Studies on New Routes for the Synthesis of 4- and 5-Aminoimidazole Nucleoside Derivatives

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The synthesis of urethane protected 4- and 5-aminoimidazole nucleoside derivatives **4** and **9** by two different routes is described. These routes are transformation of the carboxylate substituted imidazole nucleoside **1** *via* a Curtius rearrangement to give **4** and direct ribosylation of the imidazole base **6** to give a mixture of positional isomers **7** and **8**, which by deacetylation afford **4** and **9**, respectively. The convenience of each route depended on the positional isomer to be synthesized.

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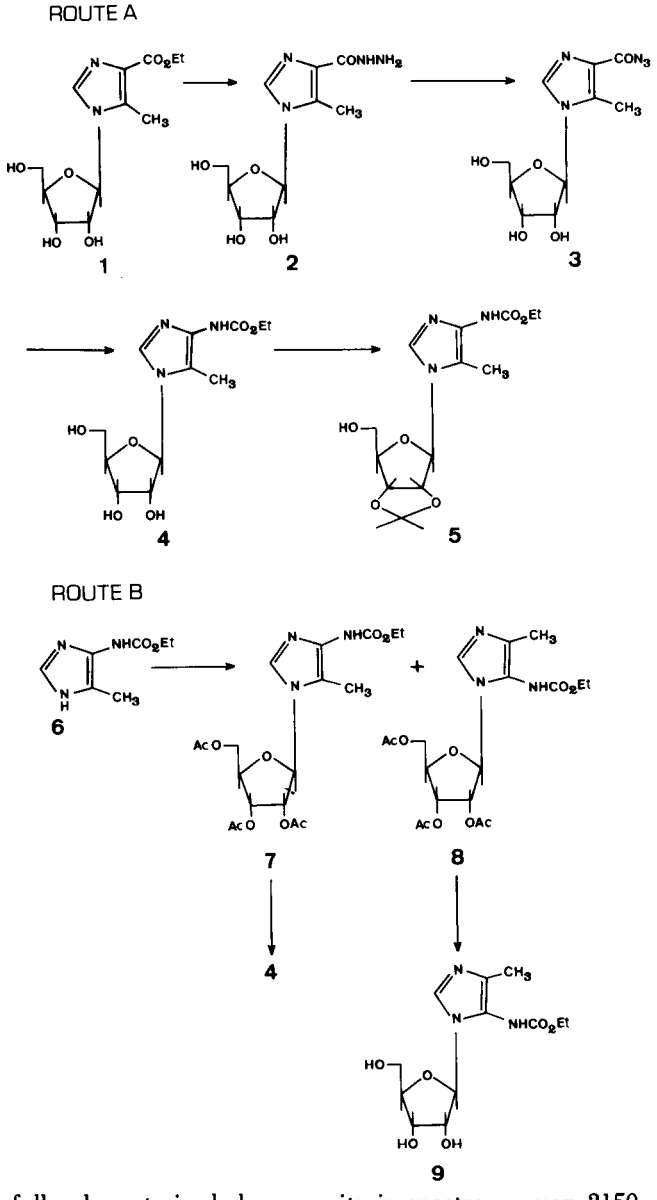
Intermediates in the *de novo* purine nucleotide biosynthetic pathway include 5-aminoimidazole ribotide and its corresponding 4-carboxamide derivative (AICA ribotide) (1). This fact has stimulated considerable interest in nucleosides related to such imidazole derivatives. Three different approaches have been reported for the synthesis of aminoimidazole nucleosides (2), namely, reduction of nitroimidazole nucleoside analogs, ring opening of purine nucleosides and ring closure of glycosylamines. These two latter methods always lead to 5-amino substituted imidazole nucleosides. The commercial availability of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside) prompted several chemical transformations of the 5-amino group (3-6). However, due to the instability of 4(5)-aminoimidazoles (7), relatively few studies have been made on the preparation of 4- or 5-aminoimidazole nucleoside derivatives bearing different substituents from carboxamide or related groups at 5- or 4-position, respectively. In order to circumvent such instability we have achieved the synthesis of certain urethane protected 4-and 5-aminoimidazole nucleosides.

