through a 2 cm × 22 cm column. After removal of the less polar components with hexanes, the product was washed from the column with ethyl acetate. The residue (0.051 g) was purified by sublimation (90 °C (1.5 mmHg)) to yield 0.032 g (23%) of clear, pale yellow crystals: mp 83.5–84.5 °C; IR (KBr) 1638 cm^{-1} (C=O stretch); ^1H NMR ($CDCl_3$) δ 1.71 (d, 3 H, CH_3CH, ^3J = 7 Hz), 4.89 (q, 1 H, $CHCH_3$, ^3J = 7 Hz), 6.85–7.44 (m, 8 H, ArH), 10.42 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) 194.25, 165.32, 146.48, 137.12, 133.77, 133.38, 129.03, 128.37, 118.23, 117.28, 116.98, 42.04, 21.67; MS 258 (21), 149 (100), 148 (61), 131 (16), 103 (31), 91 (25), 77 (26). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.61; H, 5.59.

X-ray Crystallography. A colorless, prismatic crystal of (±)-1*H*-1-hydroxy-2,3-dihydro-2,2,3-trimethyl-7-methoxyisoindolium 3,5-dinitrobenzoate (**4d**) ($C_{19}H_{21}N_3O_8$), grown from ethanol, having approximate dimensions of 0.23 × 0.20 × 0.31 mm, was determined to be monoclinic with space group $P2_1/n$ and cell constants of a = 12.826 (2) Å, b = 7.170 (1) Å, c = 21.606 (5) Å, β = 91.66 (2), Z = 4, D_c = 1.402 g cm^{-3}, and μ = 8.97 cm^{-1}. It was mounted on an Enraf-Nonius CAD4 automated diffractometer, and all intensity measurements were performed at 23 °C with Cu Kα (λ = 1.541 84 Å) radiation with a graphite crystal, incident beam monochromator, scan type ω. Of the 4229 unique reflections, 2795 having $I > 3\sigma(I)$ were used in the structure solution and refinement. The structure was solved with the direct methods program SHELXS-86,[25] and refinement was carried out by using full-matrix least-squares techniques. All H atoms attached to C were included at their calculated positions by assuming C–H = 0.95 Å. These atoms were then included in the calculations with fixed, isotropic thermal parameters 1.2 times that of the attached atom and constrained to "ride" with this atom. The H atom on the hydroxyl was located in a difference Fourier map and included in the calculations with its positional and isotropic thermal parameters refined. The final agreement factors were R_1 = 0.065, and GOF = 5.18. Figure 1 is a computer-generated perspective drawing of **4d** from the final X-ray coordinates.

Acknowledgment. We thank Professor Gary R. Weisman for helpful discussions concerning MMP2 calculations. We gratefully acknowledge support from the National Science Foundation for the purchase of the Bruker AM360 NMR spectrometer (Grant CHE-8614606).

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

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Nucleosides. 3. Reactions of AICA-Riboside with Isothiocyanates. A Convenient Synthesis of Isoguanosine and Xanthosine Derivatives[1]

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Cyclodesulfurative annulations of 5-[1-(3-substituted-thioureido)]-1-(β-D-ribofuranosyl)imidazole-4-carboxamides (**3a–h**) with *N,N'*-dicyclohexylcarbodiimide are described. Isoguanosine (**4**) and several 1-substituted isoguanosines **6a–f,h** are readily prepared by a ring closure of the appropriate resulting 5-(3-substituted-1-ureido)-1-(β-D-ribofuranosyl)imidazole-4-carbonitriles **5a–h**. Treatment of the appropriate 1-substituted isoguanosines under basic conditions has furnished the corresponding 1-substituted xanthosine **12**.

Introduction

Isoguanosine (**4**), one of the unusual naturally occurring nucleosides, was first synthesized by Fischer[2] and was subsequently isolated from plant[3] and animal sources,[4,5] for example, *Croton tiglium* and *Diaulula sandiegensis*, respectively. Later on, doridosine (**6a**), an isoguanosine derivative possessing a methyl group on the N-1 position of the purine ring, was isolated from a marine animal by three independent research groups as well.[6,7] The chemical properties of isoguanosine derivatives, such as poor solubility, are similar to those of guanosine. However, biologically and physiologically, doridosine-like adenosine analogues promote the accumulation of cyclic AMP in the brain,[8] inducing a more profound lowering of blood pressure, decreasing heart rate, and smooth muscle relaxation than that observed for isoguanosine per se.[9] Recently, several analogues of doridosine were synthesized[10] due to an appreciation of the important effect of the purine receptor on the cardiovascular system and the discovery of the mechanism of action of doridosine related to the A_2 agonists.[11]

[†] Institute of Pharmacy and Medical Laboratories.
[‡] Department of Medicinal Chemistry.

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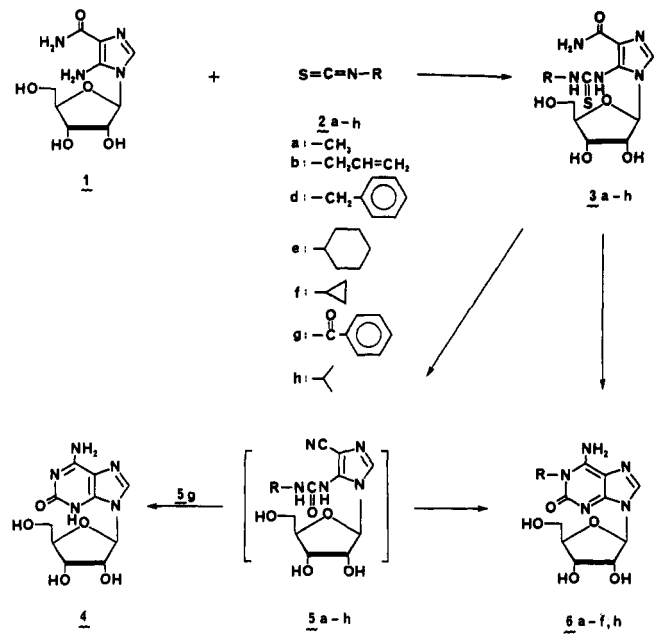
A perusal of the literature revealed that the synthesis of isoguanosine had been achieved from 4,5-dicyanoimidazole,[12] ureidoimidazolecarbonitrile,[13] and/or 2,6-diamino-9-(β-D-ribofuranosyl)purine[14] by a selective deamination with nitric acid. A photochemical preparation of isoguanosine from adenosine N^1-oxide[15] and from 2-iodoadenosine[16] has also been reported. All of these reactions involved either several steps or the use of undesirable heavy metal salts and gave a low overall yield.

