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One-step protecting-group-free synthesis of azepinomycin in water

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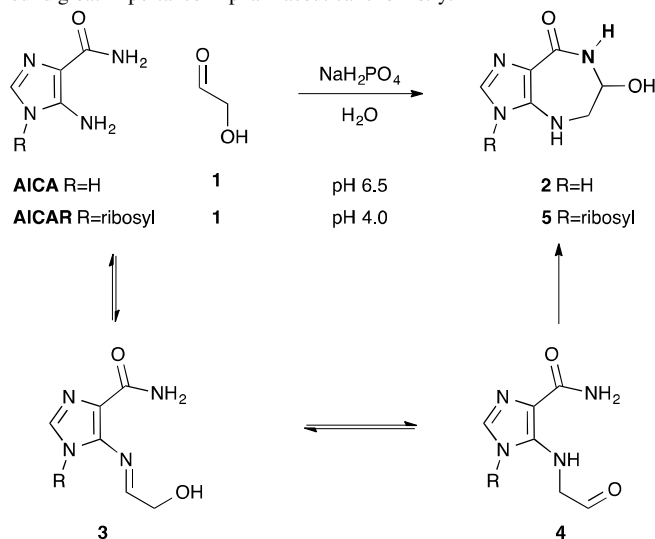
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We report an efficient, atom economical general acid-base catalyzed one-step multi-gram synthesis of azepinomycin from commercially available compounds in water. We propose that the described pH-dependent Amadori rearrangement, which couples an amino-imidazole and simple sugar, is of importance as a potential step toward predisposed purine nucleotide synthesis at the origins of life.

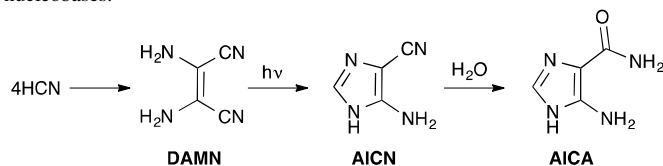
Nucleotides and nucleic acids are compounds of privileged biological importance and, consequently, nucleotide and nucleobase analogues have found great importance in pharmaceutical chemistry.¹



Scheme 1: Protecting-group-free synthesis of azepinomycin **2** (R=H) and azepinomycin riboside **5** (R=β-D-ribofuranosyl) in water. *N*-Acyl-hemiaminal *N*-H shown bold.

Here we demonstrate an amino-imidazole tethering strategy that uses an Amadori rearrangement, which couples glycolaldehyde (**1**) to 5-amino-imidazole-4-carboxamide (**AICA**), and consequently the synthesis of azepinomycin (**2**),² a guanine deaminase inhibitor isolated from the culture filtrate of *Streptomyces sp* (Scheme 1) containing an *N*-acyl hemiaminal synthesized by direct conjugation of an aldehyde and amide in neutral water.^{2,3} We propose that this could have been a key step in the regiospecific coupling of purine precursors to sugars at the onset of biology, before the advent of enzymatically-controlled biosynthesis.

The synthesis of 5-amino-imidazole-4-carbonitrile (**AICN**) and **AICA** from hydrogen cyanide tetramer (**DAMN**) was demonstrated more than 60 years ago by a remarkable photochemical rearrangement (Scheme 2).⁴ Further chemical elaboration of **AICN** and **AICA** to the canonical purine nucleobases has been reported, however poor selectivity and very low yields for purine nucleobases ribosylation with free sugars⁵ has cast doubt upon the plausibility of purine nucleoside synthesis by direct glycosylation of nucleobases.^{6,7}



Scheme 2: Oligomerisation of hydrogen cyanide to diaminomaleonitrile (**DAMN**) and subsequent photochemical isomerisation and hydrolysis to 5-amino-imidazole-4-carbonitrile (**AICN**) and 5-amino-imidazole-4-carboxamide (**AICA**)

