Synthesis of cyclopentane analogs of 1-(2′,3′-dideoxy-β-*glycero*-pentofuranosyl)pyrimidine nucleosides

LUCJAN J. J. HRONOWSKI AND WALTER A. SZAREK
Department of Chemistry, Queen's University, Kingston, Ont., Canada K7L 3N6

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Synthesis of new carbocyclic analogs of 1-(2′,3′-dideoxy-*glycero*-pentofuranosyl)pyrimidine nucleosides having the uracil (**34**), 2-thiouracil (**33**), 2-thiothymine (**31**), cytosine (**44**), and 5-methylcytosine (**43**) bases is described. The nucleoside analogs having the uracil, 2-thiouracil, and 2-thiothymine bases were prepared by coupling *cis*-3-aminocyclopentanemethanol (**8**) with 3-ethoxypropenoyl isocyanate (**26**), 3-ethoxypropenoyl isothiocyanate (**25**), and 3-methoxy-2-methylpropenoyl isothiocyanate (**23**), respectively, to give the corresponding acyl urea (**30**) and acyl thioureas (**29** and **27**). The acyl urea was cyclized in 2 *N* H_2SO_4 and the acyl thioureas in 15 *N* aqueous ammonia to give the corresponding nucleoside analogs. The nucleoside analogs containing the cytosine (**44**) and 5-methylcytosine (**43**) bases were prepared from the uracil and thymine nucleoside analogs, respectively, by way of the 4-chloropyrimidinone intermediates (**42** and **41**). The synthesis of *cis*-3-aminocyclopentanemethanol (**8**) from norbornene by way of *cis*-1,3-cyclopentanedicarboxylic acid anhydride (**3**) is also described. In addition, the ease of nucleophilic opening of compound **3** is compared to the opening of camphoric anhydride (**9**), which contains a *cis*-vicinal substituent at position 2. The relative ease of opening of compound **3** is discussed with respect to the effect, observed in an earlier study, that a *cis*-vicinal acetoxy group has on the course of the nucleophilic opening of such anhydrides. The ^1H magnetic resonance spectra at 200 MHz of all of the synthetic intermediates and of the nucleoside analogs have been determined and discussed. The nucleoside analogs were screened for cell-growth inhibition using K-562 cells. Nucleoside analogs having the 2-thiouracil (**33**), 2-thiothymine (**31**), cytosine (**44**), and 5-methylcytosine (**43**) bases showed some growth inhibition with activity 150 to 300 times lower than that shown by 5-fluorouracil in this test system.

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On décrit la synthèse de nouveaux analogues carbocycliques des nucléosides de la (didésoxy-2′,3′ *glycéro*-pentofuranno-syl)pyrimidine contenant de l'uracil (**34**), du thio-2 uracil (**33**), de la thio-2 thymine (**31**), de la cytosine (**44**) et de la méthyl-5 cytosine (**43**). On a préparé les analogues des nucléosides contenant les bases uracil, thio-2 uracil et thio-2 thymine en procédant au couplage de l'amino-3-*cis* cyclopentaneméthanol avec respectivement l'isocyanate d'éthoxy-3 propènoyle (**26**), l'isothiocyanate d'éthoxy-3 propènoyle (**25**) et l'isothiocyanate de méthoxy-3 méthyl-2 propènoyle (**23**); on obtient ainsi l'acyl urée **30** et les acyl thiourées **29** et **27** correspondantes. La cyclisation de l'acyl urée en présence de H_2SO_4 2 *N* et des acyl thiourées en présence d'ammoniac aqueux 15 *N* conduit aux analogues de nucléosides correspondants. On a préparé les analogues de nucléosides contenant de la cytosine (**44**) et de la méthyl-5 cytosine (**43**) à partir de leurs analogues de nucléosides correspondants contenant de l'uracil et de la thymine et en procédant par leurs intermédiaires chloropyrimidinones (**42** et **41**). On décrit aussi la synthèse de l'amino-3-*cis* cyclopentaneméthanol (**8**) à partir du norbornène, en passant par l'anhydride de l'acide cyclopentanedicarboxylique-1,3-*cis* (**3**). De plus, on compare la facilité d'ouverture du produit **3**, sous l'influence d'agents nucléophiles, avec celle observée pour l'anhydride de l'acide camphorique (**9**) qui contient un substituant vicinal-*cis* en position 2. On discute de la facilité relative d'ouverture du composé **3** en fonction de l'effet, observée dans une étude antérieure, qu'un groupement vicinal-*cis* peut avoir sur le cours de l'ouverture de tels anhydrides. On a déterminé les spectres en résonance magnétique du ^1H à 200 MHz de tous les intermédiaires de synthèse et de tous les analogues de nucléosides et on les discute. Utilisant des cellules K-562, on a évalué l'utilité des analogues de nucléosides comme inhibiteurs de la croissance des cellules. Comparées à l'activité du fluoro-5 uracil dans ce système, les analogues de nucléosides contenant les bases thio-2 uracil (**33**), thio-2 thymine (**31**), cytosine (**44**) et méthyl-5 cytosine (**43**) présentent des effets qui sont de 150 à 300 fois plus faibles.

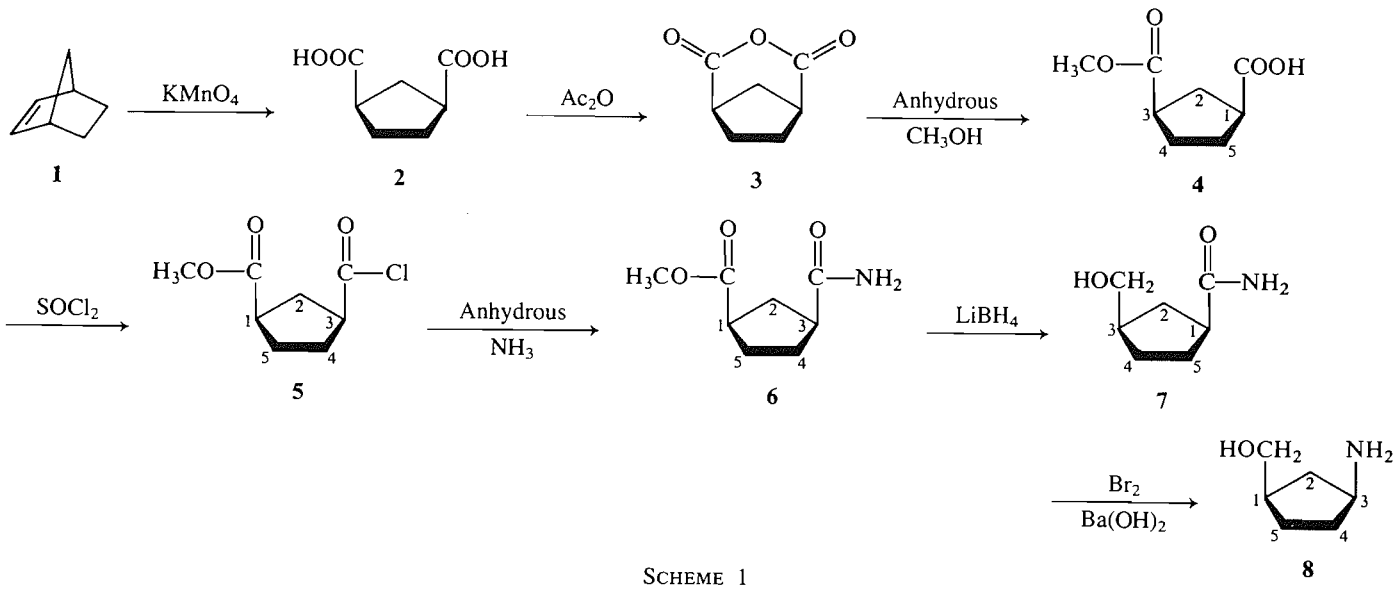
[Traduit par la revue]

Introduction

The synthesis of 2′,3′-dideoxynucleosides was first described in 1955 by Michelson and Todd (1), who synthesized a variety of 3′-deoxythymidines. Nine years later Pfitzner and Moffatt (2) described the synthesis of various 2′,3′-dideoxyuridines. The importance of the 2′,3′-dideoxynucleosides as possible chain terminators of DNA synthesis was pointed out by Robins *et al.* (3), who synthesized 2′,3′-dideoxyadenosine. 2′,3′-Dideoxyadenosine was subsequently shown by Doering *et al.* (4) to be lethal to *Escherichia coli* cultures with activity at concentrations as low as 10^{-7} *M*; however, the 2′,3′-dideoxy derivatives of uridine and cytidine were found to be inactive in their test systems. 2′,3′-Dideoxyadenosine was shown to irreversibly inhibit DNA synthesis, possibly by adding to the end of a growing polydeoxynucleotide and thus blocking further chain elongation. Such a mechanism of action was shown for 3′-deoxythymidine in a cell-free system (5). 2′,3′-Dideoxy-5-fluorouridine was shown by Khwaja and Heidelberger (6) to be lethal to *E. coli* at a concentration of 2×10^{-4} *M* and it also inhibited the growth of HeLa cells at 10^{-4} *M*. An important recent use of the 2′,3′-dideoxynucleotides is in DNA sequencing, in which they are used as specific, chain-terminating inhibitors of DNA polymerase (7).

In contrast to the relatively large number of 2′,3′-dideoxynucleosides that have been synthesized (1–3, 6–8, and references therein), there have been described relatively few syntheses of the carbocyclic analogs of the 2′,3′-dideoxynucleosides and most of these were of analogs of purine nucleosides. Schaeffer *et al.* (9), in their studies on the structural requirements in inhibitors of the enzyme adenosine deaminase, have synthesized several *cis*-3-(6-substituted-9-purinyl)cyclopentylmethanols in which the substituent was the Cl, SH, OH, NH_2, $NHCH_3$, or $N(CH_3)_2$ group. Montgomery and Hewson (10) synthesized the carbocyclic analog of 2′,3′-dideoxytubercidin.

[1]Revision received August 20, 1987.



1 2 3 4 5 6 7 8

SCHEME 1

This compound, although somewhat cytotoxic, showed no activity against leukemia L1210. Shealy *et al.* (11) have synthesized the 2′,3′-dideoxy carbocyclic analogs of 8-aza-hypoxanthine and 8-azaadenine nucleosides; only the carbocyclic analog of 2′,3′-dideoxy-8-azaadenosine showed cytotoxicity to H. Ep./2 cells in culture (ED_{50} = 42 μg/mL), and both analogs showed no activity against leukemia L1210 in mice. The only carbocyclic analog synthesized of the 2′,3′-dideoxypyrimidine nucleosides is the analog of 3′-deoxythymidine (12). This compound was shown to be noncytotoxic to human epidermoid carcinoma cells and also showed no activity against L1210 leukemia in mice. The present paper describes the synthesis of the carbocyclic analogs of 2′,3′-dideoxypyrimidine nucleosides having the uracil, 2-thiouracil, 2-thiothymine, cytosine, and 5-methylcytosine bases. In addition, preliminary results are presented on their effects on the growth of K-562 cells in culture.

