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A NOVEL AND EFFICIENT SYNTHESIS OF THE NATURALLY OCCURRING
NUCLEOSIDE DORIDOSINE¹

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Abstract: 1-Methylisoguanosine was synthesized by a one-pot reaction involving a condensation of 5-amino-1-(β -D-ribofuranosyl)imidazole-4-carboxamide (1) with methyl isothiocyanate, treatment of the resulting thiourea derivative with DCC furnished 5-(3-methyl-1-ureido)-1-(β -D-ribofuranosyl)imidazole-4-carbonitrile (4) which was then annulated with ethanolic ammonia to furnish doridosine in a 68% yield from 1.

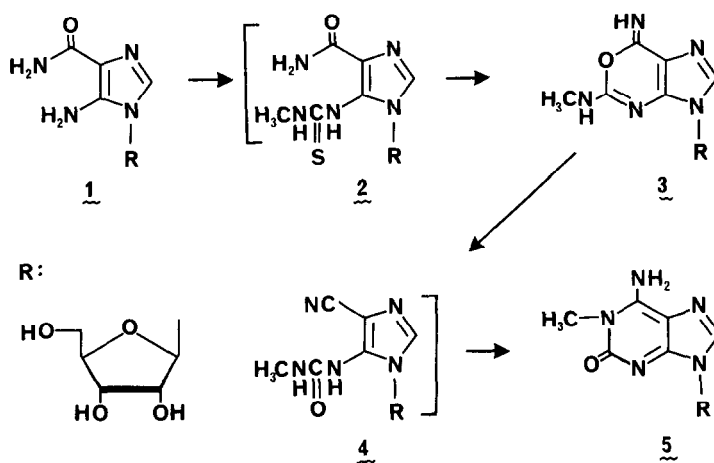
1-Methylisoguanosine (5, doridosine, 6-amino-1-methyl-9- β -D-ribofuranosylpurin-2-one) was recently isolated from three different marine animals by three independent laboratories.²⁻⁴ This compound has been shown to possess potent muscle-relaxant activity, as well as a lowering of blood pressure and antiinflammatory activity.⁵⁻⁸ Doridosine and a variety of doridosine analogs have been synthesized and studied^{9,10} because of the biological activity observed for doridosine. Doridosine, *per se*, has been synthesized^{3,9,11} by a direct methylation of isoguanosine with methyl iodide or by the cyclization of an appropriate imidazole nucleoside. The first method has furnished a mixture of 1-methylisoguanosine and 2-methoxyadenosine, both of which were obtained in relatively poor yield.³ The second method involved a conversion of the commercially available 5-amino-1-(β -D-ribofuranosyl)imidazole-4-carboxamide (AICA-riboside) into its tri-O-acetyl derivative, which was then treated with phosphorus oxychloride to obtain 5-amino-4-cyano-1-(2,3,5-tri-O-acetyl- β -D-ribofuranosyl)imidazole (tri-O-acetyl derivative of AICN-riboside). However, this nitrile derivative was contaminated with some highly colored impurities and needed extensive column chromatography in order to obtain pure material. Compound 5 was then obtained by a reaction of the protected AICN-riboside with methyl isocyanate, followed by cyclization and deprotection with methanolic ammonia. The second method gave a 39% yield of 5 from AICA-riboside.

As part of our continuing study on the development of new methodology for the formation of heterocyclic compounds, we have recently reported¹² a facile and interesting procedure for the synthesis of 5-(3-methoxycarbonyl-1-ureido)-1-(β -D-ribofuranosyl)imidazole-4-carbonitrile which involved the reaction of AICA-riboside with methoxycarbonyl isothiocyanate, followed by a cyclodesulfurization of the resulting thioureido derivative with dicyclohexylcarbodiimide. Subsequent studies (¹⁸O labeling) in our laboratory¹³ have provided strong support for a mechanism which involves the formation of a [1,3]oxazine intermediate with the carboxamide oxygen ultimately becoming part of the ureido group. Our successful synthesis of this AICN-riboside derivative from AICA-riboside under such mild conditions suggested that this approach might provide a new, novel and more efficient synthetic route for the preparation of doridosine and some structurally related derivatives.

A retro synthetic evaluation using this approach indicated that an initial condensation of

the commercially available AICA-ribose and methyl isothiocyanate should provide 5-(3-methyl-1-thioureido)-1-(β -D-ribofuranosyl)imidazole-4-carboxamide (2). A subsequent cyclodesulfurization of compound 2 with DCC should provide 5-(3-methyl-1-ureido)-1-(β -D-ribofuranosyl)imidazole-4-carbonitrile (4) which could then be annulated to provide the desired nucleoside 5.

