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C-Nucleosidations with 2,6-Diamino-5,8-diaza-7,9-dicarba-purine[1]

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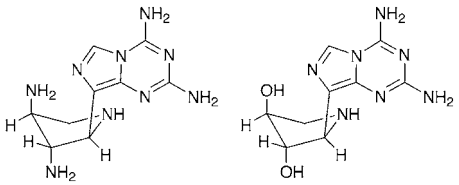
ABSTRACT

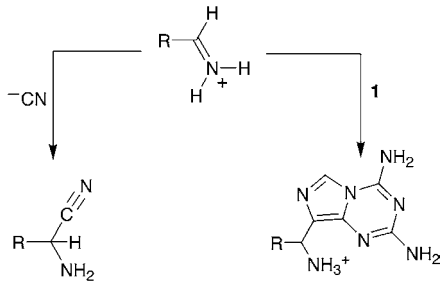


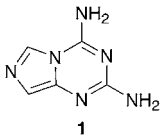
Endocyclic iminium ions derived from L-4-amino-threose derivatives smoothly react with 2,6-diamino-5,8-diaza-7,9-dicarba-purine to give corresponding C(9)-*nucleosides* in high yields.

The search for the chemistry of life's origin[2] constitutes a major and abiding challenge to chemical biology. Core-organic chemistry is also being challenged in this search by being expected to point to and explore the potentials of any type of organic molecule or chemical reactivity that conceivably could have played a role in the self-organization of matter. Experimental explorations driven by this motif can (if judiciously chosen) lead to observations that, besides their possible etiological relevance, may be of interest to chemistry in its own right.

The starting point of the study we are reporting here was the expectation that a process in which iminium ions derived from aldehydes were to react with nucleobases to form C-nucleosides capable of acting as building blocks in informational oligomers would be of interest in the context alluded to. Such a (Mannich-type) reaction of iminium ions would be chemically analogous and etiologically complementary to the addition of cyanide ion to give α-aminonitriles, an important source of α-amino acids (Strecker reaction).[3] Whereas natural purines are devoid of the capacity of reacting as nucleobase partners in C-nucleosidations, potential nucleobases of the type exemplified by the purinoid **1** described in the preceding communication[4] may be capable of fulfilling such a role (Scheme 1). Here we describe that such C-nucleosidations occur smoothly under mild conditions

Scheme 1. Formal Analogy between Strecker Reaction and C-Nucleosidation with Nucleobase Isomer **1**





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(1) *Chemistry of* α-Aminonitriles. Part 40. Part 39: ref 4.
(2) Miller, S. L.; Orgel, L. E. *The Origins of Life on Earth*; Prentice Hall Inc.: Englewood Cliffs, New Jersey, 1974.

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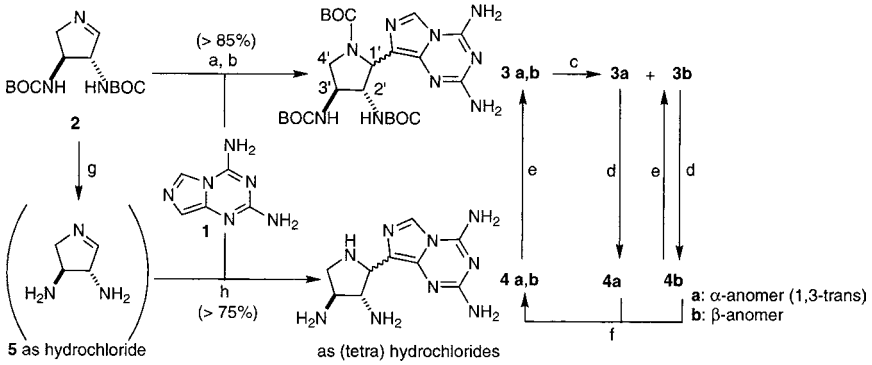
Scheme 2. C-Nucleosidation of 3,4-Diamino-pyrroline **2** and **5** Directly Followed by (NH)-Bocylation[a]