Results and discussion

cis-3-Aminocyclopentanemethanol (**8**), used in the synthesis of the carbocyclic analogs of 2′,3′-dideoxynucleosides, was prepared previously by Schaeffer *et al.* (9) from 3-oxocyclopentanecarboxylic acid (13). Shealy *et al.* (12) reported the synthesis of **8** from *cis*-1,3-cyclopentanedicarboxylic acid (**2**) without giving experimental details. In the present work **8** has been prepared from norbornene as shown in Scheme 1.

*Synthesis of (±)-*cis*-3-aminocyclopentanemethanol (8)*

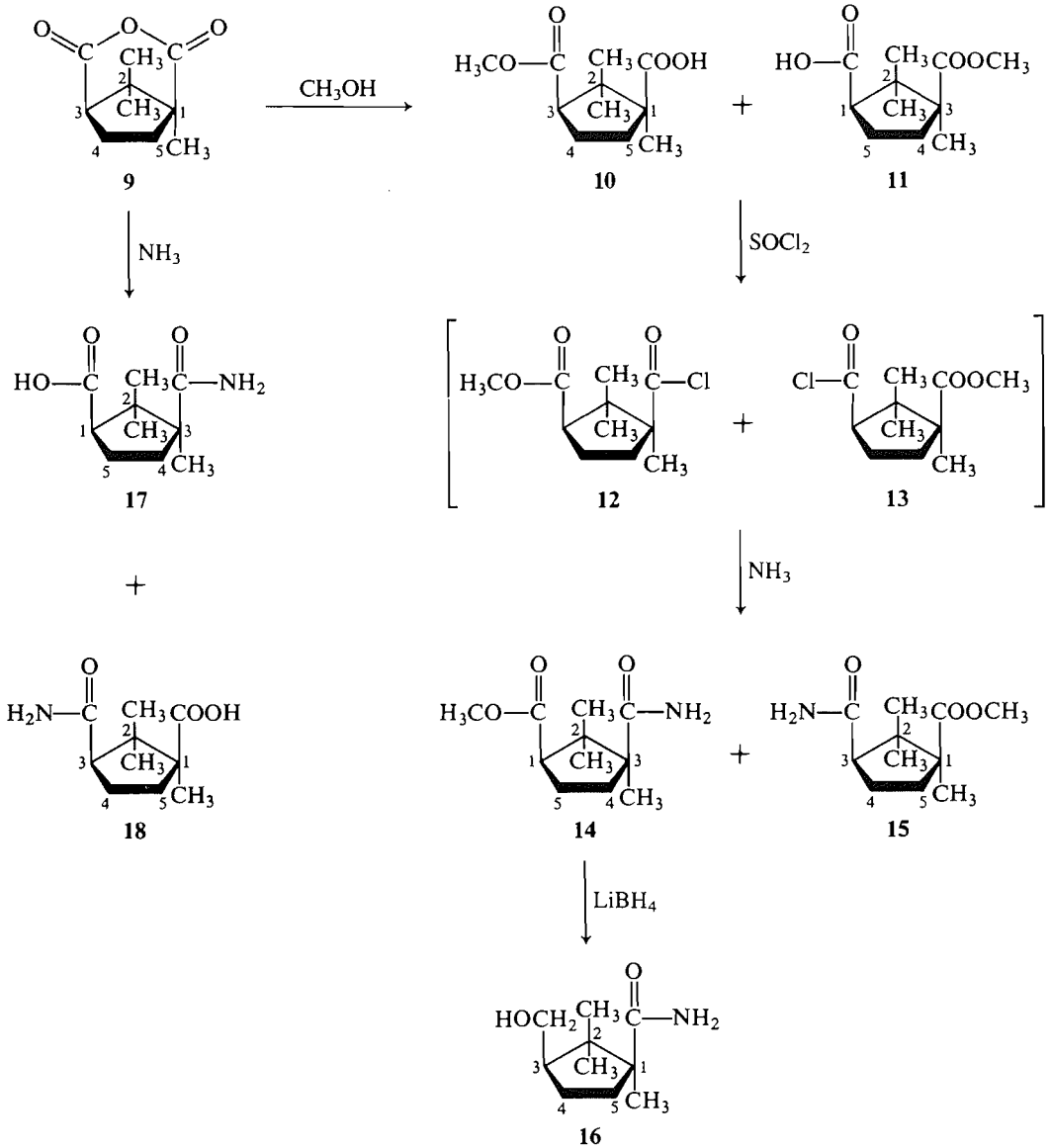
The *cis* configuration of the two substituents in the cyclopentane derivatives shown in Scheme 1 is determined by the starting material, bicyclo[2.2.1]hept-2-ene (**1**), which, in the first step, is oxidized to *cis*-1,3-cyclopentanedicarboxylic acid (**2**) using potassium permanganate by the procedure described by Birch *et al.* (14). The *cis*-diacid (**2**) was then converted into (±)-*cis*-3-aminocyclopentanemethanol (**8**) by the same series of reactions that was used by O'Dell and Shealy (15) for the preparation of the cyclopentane analogs of 2′- and 3′-deoxy-*erythro*-pentofuranosylamine. The diacid was converted first into the anhydride (**3**) by heating at reflux temperature in acetic anhydride. The anhydride (**3**) was then opened with anhydrous methanol to give an intermediate (**4**)[2] having two different functional groups at positions 1 and 3 of the cyclopentane ring. The carboxylic acid and the ester functional groups were then converted selectively into the amino and the hydroxymethyl substituents, respectively, as shown in Scheme 1. In the final reaction shown in Scheme 1 the carbamoyl group was converted into the amino substituent by the Hofmann hypobromite reaction, in which the configuration of the original carbamoyl group is retained (16–18).

The ^{1}Hmr spectra of the compounds shown in Scheme 1 were determined on a 200-MHz spectrometer. However, even with this instrument, the signals of the methylene protons at positions 4 and 5 show complex second-order patterns, and thus only the ranges of their signals are given. The chemical shifts of the protons at positions 1, 2, and 3 could be more easily determined, although the signals of these protons often overlapped other signals to make the measurement of the exact chemical shifts difficult. The chemical-shift assignments were made with the aid of spin–spin decoupling experiments.

Nucleophilic opening of cis*-1,3-cyclopentanedicarboxylic acid anhydrides*

It was observed previously that nucleophilic opening of *cis*-1,3-cyclopentanedicarboxylic acid anhydrides, substituted at position 4 with an acetoxy group, gives a mixture of isomers when this group is in the *trans* configuration (16) and a single isomer when it is in the *cis* configuration (19). In the latter case only one isomer was isolated when ammonia or methanol was used as the nucleophile. With each of these nucleophiles the attack occurred at the carbonyl carbon farthest away from the acetoxy substituent. It was of interest, therefore, to study the effect of substituents at position 2. Scheme 2 shows a series of reactions using *dl*-camphoric anhydride (**9**) as the model compound. In contrast to compound **3**, which is converted

[2]The solvolysis of *cis*-1,3-cyclopentanedicarboxylic acid anhydride (**3**) generates a racemic mixture, since the attack by methanol is equally probable at both carbonyl carbons. Consequently, all of the subsequent cyclopentane derivatives are racemates, although only one enantiomer is shown in Schemes 1, 3, and 4.



SCHEME 2

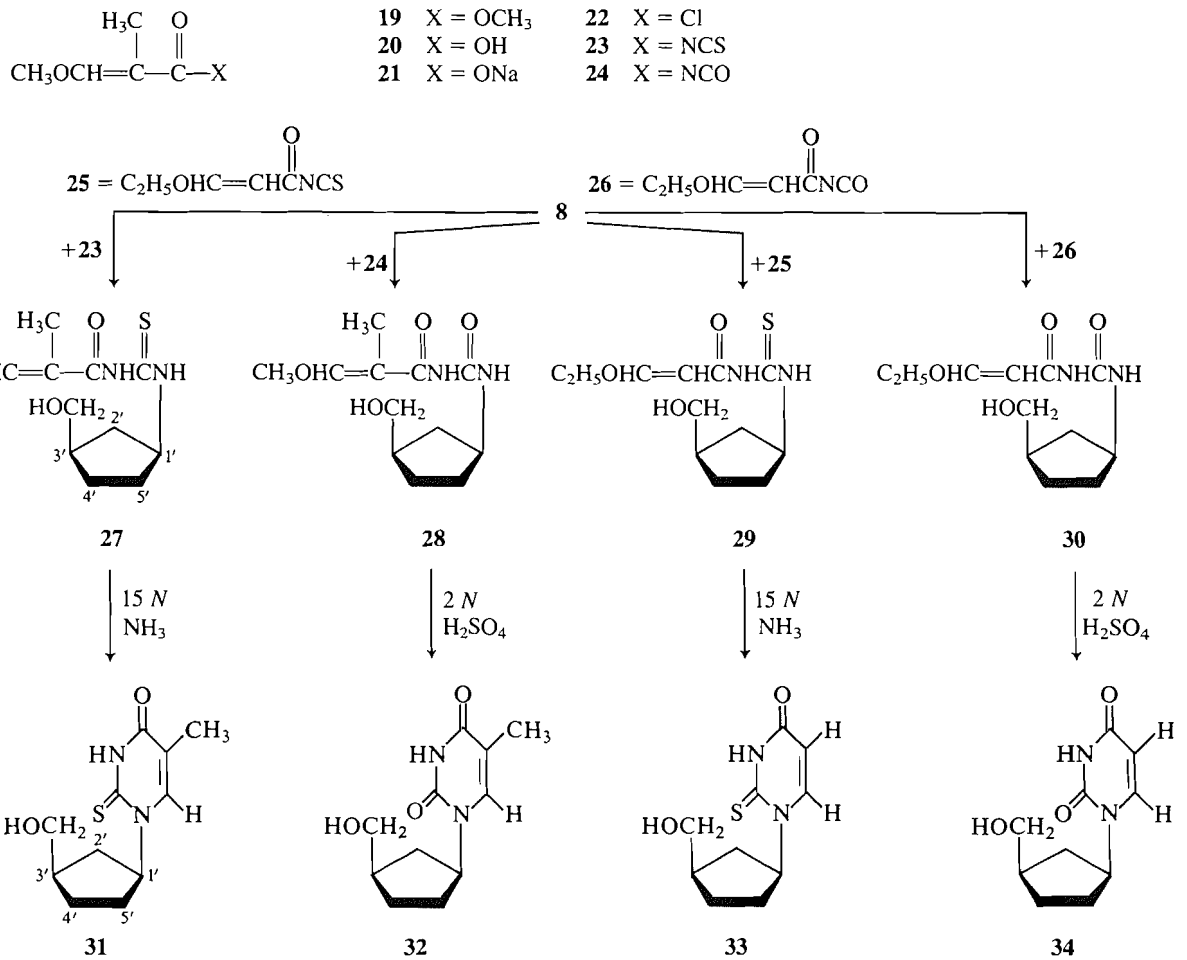
into compound **4** by stirring in anhydrous methanol at room temperature for 19 h, camphoric anhydride (**9**) is very resistant to methanolysis; no reaction was observed after 10 days of stirring in anhydrous methanol at room temperature. Moreover, even after being heated at reflux temperature for 2 days in methanol, over 81% of **9** was recovered and only a 12% yield of the solvolysis products, as a mixture of compounds **10** and **11**, was obtained. However, the opening of camphoric anhydride (**9**) was relatively rapid, when anhydrous ammonia in benzene was used, to give a mixture of compounds **17** and **18** in over 95% yield. The above observations and those with the acetoxy substituents (16, 19) indicate that steric interactions between *cis*-vicinal substituents in these compounds greatly reduce the rate of nucleophilic attack at the adjacent carbonyl carbon, thus accounting for the production of a single isomer in the nucleophilic opening of the anhydride containing the *cis*-acetoxy substituent at position 4 (19).

