Intramolecular Cyclization of Ethyl ω-(5-Amino-4-aminocarbonylimidazol-1-yl)carboxylates

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Attempted elaboration of the title compounds to purines by reaction with ethyl formate leads instead to some novel fused imidazoles by intramolecular cyclization.

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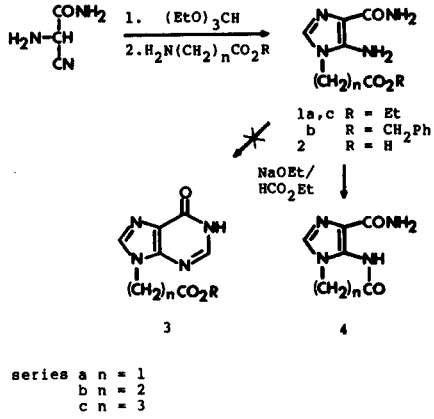
Purine nucleoside phosphorylase (PNP, E.C.2.4.2.1) is an important enzyme in the catabolism of purine nucleosides, and inhibitors of this enzyme have been determined to be of potential value as immunosuppressive agents [1]. Since PNP must bind phosphate in close proximity to the heterocyclic base, we are currently exploring the possibility that molecules incorporating both a heterocycle and a suitably spaced acidic functional group might be potent inhibitors of this enzyme. Herein we wish to report the synthesis of some novel imidazoles, and interesting observations made in attempting to elaborate these to purines.

The esters of ω-(5-amino-4-aminocarbonylimidazol-1-yl)-carboxylic acids **1** were prepared from aminocyanoacetamide by a simple modification of the conventional procedure [2]. The appropriate amino ester salt was dissolved in one equivalent of aqueous sodium hydroxide, and this solution was added directly to the reaction mixture. Yields were moderate, and the assigned structures were supported by ^{1}H NMR spectra and elemental analysis. Saponification of these esters gave the previously unreported carboxylic acids **2**, which we are currently evaluating as inhibitors of PNP.

1-Alkyl-5-aminoimidazole-4-carboxamides have been elaborated to 9-alkylhypoxanthines **3** by heating with a large excess of ethyl formate in the presence of sodium ethoxide [3]. Since we also required these compounds for our enzyme inhibition studies, we attempted this reaction for **1b** and **1c**, expecting to obtain **3b** and **3c**, which we had been unable to prepare by alkylation and hydrolysis of 6-chloropurine, the method used for the preparation of **3a** [4]. Despite the use of a large excess of ethyl formate, the only products isolated were 8-aminocarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2-one (**4b**) and 9-aminocarbonyl-1,2,3,4-tetrahydro-5*H*-imidazo[1,5-*a*][1,3]diazepin-2-one (**4c**) formed from **1b** and **1c** respectively by intramolecular reaction of the aromatic amino group with the ester function in the side-chain. These previously unreported compounds were readily characterized by elemental analysis and by their ^{1}H nmr spectra, which



showed a broad, exchangeable, two proton resonance at 7.0 ppm assigned to the unreacted amide function, an exchangeable one proton resonance around 9.5 ppm characteristic of acylation of the original 5-amino group, and only one resonance for an aromatic proton, shifted downfield to 7.4 ppm. This chemical shift is characteristic of an acylaminoimidazole, but not a purine, for which resonances between 8.0 and 8.5 ppm are observed.

Intramolecular cyclization, obviously facile for formation of the six- and seven-membered rings in **4b** and **4c**, was not observed for **1a**, presumably due to unfavorable ring strain in the putative product **4a**. Similar observations have been made for other systems with fused, planar five-membered rings [5].

Anticipating that the carboxylic acids would be much less susceptible to intramolecular cyclization than the esters, **2b** was heated at reflux with an excess of ethyl formate in ethanolic sodium ethoxide. Surprisingly, **4b** was the only product observed in this reaction also. In contrast to the cyclization of **1b** and **1c**, the presence of ethyl formate was required for the cyclization of **2b**, possibly indicating prior formation of a mixed anhydride. Thus, it is apparent that this approach to the purines **3b** and **3c** is not feasible. A convenient approach to some novel fused imidazoles has been demonstrated, however. Related com-

pounds have been determined to be of interest as purine antagonists [6], and we are currently exploring further possibilities of this synthetic method.