A solution of AICA-ribose (1, 2.35 g, 9.1 mmol) and methyl isothiocyanate (5 mL, 73 mmol) in *N,N*-dimethylformamide (20 mL) was heated at 80°C for 12 hours. The solvent was then removed to afford an oil which was dissolved in methanol (10 mL). The white solid which was formed by the addition of ether (100 mL) was collected by filtration, and washed with ether (20 mL). This solid was determined to be compound 2 by TLC and a ^1H -NMR spectrum.¹⁴



Scheme I

This solid was found to be very hygroscopic, therefore, the crude product was immediately dissolved in DMF (50 mL), dicyclohexylcarbodiimide (5.6 gm, 27.3 mmol) was added to the resulting solution and the mixture stirred at room temperature for 24 hours. The solvent was then removed to afford an oil which was dissolved in a mixture of methanol and chloroform (10 mL, v/v, 2:8) with flash chromatography being used to remove the fast-moving band of dicyclohexylthiourea and DCC. The column was then eluted with methanol to obtain a fraction

containing the nucleoside material, as determined by TLC, and the solvent removed to obtain an oil. Ethanol (100 mL) and 58% ammonium hydroxide (20 mL) was added to this oil and the mixture was stirred at room temperature. After 30 min., a white solid separated, but the reaction mixture was allowed to stir at room temperature for an additional 12 hours. The solid was then collected by filtration to give 1.3 g of pure doridosine (5). This synthetic sample was found to be identical (IR, UV, $^1\text{H-NMR}$ and MS) to the naturally occurring nucleoside doridosine based on a comparison of data for 5 and the reported³ data as follows: M.p. 270-271°C (lit.¹¹ 266- 267°C); IR(KBr): 3500, 3455, 3200, 3100, 1690, 1640, 1600, 1580, 1525, 1430, 1400, 1200, 1080, 1050, 1020, 850 cm^{-1} ; UV λ_{max} nm ($\epsilon \times 10^4$): (MeOH) 250 (0.84), 299 (1.15); (pH 1) 234 (0.7), 283 (1.37); mass spectrum, m/z 298 ($\text{M}^+ + \text{H}$), 208 ($\text{B} + 44$), 194 ($\text{B} + 30$), 166 ($\text{B} + 2\text{H}$), 108 ($\text{BH-CH}_3\text{NCO}$); $^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$); δ 8.14 (s, 2H, NH_2 , D_2O exchangeable), 7.90 (s, 1H, H-8), 5.70 (q, 1H, H-5' OH, D_2O exchangeable), 5.60 (d, 1H, H-1', $J = 6.4$ Hz), 5.33 (d, 1H, H-2' OH, $J = 6.4$ Hz, D_2O exchangeable), 5.07 (d, 1H, H-3' OH, $J = 4.3$ Hz, D_2O exchangeable), 4.53 (q, 1H, H-2'), 4.06 (q, 1H, H-3'), 3.90 (q, 1H, H-4'), 3.63-3.44 (m, 2H, H'-5), 3.59 (s, 3H, CH_3). High resolution mass spectrometry demonstrated that the base peak $\text{C}_6\text{H}_8\text{N}_5\text{O}$ (m/z 166) corresponds to a methylisoguanine fragment. We observed the loss of a N(1)-C(2) unit from the base peak (m/z 166), which is particularly relevant to the structural determination of 5. This loss was used to establish the position of methylation in the isoguanosine series^{3,5}. The filtrate was evaporated in vacuo to afford an oil, water (10 mL) was added to the oil, and the mixture allowed to stand at room temperature for 24 hours. The solid was collected by filtration to give an additional 0.5 g of pure compound 5. The total combined yield of compound 5 was 1.8 g (68%). This yield was obtained without any attempt to optimize the reaction conditions.

It would appear that this methodology may provide a new and novel general route for the preparation of various doridosine analogs containing an amino-N-alkylpyrimidinone moiety via a simple variation of the isothiocyanate and the ortho amino-carboxamide heterocycles used in the initial condensation. The scope of this methodology is under investigation in our laboratory.

Acknowledgment: This investigation was supported by PHS Grant CA 28381 awarded by the National Cancer Institute, DHHS. The authors would also like to acknowledge the NIH Biomedical Research Support (RR 01437) for funds toward the purchase of the IBMNP-270SY NMR Spectrometer and thank Ms Deanna VanSickle for assistance in the preparation of this manuscript.

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layer chromatography (TLC) was performed with Analtech silica gel GHLF TLC plates (250 microns).

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14. It is of some interest that a bis-(methylcarbamoyl) adduct was obtained³ from a condensation of 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile with excess methyl isocyanate. However, the ¹H-NMR spectrum of compound 2 revealed a doublet centered at δ2.88 which supported the presence of only a single N-CH₃ group. On the basis of this spectrum, the structure of compound 2 was assigned as the mono-N-methyl-thiocarbamoyl adduct instead of the bis-(N-methylthiocarbamoyl) derivative. ¹H-NMR (270 MHz, DMSO-d₆) spectrum of compound 2: δ 8.96 (s, 1H, NH), 7.95 (s, 1H, =C-H), 7.87 (br s, 1H, NH), 7.20 (s, 1H, NH_{2a}), 7.03 (s, 1H, NH_{2b}), 5.46 (d, 1H, H-1', J = 3.3 Hz), 5.23 (d, 1H, H-2'OH, J = 4.9 Hz), 5.09 (d, 1H, H-3'OH, J = 5.3 Hz), 5.01 (t, 1H, H-5'OH), 4.13 (q, 1H, H-2'), 4.05 (q, 1H, H-3'), 3.82 (q, 1H, H-4'), 3.57-3.51 (m, 2H, H-5'), 2.88 (d, 3H, CH₃).

(Received in USA 7 August 1985)