[a] (a) 0.10 M (1.0 mole equiv) **1**, 0.11 (1.1) of **2**, 0.10 (1.0) $TsOH \cdot H_2O$, DMSO, rt, 1 h; (b) 0.15 (2.0) Boc_2O, 0.15 (2.0) TEA, CH_2Cl_2, rt, 30 min, >85% **3a**,**b**; (c) separation of **3a** and **3b** by preparative HPLC**,** VERTEX COLUMN, Spherisorb SW, JL280, eluted with AcOEt/*i*-PrOH 20/1, 58% **3a** and 26% **3b**; (d) **3a** or **3b** suspended in saturated HCl in Et_2O, rt, 15 min, >95%; (e) **4a**,**b**, 3.0 (10.0) TEA, 1.2 (4.0) Boc_2O, DMSO; rt, 1 h, 95% **3a**,**b**; (f) 0.10 M **4a** or **4b**, in D_2O, pH 1.9, **4a**:**4b** in **4a**,**b** = 3:1; (g) (3.0) **2** suspended in Et_2O saturated with HCl, rt, 30 min; (h) 0.30 M (3.0) **5** (crude), 0.10 (1.0) **1**, in DMSO, rt, 4 h, followed by procedures (e) and (c), 48% **3a** and 26% **3b**.

and that they can lead to stable (C-9)-nucleosides in cases where the reaction partner is a cyclic iminium ion derived from L-threose derivatives.[5]

The pyrrolines **2** and **7** used as substrates in this study were prepared without giving any consideration to criteria such as the "naturalness" of a pathway of formation; they were made according to published chemical procedures by N-chlorination of the corresponding 2,3-*trans*-disubsituted pyrrolidines[6−8] with *N*-chlorosuccinimide,[7,8] followed by dehydrochlorination with DBU. Whereas pyrroline **2** could be isolated as the monomer and was characterized and stored as such,[9] the pyrroline **7** was handled and characterized as its (known[8]) trimer **6**.[10]

Pyrroline **2** in 0.1 M DMSO solution reacts with 0.9 mole equiv of purinoid **1** in the presence of 1 equiv of a Bronsted acid at room temperature within less than 1 h (conditions a) to afford a binary mixture of diastereomeric C-nucleosides, which after in situ protection of the imino group with BOC-anhydride (conditions b), was isolated in high yield as the corresponding mixtures of epimeric tri-BOC-derivatives **3a**,**b**. Chromatographic separation (conditions c) led to the pure epimers **3a** and **3b** as light-yellow solids in 58% and 26% yield, respectively (Scheme 2). The constitutional and configurational assignments of **3a** as the α-anomer (nucleobase cis to 3′NHBOC) and of **3b** as the *β*-anomer rest on their ^1H and ^{13}C NMR, UV, and mass spectroscopic data.[11] Both nucleosides could be deprotected without discernible epimerization by stirring their suspensions in dry ether saturated with HCl at room temperature within minutes to give the free nucleosides **4a** and **4b** as solid hydrochloride salts. A sample of the epimer **4a** was shown by titration and elemental analysis to contain 3.7 mole equiv of HCl (pK_a = 4.7 and 7.8). ^1H NMR spectroscopy of (acidic) solutions of pure **4a** and pure **4b** in D_2O, (pH ≈ 1.9, conditions f; *δ* H-(C1′) for α-epimer **4a** = 5.46 ppm (d, J = 7.5 Hz), for *β*-epimer **4b** = 5.61 ppm (*d*, J = 8.1 Hz)) showed configurational equilibration to the mixture of **a**:**b** = 3:1 (room temperature) with a half-life for the less stable epimer **4b** of about 140 min. Under these conditions the equilibrium mixture of the two epimers is constitutionally stable (observed during 5 months). In D_2O solutions at pH 7.7 (room temperature), the epimers still equilibrate, yet more slowly, the less stable epimer taking a week to reach equilibrium (^1H NMR). At pH 11.3 (NaOH) **4a**, the α-isomer, was observed to be configurationally equilibrated after 3 weeks, accompanied by minor amounts of a hydrolysis product (^1H NMR).