The present paper describes the preparation of nucleosides of 4(5)-ethoxycarbonylamino-5(4)-methylimidazole by two different routes, namely, transformation of the corresponding carboxylate substituted imidazole nucleoside *via* a Curtius rearrangement (Route A), and direct glycosylation of the ethoxycarbonylimidazole derivative (Route B). As it will be shown the convenience of each route depended on the positional isomer to be synthesized.

The starting material for Route A, 4-ethoxycarbonyl-5-methyl-1-β-D-ribofuranosylimidazole (**1**) was prepared by deacetylation with methanolic ammonia of the corresponding peracetylated riboside, previously described (8). As expected (5,9), since the reaction was achieved under mild conditions, no ammonolysis of the ester group took place.

Treatment of **1** with hydrazine hydrate afforded 4-hydrazinocarbonyl-5-methyl-1-β-D-ribofuranosylimidazole (**2**) in quantitative yield, which by nitrosation with sodium nitrite and aqueous hydrochloric acid in acetone gave the 4-azidocarbonyl derivative **3**. Acyl azide **3** was not fully characterized, however its ir spectra, ν max 2150 cm^{-1} as well as the subsequent chemical transformation showed that the structure of **3** was as indicated. Curtius rearrangement of **3** in refluxing ethanol gave 4-ethoxycarbonylamino-5-methyl-1-β-D-ribofuranosylimidazole (**4**),



the structure of which was deduced from its analytical and pmr data. Although the value of the coupling constant did not allow an unequivocal assignment for the anomeric configuration of **4** (J1'2' > 2 Hz), the fact that no anomerization of the starting material **2** had occurred was demonstrated by application of Imbach's criterion on the 2',3'-*O*-isopropylidene derivative **5**, whose pmr spectrum showed a difference of chemical shift for the isopropylidene methyl groups of 0.20 ppm, only consistent with a β configuration (10).

Since the previously reported ribosylation of 4(5)-ethoxycarbonyl-5(4)-methylimidazole had led to very low yield of the 5-carboxylate substituted isomer (8), the above described Route A was not followed for the preparation of the 5-ethoxycarbonylamino-4-methyl substituted riboside. However, Route B provided a convienent procedure to obtain such an isomer. Route B, consisting of direct glycosylation of the corresponding imidazole base **6** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride *via* the mercuric cyanide-nitromethane method led to a mixture of 4-ethoxycarbonylamino-5-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**7**) and 5-ethoxycarbonylamino-4-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**8**) in 30 and 58% yields, respectively.

Compound **6**, which had been previously prepared from 5-ethoxycarbonylamino-2-mercapto-4-aminothiazole followed by desulphurization of the resulting 2-mercaptoimidazole (11), was easily obtained from 4(5)-hydrazinocarbonyl-5(4)-methylimidazole (12) *via* Curtius rearrangment of the corresponding acyl azide.

Deacetylation of **7** and **8** with methanolic ammonia afforded the deprotected ribosides **4**, identical to that obtained from **1**, and 5-ethoxycarbonylamino-4-methyl-1-β-D-ribofuranosylimidazole (**9**). The structure of **9** was determined on the basis of its pmr spectrum and analytical data. As expected, the signal for the methyl group appeared at higher field than that of the corresponding 5-methyl subsituted isomer **4**, as a consequence of the deshielding effect of the adjacent glycosyl moiety in compound **4** (13). Although the anomeric configuration of **9**, as well as that of its acetylated derivative **8**, could not be established on the basis of their coupling constants J1'2' (J1'2' > 2 Hz in both cases), both compounds were assigned as β taking into account the fact that the mercuric cyanide method gives in general only 1'2'-*trans*-nucleosides.

Attempts to hydrolyze **4** and **9** to the corresponding free amino compounds by heating with 1*N* sodium hydroxide solution led to ring fission products which were not identified.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 100 MHz on a Varian XL-spectometer using TMS as the internal standard. Analytical thin layer chromatography was performed on aluminum sheets coated with a 0.2 mm layer of silica gel $60F_{254}$ (Merck), and preparative layer chromatography on 20 × 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). The compounds were detected with uv light of 254 nm or by spraying with sulfuric acid in ethanol, 30%.

