

The Synthesis of Certain 5,7-Dihydroxyimidazo[1,2-*a*]pyrimidines

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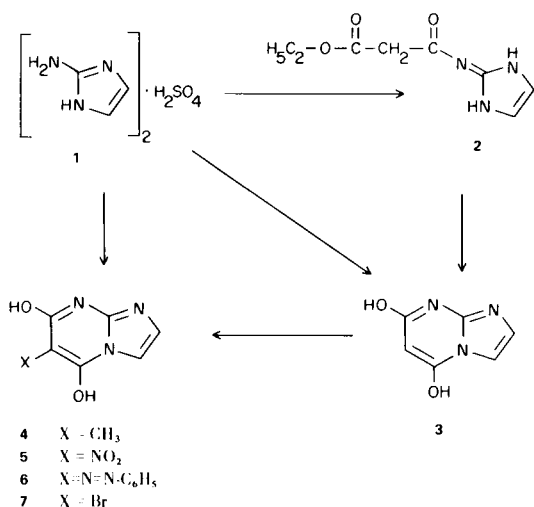
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Although several synthetic procedures have been reported for the preparation of substituted imidazo[1,2-*a*]pyrimidines, the majority of the known derivatives contain large substituent groups. Our own interest has been with the simpler purine analogs in this ring system. We now wish to report the synthesis of 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine and several 6 substituted derivatives which were of interest as potential inhibitors of certain purine enzymes.

The most common synthetic procedure that has been employed for the preparation of imidazo[1,2-*a*]pyrimidines involves the condensation of 2-aminopyrimidine derivatives with an α -halocarbonyl compound (1-17). This type of reaction proceeds quite readily, however, the nature of the substituents on the pyrimidine ring severely limits this reaction. Recently, Guerret and coworkers have synthesized several alkyl derivatives of the imidazo[1,2-*a*]pyrimidine ring system from 2-aminoimidazole derivatives (18). The possibility of utilizing this approach was then investigated for the synthesis of 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (3).

2-Aminoimidazolium sulfate (19) (1) was condensed with diethyl malonate in ethanolic sodium ethoxide. Acidification of this alcoholic reaction mixture with anhydrous hydrogen chloride afforded the intermediate 2-(*N*- α -carbethoxyacetamido)-1,2-dihydroimidazole (2).



The assignment of this structure is based on fact that the pmr spectrum of the product shows a singlet (N-H) proton at 11.40 ppm which integrates for two protons, and in addition the protons at the 4 and 5 positions of the imidazole ring appear as a sharp singlet at 6.72 δ in d_6 -DMSO. The thermal cyclization of 2 at 135° afforded 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (3). This new imidazo[1,2-*a*]pyrimidine derivative was readily purified by recrystallization from water, however, it was found that warm alkaline solution rapidly decomposed the product. Subsequently, it was found that 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (3) could be prepared directly from 1 if the sodium salt of the intermediate 2 was dissolved in cool water and the solution acidified to pH 1. Analogously, condensation of 1 with diethyl methylmalonate and with diethyl nitromalonate afforded 5,7-dihydroxy-6-methylimidazo[1,2-*a*]pyrimidine (4) and 5,7-dihydroxy-6-nitroimidazo[1,2-*a*]pyrimidine (5), respectively. Attempted replacement of the hydroxyl functions of (3-5) with phosphorus oxychloride or with phosphorus pentasulfide resulted in decomposition products.

Paudler and Kuder (9) have reported that the imidazo[1,2-*a*]pyrimidine and 5,7-dimethylimidazo[1,2-*a*]pyrimidine undergo electrophilic attack at the 3-position. Pyl and Baufeld (14-15) have studied electrophilic substitutions of 5-hydroxy-7-methyl-2-phenylimidazo[1,2-*a*]pyrimidine and have found substitutions occur at the 3-position and also at the 6-position. It was of interest to determine where electrophilic substitutions would occur in 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (3), which contains strong electron donating substituents in the 5 and 7-positions of this ring system.

Treatment of 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (3) with an aqueous solution of benzenediazonium chloride afforded the corresponding 6-phenylazo derivative (6). This product was identical in all respects to the product obtained by the base catalyzed condensation of 1 with diethyl phenylazomalonate. The treatment of 3 with bromine in acetic acid afforded 6-bromo-5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (7). Proof that electrophilic attack occurred at the 6-position was substantiated by the fact that the pmr spectrum of the product shows the

disappearance of the proton of 5.12 δ which was assigned to the proton at the 6-position of **3**.

EXPERIMENTAL (20)

2-(*N*- α -Carbethoxyacetamido)-1,2-dihydroimidazole (**2**).

