Heterocycles. 10. A Facile Synthesis of 7-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole [1]

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Reaction of imidazole with acrolein gave the title compound whose structure was confirmed by X-ray analysis.

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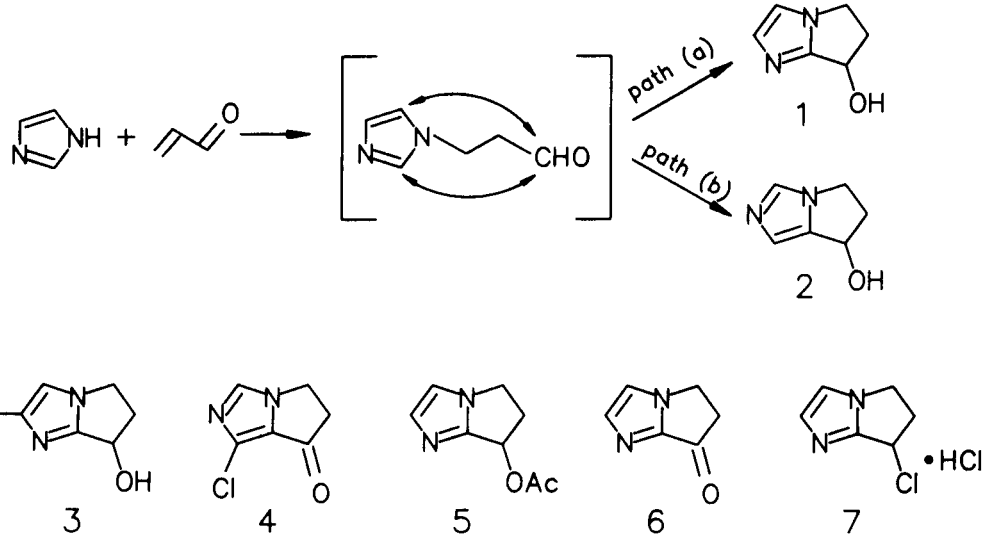
During an investigation of the synthesis of 1-alkylimidazoles as potential thromboxane synthetase inhibitors, we had occasion to react imidazole with various Michael acceptors. Reaction of imidazole with acrylic acid [2], methyl acrylate [3], acrylonitrile [4], and methyl vinyl ketone gave the expected 1,4-addition products. However, reaction of imidazole with acrolein yielded an easily isolated, white, crystalline solid whose elemental analysis indicated a 1:1 addition product corresponding to a formula of $C_6H_8N_2O$. Proton nmr of this material showed a pair of one proton doublets at 6.74 and 6.97 ppm (J's = 1.2 Hz) for the imidazole hydrogens and no aldehydic proton. Formation of an acetate upon reaction with acetic anhydride, a ketone upon oxidation with manganese dioxide, and a chloride by reaction with thionyl chloride established, in addition, the presence of a secondary alcohol.

These data led us to conclude that a reaction with acrolein had occurred followed by a cyclization. We assumed that imidazole underwent a normal Michael addition to acrolein, as shown above, from which two possible routes of cyclization are possible leading to 7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (**1**) (path a) or 7-hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole (**2**) (path b) [5]. The chemical shifts of the imidazole hydrogens in the ^1H nmr suggest the former structure for this product [6]. Rapoport, however, has shown that the chemical shifts of imidazole hydrogens cannot be relied on for structural determinations [7]. In fact, several pieces of chemical information lend support to structure **1**. For example, we were unable to see any product analogous to **1** or **2** from the reaction of 2-methylimidazole and acrolein whereas 4(5)-methylimidazole did lead to such a product **3**. Thus, when the 2 position is blocked no product is found, but when it is free a cyclized product is obtained.

Although it has been reported that imidazoleacetyl chloride on treatment with aluminum chloride gives 1-chloro-5,6-dihydro-7-oxo-7*H*-pyrrolo[1,2-*c*]imidazole (**4**) [2], a potential precursor to either **6** or **2**, we were unable to repeat the preparation.