Assignment of the ^{1}Hmr signals in the spectra of the compounds shown in Scheme 2 was made after preparation of compound **16** from **14**. The signals of the protons in compound **16** were unambiguously assigned with the aid of spin–spin decoupling experiments. In general, the signals in the spectra of compounds **10**–**18** are much better resolved than those in the spectra of compounds **4**–**7**.

Synthesis of pyrimidine nucleoside analogs shown in Scheme 3

The base moiety of the 2-thiothymine nucleoside analog (**31**) was synthesized from 3-methoxy-2-methylpropenoyl isothiocyanate (**23**), which was prepared using the method of Shaw and Warrener (20). Compound **23** was coupled with (±)-*cis*-3-aminocyclopentanemethanol (**8**) to give compound **27**; this product was then cyclized in 15 *N* aqueous ammonia to give nucleoside analog **31**. The corresponding thymine nucleoside analog (**32**) was prepared as described previously (12).

The 2-thiouracil nucleoside analog (**33**) was prepared by coupling compound **8** with 3-ethoxypropenoyl isothiocyanate (**25**) (20) to give **29**, which was then cyclized in 15 *N* aqueous ammonia to give the nucleoside analog (**33**). The uracil



SCHEME 3

nucleoside analog (**34**) was prepared by coupling compound **8** with 3-ethoxypropenoyl isocyanate (**26**) (21) to give **30**, which was then cyclized in 2 *N* H_2SO_4 to give the nucleoside analog (**34**).

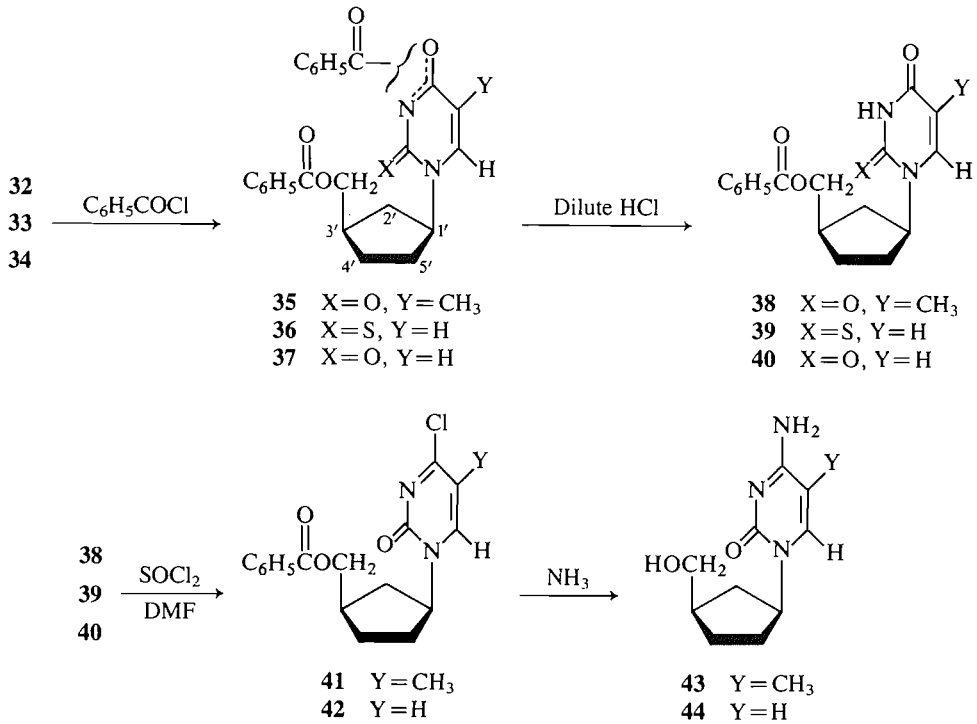
The signals of the protons on the cyclopentane rings in compounds **27**–**30** show complex patterns with many of the signals overlapping in a narrow region of the ^{1}Hmr spectrum. The signals of the other protons in each of these compounds are well resolved and allow relatively easy characterization of the different compounds (**27**–**30**). Also, as was observed previously (19, 22), the protons in the sulfur-containing compounds, in general, resonate further downfield than the corresponding protons in the oxygen-containing analogs. The only significant exception to this trend occurs for H-3 in compounds **29** and **30**; in the case of the oxygen-containing compound (**30**) this proton resonates at lower field than in the case of the sulfur-containing compound (**29**).

In the case of nucleoside analogs **31**–**34**, in a 200-MHz field all of the protons on the cyclopentane ring in each of these compounds, except for H-1′, have complex overlapping signals in the δ 1.2–2.2 region. The signals for the other protons in these nucleosides are easily resolved even at 60 MHz, and, as was seen above, protons in the sulfur-containing compounds resonate at lower fields than the corresponding protons in the oxygen-containing compounds. Also, as was seen previously (19, 22), this difference is largest for the protons nearest the sulfur atom. Thus, H-1′ and H-3 resonate 1.0 and 1.3 ppm, respectively, further downfield in the case of the sulfur-containing nucleosides (**31** and **33**) than in the case of the oxygen-containing nucleosides (**32** and **34**), whereas the methylene protons of the hydroxymethyl group have virtually the same chemical shifts in all four compounds. The chemical shifts of the protons in compound **32** were previously reported by Shealy *et al.* (12) using a 100-MHz spectrometer and agree with those observed in the present study to within ±0.02 ppm.

Synthesis of carbocyclic analogs of cytosine nucleosides

The cytosine nucleosides shown in Scheme 4 were synthesized using the method described by Žemlička and Šorm (23); however, the protection of the hydroxyl groups was performed as described by Shealy and O'Dell (24). Nucleosides **32**–**34** were treated first with an excess of benzoyl chloride in pyridine to give compounds **35**–**37**. The benzoyl group on the pyrimidine rings was then selectively removed using dilute hydrochloric acid solution to give the monobenzoyl derivatives (**38**–**40**). The protected nucleosides **38** and **40** were converted into the 4-chloropyrimidinone intermediates **41** and **42**, respectively, using a catalytic amount of *N*,*N*-dimethylformamide and an excess of thionyl chloride in chloroform; compounds **41** and **42** were then converted into the cytosine nucleosides **43** and **44**, respectively, using anhydrous ammonia in methanol. However, an attempt to prepare the 4-amino analog of the 2-thiouracil nucleoside (**33**) by the above method gave instead nucleoside **44**.

In the case of the nucleosides shown in Scheme 4, at 200 MHz the signals of the methylene protons occur as complex groups



SCHEME 4

of overlapping multiplets, and thus only their chemical-shift ranges are given. The signals of the protons at C-1′, C-2′, and C-3′ are more resolved in the spectra of most of the nucleosides and, as was observed previously, the signals of the protons in the sulfur-containing nucleosides occur further downfield than those of the corresponding protons in the oxygen-containing nucleosides. The signals for the amino protons show different patterns in the two cytosine nucleosides (**43** and **44**). In the case of the nucleoside analog **44** these protons give rise to a single broad peak, whereas in the case of the 5-methylcytosine analog **43** they give rise to two broadened singlets at δ 6.66 and 7.04, suggesting that rotation of the amino group in the 5-methylcytosine analog **43** may be restricted.

Ultraviolet spectra of nucleoside analogs 31–34

The ultraviolet spectra of the uracil-nucleoside analog **34** closely resemble the spectra of 1-methyluracil (25) at the corresponding pH's. The absorption maxima in the spectra of the thymine analog **32** occur at slightly longer wavelengths (λ = 272–273 nm) than in the case of the uracil analog **34** (λ = 266–268 nm); otherwise, the spectra closely resemble those of **34** at the corresponding pH's. The absorption spectra of the 2-thiouracil- (**33**) and of 2-thiothymine- (**31**) -nucleoside analogs are more complex than those of **32** and **34**; however, they resemble closely the behavior of 1-methyl-2-thiouracil and 1-methyl-2-thiothymine, respectively, at the corresponding pH's (25). The absorption maximum at longer wavelength in the spectrum of **33** is relatively constant in both acidic and basic solvents; however, in the case of **31** the maximum shifts from 276 nm in acidic media to 266 nm in basic media. A similar behavior had been observed in the cases of 1-methyl-2-thiouracil and 1-methyl-2-thiothymine (25).

Biological evaluation

Compounds **31–34**, **43**, and **44** were tested for cell-growth inhibition using cultured K-562 cells by methods described previously (26). Nucleoside analogs having the 2-thiouracil (**33**), 2-thiothymine (**31**), cytosine (**44**), and 5-methylcytosine (**43**) bases showed some growth inhibition, with activity 150–300 times lower (higher values of ED_{50}) than that shown by 5-fluorouracil in this test system. Compounds **31–34** have also been tested for activity against the HSV-1 and the HSV-2 viruses. None of these compounds demonstrated antiviral activity in the 0.24–500 μg/mL concentration range.

Conclusion

The synthesis of (±)-*cis*-3-aminocyclopentanemethanol (**8**) from norbornene has been described. In addition, the effect of *cis*-vicinal substituents on the nucleophilic opening of *cis*-1,3-cyclopentanedicarboxylic acid anhydrides has been studied using *dl*-camphoric anhydride as a model. The results obtained with this anhydride, together with those obtained with the *cis*-1,3-cyclopentanedicarboxylic acid anhydrides having acetoxy substituents at position 4 (19, 22), show that *cis*-vicinal substituents greatly decrease the rate of nucleophilic attack at the adjacent carbonyl carbon. In the anhydride containing the 4-*cis*-acetoxy substituent, nucleophilic attack occurred only at the carbonyl carbon farthest away from the acetoxy group, thus allowing regiospecific opening of this anhydride (19).