The great difficulties incurred by ribosylation of purine nucleobases and observed intermediacy of 5-amino-imidazole-4-carboxamide riboside (**AICAR**) in *de novo* purine synthesis have led to our interest in the reactivity of **AICA** to develop new strategies to tether sugars and purine precursors.^{7,8,9} Specifically, we have previously proposed that the 1,5-disposition of the

imidazole and amine moieties of **AICA** provide the inherent regioselectivity required to deliver the correct *N7*-ribosylation of purine nucleotides in the absence of sophisticated enzymatic control. We have previously demonstrated pH-controlled multicomponent coupling of **AICA**, aldehydes and 2-amino-azoles that leads to regiospecific coupling of **AICA** (by the correct *N1*-nitrogen atom) to masked tetrose and pentose sugars in excellent yields.⁸ Here we report a complementary tethering strategy for **AICA** and **1** by Amadori rearrangement in neutral aqueous phosphate buffer. The nature of the reaction conditions, the compounds (**AICA** and **1**) and the remarkable efficiency and selectivity signify the potential importance of the reaction in elucidating the chemical origins of life.

Four syntheses of azepinomycin (**2**) have previously been reported. Isshiki *et al.* reported both seven- and six-step sequences to **2** in 5% or 6% overall yield, respectively.² Fuji *et al.* reported an eleven-step sequence to yield **2** in 5% overall yield.¹⁰ Finally, in 2012, Hosmane and co-workers reported a seven-step synthesis providing access to **2** in 16% yield from **AICAR**.¹¹

During the course of studying of the chemical origins of ribonucleotides we noted that **2** is, constitutionally, a conjugate of glycolaldehyde (**1**) and **AICA**. We had previously observed both highly efficient trapping of **AICA** as Schiff bases **3** in water^{8,9} and the remarkable efficacy of phosphate, acting as a general acid-base catalyst, mediating neutral-pH proton transfer.¹² Our analysis of **2** suggested that, under conditions when rapid tautomerisation of imine **3** and aldehyde **4** was observed, **2** would be a privileged chemical structure, accessible in one protecting-group-free step from commercially available reagents by sequential imine formation, Amadori rearrangement and amine-tethered dehydration.

Pleasingly, incubation of **AICA** (0.08M) and **1** (0.15M) in aqueous 1M-phosphate buffer at 60°C for 24 h gave a facile and near quantitative synthesis of **2** in 83% yield. Purification of **2** (pKa 4.2; see supplementary information) can be conveniently achieved by solid-phase extraction with ion-exchange resin (proton-form Dowex® 50W) and liberation of **2** from Dowex® is then achieved at pH \geq 7 to give a 1.16 g (80%) isolated yield of **2**. Heterocycle **2** can then be further purified by (unoptimized) recrystallisation to afford crystalline **2** in 60% yield after one protecting-group-free step without any requirement for chromatography.[†]

¹H-NMR studies indicate that the *N*-acyl hemiaminal N—H bond of **2** (Scheme 1; N—H shown bold) exchanges slowly and is observed as a doublet (¹H NMR (H₂O:D₂O, 10:1) δ_{H} 8.06 ppm, *J* = 5.6 Hz) in ¹H-NMR spectra acquired of H₂O solutions of **2** (¹H NMR spectra of **2** in DMSO, H₂O:D₂O (10:1), D₂O are provided in Supplementary Information). The slow exchange of *N*-acyl hemiaminals has been observed previously and attributed to intramolecular hydrogen bonding,¹³ however the bicyclic architecture of **2** prohibits intramolecular hydrogen bonding suggesting inductive or stereoelectronic inhibition of proton-exchange in **2**. Evidence of an anomeric effect is provided by the axial position of hemiaminal moiety in crystal structure (Figure 1).[†]

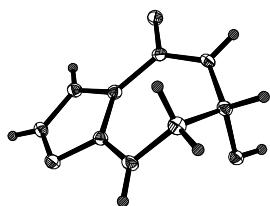


Figure 1: Single crystal X-ray structure of azepinomycin (**2**) crystallised from aqueous ethanol (H₂O:EtOH 9:1).