Confirmation of the structure **1** was obtained by X-ray analysis [8]. An ORTEP drawing of the molecular struc-



ture of **1** is depicted in Figure 1, showing that the acrolein attachment is from N_1 to C_2 of the imidazole ring. The acetate, ketone, and chloride (*loc. cit.*) prepared from **1** can, therefore, be assigned structures **5**, **6**, and **7**, respectively.

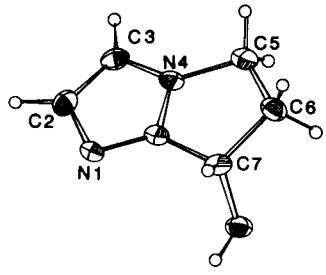


Figure 1. Molecular Structure of 1

EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (potassium bromide or neat film) were recorded on a Perkin-Elmer 521 grating spectrophotometer. Nuclear magnetic resonance spectra (deuteriochloroform with tetramethylsilane as internal standard) were run on a Varian FT-80A spectrometer. The standard drying agent was magnesium sulfate, and solvents were removed *in vacuo* on a rotary evaporator. Flash chromatography was effected with E. Merck silica gel.

6,7-Dihydro-7-hydroxy-5*H*-pyrrolo[1,2-*a*]imidazole (**1**).

A solution of imidazole (15 g, 0.22 mole), triethylamine (2 ml) and dioxane (200 ml) were treated in one portion with acrolein (16.8 g, 0.3 mole) and the reaction was heated at reflux temperature for 4 hours. The solvent was removed and the residue was dissolved in acetone-methanol and crystallized by boiling off the methanol keeping solvent level up with acetone. After cooling at 0°, the solid was filtered off and recrystallized from acetone to give **1** (10.2 g, 37%); mp 138-140°; ir: ν 3130-3060, 1510, 1090, 1020, 730 cm^{-1}; ^1H nmr: δ 2.27-3.26 (2H, m, C_6-CH_2), 3.70-4.47 (2H, m, C_5-CH_2), 5.12 + 5.23 (1H, 2 d, C_7-H), 6.82 (1H, d), 7.05 (1H, d), 8.32 (1H, s, exchangeable, OH).

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.96; H, 6.51; N, 22.36.

From another reaction, in an attempt to isolate the putative 3-imidazolepropanal by column chromatography, we only succeeded in recovering a small second crop of **1** together with some imidazole.

2-Methyl-6,7-dihydro-7-hydroxy-5*H*-pyrrolo[1,2-*a*]imidazole (**3**).

A solution of 4-methylimidazole (16.4 g, 0.20 mole) in dioxane (150 ml) and triethylamine (2 ml) was treated in one portion with acrolein (11.2 g, 0.20 mole), refluxed for 4 hours, then cooled to room temperature and concentrated. The residue was triturated with acetone and the resulting solid was filtered off and washed with acetone. The solid was crystallized from dimethylsulfoxide to give **3** (2.32 g, 8.4%), mp 196-196.5°; ir: ν 3070, 1510, 1120, 1090, 1010, 810 cm^{-1}; uv: λ 222 nm (log ϵ 3.801); ^1H nmr (perdeuteriomethanol): δ 1.53 (3H, s, CH_3), 1.73-2.50 (2H, m, C_6-CH_2), 3.17-3.57 (2H, m, C_5-CH_2), 4.25-4.45 (2H, m, C_7-H + OH), 6.10 (1H, s, C_3-H).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.86; N, 7.36; N, 20.06.

7-Acetoxy-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (**5**).

A solution of **1** (11.1 g, 0.09 mole) in pyridine (100 ml) was treated with excess acetic anhydride (20 ml) and allowed to stand at room temperature for 24 hours. The excess anhydride was decomposed with methanol and the solvent evaporated. The residue was dissolved in chloroform, washed with water, dried, and concentrated to a liquid which was distilled (Kugelrohr) to give **5** (13.0 g, 87%), bp 130-135°/0.1 T, solidified on standing mp 73-75°; ir ν 1735, 1240 cm^{-1}; uv: λ 218 (log ϵ 3.825); ^1H nmr: δ 2.08 (3H, s, CH_3), 2.67-3.40 (2H, m, C_6-CH_2), 3.95-4.33 (2H, m, C_5-CH_2), 5.96 + 6.01 (1H, 2 d), 6.98 (1H, d), 7.17 (1H, d).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.74; H, 6.22; N, 16.68.

