Synthesis of 6-Amino-1,2,4-triazolo[1,5-*a*]pyrazin-4(5*H*)one, A Bridgehead Analog of Guanine

Michael V. Pickering, Marie T. Campbell, J. T. Witkowski and Roland K. Robins

ICN Pharmaceuticals Inc., Nucleic Acid Research Institute, Irvine, CA 92715

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The synthesis of 6-amino-1,2,4-triazolo[1,5-*a*]pyrazin-4(5*H*)one, an analog of guanine with a bridgehead nitrogen, is described.

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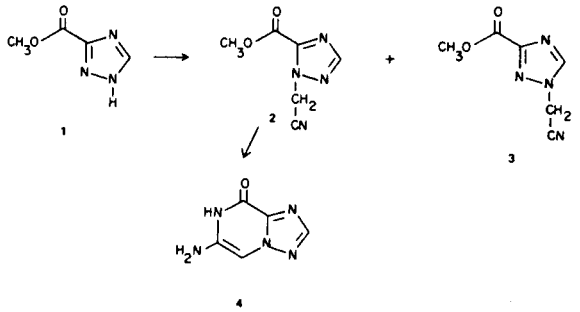
A number of aza (1) and deaza (2) analogs of purines have been investigated recently as antimetabolites. Certain heterocyclic compounds (3) and nucleosides (4) structurally related to purines and containing a bridgehead nitrogen atom have also been described. The antitumor (5) and antiviral (6) activity exhibited by 3-deazaguanine (7) prompted us to investigate similar heterocyclic compounds closely related to guanine. We now report the synthesis of a guanine analog, 6-amino-1,2,4-triazolo-[1,5-*a*]pyrazin-4(5*H*)one (**4**), which contains a bridgehead nitrogen and may be described as 3-deaza-4-azaguanine.



This synthesis was accomplished in two steps by alkylation of methyl 1,2,4-triazole-3-carboxylate (**1**) with iodoacetonitrite followed by ring-closure of methyl 1-cyanomethyl-1,2,4-triazole-5-carboxylate (**2**) with ammonia to give **4**. This is to our knowledge the first reported example of this type of ring closure giving rise to a bridgehead nitrogen atom in a condensed ring system.

Treatment of methyl 1,2,4-triazole-3-carboxylate (**8**) (1) with one mole of iodoacetonitrite in dimethylformamide in the presence of anhydrous potassium carbonate (one mole) at room temperature for 18 hours gave a mixture of two isomers identified as methyl 1-cyanomethyl-1,2,4-triazole-5-carboxylate (**2**) and methyl 1-cyanomethyl-1,2,4-triazole-3-carboxylate (**3**). These products were separated by column chromatography on silica gel (Woelm) with 20:1 chloroform-methanol as eluant. The first product from the column was crystallized from ethyl ether-petroleum ether to give a 23% yield of **2** with m.p. 64-66°; pmr (DMSO-d_6): δ 4.00 (s, 3, CH_3), 5.84 (s, 2, CH_2), 8.32 (s, 1, H-3).

Crystallization of the second product from teh column from ethyl acetate afforded a 24% yield of **3** with m.p. 122-124°; pmr (DMSO-d_6): δ 3.93 (s, 3, CH_3), 5.76 (s, 2, CH_2) 8.86 (s, 1, H-5).

These chemical shift values for the triazole protons of **2** and **3** are characteristic for 1-substituted methyl 1,2,4-triazole-5-carboxylates and 1-substituted methyl 1,2,4-triazole-3-carboxylates, respectively (9).

Treatment of **2** with methanol (saturated with anhydrous ammonia at 0°) in a sealed bomb for 18 hours at room temperature provided in 90% yield 6-amino-1,2,4-triazolo-[1,5-*a*]pyrazin-4-(5*H*)one (**4**) with m.p. > 300°; pmr (DMSO-d_6): δ 5.40 (br, s, 3, N-H), 7.08 (s, 1, H-7), 8.25 (s, 1, H-2); uv: λ max (*p*H 1) 212 nm (ε, 14,960), sh 240 (ε, 4,550); λ max (*p*H 7) 217 (ε, 16,460), 263 (ε, 5,980), 327 (ε, 3,320); λ max (*p*H 11) 262 (ε, 5,830), 320 (ε, 6,790) (10). It is of interest that ring closure of **2** apparently occurs much more readily than the analogous reaction leading to 3-deazaguanine. Ring-closure of methyl 5(4)cyanomethylimidazole-4(5)carboxylate with liquid ammonia required heating at 100° for 8 days (7).

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