A solution of sodium ethoxide in ethanol was prepared by dissolving sodium (2.3 g., 0.1 formula weights) in 150 ml. of absolute ethanol. Diethylmalonate (8.8 g., 55 mmoles) and 2-aminoimidazolium sulfate (**1**) (6.7 g., 50 mmoles) were added to the sodium ethoxide solution. The resulting solution was stirred and slowly warmed to reflux, at which time a sodium salt began to precipitate. The mixture was refluxed for six hours and then treated dropwise with 50 ml. of anhydrous ethanolic hydrogen chloride. After the addition was complete the mixture was refluxed for 20 minutes, filtered and the filtrate evaporated to dryness. The gummy residue was dissolved in 30 ml. of water and the pH of this solution brought to pH 6 by the addition of saturated sodium carbonate solution to afford a light yellow product. The product was separated by filtration, washed with water, and dried at 80°. Recrystallization from water afforded 3.35 g. (34%) of analytically pure product that slowly melts and resolidifies above 175°; pmr (DMSO- d_6): δ 1.20 (t, 3, $J = 3.5$ Hz), 3.46 (s, 2), 4.10 (q, 2, $J = 3.5$ Hz), 6.72 (s, 2), 11.40 ppm (broad, 2).

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.7; H, 5.58; N, 21.3. Found: C, 48.7; H, 5.69; N, 21.4.

5,7-Dihydroxyimidazo[1,2-*a*]pyrimidine (**3**).

Method A.

2-(*N*- α -Carbethoxyacetamido)-1,2-dihydroimidazole (**2**) (1.97 g., 10 mmoles) was heated at 200° for 45 minutes. The residue, after cooling, was recrystallized from water to afford 1.12 g. (75%) of analytically pure 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (**3**) that had a melting point $> 360^\circ$. The ultraviolet absorption spectra showed λ max (pH 1) 263 nm (ϵ , 10,600) and λ max (pH 11) 263 nm (ϵ , 11,600); pmr (DMSO- d_6): δ 5.12 (s, 1), 7.42 (d, $J = 2.5$ Hz, 1), 7.53 (d, $J = 2.5$ Hz, 1), 11.5 ppm (broad, 2).

Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.7; H, 3.31; N, 27.8. Found: C, 47.8; H, 3.31; N, 27.7.

Method B.

A solution of sodium ethoxide in ethanol was prepared by dissolving sodium (8.1 g., 0.352 formula weights) in 200 ml. of absolute ethanol. Diethylmalonate (27.4 g., 0.171 mole) and 2-aminoimidazolium sulfate (**1**) (22.2 g., 0.168 mole) were added to the sodium ethoxide solution. The resulting solution was stirred and heated at reflux for 6 hours. The mixture was cooled and the sodium salt was separated by filtration, washed with ethanol, and air dried. The sodium salt was dissolved in 100 ml. of water at 30°, and the product precipitated from the solution by the addition of 6 *N* hydrochloric acid until a pH of 1 was obtained. The mixture was cooled to 5° and the product separated by filtration, washed with ice water, and dried at 100°. Recrystallization from water afforded 11.9 g. (47%) of analytically pure 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (**3**). This product was identical in all respects to the product prepared by Method A.

5,7-Dihydroxy-6-methylimidazo[1,2-*a*]pyrimidine (**4**).

A solution of sodium ethoxide in ethanol was prepared by dissolving sodium (1.84 g., 0.08 formula weights) in 100 ml. of absolute ethanol. Diethyl methylmalonate (6.96 g., 40 mmoles) and 2-aminoimidazolium sulfate (**1**) (5.28 g., 40 mmoles) were

added to the sodium ethoxide solution. The mixture was refluxed with stirring for 8 hours and then evaporated to dryness at reduced pressure. The residue was dissolved in 100 ml. of water (30°) and the pH of the resulting solution was adjusted to 2 by the addition of 6 *N* hydrochloric acid. The product was separated by filtration, washed with cold water, and recrystallized from water to afford 2.74 g. (40%) of analytically pure product that had a melting point of 310-312° dec. The ultraviolet absorption spectra showed a λ max (pH 1) at 275 nm (ϵ , 11,900) and λ max (pH 11) at 275 nm (ϵ , 11,700); pmr (DMSO- d_6): δ 1.91 (s, 3) 7.38 (d, $J = 2.5$ Hz, 1), 7.49 (d, $J = 2.5$ Hz, 1), 11.5 ppm (broad, 2).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.9; H, 4.24; N, 25.4. Found: C, 50.91; H, 4.38; N, 25.0.

5,7-Dihydroxy-6-nitroimidazo[1,2-*a*]pyrimidine (**5**).