Several approaches for the preparation of doridosine analogues are also available. These approaches are either by a direct alkylation of isoguanosine with methyl iodide or by a condensation of protected 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile (AICN-riboside) with various isocyanates followed by cyclization and deprotection using methanolic ammonia. The latter approach provided direct access to various 1-substituted isoguanosines by the use of appropriate isocyanates.[11,17] However, the protected AICN-riboside intermediate used in the latter approach was prepared by a tedious process involving intensive column chromatography because the electron-withdrawing character of a cyano group on the 4-position decreases the basicity of the 5-exocyclic amino group and consequently increases the difficulty of effecting a reaction of AICN-riboside with certain isocyanates. As part of our synthetic study on the DCC-mediated cyclodesulfurative annulation reaction, we found that 5-[3-(methoxycarbonyl)-1-ureido]-1-(β-D-ribofuranosyl)-imidazole-4-carbonitrile could be synthesized via a condensation of AICA-riboside with methoxycarbonyl isothiocyanate following by a cyclodesulfurization of the resulting thioureido derivative with dicyclohexylcarbodiimide.[18,19] Our successful synthesis of this AICN-riboside derivative from AICA-riboside, vide supra, under such mild conditions, prompted us to study the possibility that this methodology might provide an efficient approach for the preparation of isoguanosine and various doridosine analogues containing an amino-*N*-alkylpyrimidinone moiety. These compounds would be of some interest as potential antihypertensive agents.

Results and Discussion

Preparation of Substituted Isoguanosines. A useful first generation testing ground for this concept would be the synthesis of doridosine via the cyclocondensation of AICA-riboside (1) with methyl isothiocyanate (2a). An attempt to isolate the resulting thioureido derivative (3a), which was prepared by heating AICA-riboside with 2a in DMF at 80 °C for 12 h, was unsuccessful because the product was found to be very hygroscopic. Thus, compound 3a was subjected to cyclodesulfurization with an excess amount of DCC in DMF at room temperature for 24 h. The mixture was applied to flash chromatography to afford an oily residue identified as 5-(3-methyl-1-ureido)-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile (5a), after removing the fast-moving band of dicyclohexylurea and DCC. The ring closure of 5a was effected in a mixture of

Scheme I



methanol and ammonia water (58%). The overall yield of doridosine from AICA-riboside is 68% (Scheme I). Although this approach was more efficient than previously reported, we felt that it could be even more practical if the reaction could be run in a one-pot reaction. Therefore, after the initial condensation of AICA-riboside with 2a in DMF, we added DCC directly to the mixture. When the reaction was complete (followed by TLC), the solvent from the reaction mixture was replaced by ethanol and concentrated ammonia was added to this solution to give doridosine. Unfortunately, the product obtained from this process was contaminated with DCC and dicyclohexylurea. These impurities were difficult to remove by recrystallization. Interestingly, in an attempt to isolate 5a after column chromatography, we added methanol to the oily residue and allowed the mixture to stand at room temperature for 2 days. We obtained a solid that was found to be doridosine (64% overall yield from AICA-riboside). Since we assumed, a priori, that 5a was ready to cyclize in methanol without any base, we were encouraged to find that heating the initial condensation product with DCC in ethanol at reflux temperature facilitated the reaction. We established that the AICN derivative was formed during the reaction and was then gradually converted into doridosine. Due to the poor solubility of doridosine in ethanol, the mixture gradually became a suspension during the course of this reaction. After the reaction was complete, the mixture was cooled to room temperature to obtain doridosine in 64% yield. It is of some interest that another compound that was established to have the structure of 6-(*N*,*N*′-dicyclohexylguanidinyl)-1-methyl-9-(β-D-ribofuranosyl)purin-2(1*H*)-one (7) was isolated in 11% yield from the filtrate. Thus, the high temperature used in the reaction not only promoted the ring closure of 5a under neutral conditions and but also enhanced the nucleophilicity of the 6-amino group of doridosine toward the DCC to form compound 7.

Surprisingly, when the earlier reaction was repeated using the benzyl and cyclohexyl isothiocyanates 2d,e, we did not obtain 5-(3-benzyl-1-thioureido)-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (3d) and 5-(3-cyclohexyl-1-thioureido)-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (3e). On the assumption that the nucleophilicity of the exocyclic nitrogen on the 5-position of

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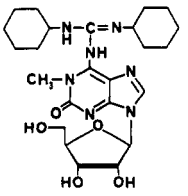