4-Ethoxycarbonyl-5-methyl-1-β-D-ribofuranosylimidazole (**1**).

A solution of 8.24 g (0.02 mole) of 4-ethoxycarbonyl-5-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl) imidazole (**8**) in 200 ml of methanol saturated with ammonia at 0° was allowed to stand at room temperature for 24 hours. Evaporation of the solvent left a residue which was crystallized from acetone to give 5.43 g (93%) of **1** with mp 144-145°; pmr (DMSO-d_6): δ 8.10 (s, 1, H-2), 5.65 (d, 1, J1'2' = 5 Hz, H-1').

Anal. Calcd. for $C_{12}H_{18}O_6N_2$: C, 50.34; H, 6.33; N, 9.78. Found: C, 50.46; H, 6.20; N, 9.92.

4-Hydrazinocarbonyl-5-methyl-1-β-D-ribofuranosylimidazole (**2**).

A mixture of 4.90 g (0.017 mole) of **1** and 40 ml of hydrazine hydrate in 125 ml of ethanol was refluxed for 3 hours. Then, the solution was evaporated and co-evaporated with ethanol to give **2** in quantitative yield, mp 213-215° (from ethanol); pmr (DMSO-d_6-deuterium oxide): δ 8.08 (s, 1 H-2); 5.65 (d, 1, J1'2' = 5 Hz, H-1').

Anal. Calcd. for $C_{10}H_{16}N_4O_5$: C, 44.11; H, 5.92; N, 20.58. Found: C, 44.10; H, 6.03; N, 20.42.

4-Ethoxycarbonylamino-5-methyl-1-β-D-ribofuranosylimidazole (**4**).

To a cooled stirred suspension of 4.60 g (0.017 mole) of **2** in 20 ml of acetone and 4 ml of 6*N* hydrochloric acid, a solution of 1.80 g of sodium nitrite in 6 ml of water was added dropwise, while the reaction temperature was kept under 10°. The mixture was stirred for 15 minutes and then it was allowed to stand at room temperature for 24 hours while stirring. After this time solution was obtained. The solvent was removed *in vacuo* under 30° and the residue was extracted with dry acetone. Evaporation of the acetone extract left 4.01 g of the acyl azide **3**: ir (nujol): 2150 cm^{-1} (N_3). Heating crude **3** in refluxing ethanol for 6 hours afforded, after evaporation of the solvent and tlc chromatography of the residue (4:1 ethyl acetate-methanol), 2.15 g. (51%) of **4** as a syrup: pmr (DMSO-d_6): δ 8.75 (s, 1, NH exchangeable with deuterium oxide), 7.82 (s, 1, H-2), 5.54 (d, 1, $J_{1'2'}$ = 5.5 Hz, H-1'), 2.10 (s, 3, CH_3).

Anal. Calcd. for $C_{12}H_{19}N_3O_6 \cdot H_2O$: C, 45.14; H, 6.58; N, 13.17. Found: C, 45.48; H, 6.46; N, 13.54.

4-Ethoxycarbonylamino-5-methyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole (**5**).

To a solution of 0.78 g (0.0026 mole) of **4** in 20 ml of dry acetone and 10 ml of 2,2-dimethoxypropane was added 0.32 g of perchloric acid. After 24 hours at room temperature, the solution was neutralized with 0.4 ml of saturated solution of sodium carbonate and evaporated to dryness. The residue was partitioned between ethyl acetate and water and the organic phase was dried over sodium sulfate and then evaporated, leaving a residue which was purified by tlc (9:1 ethyl acetate-methanol). Elution of the major band gave 0.80 g (96%) of **5** as a syrup; pmr (DMSO-d_6-deuterium oxide): δ 8.05 (s, 1, H-2), 5.87 (d, 1, J1'2' = 3 Hz, H-1') 2.14 (s, 3, CH_3), 1.54 and 1.34 (2s, $2CH_3$ isopropylidene group).