(±)-*cis*-3-Aminocyclopentanemethanol was utilized for the synthesis of carbocyclic analogs of nucleosides having uracil, 2-thiouracil, 2-thiothymine, thymine, cytosine, and 5-methylcytosine bases. The 200-MHz ^{1}Hmr spectra of all of these nucleosides, as well as of the cyclopentane derivatives, have also been determined and discussed.

Experimental

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. The ^{1}Hmr spectra were recorded on a Bruker CXP-200 spectrometer at 200 MHz. The proton chemical shifts (δ) are given relative to Me_4Si (δ = 0). Assignments of chemical shifts and coupling constants were made with the aid of spin-decoupling experiments. The following abbreviations are used in describing ^{1}Hmr signals: singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (qu), sextuplet (se),

multiplet (m), and broadened (br). Ultraviolet spectra were recorded on a Perkin–Elmer 552 spectrophotometer. Thin-layer chromatography (tlc) was performed using silica gel 60 F-254 plates and column chromatography on silica gel 60. The plates and silica gel 60 were purchased from BDH Chemicals. The developed plates were dried and sprayed with a solution of ceric sulfate (1%) and molybdic acid (1.5%) in 10% aqueous sulfuric acid, and heated at ~150°C. Unless otherwise indicated, the same solvent was used for both tlc and column chromatography.

cis-1,3-Cyclopentanedicarboxylic acid (2)

Compound **2** was prepared from bicyclo[2.2.1]hept-2-ene (**1**) by the procedure of Birch *et al.* (14) using potassium permanganate instead of sodium permanganate. A solution of norbornene (**1**) (28.2 g, 0.30 mmol) in 2,2,4-trimethylpentane (200 mL) was added to water (1 L). To the stirred mixture, a solution of $KMnO_4$ (147 g, 0.93 mol) in water (2.5 L) was added over a period of 5 h (temperature 25–37°C), during which time CO_2 was vigorously bubbled through the reaction mixture. Immediately after the permanganate addition was complete, SO_2 was passed through the reaction mixture until it became colorless. The volume of the reaction solution was reduced to 825 mL. The solution was then cooled in an ice bath and acidified with concentrated HCl (90 mL). Extraction with diethyl ether (9 × 200 mL) gave a white solid (33.26 g, 70%), mp 104–114°C. After recrystallization of this material from diethyl ether – hexanes, the mp was 120°C (lit. (14) mp 119.9–120.6°C (corr.)); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.67–1.94 (5H, m, H-2, H-4, H-4′, H-5, and H-5′), 2.11 (1H, d of t, J_{gem} = 13.2, ^3J = 8.0 Hz, H-2′), 2.64–2.80 (2H, m, H-1 and H-3), 12.1 (2H, br s, CO_2H). *Anal.* calcd. for $C_7H_{10}O_4$: C 53.16, H 6.37; found: C 53.19, H 6.45.

cis-1,3-Cyclopentanedicarboxylic acid anhydride (3)

Compound **2** (36.4 g, 230 mmol) was dissolved in acetic anhydride (100 mL) and 31 mL of solvent were removed by distillation. The reaction solution was heated at reflux temperature for a further 0.5 h and cooled. The solvent was removed under vacuum and the residue was recrystallized from tetrahydrofuran–hexanes to give a light-grey solid (25.56 g, 79%); in a melting point determination, this material turned from an opaque solid to a stiff, clear gel in the range 128–145°C and melted at 159–160°C (lit. (27) mp 161°C). Repeated recrystallizations from tetrahydrofuran–hexanes gave a white solid but did not alter the above melting behavior; ^{1}Hmr (200 MHz, $CDCl_3$), δ: 1.77 (1H, d of t, J_{gem} = 12.8, ^3J = 4.2 Hz, H-2), 1.98–2.33 (5H, m, H-2′, H-4, H-4′, H-5, and H-5′), 3.21–3.33 (2H, m, H-1 and H-3); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.69 (1H, d of t, J_{gem} = 12.5, ^3J = 4.2 Hz, H-2), 1.82–2.21 (4H, m, H-4, H-4′, H-5, and H-5′), 2.36 (1H, br d, J_{gem} = 12.5 Hz, H-2′), 3.18 (2H, m, H-1 and H-3); spin–spin decoupling was performed at δ 1.69 and 2.36. *Anal.* calcd. for $C_7H_8O_3$: C 60.00, H 5.75; found: C 59.99, H 5.99.

(±)-Methyl hydrogen cis-1,3-cyclopentanedicarboxylate (4)

A solution of **3** (19.34 g, 138 mmol) in anhydrous methanol (400 mL) was stirred at room temperature for 19 h and left in the cold room (2°C) for 12 days. The solvent was removed on a rotary evaporator to give **4** as a light-brown oil (23.6 g); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.68–2.05 (5H, m, H-2, H-4, H-4′, H-5, and H-5′), 2.13 (1H, d of t, J_{gem} = 12.7, ^3J = 8.0 Hz, H-2′), 2.66–2.97 (2H, m, H-1 and H-3), 3.60 (3H, s, OMe), 12.1 (1H, br s, CO_2H); ^{1}Hmr (200 MHz, $CDCl_3$), δ: 1.9–2.5 (6H, m, H-2, H-2′, H-4, H-4′, H-5, and H-5′), 2.8–3.0 (2H, m, H-1 and H-3), 3.71 (3H, s, OMe), 11.3 (1H, br s, CO_2H).

(±)-Methyl cis-3-(chloromethanoyl)cyclopentanecarboxylate (5)

Compound **4** (23.6 g) was dissolved in benzene (550 mL) and 50 mL were removed by distillation to remove traces of water. To the hot, benzene solution, thionyl chloride (50 mL, 0.68 mol) was added dropwise, and the solution was stirred for 5 min. Two drops of pyridine were then added and stirring was continued until the vigorous evolution of gases subsided; then 2 drops of *N*,*N*-dimethylformamide were added and the solution was heated at reflux temperature for 2 h. The mixture was kept at room temperature overnight, and the solvent was removed on a rotary evaporator to give **5** as a yellow oil (26.2 g); ^{1}Hmr (200 MHz, $CDCl_3$), δ: 1.95–2.48 (6H, m, H-2, H-2′, H-4, H-4′, H-5, and H-5′), 2.87 (1H, qu, ^3J = 8.1 Hz, H-1), 3.30 (1H, m, H-3), 3.70 (3H, s, OMe).

(±)-Methyl cis-3-carbamoylcyclopentanecarboxylate (6)

Compound **5** (26.2 g) was dissolved in dry benzene (450 mL) and anhydrous ammonia was bubbled through the reaction solution for 0.5 h. The resulting mixture was purged with nitrogen for 10 min. It was then diluted with ethyl acetate (400 mL), heated to boiling, and treated with charcoal. The hot mixture was filtered and the solid residue was washed with hot ethyl acetate. The combined filtrate and washings were cooled and the white crystalline solid was collected by filtration to give **6** (13.56 g), mp 122–123°C. The volume of the filtrate was reduced to 75 mL and additional **6** (2.21 g), mp 122–123°C, was collected by filtration. A final third crop of **6** (0.24 g) was obtained and had mp 117–121°C (total yield of 16.01 g, 67.8%, from **3**); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.61–1.89 (5H, m, H-2, H-4, H-4′, H-5, and H-5′), 2.04 (1H, d of t, J_{gem} = 12.6, ^3J = 7.6 Hz, H-2′), 2.59 (1H, m, H-3), 2.78 (1H, m, H-1), 3.59 (3H, s, OMe), 6.78 (1H, br s, $CONH_2$), 7.29 (1H, br s, $CONH_2$). *Anal.* calcd. for $C_8H_{13}O_3N$: C 56.13, H 7.65, N 8.18; found: C 56.07, H 7.98, N 8.32.

(±)-cis-3-(Hydroxymethyl)cyclopentanecarboxamide (7)

A solution containing lithium borohydride (3.58 g, 164 mmol) in tetrahydrofuran (200 mL) was heated at reflux temperature for 1 h; heating was discontinued, compound **6** (14.09 g, 82 mmol) was added to the hot tetrahydrofuran solution, and heating at reflux temperature was then continued for 2 h. The reaction solution was cooled in an ice bath and diluted slowly with water (150 mL), then a slow addition of Amberlite CG-120 (H^+) cation-exchange resin (90 g) was made. The mixture was stirred overnight at room temperature. The resin was removed by filtration and washed with water (3 × 90 mL). The combined filtrate and washings were treated with Dowex 1-X8 (^-OH) anion-exchange resin to adjust the pH to 7. The resin was removed by filtration and washed with water (3 × 90 mL). The combined filtrate and washings were evaporated and the residue was evaporated with methanol (3 × 30 mL) to give a white solid (11.6 g), mp 112–117°C. This material was recrystallized from methanol–tetrahydrofuran to give **7** in two crops (9.14 g, mp 121–123°C, and 0.91 g, mp 119–122°C) for a total yield of 10.05 g (85.7%); R_f 0.49 (9:1 (v/v) acetonitrile–water), component visualized using iodine vapor; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.15–1.76 (5H, m, H-2, H-4, H-4′, H-5, and H-5′), 1.78–2.09 (2H, m, H-2′ and H-3), 2.55 (1H, m, H-1), 3.29 (2H, d of d, $^3J_{to\ H\text{-}3}$ = 6.4, $^3J_{to\ CH_2OH}$ = 5.3 Hz, CH_2OH), 4.46 (1H, t, ^3J = 5.3 Hz, CH_2OH), 6.68 (1H, br s, $CONH_2$), 7.21 (1H, br s, $CONH_2$); the $CONH_2$ and OH protons exchanged with D_2O. *Anal.* calcd. for $C_7H_{13}O_2N$: C 58.72, H 9.15, N 9.78; found: C 59.16, H 9.17, N 10.28.

(±)-cis-3-Aminocyclopentanemethanol (8)

To a solution at 5°C containing $Ba(OH)_2 \cdot 8H_2O$ (95.4 g, 0.302 mol) in water (1.9 L), bromine (3.8 mL, 74 mmol) was added. Immediately after the bromine had dissolved, a solution of compound **7** (9.63 g, 67.2 mmol) in water (50 mL) was added in one portion, and the reaction solution was allowed to warm to room temperature over a period of 2 h. The solution was then heated at 50–65°C for 1.25 h, cooled to ice-bath temperature, and acidified with 3 *M* H_2SO_4 (85 mL). The mixture was stirred for 1 h and the precipitate was removed by centrifugation. The solution was stored in the cold room (2°C) overnight and then passed through Amberlite CG-120 (H^+) cation-exchange resin (150 g). The resin was washed with water (1.5 L) and then eluted with 2 *N* NH_3 in water; the elution was monitored by tlc (5:3:2 (v/v/v) *n*-butanol–water–acetic acid). No product was eluted in the first 2 L; an additional 2.5 L of 2 *N* NH_3 in water was required to elute the product from the column. The solvent was evaporated and the residual oil was dissolved in ethanol; the mixture was filtered to remove small amounts of insoluble matter. The solvent was evaporated to afford **8** as a yellow oil (5.70 g, 74%). The ^{1}Hmr spectrum showed no signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 0.95 (1H, d of t, J_{gem} = 12.4, ^3J = 7.0 Hz, H-2), 1.17–1.73 (4H, m, H-4, H-4′, H-5,

and H-5′), 1.79–2.11 (2H, m, H-2′ and H-1), 3.17 (1H, m, H-3), 3.28 (2H, d, J = 6.0 Hz, HOCH_2); spin–spin decoupling was performed at δ 0.95 and 3.17.