EXPERIMENTAL

Melting points were determined on a Laboratory Devices Mel-Temp capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded at 60 MHz in DMSO-d_6 and chemical shifts are reported in ppm downfield from TMS.

(5-Amino-4-aminocarbonylimidazol-1-yl)carboxylates **1**.

General Procedure.

A solution of aminocyanoacetamide (6 g, 60 mmoles) and triethyl orthoformate (9.5 g, 60 mmoles) in acetonitrile (40 ml) was heated at reflux for 50 minutes. After cooling, a solution of the appropriate amino-acid ester salt (25 mmoles) in 5*M* aqueous sodium hydroxide (5 ml) was added. The solution was heated at reflux for 40 minutes, cooled, and concentrated *in vacuo*. The residue was dissolved in brine, and the product was extracted into dichloromethane. After drying over magnesium sulfate, the solvent was removed *in vacuo*.

Ethyl 2-(5-Amino-4-aminocarbonylimidazol-1-yl)acetate (**1a**).

This compound was isolated in 50% yield after crystallization from isopropyl alcohol, mp 170-171°; ^{1}H nmr: 1.2 (t, 3H, C*H*$_3$CH$_2$), 4.2 (q, 2H, CH$_3$C*H*$_2$O), 4.8 (s, 2H, NC*H*$_2$CO), 5.7 (broad s, 2H, ArN*H*$_2$), 6.6 (broad s, 2H, CON*H*$_2$), 7.1 (s, 1H, Ar*H*).

Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.66; N, 26.41. Found: C, 45.37; H, 5.56; N, 26.06.

Benzyl 3-(5-Amino-4-aminocarbonylimidazol-1-yl)propanoate (**1b**).

This compound was isolated in 53% yield after crystallization from water, mp 191-193°; ^{1}H nmr: 2.8 (t, 2H, CH$_2$C*H*$_2$CO), 4.0 (t, 2H, NC*H*$_2$), 5.1 (s, 2H, PhC*H*$_2$O), 5.7 (broad s, 2H, ArN*H*$_2$), 6.6 (broad s, 2H, CON*H*$_2$), 7.0 (s, 1H, Ar*H*), 7.3 (s, 5H, *Ph*).

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.56; N, 19.44. Found: C, 58.26; H, 5.63; N, 19.41.

Ethyl 4-(5-Amino-4-aminocarbonylimidazol-1-yl)butanoate (**1c**).

This compound was isolated in 69% yield after crystallization from isopropyl alcohol; mp 164-165°; ^{1}H nmr: 1.2 (t, 3H, C*H*$_3$CH$_2$O), 1.8-2.4 (overlapping m, 4H, C*H*$_2$C*H*$_2$CO), 3.8 (t, 2H, NC*H*$_2$CH$_2$), 4.1 (q, 2H, CH$_3$C*H*$_2$O), 5.7 (broad s, 2H, ArN*H*$_2$), 6.6 (broad s, 2H, CON*H*$_2$), 7.1 (s, 1H, Ar*H*).

Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 50.00; H, 6.67; N, 23.33. Found: C, 50.11; H, 6.72; N, 23.33.

General Procedure for the Saponification of **1**.

The ester **1** (10 mmoles) was dissolved in 95% ethanol (100 ml), 5*M* aqueous sodium hydroxide was added, and the solution was heated at reflux for 3 hours. After cooling, the solvent was removed *in vacuo*. The residue was dissolved in a minimum amount of water and the solution brought to *p*H 5 by addition of concentrated hydrochloric acid. The precipitated product was separated by filtration, washed with water, and dried *in vacuo*.