En route to **2**, Hosmane *et al.* isolated the two diastereomeric ribosides **5** in a combined 27% yield.¹¹ Though it was predicted that ribosylation of **2** may improve bioactivity, it was observed to diminish guanine deaminase inhibitor activity. Though our primary goal was to establish the chemical reactivity of **AICA** and **1**, we thought it imperative to also investigate the reactivity of **AICAR**. Firstly, to demonstrate the stability of the glycosidic bond of **AICAR** under the conditions that facilitate Amadori rearrangement, and secondly, to investigate the potential derivatisation of **AICAR**. **AICAR** Amadori rearrangement provides a rapid, protecting-group-free method to access **5**, however could be highly detrimental to further development of purine nucleotide synthesis under phosphate buffer reaction conditions.

Interestingly, we observed no reaction between **AICAR** and **1** in pH 6-phosphate buffer. Indeed, **1** was completely consumed in a slow homoaldol/Lobry de Bruyn-Alberda van Ekenstein rearrangement over the course of 4 - 5 days at 60°C to give erythulose, whereas **AICAR** (within the limits of ¹H-NMR detection) remain unaltered by phosphate buffer or glycolaldehyde-modification at pH 6.5.[‡] We hypothesise that the change in pKa¹⁴ of **AICAR** relative to the aglycone, **AICA**, prohibited iminium formation and, therefore, protected **AICAR** from derivatisation by inhibition of the Amadori rearrangement. Interestingly, with respect to further elaboration of purine ribonucleotides, the switch in reactivity observed protects **AICAR** from subsequent (undesirable) derivatisation by the aldehydic precursors of nucleotides in phosphate buffer.

In support of our hypothesis that the observed pK_a shift protects **AICAR** from derivatisation at neutral pH, we found that Amadori rearrangement of **AICA** and **1** was not observed at pH > 8. Consequently, we proposed that Amadori rearrangement of **AICAR** would be observed at low pH. We were pleased to observe that at pH 3 - 4 in phosphate or acetate buffer, conversion of **AICAR** to **5** was indeed switched on, such that in aqueous solution at pH 4 preparation of **5** could be achieved in 50 - 65% yield over 3 - 4 days at 60°C directly from **AICAR**. The equilibrating diastereomers of **5** (H₂O, 1.2:1),¹¹ were then isolated by solid-phase extraction with ion-exchange resin (proton-form Dowex® 50W) and separated for individual analysis by preparative RP-HPLC.

Conclusions

We have demonstrated a high-yielding, atom-economical, chromatography-free, and protecting-group-free strategy for the synthesis of azepinomycin (**2**). Additionally, we described the pH dependence of aminoimidazole—glycolaldehyde Amadori rearrangement leading to differential synthesis of azepinomycin ribosides (**5**) and azepinomycin (**2**).

Importantly, with respect to the origins of life, these results demonstrate highly effective sugar-C2'—(5-amino)-imidazole tethering of carbohydrates and 5-aminoimidazoles, which are important purine nucleobase precursors. An investigation of the predisposed¹⁵ Amadori rearrangement towards the origin of purine ribonucleotides in biology is underway in our laboratory.

Experimental

Glycolaldehyde dimer was purchased from Sigma-Aldrich, 5-aminoimidazole-4-carboxamide (**AICA**) was purchased from Acros

Organics, and AICA-riboside (**AICAR**) was purchased from Fluorochem. Solvents were obtained from Fischer Scientific. All reagents and solvents were used without further purification. Dowex 50WX8 200-400 mesh ion exchange resin was purchased from Acros Organics and was washed with methanol and sodium hydroxide solution before being regenerated with hydrochloric acid solution. NMR spectra were recorded on either a Bruker 600 MHz or Oxford 400 MHz spectrometer in D₂O, DMSO-*d*₆ or a mixture of H₂O and D₂O and chemical shifts are reported in ppm, referenced to the residual solvent signals. Mass spectrometry was carried out on a Waters LCT Premier XE spectrometer. HPLC was carried out on an Agilent 1260 system with a Polaris 5 C18-A analytical (150 x 4.6 mm) or semi-preparative (150 x 10 mm) column at 30°C with injection volumes of 5 or 100 μL (10 mg/mL) and flow rates of 1 or 5 mL/min respectively.