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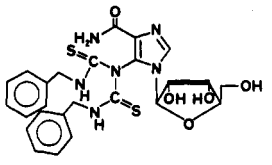
AICA-riboside could be enhanced under basic conditions, 1-benzyl- and 1-cyclohexylisoguanosine (**6d,e**) were obtained in good yield by a one-pot reaction. This reaction involved an initial condensation of AICA-riboside with **2d** and **2e** in pyridine at 80 °C, followed by the treatment of the resulting thiourea derivatives **3d** and **3e** with DCC to afford **5d** and **5e**, which were then annulated with methanolic ammonia to afford **6d** and **6e**. It is worthy to note that in a condensation of AICA-riboside with **2d**, we isolated another compound (small spot on TLC R_f = 0.58) that migrated just higher than the spot observed for the desired product. In view of a previous report[17] on the isolation of a 5-bis(methylcarbamoyl)amino adduct from a reaction of 5-amino-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile with methyl isocyanate, we presumed that our product might be 5-[bis(benzylthiocarbamoyl)amino]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**8**). The ^{1}H NMR spectrum of the product showed one absorption singlet at δ 9.11 corresponding to an NH proton and one triplet centered at δ 9.85 corresponding to another NH proton. This was indicative of two chemically nonequivalent protons on the thioureido side chain. The ^{13}C NMR spectrum of the product showed two peaks at δ 183 and 189, which confirmed the presence of two chemically nonequivalent thiocarbonyl group. Therefore, the structure of this minor product was assigned as 5-[1-[3-(benzylthiocarbamoyl)-3-benzylthioureido]]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**9**) instead of **8**. Similarly, 1-allylisoguanosine (**6b**) and 1-cyclopropylisoguanosine (**6f**) were obtained in good yield by a direct treatment of the condensed products **3b** and **3f** obtained from AICA-riboside and allyl isothiocyanate (**2b**) or cyclopropyl isothiocyanate (**2f**) in DMF with DCC, followed by column chromatography and subsequent treatment with methanolic ammonia.



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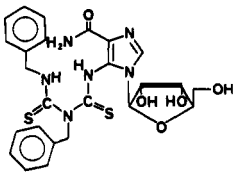

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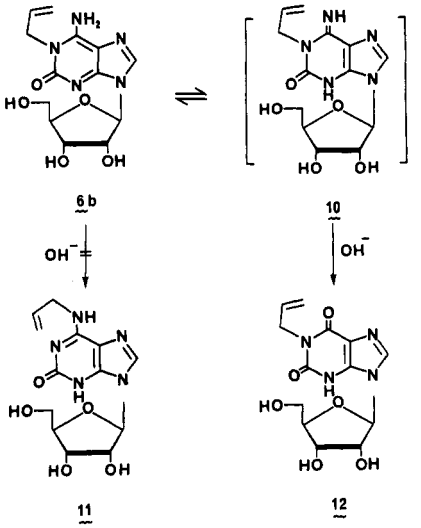
Although the synthesis of isoguanosine from **1** has been reported by Yamazaki and co-workers,[20,21] we felt that the use of 1,3-dicyclohexylcarbodiimide-mediated cyclodesulfurative methodology would provide a milder and more efficient alternative approach for the preparation of isoguanosine. Thus, the mixture that was obtained by a reaction of **1** with benzoyl isothiocyanate (**2g**) in DMF at room temperature was treated with DCC. The oily residue **3g** obtained by evaporating the mixture was then extracted with chloroform and water to remove DCC and dicyclohexylthiourea. The aqueous layer was then evaporated to dryness, and the residue was redissolved in methanol, which was subsequently treated with ammonia to give **4** in 78% overall yield from AICA-riboside.

Scheme II



6b **10** **11** **12**

Synthetic Application to the Synthesis of Xanthosine Derivatives. Since we had 1-allylisoguanosine (**6b**) in hand, we attempted to effect a Claisen rearrangement between the 1-allyl group and the 6-amino group of **6b** to give **11**. However, when **6b** was treated with a 0.2 N sodium hydroxide solution, we isolated 1-allylxanthosine (**12**) in 68% yield (Scheme II). The structure of this product was determined on the basis of elemental analysis, IR, and ^{1}H and ^{13}C NMR spectral data. The infrared spectra showed two absorption peaks at 1720 and 1661 cm^{-1} for the two carbonyl groups. Furthermore, the ^{1}H NMR spectrum revealed a peak for the 6-amino group proton of **6b** at δ 8.11 had disappeared and a new broad peak (singlet) had appeared at δ 12.04. This latter peak would correspond to the N_3H in a pyrimidinone ring of **12**. Hydrolysis of **6b** under basic conditions can most likely be attributed to the existence of a tautomeric form of **6b** (the imino tautomer **10**), which was readily hydrolyzed by aqueous base. We found that isoguanosine, per se, did not react under these conditions.

Synthetic Application to the Synthesis of Tricyclic Nucleoside. It has been reported that a direct cyclocondensation of *o*-aminobenzamide with alkyl or aryl isothiocyanates gave the corresponding 3-substituted quinazolinones.[22] Interestingly, by replacing the *o*-aminobenzamide with **1**, no 1-substituted 2-thioxoxanthosines **15** were observed when AICA-riboside was treated with various alkyl or aryl isothiocyanates in DMF at 80 °C (Scheme III). The fact that no bicyclic product was isolated from an imidazole ring system containing *o*-aminocarboxamide is probably due to the lone pair electrons of the nitrogen atom on the 5-amino group being delocalized into the imidazole ring system and being conjugated with the carbonyl group of the 4-carboxamide moiety. This enamine-type conjugation would reduce the electrophilicity of the sp^2 carbon of the carboxamide group. The ^{1}H NMR spectrum of **1** showed that two broad singlets at δ 6.65 and 6.79, which are corresponding to two protons of 5-amino, lend some support to the fact that the lone pair of electrons on the 5-exocyclic nitrogen is being conjugated into the ring