*(±)-3-Methyl hydrogen 1,2,2-trimethyl-*cis*-1,3-cyclopentanedicarboxylate (**10**) and (±)-3-methyl hydrogen 2,2,3-trimethyl-*cis*-1,3-cyclopentanedicarboxylate (**11**)*

A mixture of *dl*-camphoric anhydride (**9**, 50 g, 274 mmol) in anhydrous methanol (650 mL) was heated at reflux temperature for 2 days, cooled to room temperature, and a white solid (28.6 g) was collected by filtration, which was shown by ^{1}Hmr spectroscopy and a melting-point determination to be starting material (**9**). The volume of the filtrate was reduced to 150 mL, the solution was cooled to 4°C, and additional **9** (11.72 g) was collected by filtration. The solvent was evaporated and the resulting oil was fractionated by column chromatography on silica gel to give a component (6.96 g, 12%), R_f = 0.43 (9:1 (v/v) toluene–2-propanol), which was shown by ^{1}Hmr spectroscopy to be a mixture of compounds **10** and **11**, with compound **10** being the major isomer. Compound **10**, ^{1}Hmr (200 MHz, $CDCl_3$), δ: 0.84 (3H, s, Me), 1.25 (3H, s, Me), 1.27 (3H, s, Me), 1.52 (1H, m, J_{gem} = 13.5, $^3J_{5,4}$ = 9.6, $^3J_{5,4'}$ = 3.9 Hz, H-5), 1.72–1.94 (1H, m, H-4), 2.08–2.30 (1H, m, H-4′), 2.47–2.67 (1H, m, H-5′), 2.78–2.88 (1H, m, H-3), 3.70 (3H, s, OMe); compound **11**, ^{1}Hmr (200 MHz, $CDCl_3$), δ: 0.82 (3H, s, Me), 1.21 (3H, s, Me), 1.29 (3H, s, Me), 1.52 (1H, m, J_{gem} = 13.5, $^3J_{4,5}$ = 9.6, $^3J_{4,5'}$ = 3.9 Hz, H-4), 1.72–1.94 (1H, m, H-5), 2.08–2.30 (1H, m, H-5′), 2.47–2.67 (1H, m, H-4′), 2.78–2.88 (1H, m, H-1), 3.69 (3H, s, OMe); spin–spin decoupling was performed at δ 1.52 and 2.83.

*(±)-Methyl 2,2,3-trimethyl-*cis*-3-carbamoylcyclopentanecarboxylate (**14**) and (±)-methyl 1,2,2-trimethyl-*cis*-3-carbamoylcyclopentanecarboxylate (**15**)*

A solution of compounds **10** and **11** (6.64 g, 31.0 mmol) in benzene (100 mL) was treated with thionyl chloride (11 mL, 153 mmol), as described above for the preparation of **5**, to give an oily mixture of compounds **12** and **13**. The oil was dissolved in dry benzene (100 mL) and anhydrous ammonia was bubbled through the reaction solution for 0.5 h. The reaction mixture was then flushed with nitrogen for 10 min, heated to boiling, and filtered. The filtrate was evaporated to give a pale-yellow solid (5.68 g), which was fractionated by column chromatography on silica gel to give **14** (3.024 g) and a mixture of **14** and **15** (0.584 g), with **14** as the major component, for a total yield of 3.608 g (55% from **10** and **11**). An analytical sample of **14** was prepared by recrystallization from ethyl acetate – hexanes, mp 135°C, R_f 0.35 (tlc) (7:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol); ^{1}Hmr (200 MHz, $CDCl_3$), δ: 0.83 (3H, s, Me), 1.22 (3H, s, Me), 1.30 (3H, s, Me), 1.55 (1H, m, H-4), 1.75–1.95 (1H, m, H-5), 2.16–2.48 (2H, m, H-4′ and H-5′), 2.82 (1H, d of d, ^3J = 10.5, ^3J = 7.6 Hz, H-1), 3.69 (3H, s, OMe), 5.55 (2H, br s, $CONH_2$); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 0.66 (3H, s, Me), 1.08 (3H, s, Me), 1.16 (3H, s, Me), 1.35 (1H, m, J_{gem} = 12.6, $^3J_{4,5}$ = 9.3, $^3J_{4,5'}$ = 3.2 Hz, H-4), 1.74 (1H, m, H-5), 1.99 (1H, m, H-5′), 2.33 (1H, t of d, J = 12.2, ^3J = 8.6 Hz, H-4′), 2.79 (1H, d of d, ^3J = 10.2, ^3J = 8.0 Hz, H-1), 3.60 (3H, s, OMe), 6.86 (1H, br s, $CONH_2$), 6.91 (1H, br s, $CONH_2$); spin–spin decoupling was performed at δ 2.79. *Anal.* calcd. for $C_{11}H_{19}O_3N$: C 61.95, H 8.98, N 6.57; found: C 61.86, H 9.00, N 7.04.

The mixture of **14** and **15** was fractionated again by column chromatography on silica gel to give a sample of **15**. An analytical sample of **15** was prepared by recrystallization from ethyl acetate – hexanes, mp 116–118°C, R_f 0.24 (tlc); ^{1}Hmr (200 MHz, $CDCl_3$), δ: 0.82 (3H, s, Me), 1.20 (3H, s, Me), 1.27 (3H, s, Me), 1.51 (1H, m, J_{gem} = 13.8, $^3J_{5,4}$ = 9.6, $^3J_{5,4'}$ = 4.3 Hz, H-5), 1.81 (1H, m, J_{gem} = 13.6, ^3J = 9.6, $^3J_{4,5'}$ = 6.9 Hz, H-4), 2.18 (1H, m, J_{gem} = 13.6, $^3J_{4',5'}$ = 11.6, $^3J_{4',3}$ = 9.1, $^3J_{4',5}$ = 4.3 Hz, H-4′), 2.61 (1H, m, H-5′), 2.63 (1H, t, ^3J = 9.3 Hz, H-3), 3.68 (3H, s, OMe), 5.35 (1H, br s, $CONH_2$), 5.54 (1H, br s, $CONH_2$); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 0.63 (3H, s, Me), 1.11 (6H, s, Me), 1.38 (1H, m, J_{gem} = 13.3, $^3J_{5,4}$ = 9.4, $^3J_{5,4'}$ = 4.0 Hz, H-5), 1.62 (1H, m, J_{gem} = 12.9, $^3J_{4,5}$ = $^3J_{4,3}$ = 9.6, $^3J_{4,5'}$ = 6.8 Hz, H-4), 1.97 (1H, m, H-4′), 2.42 (1H, t of d, J = 12.8, $^3J_{5',4}$ = 6.8 Hz, H-5′), 2.62 (1H, t, ^3J = 9.6 Hz, H-3), 3.59 (3H, s, OMe), 6.88 (1H, br s, $CONH_2$), 7.13 (1H, br s, $CONH_2$). *Anal.* calcd. for $C_{11}H_{19}O_3N$: C 61.95, H 8.98, N 6.57; found: C 62.05, H 9.16, N 6.91.

*(±)-1,2,2-Trimethyl-*cis*-3-(hydroxymethyl)cyclopentanecarboxamide (**16**)*

Compound **14** (1.43 g, 6.70 mmol) was treated with lithium borohydride (0.5 g, 23 mmol) in tetrahydrofuran (100 mL) as described for the preparation of **7**. After treatment with cation- and anion-exchange resins, the solvent was evaporated and the residue was evaporated with methanol (10 × 2 mL). The residue was then stirred in tetrahydrofuran–hexanes, and the resulting white solid was collected by filtration to give 0.84 g of material. This material was fractionated by column chromatography on silica gel to give **16** (0.102 g, 8.2%), mp 159°C, R_f 0.26 (tlc) (4:1 (v/v) toluene–2-propanol). An analytical sample was prepared by recrystallization from ethyl acetate – methanol–hexanes, mp 162–163°C; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 0.65 (3H, s, Me), 1.05 (6H, s, Me), 1.15–1.38 (2H, m, H-4 and H-5), 1.68–1.99 (2H, m, H-3 and H-4′), 2.27 (1H, t of d, J = 13.2, ^3J = 6.9 Hz, H-5′), 3.24 (1H, d of d of d, J_{gem} = 10.2, $^3J_{\text{to H-3}}$ = 7.6, $^3J_{\text{to HOCH}_2}$ = 5.0 Hz, HOCH_2), 3.47 (1H, m, J_{gem} = 10.2, ^3J = 5.1 Hz, HOCH_2), 4.27 (1H, t, ^3J = 5.0 Hz, HOCH$_2$), 6.76 (1H, br s, $CONH_2$), 6.79 (1H, br s, $CONH_2$); spin–spin decoupling was performed at δ 2.27, 3.47, and 4.27. *Anal.* calcd. for $C_{10}H_{19}O_2N$: C 64.83, H 10.34, N 7.56; found: C 64.92, H 10.12, N 7.81.

*(±)-2,2,3-Trimethyl-*cis*-3-carbamoylcyclopentanecarboxylic acid (**17**) and (±)-1,2,2-trimethyl-*cis*-3-carbamoylcyclopentanecarboxylic acid (**18**)*

Dry ammonia was bubbled through a solution of *dl*-camphoric anhydride (**9**, 40.0 g, 220 mmol) in tetrahydrofuran (500 mL) (which had been cooled initially to 5°C) for 40 min. The mixture was left at 0°C overnight and then flushed with nitrogen for 30 min. The ice-cold mixture was filtered and the solid was dissolved in water (250 mL). Insoluble material was removed by filtration, and the filtrate was cooled to ice-bath temperature and acidified to pH 2. The solution was kept in the cold room (2°C) for 2 days; the crystalline solid was collected by filtration and washed with ice-cold water to give a mixture of **17** and **18** (39.2 g) that, by integration of the ^{1}Hmr signals, was shown to contain **17** and **18** in a 1:3 ratio, respectively. Compound **18**, ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 0.72 (3H, s, Me), 1.11 (3H, s, Me), 1.13 (3H, s, Me), 1.28–2.46 (4H, m, H-4, H-4′, H-5, and H-5′), 2.61 (1H, t, ^3J = 9.4 Hz, H-3), 6.83 (1H, br s, $CONH_2$), 7.06 (1H, br s, $CONH_2$), 12.1 (1H, br s, CO_2H). The volume of the filtrate was reduced to 50 mL, the solution was cooled for 8 h at 0°C, and an additional crop of a mixture of **17** and **18** (2.62 g) was obtained for a total yield of 41.82 g (95.4%); the second crop contained compounds **17** and **18** in a 4:1 ratio, respectively. Compound **17**, ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 0.72 (3H, s, Me), 1.08 (3H, s, Me), 1.18 (3H, s, Me), 1.28–2.46 (4H, H-4, H-4′, H-5, and H-5′), 2.69 (1H, d of d, ^3J = 10.0, ^3J = 8.0 Hz, H-1), 6.85 (1H, br s, $CONH_2$), 6.89 (1H, br s, $CONH_2$), 12.1 (1H, br s, CO_2H).