Azepinomycin 2

A solution of 5-aminoimidazole-4-carboxamide hydrochloride **AICA** (1.38 g, 8.5 mmol) and glycolaldehyde dimer (0.90 g, 15 mmol) in aqueous sodium phosphate (1M, 100 mL, pH 6) was prepared and incubated at 60°C for 24 h. The solution was diluted to 500 mL with water and run through a column of Dowex® 50WX8 ion exchange resin (H⁺ form, ca. 300 mL, 1.7 meq/mL) and the resin was then washed with 1 bed volume of water. The resin was suspended in water (300 mL), the pH was raised to pH 7 with sodium hydroxide (4M) and the suspension was filtered. The resin was further washed with water and the combined filtrate and washings were lyophilised. The resulting solid was dried over P₂O₅ giving **2** (1.16 g, 80%) as a fine cream powder. A portion (1.0 g) of material was further purified by crystallisation from water:ethanol (1:1, 20 mL) at 0°C. The solids were collected by filtration and washed with ice-cold ethanol and then diethyl ether giving an off white solid (0.6 g, 60%). Analytical samples of x-ray quality crystals were obtained by vapour diffusion of ethanol into an aqueous solution of compound **2**. R_f: 0.24 (CH₂Cl₂; 1% NH₃ in MeOH, 5 : 3). M.p. 194-230°C (dec) [lit. 208-220°C (dec.)]¹⁰. IR (cm⁻¹) 3285 (NH); 3105 br (OH); 2279, 2823 (CH); 1592, 1546 (C=O, C=N). ¹H NMR (600 MHz, DMSO) δ_H 11.83 (1H, br s, N1-H); 7.75 (1H, d, *J* = 5.6 Hz, N9-H); 7.32 (1H, d, *J* = 1.1 Hz, C2-H); 6.28 (1H, dd, *J* = 5.6, 2.2 Hz, N6-H); 5.39 (1H, d, *J* = 5.6 Hz, OH); 4.74 (1H, q, *J* = 5.6 Hz, C8-H); 3.36 (signal obscured by HDO peak, C7-H_a); 2.87 (1H, dd, *J* = 13.2, 2.2 Hz, C7-H_b). ¹H NMR (600 MHz, D₂O:H₂O 1:10) δ_H 8.05 (0.5H, br d, 5.6 Hz, N9-H); 7.58 (1H, s, C2-H); 5.16 (1H, t, *J* = 5.6 Hz, C8-H); 3.69 (1H, dt, *J* = 13.8, 5.6 Hz, C7-H_a); 3.12 (1H, d, *J* = 13.8 Hz, C7-H_b). ¹H NMR (600 MHz, D₂O) δ_H 7.59 (1H, s, C2-H); 5.16 (1H, d, *J* = 5.6 Hz, C8-H); 3.70 (1H, dd, *J* = 13.8, 5.6 Hz, C7-H_a); 3.13 (1H, d, *J* = 13.8 Hz, C7-H_b). ¹³C NMR (150 MHz, DMSO) δ_C 161.3 (q, C10); 150.8 (q, C5); 136.2 (CH, C2); 105.5 (q, C4); 72.6 (CH, C8); 48.5 (CH₂, C7). UV-vis: λ_{max} (H₂O, pH 8) 287 nm (ε 9100). m/z (EI⁺) 168 (100%, [M⁺]); 169 (92%, [M+H⁺]); 95 (38%); 123 (29%); 68 (26%); 122 (25%) 140 (25%). HRMS C₆H₈N₄O₂ calcd. 168.06473, found 168.06512.