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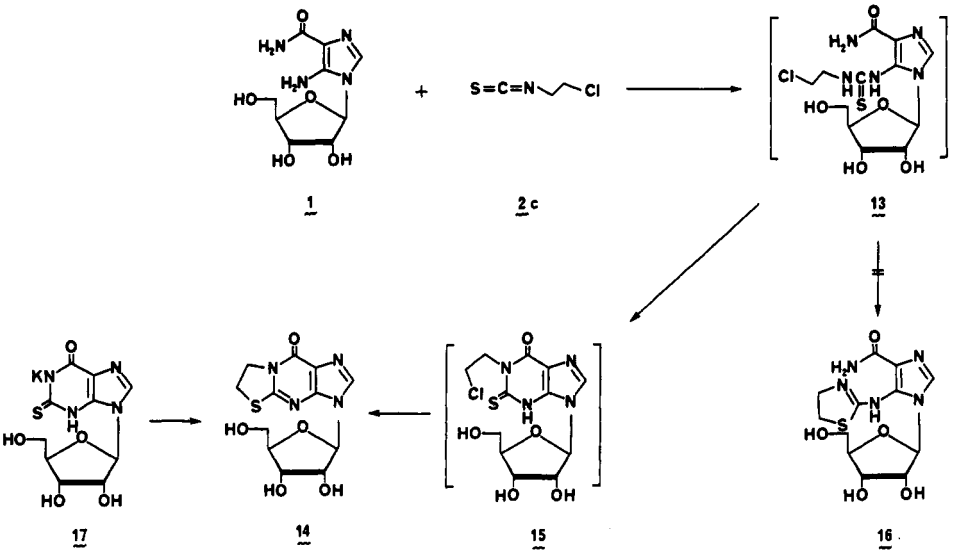
Scheme III



system.[22] The results obtained from the previous reactions prompted us to examine the behavior of 2-chloroethyl isothiocyanate toward a condensation with 1. Chloroalkyl isothiocyanates have been previously employed for the synthesis of some condensed tricyclic heterocycles.[23] On the basis of the poor electrophilic character of the carbon atom of 4-carboxamide moiety of AICA-riboside, we assumed that 5-[[2-(4,5-dihydrothiazolyl)]amino]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (16) could be obtained by simply reacting AICA-riboside (1) with 2-chloroethyl isothiocyanate. This should occur as the result of an intramolecular reaction of the initially formed product, 5-[3-(2′-chloroethyl)thioureido]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (13). However, when 1 and 2-chloroethyl isothiocyanate were heated in pyridine at 50 °C for 72 h, the product we isolated was found to be 3-(β-D-ribofuranosyl)-6,7-dihydrothiazolo[3,2-*a*]purin-9-one (14) instead of the expected 15 or 16 on the basis of elemental analysis, ^{1}H NMR, and ^{13}C NMR spectral data. A literature survey revealed that compound 14 has been prepared by the reaction of an aqueous solution of 2-mercaptoinosine potassium salt with an excess of dibromoethane in the presence of alkali at room temperature.[24] The mechanism of this reaction is probably through an initial intramolecular nucleophilic attack of the nitrogen atom of the (2-chloroethyl)thioureido side chain to the sp^2 carbon atom of the 4-carboxamide, followed by an elimination of ammonia to form of 16. Subsequently, a base catalyzed the intramolecular cyclization of 16 to 14.

Conclusion

Cyclodesulfurative annulation of *o*-thioureidoimidazolecarboxamide derivatives mediated by DCC can be used to construct various analogues of isoguanosine under experimentally convenient and exceptionally mild conditions. The resultant 1-substituted isoguanosines are good precursors for the synthesis of 1-substituted xanthosine derivatives. The detailed biological results will be published elsewhere.

Experimental Section

General Methods. Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a JEOL FX-100 spectrometer from National Taiwan Normal University or on a Bruker Model AM 300 spectrometer from National Taiwan University, Taipei, and are reported in parts per million with DMSO-d_6 as internal standard on a δ scale. Elemental analysis was carried out either on a Heraeus Elemental Analyzer in Cheng-Kong University, Tainan, or on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University, Taipei.

5-[1-(3-Methylthioureido)]-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (3a). A mixture of AICA-riboside (1; 3.1 g, 12 mmol) and methyl isothiocyanate (2a; 8.8 mL, 0.12 mol) in dimethylformamide (40 mL) was heated at 60 °C under nitrogen for 36 h. The solvent was then removed in vacuo, and the residue was applied to a column (silica gel, 70–230 mesh, 3.5 × 30 cm; solvent system, chloroform/methanol (gradient from 99/1 to 85/15)). The desired fraction (R_f = 0.09, solvent system, chloroform/methanol/water = 8/2/0.2) was collected and evaporated to afford the solid. The solid was recrystallized from methanol to afford 2.98 g (75%) of **3a**: mp 185 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.92 (d, 3 H, CH_3), 3.55 (br s, 2 H, 5′-CH_2), 3.80 (br s, 1 H, 4′-CH), 4.15 (m, 2 H, 2′-CH + 3′-CH), 4.95 (m, 2 H, 3′-OH + 5′-OH), 5.30 (br s, 1 H, 2′-OH), 5.50 (br s, 1 H, 1′-CH), 7.05 (br s, 1 H, NH_a), 7.15 (br s, 1 H, NH_b), 7.96 (s, 2 H, 8-CH + NH), 8.95 (br s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.57, 60.57, 69.47, 75.28, 84.26, 88.23, 128.59, 128.69, 132.77, 163.77, 183.57. Anal. Calcd for $C_{11}H_{17}N_5O_5S \cdot {}^1/_4H_2O$ (335.79): C, 39.35; H, 5.25; N, 20.86. Found: C, 39.46; H, 5.28; N, 20.74.

