290 (sh), 221 (11.5) in 0.1 *N* HCl; 293 (18.3), 286 (18.7), 221 (11.8) in 0.1 *N* NaOH and at pH 7.

Anal. Calcd for $C_{12}H_{16}N_4O_3S$: C, 48.63; H, 5.44; N, 18.91; S, 10.82. Found: C, 48.76; H, 5.52; N, 18.63; S, 11.10.

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Communications to the Editor

Remote Oxidation of Unactivated Methylene Groups

Sir:

Nature's ability to carry out selective functionalization of simple substrates (*e.g.* stearic → oleic acid) utilizes a principle of great power which has not been applied by chemists: any intrinsic reactivity of the substrate, dictated by its own functional groups, can be overridden by combining the substrate with a reagent (*i.e.*, the enzyme) whose selectivity is dominant. In particular, even a single unactivated CH_2 group of a chain can be attacked selectively within an enzyme–substrate complex by steric approximation to the attacking atom. We wish to report the first chemical example of the application of this principle.

As the reagent to attack an unactivated CH_2 group we selected benzophenone triplet.[1] After hydrogen atom transfer the resulting pair of radicals, still held together by the link between reagent and substrate, should couple as in the Yang reaction;[2] it should be noted, however, that in contrast to the four-membered products of the Yang reaction our products (II) have rings of 20 and more members. A series of *p*-benzophenonecarboxylic esters (I)[3] of long-chain alcohols was prepared; the reversible ester link attaches the reagent benzophenone to the substrate alcohol at a site remote from that involved in subsequent chemistry. Irradiation of 10^{-3} *M* solutions of the esters I in CCl_4 with a 450-W Hanovia medium-pressure mercury lamp using a uranium glass filter led to rapid (quantum yield ~0.2) disappearance of the benzophenone chromophore. The crude alcohol product II was dehydrated

(1) C. Walling and M. J. Gibian, *J. Am. Chem. Soc.*, 87, 3361 (1965).

(2) N. C. Yang and D. H. Yang, *ibid.*, 80, 2913 (1958).

(3) All compounds had mass, nmr, and infrared spectra consistent with the assigned structures.