*3-Methoxy-2-methylpropenoic acid (**20**)*

Compound **20** was prepared from methyl 2-methylpropenoate by way of the intermediacy of methyl 2,3-dibromo-2-methylpropanoate and methyl 3-methoxy-2-methylpropenoate (**19**) as described previously (12, 20). Compound **20**, ^{1}Hmr (200 MHz, $CDCl_3$), δ: 1.73 (3H, d, $^4J_{\text{to H-3}}$ = 1.2 Hz, Me), 3.86 (3H, s, OMe), 7.40 (1H, q, ^4J = 1.2 Hz, H-3); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.59 (3H, d, $^4J_{\text{to H-3}}$ = 1.4 Hz, Me), 3.80 (3H, s, OMe), 7.31 (1H, q, ^4J = 1.4 Hz, H-3), 11.8 (1H, br s, CO_2H).

*3-Methoxy-2-methylpropenoyl chloride (**22**)*

Compound **20** was converted into its sodium salt (**21**) as described by Shaw and Warrener (20); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.54 (3H, d, $^4J_{\text{to H-3}}$ = 1.3 Hz, Me), 3.60 (3H, s, OMe), 6.91 (1H, q, ^4J = 1.3 Hz, H-3). The sodium salt was then treated with $SOCl_2$ in ether as described previously (20); distillation gave **22**, ^{1}Hmr (200 MHz, $CDCl_3$), δ: 1.74 (3H, d, Me), 3.96 (3H, s, OMe), 7.66 (1H, q, ^4J = 1.2 Hz, H-3).

(±)-N-{N′-[cis-*3*-*(Hydroxymethyl)cyclopentyl]thiocarbamoyl}-3-methoxy-2-methylpropenamide (27)*

3-Methoxy-2-methylpropenoyl isothiocyanate (**23**) was prepared from equivalent amounts of compound **22** and potassium thiocyanate in acetonitrile as described previously (20). Compound **23** was purified by distillation under vacuum and used immediately for the preparation of **27**. Compound **23** (0.28 g, 1.8 mmol) was added to a solution of **8** (0.21 g, 1.8 mmol) in methanol (5 mL) and diethyl ether (5 mL) and the reaction solution was kept at room temperature overnight; the mixture was filtered and the solvent was evaporated. The residue was fractionated by column chromatography on silica gel to give **27** (0.337 g, 77%) as a colorless oil, R_f 0.50 (8:8:1 (v/v/v) toluene – ethyl acetate – 2-propanol). The ^{1}Hmr spectrum showed minor signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.14–2.23 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 1.61 (3H, d, $^4J_{\text{to H-3}}$ = 1.1 Hz, Me), 3.29–3.36 (2H, m, HOCH_2), 3.85 (3H, s, OMe), 4.50 (1H, se, ^3J = 7.0 Hz, H-1′), 4.61 (1H, t, ^3J = 5.3 Hz, *H*OCH$_2$), 7.52 (1H, q, ^4J = 1.1 Hz, H-3), 10.40 (1H, br s, CON*H*CSNH), 10.97 (1H, br d, $^3J_{\text{to H-1′}}$ = 7.3 Hz, CONHCSN*H*); spin–spin decoupling was performed at δ 4.50.

(±)-N-{N′-[cis-*3*-*(Hydroxymethyl)cyclopentyl]carbamoyl}-3-methoxy-2-methylpropenamide (28)*

A solution of 3-methoxy-2-methylpropenoyl isocyanate (**24**) in benzene was prepared from **22** and silver cyanate as described by Shealy *et al.* (12) and was used immediately for the preparation of **28** without further purification. To a solution of **8** (0.67 g, 5.8 mmol) in dry *N*,*N*-dimethylformamide (12.2 mL), cooled to −15°C, a solution of **24** (1.22 equiv., theoretical) in benzene was added dropwise; the temperature of the reaction solution was maintained below −10°C with a cooling bath. After the addition of **24** was complete, the reaction solution was kept at room temperature overnight; the mixture was filtered and the solvent was evaporated. The residue was fractionated by column chromatography on silica gel to give **28** (1.05 g, 71%) as a white solid, R_f 0.44 (3:3:1 (v/v/v) toluene – ethyl acetate – 2-propanol). The ^{1}Hmr spectrum revealed only minute signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.02–1.18 (1H, m, H-2′), 1.29–2.11 (6H, m, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 1.61 (3H, d, $^4J_{\text{to H-3}}$ = 1.3 Hz, Me), 3.30 (2H, t, ^3J = 5.2 Hz, HOCH_2), 3.79 (3H, s, OMe), 3.99 (1H, se, ^3J = 6.9 Hz, H-1′), 4.55 (1H, t, ^3J = 5.2 Hz, *H*OCH$_2$), 7.45 (1H, q, ^4J = 1.3 Hz, H-3), 8.65 (1H, br d, $^3J_{\text{to H-1′}}$ = 7.3 Hz, CONHCON*H*), 9.67 (1H, br s, CON*H*CONH); spin–spin decoupling was performed at δ 1.10, 3.30, and 3.99.

(±)-3-Ethoxy-N-{N′-[cis-*3*-*(hydroxymethyl)cyclopentyl]thiocarbamoyl}propenamide (29)*

3-Ethoxypropenoyl isothiocyanate (**25**) was prepared as described previously (20) and used immediately after distillation for the preparation of **29**. Compound **25** (1.41 g, 8.97 mmol) was added to a solution of **8** (0.934 g, 8.11 mmol) in methanol (13 mL) and diethyl ether (20 mL), and the reaction solution was kept at room temperature overnight; the mixture was filtered and the solvent was evaporated. The resulting oil was fractionated by column chromatography on silica gel to give **29** (1.54 g, 70%) as a pale yellow-green oil; R_f 0.50 (8:8:1 (v/v/v) toluene – ethyl acetate – 2-propanol). The ^{1}Hmr spectrum showed minor signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.10–2.23 (6H, m, H-2′, H-2″, H-4′, H-4″, H-5′, and H-5″), 1.24 (3H, t, ^3J = 7.0 Hz, Me), 1.85–2.23 (1H, m, H-3′), 3.32 (2H, t, ^3J = 5.6 Hz, HOCH_2), 3.98 (2H, q, ^3J = 7.0 Hz, CH_3CH_2O), 4.48 (1H, se, ^3J = 6.9 Hz, H-1′), 4.56 (1H, t, ^3J = 5.0 Hz, *H*OCH$_2$), 5.70 (1H, d, $^3J_{2,3}$ = 12.2 Hz, H-2), 7.59 (1H, d, $^3J_{3,2}$ = 12.2 Hz, H-3), 10.84 (1H, br s, CON*H*CSNH), 10.96 (1H, br d, $^3J_{\text{to H-1′}}$ = 7.2 Hz, CONHCSN*H*); spin–spin decoupling was performed at δ 3.32, 4.48, and 10.96.

(±)-3-Ethoxy-N-{N′-[cis-*3*-*(hydroxymethyl)cyclopentyl]carbamoyl}propenamide (30)*

A solution of 3-ethoxypropenoyl isocyanate (**26**) in benzene was prepared as described previously (21, 28). A solution of compound **26** (26.6 mmol, theoretical) in benzene (60 mL) was added to a solution of **8** (2.73 g, 23.7 mmol) in *N*,*N*-dimethylformamide (60 mL) that had been cooled to −15°C; the temperature was maintained below −10°C during the addition. The reaction solution was kept at room temperature overnight. The mixture was filtered and the solvent was evaporated with ethanol (2 × 20 mL); fractionation of the residue by column chromatography on silica gel gave **30** (2.59 g, 43%) as a semisolid, R_f 0.57 (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol). The ^{1}Hmr spectrum showed minor signals attributable to impurities; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.05–2.15 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 1.26 (3H, t, ^3J = 7.0 Hz, Me), 3.32 (2H, t, ^3J = 5.6 Hz, HOCH_2), 3.98 (1H, se, ^3J = 7.0 Hz, H-1′), 4.02 (2H, q, ^3J = 7.0 Hz, CH_3CH_2O), 4.53 (1H, t, ^3J = 5.3 Hz, *H*OCH$_2$), 5.59 (1H, d, $^3J_{2,3}$ = 12.7 Hz, H-2), 7.69 (1H, d, $^3J_{3,2}$ = 12.7 Hz, H-3), 7.98 (1H, br d, $^3J_{\text{to H-1′}}$ = 7.4 Hz, CONHCON*H*); spin–spin decoupling was performed at δ 3.32 and 4.00.

(±)-2,3-Dihydro-1-{cis-*3-(hydroxymethyl)cyclopentyl}-5-methyl-2-thioxo-4(1*H*)-pyrimidinone (31)*

A solution of compound **27** (0.359 g, 1.32 mmol) in 15 *N* aqueous ammonia (15 mL) was heated at 100°C in an oil bath for 30 min. After the reaction solution had cooled to room temperature, the solvent was evaporated and the residue was evaporated with ethanol (2 × 10 mL). The resulting material was fractionated by column chromatography on silica gel to give **31** (0.195 g, 62%). Recrystallization from ethanol–hexanes gave **31** (0.116 g) as a white crystalline solid, mp 138.5–139.5°C, R_f 0.39 (4:4:1 (v/v/v) toluene – ethyl acetate – 2-propanol); uv λ_{max} (C_2H_5OH): 221 (ε 15 300), 276 (15 400) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 221 (ε 15 300), 276 (15 300) nm; λ_{max} (0.01 *M* NaOH in C_2H_5OH): 242 (ε 20 300), 255 (17 800), 266 (17 600) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), 1.26–2.21 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 1.85 (3H, m, Me), 3.40 (2H, m, HOCH_2), 4.61 (1H, t, ^3J = 5.2 Hz, *H*OCH$_2$), 5.74 (1H, m, H-1′), 7.76 (1H, m, H-6), 12.51 (1H, br s, H-3). *Anal.* calcd. for $C_{11}H_{16}O_2N_2S$: C 54.98, H 6.71, N 11.66, S 13.34; found: C 55.19, H 6.96, N 11.73, S 13.52.