The C-nucleosidation reaction proceeds comparably well with the underivatized 3,4-diamino-1-pyrroline **5**[12] used in

(3) Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27; *Liebigs Ann. Chem.* **1854**, *91*, 349. Miller, S. L. *Science* **1953**, *117*, 528.

(4) Wang, Z.; Huynh, H. K.; Han, B.; Krishnamurthy, R.; Eschenmoser, A. *Org. Lett.* **2003**, *5*, 2067.

(5) For reviews on the chemical synthesis of C-nucleosides and C-glucosides see: Hanessian, S.; Peruet, A. G. *Adv. Carbohydrate. Chem. Biochem*. **1976**, *33*, 111. Postema, M. H. D. *Tetrahedron* **1992**, *48*, 9545.

(6) Brouwer, A. J.; van der Linden, H. J.; Liskamp, R. M. J. *J. Org. Chem*. **2000**, *65*, 1750.

(7) Arakawa, Y.; Yoshifuji, S. *Chem. Pharm. Bull*. **1991**, *39*, 2219.

(8) Folkersen, B. M.; Lundt, I.; Foged, C.; Valsborg, J. S. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 1145.

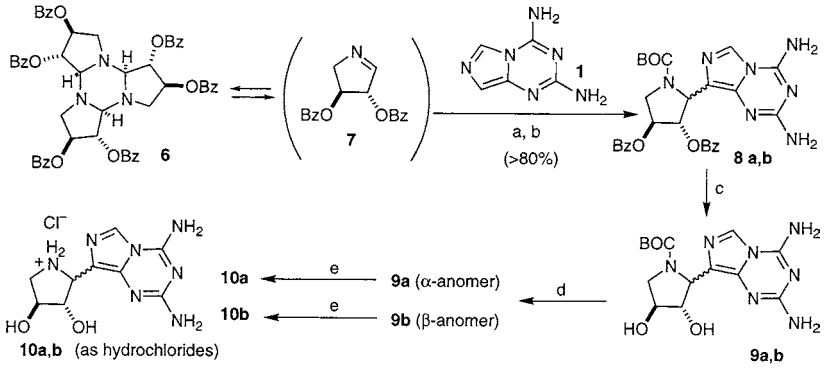
(9) Data of **2** and **6** in Supporting Information.

(10) The constitution and configuration of the trimer **6** is clearly deducible from its mass and the ^1H and ^{13}C NMR spectra; the latter show the single set of signals belonging to the monomer-derived units. This indicates the configuration at the stereogenic carbon centers of the tricycle's inner (six-membered) ring to be all *cis*, the configuration shown in the formula **6** being the (sterically) more favourable of the two possibilities.

(11) Data of **3a** and **3b** in Supporting Information. The ^1H NMR spectra of **3a** and **3b** show several slowly interconverting rotomers about the BOC−N bonds, which lead to strong exchange cross-peaks in the ROESY spectra, thus obscuring some of the expected NOEs. The assignment of **3a** and **3b** to the α- and *β*-epimers, respectively, is based on the medium to strong NOEs from the NH-(C3′) proton to H-(C1′), H-(C2′), and Hα-(C4′) in the ROESY spectrum of **3b** and was later corroborated by a strong 1D-NOE (CD_3OD) between H-(C3′) and H-(C1′) in **4b**, the product from the deprotection of **3b**.

(12) ^1H NMR spectrum of crude **5** (hydrochlorides) showed absence of *tert*-BOC groups; MS (of methanolic solution of **5**): 100.2 (52, $[M + H]^+$), 116.1 (100, $[M - 2H + H_2O + H]^+$), 132.1 (36, $[M + CH_3OH + H]^+$.