5-[1-(3-Benzylthioureido)]-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (3d) and 5-[1-[3-(Benzylthiocarbamoyl)-3-benzylthioureido]]-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (9). A mixture of AICA-riboside (1, 3.0 g, 12 mmol) and benzyl isothiocyanate (2d; 17 mL, 0.12 mol) in pyridine was heated in an oil bath at 45–55 °C under nitrogen for 48 h. The solvent was then removed in vacuo, and the residue was purified by column chromatography (silica gel, 70–230 mesh, 3.5 × 30 cm; solvent, chloroform/methanol (gradient from 99/1 to 85/15)). The first UV absorbing fraction was collected, and the solvent was removed in vacuo to give 0.47 g (7%) of **9**. An analytical sample was obtained by recrystallization from methanol: mp 203 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.11 (s, 2 H, 5′-CH_2), 4.31 (m, 1 H, 4′-CH), 4.48 (m, 1 H, 3′-CH), 4.65 (m, 4 H, 2-CH_2), 4.75 (m, 1 H, 2′-CH), 5.39 (br s, 3 H, 2′ + 3′ + 5′-OH), 5.53 (br s, 1 H, 1′-CH), 7.13–7.31 (m, 12 H, 2 C_6H_5 + NH_2), 7.78

(23) ^{1}H NMR (300 MHz, DMSO-d_6) of AICA-riboside that was purchased from Sigma Co.): δ 3.58 (br s, 2 H, 5′-CH_2), 3.88 (d, 1 H, J = 2.6 Hz, C-4′H), 4.03 (q, 1 H, C-3′H), 4.27 (q, 1 H, C-2′H), 5.15 (d, 1 H, J = 4.5 Hz, C-3′OH), 5.23 (t, 1 H, C-5′OH), 5.36 (d, 1 H, J = 6.6 Hz, C-2′OH), 5.45 (d, 1 H, J = 6.3 Hz, C-1′H), 5.92 (s, 2 H, carboxamide NH_2), 6.65 (br s, 1 H, 5-NH_a), 6.79 (br s, 1 H, 5-NH_b), 7.30 (s, 1 H, =CH).

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(s, 1 H, 8-CH), 9.11 (s, 1 H, NH), 9.85 (t, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 47.75, 47.95, 69.59, 70.13, 74.49, 81.00, 88.05, 127.06, 127.18, 127.37, 127.56, 128.18, 128.31, 132.76, 137.78, 138.54, 163.60, 183.67, 189.95. Anal. Calcd for $C_{25}H_{28}N_6O_5S_2 \cdot {}^1/_2H_2O$ (565.664): C, 53.08; H, 5.17; N, 14.86. Found: C, 53.34; H, 5.05; N, 14.91. The last UV absorbing fraction was collected and furnished 2.0 g (41%) of **3d**. An analytical sample was obtained by recrystallization from methanol: mp 193–195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.52–3.64 (m, 2 H, CH_2), 3.86 (s, 1 H, 4′-CH), 4.09 (m, 1 H, 3′-CH), 4.18 (s, 1 H, 2′-CH), 4.63–4.79 (m, 2 H, CH_2), 5.02 (t, 1 H, 5′-OH, J = 4.84 Hz), 5.12 (d, 1 H, 3′-OH, J = 5.28 Hz), 5.30 (d, 1 H, 2′-OH, J = 4.61 Hz), 5.54 (s, 1 H, 1′-CH), 7.09–7.33 (m, 7 H, C_6H_5 + NH_2), 7.97 (s, 1 H, 8-CH), 8.43 (br s, 1 H, NH), 9.08 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 47.75, 60.47, 69.39, 75.24, 84.21, 88.29, 126.77, 127.20, 128.20, 128.69, 132.63, 139.58, 163.73, 183.63. Anal. Calcd for $C_{17}H_{21}N_5O_5S$ (407.445): C, 50.11; H, 5.20; N, 17.19. Found: C, 49.81; H, 5.25; N, 17.14.

5-[1-(3-Cyclohexylthioureido)]-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (3e). A mixture of AICA-riboside (1; 2.5 g, 9.7 mmol) and cyclohexyl isothiocyanate (**2e**; 14 g, 97 mmol) in pyridine (40 mL) was heated in an oil bath under nitrogen. After 3 days, the reaction had not progressed to completion. Thus, more cyclohexyl isothiocyanate (14 g, 97 mmol) was added and the mixture was heated for an additional 3 days. The solvent was then removed, and the residue was purified by low-pressure column chromatography (silica gel, 4 × 12 cm, 230–400 mesh; solvent, chloroform/methanol (gradient from 99/1 to 85/15)). The desired fraction (R_f = 0.27, solvent system, chloroform/methanol/water = 8/2/0.2) was collected and evaporated in vacuo. The solid that was obtained by the addition of acetone was recrystallized from methanol to afford 2.25 g (58%) of **3e**: mp 165–167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22–2.07 (m, 11 H, C_6H_{11}), 3.54–3.63 (m, 2 H, 5′-CH_2), 3.82 (s, 1 H, 4′-CH), 4.04–4.12 (m, 2 H, 2′-CH + 3′-CH), 5.01 (br s, 1 H, 5′-OH), 5.10 (d, 1 H, 3′-OH, J = 5.07 Hz), 5.26 (d, 1 H, 2′-OH, J = 4.72 Hz), 5.52 (s, 1 H, 1′-CH), 7.04 (s, 1 H, NH_a), 7.22 (s, 1 H, NH_b), 7.92 (s, 1 H, 8-CH), 7.96 (br s, 1 H, NH), 8.72 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.44, 25.13, 31.79, 52.97, 60.52, 69.41, 75.30, 84.16, 88.36, 128.14, 129.29, 132.45, 163.87, 181.98. Anal. Calcd for $C_{16}H_{25}N_5O_5S \cdot {}^1/_2H_2O$ (408.414): C, 47.05; H, 6.41; N, 17.15. Found: C, 47.29; H, 6.27; N, 17.28.