Anal. Calcd. for $C_{15}H_{23}N_3O_6 \cdot H_2O$: C, 50.13; H, 6.96; N, 11.69. Found: C, 50.27; H, 6.73; N, 11.47.

4(5)-Ethoxycarbonylamino-5(4)-methylimidazole (**6**).

To a cooled stirred solution of 10.70 g (0.07 mole) of 4(5)-hydrazinocarbonyl-5(4)-methylimidazole (12) in 200 ml of water and 20 ml of 6*N*-hydrochloric acid, a solution of 6.60 g of sodium nitrite in 35 ml of water was added dropwise, while the reaction temperature was kept under 10°. Then, the mixture was stirred for 10 minutes and 9.59 g of solid 4(5)-azidocarbonyl-5(4)-methylimidazole was filtered and dried at room temperature; ir (nujol): 2150 cm^{-1} (N_3). Heating the foregoing crude

product in refluxing ethanol for 8 hours afforded, after evaporation of the solvent, a solid which was recrystallized from nitromethane to give 8.67 g (90%) of **6** with mp 185-186° (literature (11) 187°).

4-Ethoxycarbonylamino-5-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (**7**) and 5-Ethoxycarbonylamino-4-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**8**).

To a mixture of 8.83 g (0.03 mole) of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride, 7.56 g (0.03 mole) of mercuric cyanide and molecular sieve in 300 ml of dry nitromethane was added 3.06 g (0.02 mole) of **6** and the mixture was refluxed for 3 hours. After this, it was filtered while still hot in order to remove the insoluble residue which was washed with more hot nitromethane. The chloroform extract was washed with 30% aqueous potassium iodide, water and dried over sodium sulfate. The residue obtained after removing the solvent was chromatographed by tlc (1:3 acetone-chloroform). The fastest moving band afforded 2.56 g (30%) of **7** as a foam; pmr (deuteriochloroform): δ 7.55 (s, 1, H-2), 6.68 (s, 1, NH exchangeable with deuterium oxide), 5.74 (d, 1, J1'2' = 5 Hz, H-1').

Anal. Calcd. for $C_{18}H_{25}N_3O_9 \cdot H_2O$: C, 48.54; H, 6.07; N, 9.43. Found: C, 48.71; H, 6.24; N, 9.15.

The slowest moving band yielded 4.96 g (58%) of **8** as a foam; pmr (deuteriochloroform): δ 7.77 (s, 1, H-2), 6.76 (s, 1, NH exchangeable with deuterium oxide), 5.72 (d, 1, J1'2' = 5 Hz, H-1').

Anal. Calcd. for $C_{18}H_{25}N_3O_9 \cdot H_2O$: C, 48.54; H, 6.07; N, 9.43. Found: C, 48.55; H, 6.26; N, 9.20.

4-Ethoxycarbonylamino-5-methyl-1-β-D-ribofuranosylimidazole (**4**).

A solution of 2.13 g (0.005 mole) of **7** in 50 ml of methanol saturated with ammonia at 0° was allowed to stand at room temperature for 24 hours. The solvent was removed and the residue was purified by tlc (4:1 ethyl acetate-methanol) to give 1.42 g (94%) of **4** identical in all respects to that described above.

5-Ethoxycarbonylamino-4-methyl-1-β-D-ribofuranosylimidazole (**9**).

A solution of 2.13 g (0.005 mole) of **8** in 50 ml of methanol saturated with ammonia was allowed to stand at room temperature for 24 hours. The solvent was removed and the residue was purified by tlc (9:1 acetone-methanol) to give 1.39 g (92%) of **9** as a syrup; pmr (DMSO-d_6): δ 8.70 (s, 1, NH exchangeable with deuterium oxide), 7.90 (s, 1, H-2) 5.42 (d, 1, J1'2' = 3 Hz, H-1'), 1.97 (s, 3, CH_3).

Anal. Calcd. for $C_{12}H_{19}N_3O_6 \cdot H_2O$: C, 45.14; H, 6.58; N, 13.17. Found: C, 45.37; H, 6.47; N, 13.39.

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