Scheme 3. C-Nucleosidation with 3,4-Dihydroxy-pyrrroline **7** Derived from Trimer **6**, Directly Followed by Bocylation[a]



[a] (a) 0.2 M (1.0 mole equiv, corresponding to 3.0 equiv of **7**) of **6**, 0.2 (1.0) TsOH·H_2O, DMSO, rt, 30 min; (b) 0.1 (1.0) Boc_2O, 1.0 (10.0) TEA, MeOH/CH_2Cl_2 1/1, rt, 0.5 h, 80% **8a**,**b**; (c) 0.1 M **8a**,**b** in MeOH saturated with NH_3, rt, 24 h; (d) separation by CC on silica gel, CH_2Cl_2/MeOH 5/1, 50% **9a** and 32% **9b**; (e) **9a** or **9b** suspended in saturated HCl in Et_2O, rt, 1 h, 80% and 92%, respectively.

situ as the hydrochloride salt after deprotection of **2** in ethereal HCl (conditions g). The primary C-nucleosidation product of the reaction **5** + **1** → **4a**,**b** (conditions h) was not characterized as such but directly converted (by the addition of BOC-anhydride and triethylamine to the reaction mixture, conditions e) and isolated as the mixture of epimers **3a**,**b**. Chromatographic separation (conditions c) gave the pure epimers **3a** (48%) and **3b** (26%) identical with the nucleosides isolated from the reactions **2** + **1** → **3a**,**b** → **3a** + **3b** (^{1}H and ^{13}C NMR). In a test experiment starting with a 3:1 equilibrium mixture of authentic **4a**,**b**, the re-bocylation step under conditions e followed by chromatographic separations under conditions c gave the pure tri-BOC-nucleosides **3a** and **3b** in yields of 58% and 17%, respectively. This indicates that the C-nucleosidation step starting from the free 2,3-diaminopyrroline hydrochloride (conditions h) is proceding comparably well as that of **2**. Re-bocylation of the less stable epimer **4b** under conditions e did not lead to any discernible epimerization.

The C-nucleosidation chemistry between 3,4-dibenzoyloxy-1-pyrroline **7** and purinoid **1** (Scheme 3) proceeds similarly as in the diamino series, except that the actual starting material for the nucleosidation step could not be **7** but had to be its trimer **6**, which however forms **7** in situ under the influence of the protons that mediate the nucleosidation reaction.[13] Trimer **6** in 0.2 M DMSO solution reacts with 1.0 mole quiv of **1** in the presence of 1.0 mole quiv of TsOH·H_2O at room temperature within 30 min to the mixture of epimeric C-nucleosides, isolated as a mixture of BOC-derivatives **8a**,**b** in over 80% yield.[14] The reaction has been shown to proceed comparably well when the solvent DMSO contains 10% water. Separation into pure epimers was achieved after base-catalyzed methanolic removal of the benzoyl groups in **8a**,**b** to give **9a**,**b**, directly followed by chromatography on silica gel to give the epimers **9a** (50%) and **9b** (32%) as slightly yellow solids.[15] The deprotected nucleosides **10a** and **10b**, derived from **9a** and **9b** without epimerization by de-bocylation with HCl in dry ether, were isolated as crystalline bishydrochlorides, the ^{1}H NMR analyses of which unambiguously allowed the configurational assignment **10a** and **10b** to the two epimers.[16]