2-(5-Amino-4-aminocarbonylimidazol-1-yl)acetic Acid (**2a**).

This compound was obtained in 58% yield, mp >290° dec; ^{1}H nmr: 4.7 (s, 2H, NC*H*$_2$CO), 6.5-6.9 (broad, 5H, ArN*H*$_2$, CON*H*$_2$, CO$_2$*H*), 7.1 (s, 1H, Ar*H*).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.35; N, 30.43. Found: C, 39.18; H, 4.39; N, 30.40.

3-(5-Amino-4-aminocarbonylimidazol-1-yl)propanoic Acid (**2b**).

This compound was obtained in a yield of 40%, mp 263-264°; ^{1}H nmr: 2.7 (t, 2H, CH$_2$C*H*$_2$CO), 4.0 (t, 2H, NC*H*$_2$CH$_2$), 5.8 (broad s, 3H, ArN*H*$_2$, CO$_2$*H*), 6.6 (broad s, 2H, CON*H*$_2$), 7.1 (s, 1H, Ar*H*).

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.49; H, 5.05; N, 27.99.

4-(5-Amino-4-aminocarbonylimidazol-1-yl)butanoic Acid (**2c**).

This compound was obtained in a yield of 70%, mp 208-210°; ^{1}H nmr: 1.8-2.4 (overlapping m, 4H, C*H*$_2$C*H*$_2$CO), 3.9 (t, 2H, NC*H*$_2$CH$_2$), 5.6-6.6 (broad, 3H, ArN*H*$_2$, CO$_2$*H*), 7.0 (broad s, 2H, CON*H*$_2$), 7.6 (s, 1H, Ar*H*).

Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.66; N, 26.42. Found: C, 45.11; H, 5.71; N, 26.27.

8-Aminocarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2-one (**4b**).

a) Benzyl 3-(5-amino-4-aminocarbonylimidazol-1-yl)propanoate (**1b**) (1.0 g, 3.5 mmoles) was added to a solution of sodium ethoxide (17.5 mmoles) in absolute ethanol (25 ml). Ethyl formate (1.5 ml, 17.5 mmoles) was added and the solution was heated under reflux for 3 hours. After cooling, the solution was neutralized with concentrated hydrochloric acid. Ethanol was removed *in vacuo*, and the residue was crystallized from water yielding **4b** (0.36 g, 57%), mp 262-264°; ^{1}H nmr: 2.8 (t, 2H, C*H*$_2$CO), 4.2 (t, 2H, NC*H*$_2$), 7.0 (broad s, 2H, CON*H*$_2$), 7.4 (s, 1H, Ar*H*), 9.2 (broad, 1H, ArN*H*CO).

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.65; H, 4.48; N, 31.10. Found: C, 46.57; H, 4.59; N, 30.81.

b) The acid **2b** was treated as in (a), yielding 33% of a product identical in all respects with that isolated from (a).

9-Aminocarbonyl-1,2,3,4-tetrahydro-5*H*-imidazo[1,5-*a*][1,3]diazepin-2-one (**4c**).

To a solution of sodium ethoxide (21 mmoles) in ethanol (25 ml) was added ethyl 4-(5-amino-4-aminocarbonylimidazol-1-yl)butanoate (**4c**) (1.0 g, 4.2 mmoles) and ethyl formate (1.7 ml, 21 mmoles), and the solution was heated under reflux for 3 hours. After cooling, the solution was neutralized with hydrochloric acid and concentrated. The residue was crystallized from water, yielding **4c** (0.31 g, 38%), mp 294-296°; ^{1}H nmr: 2.2 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 2.7 (m, 2H, C*H*$_2$CO), 4.2 (m, 2H, NC*H*$_2$CH$_2$), 7.1 (broad s, 2H, CON*H*$_2$), 7.4 (s, 1H, Ar*H*), 9.8 (broad, 1H, ArN*H*CO).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.15; N, 28.86. Found: C, 49.55; H, 5.14; N, 28.67.

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