*N*1-(β-D-ribofuranosyl)-(8*R*)-azepinomycin **5_A** and *N*1-(β-D-ribofuranosyl)-(8*S*)-azepinomycin **5_B**

A solution of **AICAR** (200 mg, 0.75 mmol) and glycolaldehyde dimer (450 mg, 7.5 mmol) in aqueous sodium phosphate (1M, 7.9 mL, pH 6)

was prepared and incubated at 60°C for 96 h. The solution was diluted with water (16 mL) and passed through a column of Dowex® 50WX8 ion exchange resin (H⁺ form, ca. 50 mL, 1.7 meq/mL), which was subsequently washed with water (100 mL). The resin was then removed from the column, suspended in water and the pH was adjusted to pH 7 with sodium hydroxide (4M). The suspension was filtered and the resin washed with water (100 mL). The combined filtrate and washings were lyophilised returning crude **5** (180 mg) as a mixture of diastereoisomers. A small sample of this material was subjected to semi-preparative HPLC (isocratic water), returning each of the diastereoisomers (retention times 3.9 and 4.9 min, respectively) as fine white powders after lyophilisation.

5_A. ¹H NMR (600 MHz, D₂O) δ_H 7.59 (1H, s, C2-H); 5.70 (1H, d, *J* = 6.0 Hz, C1'-H); 5.17 (1H, d, *J* = 5.4 Hz, C8-H); 4.64 (1H, t, *J* = 6.0 Hz, C2'-H); 4.37 (1H, dd, *J* = 6.0, 3.2 Hz, C3'-H); 4.22 (1H, q, *J* = 3.2 Hz, C4'-H); 3.89 (1H, dd, *J* = 12.6, 3.2 Hz, C5'-H_a); 3.85 (1H, dd, *J* = 12.6, 3.2 Hz, C5'-H_b); 3.76 (1H, dd, *J* = 14.0, 5.4 Hz, C7-H_a); 3.21 (1H, d, *J* = 14.0 Hz, C7-H_b). ¹³C NMR (150 MHz, D₂O) δ_C 167.2 (C10); 144.1 (C5); 133.4 (C2); 114.4 (C4); 88.8 (C1'); 85.9 (C4'); 73.0 (C2'); 72.8 (C8); 70.9 (C3'); 61.5 (C5'); 47.7 (C7). m/z (ES⁺) 301 (100%, [M+H⁺]). HRMS C₁₁H₁₇N₄O₆ calcd. 301.1148, found 301.1150.

5_B. ¹H NMR (600 MHz, D₂O) δ_H 7.60 (1H, s, C2-H); 5.66 (1H, d, *J* = 5.7 Hz, C1'-H); 5.18 (1H, d, *J* = 5.8 Hz, C8-H); 4.68 (1H, t, *J* = 5.7 Hz, C2'-H); 4.36 (1H, dd, *J* = 5.7, 3.4 Hz, C3'-H); 4.23 (1H, q, *J* = 3.4 Hz, C4'-H); 3.85 (1H, dd, *J* = 12.8, 3.4 Hz, C5'-H_a); 3.80 (1H, dd, *J* = 12.8, 3.4 Hz, C5'-H_b); 3.77 (1H, dd, *J* = 14.0, 5.8 Hz, C7-H_a); 3.22 (1H, d, *J* = 14.0 Hz, C7-H_b). ¹³C NMR (150 MHz, D₂O) δ_C 167.1 (C10); 144.6 (C5); 132.9 (C2); 114.0 (C4); 88.2 (C1'); 85.9 (C4'); 73.3 (C2'); 72.8 (C8); 71.0 (C3'); 61.6 (C5'); 47.7 (C7). m/z (ES⁺) 301 (100%, [M+H⁺]). HRMS C₁₁H₁₇N₄O₆ calcd. 301.1148, found 301.1146.

Notes and references

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† Cell packing and intermolecular hydrogen bond diagrams are provided in Supplementary Information. The *N*-acyl hemiaminal N—H is the only N—H not involved in intermolecular hydrogen bonding in the crystal lattice. CIF available free of charge from the Cambridge crystallographic data centre: CCDC deposit # 1034270.

‡ Glycolaldehyde (**1**) derivatisation of **AICAR** and **AICA** was not observed above pH 5 and pH 8 respectively, however deuterium exchange at imidazole-C2 carbon atom is observed in D₂O.

Electronic Supplementary Information (ESI) available: Product spectra, reaction spectra, pH-titration and crystallographic data and plots are provided in supplementary information. See DOI: 10.1039/c000000x/

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