The very mechanistic reasons that make purinoid **1** susceptible to C-nucleosidation with iminium cations are expected to render the corresponding C-nucleosides potentially labile toward epimerization at the anomeric center, as well as, in principle, toward constitutional change. Whereas we have not encountered any constitutional lability of (either protected or deprotected) C-nucleosides derived from the cyclic pyrrolines **2** and **7** under the conditions we employed, such instability was observed, however, in reaction products derived from noncyclic iminium salts. Exploratory experiments with aliphatic iminium ions (e.g., *n*-butanal, ammonia, and ammonium chloride) showed that the C-nucleosidation products are formed quickly even below room temperature (TLC, ^{1}H NMR, and MS),[17] but they were too labile in our hands for purification and isolation by chromatography on silica gel.[18] We see the reason for this marked contrast to the behavior of the corresponding C-nucleosides derived from pyrrolines in the susceptibility of the α-amino group in the C-nucleoside to undergo a conjugatively assisted elimination which, because of its reversibility, does not result in a constitutional change in the case of a pyrroline-derived

(13) The higher propensity of pyrroline **7** as compared to that of **2** to form a trimer corresponds to the (presumably) higher reactivity of its imine double bond (less "polarized" carbonyl systems are *more*, and not *less*, reactive than more "polarized" systems), as well as to the difference in steric bulk of the substituents.

(14) Note that the molar ratio monomer equivalent **7** to **1** is 3:1.

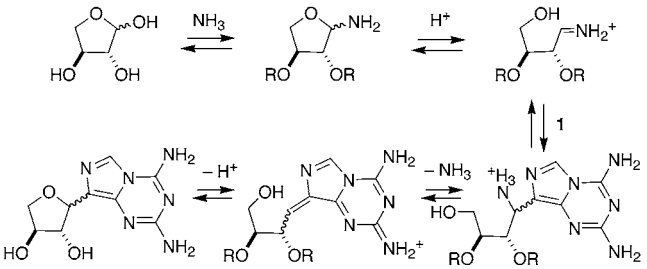
(15) Data of **9a** and **9b** in Supporting Information.

(16) Data of **10a** and **10b** in Supporting Information. The assignment of **10a** and **10b** to the α- and *β*-epimers, respectively, is based on the mutually consistent results of the 1D-NOE experiments with both **10a** and **10b** in acidified CD_3OD and D_2O solution, respectively.

(17) Reaction conditions: (c) (**1**) = 0.17 M; 4 equiv each of aldehyde, NH_4Cl, and NH_3 (2 M MeOH) in DMSO; 4 °C, 0.5 h. No reaction was observed in the absence of NH_4Cl or NH_3 or both, under otherwise identical conditions (TLC).

(18) The (polar) products of "decomposition" have not been identified.

Scheme 4. Presumed Pathway for C-Nucleosidation of Aldosugar with Purinoid **1**



C-nucleoside, but may well do so in acyclic systems (cf. also Scheme 4).

We naturally were interested in whether C-nucleosides of purinoid **1** could also be accessible from aldosugars, such as threose or ribose, under conditions in which, according to Scheme 4, an iminium derivative of the aldehyde group would be transiently formed and, after the nucleosidation step, the product's amino group would be replaced by a ring oxygen via an elimination and (cyclizing) re-addition step to form a normal furanose (C)-nucleoside.

For each threose and ribofuranose derivative we found such nucleosidations to be feasible yet to proceed rather sluggishly and to produce nucleosides in low (isolated) yields only, at least under the conditions explored (Scheme 5). L-α-Di-*O*-benzyl-threose **11**,[19] when kept in DMSO in a closed tube for 5 h at 60 °C[20] in the presence of 1 equiv of **1** and 4 equiv each of NH_4Cl and NH_3, followed by direct chromatographic separation of the reaction mixture on silica gel, gave a nucleoside in 27% yield. Its structure was shown to be the α-nucleoside derivative **12** by X-ray analysis.[21] Surprisingly as well as importantly, the corresponding nucleoside formed under the same conditions from L-threose itself turned out to be labile during purification by silica gel chromatography. On the other hand, nucleosidation of the 2,3-acetonide of D-ribofuranose **13**[22] under similar[23] conditions gave regioselectively the *β*-(C)-nucleoside **14**, which could be purified without complications.[24] Its constitution and configuration follows unambiguously from its ^1H and ^{13}C NMR, UV, and mass spectral data.[25]

(19) Prepared by treatment of L-methyl-threofuranoside in DMF with NaH and benzylbromide, followed by acid hydrolysis (1 M H_2SO_4/HOAc (1:1), 98 °C, 1 h).