Isoguanosine (4). To a suspension of AICA-riboside (1; 6.0 g, 23.24 mmol) in dry DMF (60 mL) was added benzoyl isothiocyanate (**2g**; 3.7 mL, 27.54 mmol). After the mixture was stirred at room temperature for 6 h, DCC (9.6 g, 46.53 mmol) was added with stirring. The mixture was allowed to stir at room temperature for 24 h and then concentrated in vacuo to afford an oily residue. The residue was subsequently partitioned into a mixture of chloroform and water (150 mL/150 mL). The aqueous layer was extracted with chloroform (3 × 50 mL) and then concentrated in vacuo. The residue was redissolved in methanol (50 mL). Ammonia water (50 mL) was added to this solution, and the solution was stirred at room temperature for 20 h. After the reaction was complete, the suspension was evaporated in vacuo to afford an solid. To this residue was added acetonitrile (100 mL) to obtain 5.13 g of **4** in 78% yield.

1-Methylisoguanosine (Doridosine, 6a) and 6-(*N*,*N*′-Dicyclohexylguanidinyl)-1-methyl-9-(β-D-ribofuranosyl)-purin-2(1*H*)-one (7). A solution of AICA-riboside (1; 10 g, 38.7 mmol) and methyl isothiocyanate (**2a**; 28.27 mL, 0.39 mol) in DMF (100 mL) was heated at 60 °C in an oil bath under nitrogen for 36 h. The solvent was then evaporated in vacuo to afford an oily residue. To the residue was added anhydrous ethanol (100 mL) and DCC (11.98 g, 58 mmol) and the solution was heated to reflux. A solid started to separate from solution after 3 h. After 12 h, the mixture was cooled to room temperature and the solid was collected by filtration and washed with ether to furnish 8.07 g (64%) of **6a**. The filtrate was purified by column chromatography (R_f = 0.61 ($CHCl_3$/MeOH/H_2O = 8/2/0.2), silica gel, 230–400 mesh, 4.0 × 12 cm; solvent system, chloroform/methanol (gradient from 99/1 to 90/10)) to afford 2.17 g (11%) of **7**. An analytical sample was recrystallized from methanol: mp 140 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 1.02–1.80 (m, 22 H, 2 C_6H_{11}), 3.42 (s, 3 H, CH_3), 3.52 (br s, 2 H, 5′-CH_2), 3.78 (br s, 1 H, 4′-CH), 4.05 (br m, 2 H, 2′ + 3′-CH), 4.95 (m, 1 H, 5′-OH), 5.16 (d, 1 H, 3′-OH, J = 4.0 Hz), 5.39 (d, 1 H, 2′-OH, J = 4.5 Hz), 5.68 (d, 1 H, 1′-CH, J = 6.2 Hz), 6.42 (br s, 1 H, NH), 7.63 (s, 1 H, 8-CH), 7.74 (br m, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 24.78, 25.31, 32.81, 49.80, 60.99, 69.84, 74.24, 84.37, 86.72, 96.46, 118.86, 132.49, 150.02, 152.60, 152.93, 154.87. Anal. Calcd for $C_{24}H_{37}N_7O_5 \cdot {}^1/_4H_2O$: C, 56.73; H, 7.44; N, 19.29. Found: C, 56.91; H, 7.49; N, 19.63.

1-Allylisoguanosine (6b). A mixture of AICA-riboside (1, 5.0 g, 19 mmol) and allyl isothiocyanate (**2b**; 19 g, 190 mmol) in DMF (50 mL) was heated in an oil bath at 45–55 °C under nitrogen for 44 h. After the mixture was cooled to room temperature, DCC (6.0 g, 28 mmol) was added to the mixture. The mixture was stirred at room temperature for 30 h. After the solvent was removed in vacuo, the residue was purified by column chromatography (silica gel, 3.5 × 30 cm, 70–230 mesh; solvent, chloroform:methanol:water = 8:2:0.2, R_f = 0.30). The desired portion was collected and evaporated in vacuo to give an oily residue. To the residue was added a mixture of methanol and ammonia water (28%; 30 mL, 4:1). The mixture was allowed to stir at room temperature for 2 days, and the solid was collected by filtration and recrystallized from methanol to furnish 3.8 g (62%) of **6b**: mp 210 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.46–3.64 (m, 2 H, 5′-CH_2), 3.91 (s, 1 H, 4′-CH), 4.07 (s, 1 H, 3′-CH), 4.52–4.59 (m, 3 H, 2′-CH + CH_2), 4.99–5.10 (m, 3 H, 3′-OH + CH_2), 5.35 (d, 1 H, 2′-OH, J = 6.28 Hz), 5.66 (d, 1 H, 1′-CH, J = 6.64 Hz), 5.69 (m, 1 H, 5′-OH), 5.76–5.87 (m, 1 H, CH), 7.91 (s, 1 H, 8-CH), 8.11 (br s, 2 H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.88, 61.86, 70.82, 72.81, 86.07, 87.62, 108.86, 115.74, 132.08, 138.14, 150.97, 152.46, 153.30. Anal. Calcd for $C_{13}H_{17}N_5O_5$ (323.309): C, 48.29; H, 5.30; N, 21.66. Found: C, 48.00; H, 5.37; N, 21.38.