A solution of sodium ethoxide was prepared by dissolving sodium (4.6 g., 0.2 formula weights) in 250 ml. of absolute ethanol. Diethyl nitromalonate (20.5 g., 0.1 mole) and 2-aminoimidazolium sulfate (**1**) (13.2 g., 0.1 mole) were added to the sodium ethoxide solution. The mixture was refluxed with stirring for 9 hours, and then evaporated to dryness at reduced pressure. The residue was dissolved in 250 ml. of water, and the pH adjusted to 1-2 by the addition of 6 *N* hydrochloric acid. The product was separated by filtration, washed thoroughly with water and dried. Purification was afforded by reprecipitating the product from dilute sodium hydroxide solution by the addition of 6 *N* hydrochloric acid to afford 5.9 g. (30%) of analytically pure product, m.p. 305-307° dec. The ultraviolet absorption spectra shows λ max (pH 1) 228 nm (ϵ , 14,100) and 312 nm (ϵ , 7,050) and λ max (pH 11) at 217 nm (ϵ , 26,600) and 333 nm (ϵ , 7,250); pmr (DMSO- d_6): δ 7.27 (d, $J = 2.5$ Hz, 1), 7.44 (d, $J = 2.5$ Hz, 1), 11.0 ppm (broad, 2).

Anal. Calcd. for $C_6H_4N_4O_4$: C, 36.7; H, 2.04; N, 28.6. Found: C, 36.8; H, 2.16; N, 28.4.

5,7-Dihydroxy-6-phenylazoimidazo[1,2-*a*]pyrimidine (**6**).

Method A.

A solution of benzenediazonium chloride was prepared by treating a solution of aniline (0.31 g., 3.3 mmoles) in 7 ml. of 1.7 *N* hydrochloric acid with a solution of sodium nitrite (0.25 g., 0.0036 formula weights) in 5 ml. of water at 5°. The benzenediazonium chloride solution was added dropwise to a stirred solution of 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (**3**) (0.5 g., 3.3 mmoles) in 10 ml. of 1.25 *N* sodium hydroxide solution at 10°. After the addition was complete, the mixture was stirred at 10° for 30 minutes and then at room temperature for 30 minutes. The solid was separated by filtration, and purified by reprecipitating from a dilute sodium hydroxide solution by the addition of acetic acid. A final purification by recrystallizing from absolute ethanol afforded 0.41 g. (40%) of analytically pure product that had a melting point of 227-228° dec. The ultraviolet absorption spectra shows λ max (pH 1) 244 nm (ϵ , 11,700) and 391 nm (ϵ , 21,900) and λ max (pH 11) 235 nm (ϵ , 16,150) and 371 nm (ϵ , 21,600); pmr (DMSO- d_6): δ 7.05 (d, $J = 2.5$ Hz, 1), 7.46 (d, $J = 2.5$ Hz, 1), 7.55 (m, 5), 11.5 ppm (broad, 2).

Anal. Calcd. for $C_{12}H_9N_5O_2$: C, 56.5; H, 3.53; N, 27.4. Found: C, 56.7; H, 3.62; N, 27.6.

Method B.

A solution of sodium ethoxide was prepared by dissolving sodium (1.98 g., 0.086 formula weights) in 150 ml. of absolute ethanol. Diethylphenylazomalonate (11.35 g., 43 mmoles) and 2-aminoimidazolium sulfate (**1**) (5.68 g., 43 mmoles) were added

to the sodium ethoxide solution. The mixture was refluxed with stirring for 8 hours and then evaporated to dryness at reduced pressure. The residue was dissolved in 300 ml. of water and the pH adjusted to 5-6 by the addition of a glacial acetic acid. The product was separated by filtration, washed with water, and purified by recrystallizing from ethanol to afford 3.40 g. (31%) of analytically pure product that had a melting point of 277-279° dec. This product is identical in all respects to the product prepared by Method A.

6-Bromo-5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (7).

Bromine (0.6 g., 0.00375 formula weights) in 10 ml. of acetic acid was added dropwise to a solution of 5,7-dihydroxyimidazo[1,2-*a*]pyrimidine (3) (0.5 g., 3.3 mmoles) in 20 ml. of acetic acid with good stirring at room temperature. After the addition was complete, the mixture was stirred at room temperature for 3 hours. The solid was separated by filtration, washed with ethanol (25 ml.) and dried to afford 0.68 g. (90%) of product. Recrystallization from water afforded an analytically pure sample that decomposed above 225°. The ultraviolet absorption spectra showed λ max (pH 1) at 219 nm (ϵ , 28,200) and 273 nm (ϵ , 10,300) and λ max (pH 11) at 227 nm (ϵ , 34,600) and 270 nm (ϵ , 7,880); pmr (DMSO- d_6): δ 7.15 (d, J = 2.5 Hz, 1), 7.49 (d, J = 2.5 Hz, 1), 11.5 ppm (broad, 2).

Anal. Calcd. for $C_6H_4BrO_2$: C, 31.3; H, 1.69; N, 18.3. Found: C, 31.2; H, 1.68; N, 18.0.

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- (20) Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet and nuclear magnetic resonance spectra were determined on a Cary-15 ultraviolet spectrophotometer and on a Hitachi Perkin-Elmer R-20A high resolution nuclear magnetic resonance spectrophotometer, respectively. All samples displayed a single spot on thin layer chromatography and were analyzed by the Heterocyclic Chemical Corporation of Harrisonville, Missouri.