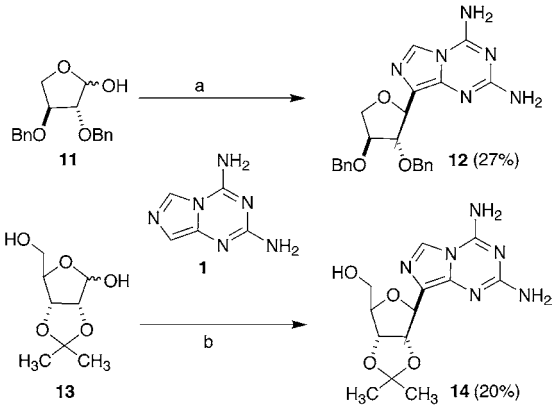
(20) The elevated reaction temperature was found to be required to induce the elimination−cyclization step (see Scheme 5).

(21) See Supporting Information. The analysis was carried out by Raj K. Chadha, TSRI. Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Center as deposition no. CCDC 180980. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 union Road, Cambridge CB12 1EZ UK (fax, + 44 (1233) 336 0333; E-mail, deposit@ccdc.cam.ac.uk).

(22) Maqbool, Z.; Hasan, M.; Pott, K. T.; Malik, A.; Zizami, T. A.; Voelter, W. *Z. Naturforsch.* **1997**, *B 52*, 1383.

(23) Except ratio **13**:**1** = 2:1 and reaction time 65 h.

Scheme 5. C-Nucleosidation of Aldosugar Furanose Derivatives with Purinoid **1**[a]



[a] **(**a) 0.3 M (1.2 mole equiv) **1**, 0.25 (1.0) **11**, 1.0 (4.0) NH_4Cl, 1.0 (4.0) NH_3, DMSO, 60 °C, 5 h, 27%; (b) 0.2 M (1.0 mole equiv) **1**, 0.4 (2.0) **13**, 0.8 (4.0) NH_4Cl, 0.8 (4.0) NH_3, DMSO, 60 °C, 5 h, 20%; Bn = benzyl.

2,6-Diamino-5,8-diaza-7,9-dicarba-purine **1** is just one member of a family of 5,8-diaza-7,9-dicarba-purines the propensity of which to undergo C-nucleosidation with iminium ions and aldosugars is worth investigating. Among these members, C-nucleosidation propensity is expected to correlate inversely with the relative stability of the corresponding C-nucleosides. We intend to report in a forthcoming paper on the behavior of other members of this family of alternative nucleobases, as well as on an extension of theC-nucleosidation chemistry to pyrimidines and still another family of purinoids.

Acknowledgment. This work was supported by the Skaggs Research Foundation (La Jolla) and Novartis A.G. (Basel). Z.W. has been a Skaggs Postdoctoral Fellow. We thank Dr. Touraj Etezady-Esfarjani (Wüthrich group, TSRI) for the ROESY measurements.

Supporting Information Available: Experimental procedure for the synthesis of pyrroline derivatives **2** and **6**; C-nucleosidation reactions of **1**; X-ray structure of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) In the absence of NH_3 and NH_4Cl but otherwise comparable conditions the formation of small amounts of a ca. 1:1 mixture of the two epimeric purinoid nucleoside was observed (TLC, ^1H NMR, MS).

(25) Data of **14** in Supporting Information. Assignment of the *β*-configuration was based on the correlation observed between the signal at δ = 8.01 ppm (NH_2-(C2)) with the signal at δ = 5.16 ppm (HO-(C5′)) by ROESY (in DMSO(D_6)).