1-Benzylisoguanosine (6d). A solution of **3d** (0.5 g, 1.2 mmol) and DCC (0.38 g, 1.4 mmol) in DMF (10 mL) was stirred at room temperature for 24 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (silica gel, 70–230 mesh, 2.5 × 10 cm; solvent, chloroform/methanol (gradient from 99/1 to 85/15)). The desired portion (R_f = 0.29, solvent system, chloroform:methanol:water = 8:2:0.2) was collected and evaporated in vacuo to afford an oily residue. To the oily residue was added a mixture of methanol and ammonia (28%; 30 mL, 3:1). The mixture was stirred at room temperature for 24 h, and the solid was collected by filtration and recrystallized from methanol to furnish 0.28 g (60%) of **6d**: mp 223 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.47–3.65 (m, 2 H, 5′-CH_2), 3.93 (s, 1 H, 4′-CH), 4.08 (s, 1 H, 3′-CH), 4.57 (m, 1 H, 2′-CH), 5.11 (d, 1 H, 3′-OH, J = 4.22 Hz), 5.22 (s, 2 H, CH_2), 5.38 (d, 1 H, 2′-OH, J = 6.22 Hz), 5.63–5.67 (m, 2 H, 1′-CH + 5′-OH), 7.16–7.33 (m, 5 H, ArH), 7.95 (s, 1 H, 8-CH), 8.20 (br s, 2 H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.90, 61.85, 70.80, 72.87, 86.07, 87.60, 108.94, 126.56, 126.96, 128.29, 136.48, 138.30, 151.32, 152.65, 153.68. Anal. Calcd for $C_{17}H_{19}N_5O_5 \cdot {}^1/_2H_2O$ (382.376): C, 53.39; H, 5.27; N, 18.31. Found: C, 53.54; H, 5.41; N, 18.18.

1-Cyclohexylisoguanosine (6e). Compound **6e** was obtained in 40% yield using a procedure similar to that which afforded **6d**: mp 229 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18–1.75 (m, 11 H, C_6H_{11}), 3.51–3.63 (m, 2 H, 5′-CH_2), 3.91 (s, 1 H, 4′-CH), 4.06 (s, 1 H, 3′-CH), 4.52–4.58 (m, 1 H, 2′-CH), 5.10 (d, 1 H, 3′-OH, J = 4.14 Hz), 5.36 (d, 1 H, 2′-OH, J = 6.45 Hz), 5.58 (d, 1 H, 1′-CH, J = 6.49 Hz), 5.82 (s, 1 H, 5′-OH), 7.86 (s, 1 H, 8-CH), 8.09 (br s, 2 H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.75, 25.53, 27.82, 55.44, 61.97, 70.93, 72.72, 86.24, 87.79, 109.46, 138.13, 151.53, 151.99, 153.69. Anal. Calcd for $C_{16}H_{23}N_5O_5$ (365.39): C, 52.59; H, 6.34; N, 19.17. Found; C, 52.36; H, 6.30; N, 19.08.

1-Cyclopropylisoguanosine (6f). Compound **6f** was obtained in 25% yield using a procedure similar to that which afforded **6b**: mp 227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.67 (s, 2 H, CH_2), 1.16–1.22 (m, 2 H, CH_2), 2.56–2.59 (m, 1 H, CH), 3.42–3.63 (m, 2 H, 5′-CH_2), 3.91 (s, 1 H, 4′-CH), 4.06 (s, 1 H, 3′-CH), 4.51–4.57 (m, 1 H, 2′-CH), 5.11 (d, 1 H, 3′-OH, J = 3.94 Hz), 5.36 (d, 1 H, 2′-OH, J = 6.16 Hz), 5.59 (d, 1 H, 1′-CH, J = 6.53 Hz), 5.79 (m, 1 H, 5′-OH), 7.87 (s, 1 H, 8-CH), 8.56 (br s, 2 H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.31, 25.52, 51.90, 70.85, 72.74, 86.11, 87.71, 108.84, 138.03, 152.63, 152.97, 154.21. Anal. Calcd for $C_{13}H_{17}N_5O_5$ (323.309): C, 48.30; H, 5.30; N, 21.66. Found: C, 48.16; H, 5.35; N, 21.64.

1-Isopropylisoguanosine (6h). To a solution of AICA-riboside (1; 2.0 g, 7.75 mmol) in pyridine (70 mL) was added isopropyl isothiocyanate (**2h**; 7.37 g, 70 mmol). The mixture was heated

in an oil bath at 60 °C for 14 days. The solvent was then changed to DMF, and DCC (1.6 g, 7.75 mmol) was added to the solution. The mixture was allowed to stir at room temperature for 24 h. The mixture was applied to column chromatography (silica gel, 3.5 × 25 cm, 70–230 mesh; solvent, chloroform/methanol (gradient from 95/5 to 80/20)). The desired portion (R_f = 0.31, solvent system, chloroform:methanol:water = 8:2:0.2) was collected and treated with methanolic ammonia (10 mL) for 2 days. The solvent was then removed in vacuo and the oily residue was added to a mixture of methanol and ether to obtain 0.1 g (4%) of **6h**: mp 215 °C dec.; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (d, 6 H, $2CH_3$), 3.44–3.53 (m, 2 H, 5′-CH_2), 3.91 (d, 1 H, 4′-CH), 4.08 (t, 1 H, 3′-CH), 4.54–4.59 (m, 2 H, 2′-CH + CH), 5.09 (d, 1 H, 3′-OH), 5.34 (d, 1 H, 2′-OH), 5.59 (d, 1 H, 1′-CH), 5.82 (m, 1 H, 5′-OH), 7.86 (s, 1 H, 8-CH), 8.04 (s, 2 H, NH_2). Anal. Calcd for $C_{13}H_{19}N_5O_5$ (325.325): C, 47.99; H, 5.89; N, 21.53. Found: C, 47.76; H, 5.88; N, 21.30.