(±)-1-{cis-*3-(Hydroxymethyl)cyclopentyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (32)*

A solution of **28** (1.106 g, 3.96 mmol) in aqueous ammonia (35 mL) was heated at 100°C in an oil bath for 65 min. After the solution had cooled to room temperature, the solvent was evaporated and the residue was then evaporated with ethanol (2 × 10 mL). The resulting material was fractionated by column chromatography on silica gel to give **32** (0.724 g, 82%) as a white solid. Recrystallization from ethanol–hexanes gave **32** (0.596 g) having mp 165–168°C (lit. (12) mp 173–174°C). Repeated recrystallization gave material having mp 166–168°C; R_f 0.34 (2:2:1 (v/v/v) toluene – ethyl acetate – 2-propanol); uv λ_{max} (C_2H_5OH): 210 (ε 9990), 272 (9980) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 210 (ε 9960), 272 (9930) nm; λ_{max} (0.01 *M* NaOH in C_2H_5OH): 220 (ε 9590), 272 (7400) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.29–2.18 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 1.79 (3H, d, $^4J_{\text{to H-6}}$ = 0.9 Hz, Me), 3.38 (2H, m, HOCH_2), 4.58 (1H, t, ^3J = 5.3 Hz, *H*OCH$_2$), 4.73 (1H, m, H-1′), 7.56 (1H, m, H-6), 11.19 (1H, br s, H-3). *Anal.* calcd. for $C_{11}H_{16}O_3N_2$: C 58.91, H 7.19, N 12.49; found: C 59.04, H 7.30, N 12.44.

(±)-2,3-Dihydro-1-{cis-*3-(hydroxymethyl)cyclopentyl}-2-thioxo-4(1*H*)-pyrimidinone (33)*

A solution of **29** (1.491 g, 5.47 mmol) in 15 *N* aqueous ammonia (50 mL) was heated at 100°C in an oil bath for 25 min. After the reaction solution had cooled to room temperature, the solvent was evaporated and the residue was then evaporated with ethanol (2 × 10 mL). The resulting material was fractionated by column chromatography on silica gel to give **33** (1.001 g, 81%) as a white solid, R_f 0.41 (3:3:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol–hexanes, mp 145–147°C; uv λ_{max} (C_2H_5OH): 219 (ε 16 000), 272 (13 600) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 219 (ε 16 700), 273 (13 700) nm;

λ_{max} (0.01 *M* NaOH in C_2H_5OH): 240 (ε 18 500), 273 (16 000) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.23–2.19 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 3.39 (2H, t, ^3J = 5.1 Hz, $HOCH_2$), 4.62 (1H, t, ^3J = 5.2 Hz, $HOCH_2$), 5.73 (1H, m, H-1′), 5.99 (1H, br d, $^3J_{5,6}$ = 7.8 Hz, H-5), 7.90 (1H, d, $^3J_{6,5}$ = 7.8 Hz, H-6), 12.63 (1H, br s, H-3). *Anal.* calcd. for $C_{10}H_{14}O_2N_2S$: C 53.08, H 6.24, N 12.38, S 14.17; found: C 53.13, H 6.40, N 12.20, S 13.95.

*(±)-1-{*cis*-3-(Hydroxymethyl)cyclopentyl}-2,4(1*H*,3*H*)-pyrimidinedione (**34**)*

A solution of **30** (2.47 g, 9.64 mmol) in 2 *N* H_2SO_4 (65 mL) was heated at reflux temperature for 30 min. After the solution had cooled to room temperature, it was treated with charcoal and the mixture was filtered. The filtrate was cooled to ice-bath temperature and neutralized with 2 *M* NaOH. The solvent was evaporated and the residue was extracted with ethanol (4 × 30 mL). The ethanol was then evaporated and the residue was fractionated by column chromatography on silica gel to give **34** (1.401 g, 69%) as a pale-yellow solid, mp 150–155°C, R_f 0.43 (1:1:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol–hexanes, mp 158–159°C; uv λ_{max} (C_2H_5OH): 209 (ε 9490), 268 (10 400) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 209 (ε 9460), 268 (10 300) nm; λ_{max} (0.01 *M* NaOH in C_2H_5OH): 220 (ε 8220), 266 (7490) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.27–2.18 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 3.38 (2H, t, ^3J = 5.6 Hz, $HOCH_2$), 4.57 (1H, t, ^3J = 5.1 Hz, $HOCH_2$), 4.74 (1H, m, H-1′), 5.57 (1H, d of d, $^3J_{5,6}$ = 8.1, $^4J_{5,3}$ = 2.2 Hz, H-5), 7.69 (1H, d, $^3J_{6,5}$ = 8.1 Hz, H-6), 11.24 (1H, br s, H-3). *Anal.* calcd. for $C_{10}H_{14}O_3N_2$: C 57.13, H 6.71, N 13.32; found: C 57.18, H 6.83, N 13.35.

*(±)-1-{*cis*-3-(Hydroxymethyl)cyclopentyl}-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione benzoate (**38**)*

A solution of benzoyl chloride (0.66 mL, 5.7 mmol) in pyridine (5 mL) was added to a solution of compound **32** (0.424 g, 1.89 mmol) in pyridine (20 mL). The reaction solution was kept at 55°C in a water bath for 48 h and then poured into a water–ice mixture (150 mL). An oil separated, which was extracted with chloroform (3 × 25 mL). The solvent was evaporated and the residue was evaporated with ethanol–water (1:1 (v/v), 2 × 20 mL). The resulting oil was fractionated by column chromatography on silica gel to give **35** (0.822 g) as a colorless solid foam, R_f 0.56 (3:2 (v/v) toluene – ethyl acetate). The ^{1}Hmr spectrum showed this sample to be contaminated by a small amount of benzoic acid; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.58–2.12 (5H, m, H-2′, H-4′, H-4″, H-5′, and H-5″), 1.88 (3H, m, Me), 2.22 (1H, d of t, J_{gem} = 12.4, ^3J = 7.0 Hz, H-2″), 2.45 (1H, m, H-3′), 4.24–4.41 (2H, m, OCH_2C), 4.83 (1H, m, H-1′), 7.47–8.02 (10H, m, C_6H_5), 7.88 (1H, m, H-6); spin–spin decoupling was performed at δ 1.88. Compound **35** (0.758 g) was dissolved in hot ethanol (70 mL), and to this solution water (25 mL) and 1 *M* hydrochloric acid (6 mL) were added; the reaction solution was heated at reflux temperature for 24 h. The solution was cooled and the solvent was evaporated. The residue was fractionated by column chromatography on silica gel to give **38** (0.429 g, 75% from **32**) as a white crystalline solid, R_f 0.46 (8:8:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol, mp 159–161°C; uv λ_{max} (C_2H_5OH): 202 (ε 17 300), 224 (16 600), 273 (10 800) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 202 (ε 16 500), 224 (16 500), 273 (10 800) nm; λ_{max} (0.01 *M* NaOH in C_2H_5OH): 228 (ε 20 400), 272 (8170) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.47–2.00 (5H, m, H-2′, H-4′, H-4″, H-5′, and H-5″), 1.78 (3H, m, Me), 2.12 (1H, d of t, J_{gem} = 12.0, ^3J = 6.9 Hz, H-2″), 2.43 (1H, m, H-3′), 4.21–4.37 (2H, m, OCH_2), 4.82 (1H, m, H-1′), 7.50–8.02 (5H, m, C_6H_5), 7.63 (1H, m, H-6), 11.26 (1H, br s, H-3); spin–spin decoupling was performed at δ 1.78, 2.43, and 4.82. *Anal.* calcd. for $C_{18}H_{20}O_4N_2$: C 65.84, H 6.14, N 8.53; found: C 66.19, H 6.10, N 8.57.

*(±)-2,3-Dihydro-1-{*cis*-3-(hydroxymethyl)cyclopentyl}-2-thioxo-4(1*H*)-pyrimidinone benzoate (**39**)*

A solution of benzoyl chloride (0.60 mL, 5.2 mmol) in pyridine (5 mL) was added dropwise to a solution of compound **33** (0.338 g, 1.49 mmol) in pyridine (15 mL). The reaction solution was treated as for the preparation of **35**, and, after fractionation by column chromatography on silica gel, two major components were isolated, namely **36** (0.386 g) as a solid foam, R_f 0.54 (3:2 (v/v) toluene – ethyl acetate), and **39** (0.192 g) as a crystalline solid that, after recrystallization from ethanol–water, gave a sample of **39** (0.111 g) having mp 179–182°C, R_f 0.34. Compound **36**, ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.42–2.50 (7H, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 4.22–4.42 (2H, m, OCH_2), 5.72 (1H, m, H-1′), 6.32 (1H, d, $^3J_{5,6}$ = 8.3 Hz, H-5), 7.46–8.02 (10H, m, C_6H_5), 8.22 (1H, d of d, $^3J_{6,5}$ = 8.3, J = 1.3 Hz, H-6); spin–spin decoupling was performed at δ 6.32 and 5.72. To a solution of compound **36** (0.362 g, 0.83 mmol) in hot ethanol (50 mL) were added water (25 mL) and 1 *M* hydrochloric acid (5 mL), and the reaction solution was heated at reflux temperature for 4 h. After the solution had cooled to room temperature, a white solid precipitated that, after reduction of the volume of the reaction mixture to 20 mL, was collected by filtration to give **39** (0.244 g), mp 179–182°C, for a total yield of 0.355 g (75% from **33**). An analytical sample was prepared by recrystallization from ethanol, mp 180–182°C; uv λ_{max} (C_2H_5OH): 203 (ε 17 200), 223 (26 700), 273 (15 600) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 203 (ε 16 700), 223 (26 700), 273 (15 400) nm; λ_{max} (0.01 *M* NaOH in C_2H_5OH): 234 (ε 29 600), 273 (18 100) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.51 (1H, m, H-2′), 1.62–2.13 (4H, m, H-4′, H-4″, H-5′, and H-5″), 2.26 (1H, d of t, J_{gem} = 11.9, ^3J = 6.9 Hz, H-2″), 2.46 (1H, m, H-3′), 4.21–4.38 (2H, m, OCH_2), 5.82 (1H, m, H-1′), 6.01 (1H, d of d, $^3J_{5,6}$ = 8.1, $^4J_{5,3}$ = 1.3 Hz, H-5), 7.50–8.02 (5H, m, C_6H_5), 7.96 (1H, d, $^3J_{6,5}$ = 8.1 Hz, H-6), 12.62 (1H, br s, H-3); spin–spin decoupling was performed at δ 4.30 and 6.01. *Anal.* calcd. for $C_{17}H_{18}O_3N_2S$: C 61.80, H 5.49, N 8.48, S 9.70; found: C 62.17, H 4.97, N 8.46, S 10.17.