1-Allylxanthosine (12). Compound **6b** was dissolved in 0.2 N sodium hydroxide solution (30 mL). The solution was heated at 80 °C in an oil bath for 40 h. The pH of the mixture was adjusted to pH 5 with acetic acid, and the mixture was allowed to stand at room temperature. The crude product was collected by filtration and purified from a mixture of DMF and water to give 0.34 g (68%) of **12**: mp 250 °C dec; IR (KBr) 3516, 3126, 2864, 1712 (C=O), 1661 (C=O), 1617, 1573, 1450, 1312, 1123, 1082, 904, 869 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.64 (s, 2 H, 5′-CH_2), 3.99 (s, 1 H, 4′-CH), 4.05 (s, 1 H, 3′-CH), 4.23 (m, 1 H, 2′-CH), 4.42 (d, 2 H, CH_2, J = 4.86 Hz), 5.00–5.07 (m, 2 H, 5′-OH + CH), 5.28 (d, 1 H, 3′-OH, J = 3.81 Hz), 5.48 (d, 1 H, 2′-OH, J = 6.12 Hz), 5.77 (d, 1 H, 1′-CH, J = 6.87 Hz), 5.79–5.87 (m, 1 H, CH), 6.05 (br s, 1 H, NH), 7.90 (s, 1 H, 8-CH), 12.04 (br s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.82, 61.25, 70.82, 74.05, 86.11, 88.69, 115.67, 115.97, 133.13, 135.71, 137.96, 149.94, 156.94. Anal. Calcd for $C_{13}H_{16}N_4O_6 \cdot {}^1/_2\ H_2O$ (333.301): C, 46.85; H, 5.14; N, 16.81. Found: C, 47.06; H, 5.05; N, 17.06.

3-(β-D-Ribofuranosyl)-6,7-dihydrothiazolo[3,2-*a*]purin-9-one (14). A mixture of AICA-riboside (**1**; 1.0 g, 3.87 mmol) and 2-chloroethyl isothiocyanate (**2c**; 4.7 g, 38.7 mmol) in pyridine (40 mL) was heated at 50 °C for 3 days. The solvent was evaporated in vacuo, and the residue was purified by column chromatography (silica gel, 60 g; solvent system, chloroform/methanol/water = 8/2/0.2; column diameter, 2.0 cm). The right fraction (R_f = 0.33, solvent system, chloroform:methanol:water = 8:2:0.2) was collected and recrystallized from water to give 0.28 g (22%) of **14**: mp 221–225 °C (lit.[24] mp 220–221 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.51–3.62 (m, 4 H, 5′-CH_2 + CH_2), 3.91 (d, 1 H, 4′-CH), 4.09 (d, 1 H, 3′-CH), 4.41 (m, 3 H, 2′-CH + CH_2), 5.03 (br s, 1 H, 3′-OH), 5.20 (br s, 1 H, 2′-OH), 5.46 (br s, 1 H, 5′-OH), 5.76 (d, 1 H, 1′-CH), 8.22 (s, 1 H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.37, 48.66, 61.25, 70.28, 74.03, 85.62, 87.17, 120.83, 138.24, 148.70, 155.27, 161.28. Anal. Calcd for $C_{12}H_{14}N_4O_5S \cdot {}^1/_4H_2O$ (330.83): C, 43.56; H, 4.42; N, 16.93. Found: C, 43.26; H, 4.38; N, 16.80.

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Heterocyclic Aromatic Anions with 4*n* + 2 π-Electrons

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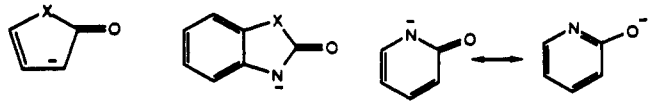
Equilibrium acidities in DMSO for several cyclic carboxamides, thiocarboxamides, esters, and sulfones that form anions possessing 4*n* + 2 electrons have been measured. Aromatic stabilization energies (ASEs) for these anions have been estimated by comparing their pK_{HA} values with those of open-chain analogues. The ASEs (kcal/mol) are 8.3 for *N*-methylindolin-2-one, 15.5 for *N*-methylindoline-2-thione, 7.1 for 2-oxo-2,3-dihydrobenzo[*b*]furan, 8.5 for 2-oxo-2,3-dihydrobenzo[*b*]thiophene, 11.4 for 3-phenyl-2*H*-thiopyran 1,1-dioxide, and 23 for cyclopentadiene. These values need to be corrected, however, for the effects of cyclization on pK_{HA} values, which are about 3 kcal/mol for carboxamides and 5 kcal/mol for esters.

Five- and six-membered ring heterocycles with 4*n* + 2 π-electrons, such as furan, thiophene, pyrrole, and pyridine, are known to display aromatic properties and to have aromatic stabilization (resonance) energies estimated to range from about 15 to 32 kcal/mol.[1] Cyclic carbanions bearing a 4*n* + 2 π-electron system, such as those formed on deprotonating 1,3-cyclopentadiene or indene, are also believed to possess aromatic stabilization energies (ASEs), and this concept has been extended to comparable heterocyclic anions of the type **1**–**3**. Two criteria have been



1 **2** **3a** **3b**

used to detect aromaticity in anionic systems: (1) the existence of aromatic ring currents and (2) the demonstration of exceptional stability. The former, frequently probed using ^{1}H NMR spectroscopy, has been branded as unreliable because of the complexity of the factors affecting chemical shifts (diamagnetic ring current, charge distribution, anisotropy, and geometry of the heteroatom).[2] Alternatively, acidity measurements have been used to detect exceptional stability in cyclic anions with 4*n* + 2 π-electrons formed by deprotonation. Comparison with a suitable model (ΔpK_{HA}) may then afford an estimate of the ASE for the ion. In practice, the acidity method has been difficult to apply since thermodynamic techniques capable of determining the pK_{HA} values of weak carbon acids have not been available until recently. Consequently, kinetic methods, which may not reflect true thermodynamic acidities, have been employed. For example, since 1,3-dithia-4,6-cycloheptadiene (**4a**) was found to undergo H/D exchange in *t*-BuOD/*t*-BuOK at 83 °C at least 150 times faster than the saturated analogue (**4b**), a minimum

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