*(±)-1-{*cis*-3-(Hydroxymethyl)cyclopentyl}-2,4(1*H*,3*H*)-pyrimidinedione benzoate (**40**)*

Compound **34** (0.448 g, 2.13 mmol) was treated with benzoyl chloride (0.75 mL, 6.5 mmol) as described for the preparation of **35**, and, after fractionation by column chromatography on silica gel, **37** (0.85 g) was obtained as a colorless solid foam, R_f 0.44 (3:2 (v/v) toluene – ethyl acetate); ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.57–2.15 (5H, m, H-2′, H-4′, H-4″, H-5′, and H-5″), 2.24 (1H, d of t, J_{gem} = 12.2, ^3J = 7.0 Hz, H-2″), 2.43 (1H, m, H-3′), 4.22–4.38 (2H, m, OCH_2), 4.81 (1H, m, H-1′), 5.88 (1H, d, $^3J_{5,6}$ = 7.9 Hz, H-5), 7.50–8.01 (10H, m, C_6H_5), 8.03 (1H, d, $^3J_{6,5}$ = 7.9 Hz, H-6); spin–spin decoupling was performed at δ 2.43, 4.81, and 5.88. Compound **37** (0.81 g) was treated as described for the preparation of **38**, and, after fractionation by column chromatography on silica gel, **40** (0.449 g, 70% from **34**) was obtained as a white crystalline solid, mp 153–155°C, R_f 0.56 (4:4:1 (v/v/v) toluene – ethyl acetate – 2-propanol). An analytical sample was prepared by recrystallization from ethanol, mp 154–155°C; uv λ_{max} (C_2H_5OH): 202 (ε 17 700), 226 (14 700), 268 (11 000) nm; λ_{max} (0.01 *M* HCl in C_2H_5OH): 203 (ε 15 800), 227 (14 500), 268 (10 900) nm; λ_{max} (0.01 *M* NaOH in C_2H_5OH): 227 (ε 19 400), 266 (8040) nm; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.47–2.02 (5H, m, H-2′, H-4′, H-4″, H-5′, and H-5″), 2.14 (1H, d of t, J_{gem} = 12.1, ^3J = 7.0 Hz, H-2″), 2.43 (1H, m, H-3′), 4.20–4.36 (2H, m, OCH_2), 4.79 (1H, m, H-1′), 5.59 (1H, d of d, $^3J_{5,6}$ = 8.0, $^4J_{5,3}$ = 2.0 Hz, H-5), 7.49–8.00 (5H, m, C_6H_5), 7.77 (1H, d, $^3J_{6,5}$ = 8.0 Hz, H-6), 11.28 (1H, br d, $^4J_{3,5}$ = 2.0 Hz, H-3); spin–spin decoupling was performed at δ 2.43, 4.79, and 5.59. *Anal.* calcd. for $C_{17}H_{18}O_4N_2$: C 64.96, H 5.77, N 8.91; found: C 64.93, H 6.02, N 8.87.

*(±)-4-Amino-1-{*cis*-3-(hydroxymethyl)cyclopentyl}-5-methyl-2(1*H*)-pyrimidinone (**43**)*

A solution of **38** (0.315 g, 0.96 mmol), thionyl chloride (1 mL, 13.8 mmol), *N*,*N*-dimethylformamide (55 mg, 0.75 mmol), and chloroform (16 mL) was heated at reflux temperature for 6 h. The solution was cooled and the solvent evaporated; the residue was dried overnight using a vacuum pump. The residue was transferred to a Teflon-lined steel bomb with dry methanol (11 mL). The steel bomb

was cooled by immersion in crushed Dry Ice for a few min, and then anhydrous ammonia (11 mL) was added. The bomb was sealed and kept in an oil bath at 100°C for 21 h. The bomb was then cooled with Dry Ice, opened, and allowed to warm to room temperature. The contents were transferred with the aid of methanol and, after reduction of the volume using a rotary evaporator, the material was fractionated by column chromatography on silica gel to give **43** (0.158 g, 74%) as a light-yellow oil, R_f 0.33 (5:3:1 (v/v/v) acetonitrile – 1,2-dimethoxyethane – 15 *N* aqueous ammonia). An analytical sample was prepared by crystallization from ethanol–acetonitrile – diethyl ether, mp 217–220°C; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.24–2.16 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 1.84 (3H, s, Me), 3.39 (2H, t, ^3J = 5.8 Hz, HOCH_2), 4.54 (1H, t, ^3J = 5.4 Hz, HOCH$_2$), 4.79 (1H, m, H-1′), 6.66 (1H, br s, NH_2),[3] 7.04 (1H, br s, NH_2),[3] 7.46 (1H, s, H-6). *Anal.* calcd. for $C_{11}H_{17}O_2N_3$: C 59.16, H 7.67, N 18.82; found: C 58.89, H 7.55, N 18.73.

*(±)-4-Amino-1-{*cis*-3-(hydroxymethyl)cyclopentyl}-2(1*H*)-pyrimidinone (**44**)*

A solution of **40** (0.375 g, 1.19 mmol), thionyl chloride (1 mL, 13.8 mmol), *N*,*N*-dimethylformamide (51 mg, 0.70 mmol), and chloroform (17 mL) was treated as described for the preparation of **43**. After having been dried in a vacuum, compound **42** was dissolved in methanol – anhydrous ammonia (20 mL, 1:1 (v/v)) and the solution was heated in a Teflon-lined steel bomb at 100°C for 8.5 h. The bomb was opened as described for the preparation of **43**, and the material was fractionated by column chromatography on silica gel to give **44** (173 mg, 69%) as an oil, R_f 0.35 (5:3:1 (v/v/v) acetonitrile–1,2-dimethoxyethane – 15 *N* aqueous ammonia). An analytical sample was prepared by recrystallization from ethanol – diethyl ether, mp 200–202°C; ^{1}Hmr (200 MHz, Me_2SO-d_6), δ: 1.23–2.18 (7H, m, H-2′, H-2″, H-3′, H-4′, H-4″, H-5′, and H-5″), 3.3–3.45 (2H, m, HOCH_2), 4.58 (1H, br t, HOCH$_2$), 4.80 (1H, m, H-1′), 5.69 (1H, d, $^3J_{5,6}$ = 7.3 Hz, H-5), 7.05 (2H, br s, NH_2), 7.64 (1H, d, $^3J_{6,5}$ = 7.3 Hz, H-6). *Anal.* calcd. for $C_{10}H_{15}O_2N_3$: C 57.40, H 7.23, N 20.08; found: C 57.16, H 7.50, N 19.70.

Treatment of compound **39** as described for the preparation of **44** gave material having mp 195–199°C and an ^{1}Hmr spectrum identical to that obtained for compound **44**.

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1. A. M. Michelson and A. R. Todd. J. Chem. Soc. 816 (1955).
2. K. E. Pfitzner and J. G. Moffatt. J. Org. Chem. **29**, 1508 (1964).
3. (*a*) M. J. Robins and R. K. Robins. J. Am. Chem. Soc. **86**, 3585 (1964); (*b*) M. J. Robins, J. R. McCarthy, and R. K. Robins. Biochemistry, **5**, 224 (1966); (*c*) M. J. Robins, F. Hansske, N. H. Low, and J. I. Park. Tetrahedron Lett. **25**, 367 (1984).
4. A. M. Doering, M. Jansen, and S. S. Cohen. J. Bacteriol. **92**, 565 (1966).
5. M. R. Atkinson, M. P. Deutscher, A. Kornberg, A. F. Russell, and J. G. Moffatt. Biochemistry, **8**, 4897 (1969).
6. T. A. Khwaja and C. Heidelberger. J. Med. Chem. **10**, 1066 (1967).
7. F. Sanger, S. Nicklen, and A. R. Coulson. Proc. Natl. Acad. Sci. U.S.A. **74**, 5463 (1977).
8. J. P. Horwitz, J. Chua, M. A. Darooge, M. Noel, and I. L. Klundt. J. Org. Chem. **31**, 205 (1966).
9. H. J. Schaeffer, D. D. Godse, and G. Liu. J. Pharm. Sci. **53**, 1510 (1964).
10. J. A. Montgomery and K. Hewson. J. Med. Chem. **10**, 665 (1967).
11. Y. F. Shealy, J. D. Clayton, and C. A. O'Dell. J. Heterocycl. Chem. **10**, 601 (1973).
12. Y. F. Shealy, C. A. O'Dell, and M. C. Thorpe. J. Heterocycl. Chem. **18**, 383 (1981).
13. A. P. Arendaruk, E. I. Budovskii, B. P. Gottikh, M. Ya. Karpeiskii, L. I. Kudryashov, A. P. Skoldinov, N. V. Smirnova, A. Ya. Khorlin, and N. K. Kochetkov. Zh. Obshch. Khim. **27**, 1312 (1957); Chem. Abstr. **52**, 4508d (1958).
14. S. F. Birch, W. J. Oldham, and E. A. Johnson. J. Chem. Soc. 818 (1947).
15. C. A. O'Dell and Y. F. Shealy. *In* Nucleic acid chemistry. Part I. *Edited by* L. B. Townsend and R. S. Tipson. John Wiley and Sons, Inc., New York. 1978. pp. 161–167.
16. Y. F. Shealy and C. A. O'Dell. Tetrahedron Lett. 2231 (1969).
17. Y. F. Shealy, C. A. O'Dell, M. C. Thorpe, and W. C. Coburn, Jr. J. Heterocycl. Chem. **20**, 655 (1983).
18. E. S. Wallis and J. F. Lane. *In* Organic reactions. Vol. III. *Edited by* R. Adams. John Wiley and Sons, Inc., New York. 1946. pp. 267–306.
19. L. J. J. Hronowski and W. A. Szarek. Can. J. Chem. **63**, 2787 (1985).
20. G. Shaw and R. N. Warrener. J. Chem. Soc. 153 (1958).
21. G. Shaw and R. N. Warrener. J. Chem. Soc. 157 (1958).
22. L. J. J. Hronowski and W. A. Szarek. Can. J. Chem. **64**, 1620 (1986).
23. J. Žemlička and F. Šorm. Collect. Czech. Chem. Commun. **30**, 2052 (1965).
24. Y. F. Shealy and C. A. O'Dell. J. Heterocycl. Chem. **17**, 353 (1980).
25. M. Sano. Chem. Pharm. Bull. **10**, 320 (1962).
26. L. J. J. Hronowski and W. A. Szarek. J. Med. Chem. **25**, 522 (1982).
27. Dictionary of organic compounds. 5th ed. Vol. 2. Chapman and Hall, New York. 1982. p. 1404.
28. Y. F. Shealy and C. A. O'Dell. J. Heterocycl. Chem. **13**, 1015 (1976).
29. E. D. Becker, H. T. Miles, and R. B. Bradley. J. Am. Chem. Soc. **87**, 5575 (1965).
30. Y. F. Shealy, C. A. O'Dell, G. Arnett, W. M. Shannon, M. C. Thorpe, J. M. Riordan, and W. C. Coburn, Jr. J. Med. Chem. **29**, 1720 (1986).

[3]The observation of two broadened singlets arising from the amino group of 5-substituted cytosines has been documented previously (see refs. 29 and 30).