6,7-Dihydro-7-oxo-5*H*-pyrrolo[1,2-*a*]imidazole (**6**).

A solution of **1** (12.3 g, 99.1 mmoles) in chloroform (500 ml) was treated with activated manganese dioxide (60 g) and stirred overnight at room temperature. The mixture was filtered and the filter cake washed with chloroform. The combined filtrate and wash were concentrated to a green solid (4.5 g) which was purified by flash chromatography (ethyl acetate and ethyl acetate-20%, acetone-0.5%, triethylamine) followed by crystallization (dichloromethane-hexane) to give **6** (1.05 g, 8.7%), mp 131-132°; ir: ν 1730, 1720, 1370 cm^{-1}; ^1H nmr: δ 3.06 (2H, t, C_6-CH_2), 4.34 (2H, t, C_5-CH_2), 7.28 (1H, s), 7.45 (1H, s); ^{13}C nmr: δ 186.7 (C=O), 146.4 (N-C=N), 138.6, 120.0, 40.4, 38.4.

Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.04; H, 5.01; N, 23.01.

6,7-Dihydro-7-chloro-5*H*-pyrrolo[1,2-*a*]imidazole Hydrochloride (**7**).

To the alcohol **1** (10.15 g, 81.7 mmoles) was added ice cold thionyl chloride (50 ml). After 15 minutes, the cooling bath was removed and the light brown solution was heated on a steam bath whereupon the solution became dark brown. After 5 minutes the thionyl chloride was removed under reduced pressure and the residue was taken up in ethanol (50 ml), treated with charcoal and filtered. The filtrate was diluted with anhydrous diethyl ether (400 ml). The resulting precipitate was filtered off, washed consecutively with diethyl ether, toluene and hexane, then dried under high vacuum to give **7** (11.87 g, 81%), mp 160-162°; ir (nujol): ν 2700-2400, 1300 cm^{-1}; uv (ethanol): λ 215 nm (log ϵ 3.798); ^1H nmr (DMSO-d_6): δ 2.37-3.83 (2H, m, C_6-CH_2), 4.17-4.65 (2H, m, C_5-CH_2), 5.88 + 5.93 (1H, 2 d), 7.63-7.75 + 7.78-7.91 (2H, 2 m, C_2-H + C_3-H); on treatment with deuterium oxide an additional pair of doublets appear at 5.35 and 5.43 (alcohol methine) and the pair of multiplets at 7.63-7.91 collapse to a pair of singlets of 7.61 and 7.72.

Anal. Calcd. for $C_6H_6Cl_2N_2$: C, 40.25; H, 4.50; N, 15.65. Found: C, 40.26; H, 4.57; N, 15.46.

4-(Imidazol-1-yl)-2-butanone.

A solution of imidazole (15 g, 0.22 mole), 1-buten-3-one (15.4 g, 0.22 mole), triethylamine (5 ml) and dioxane (200 ml) was heated under reflux for 24 hours. The solvent was removed and the residue distilled (Kugelrohr) to give 4-(imidazol-1-yl)-2-butanone (26 g, 86%), bp 125-130°/0.1 T [9].

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[5] For a recent review of these ring systems see P. N. Preston, in "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor, eds, John Wiley and Sons, New York, NY, 1986, p 15-76.

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[8] Crystal data for **2**: $C_6H_8N_2O$, M = 124.14, space group P1bar, a = 7.975 (4), b = 6.803 (3), c = 6.357 (3), V = 291.8 Å^3, Z = 2, and D_c = 1.413 gcm^{-3}. The diffractometer utilized for data collection was designed and constructed locally. A Picker four-cycle goniostat equipped with a Furnas monochromator (HOG crystal) and Picker X-ray generator is interfaced to a TI980 minicomputer and Slo-Syn stepping motors to drive angles. Centering is accomplished using automated Top/Bottom speed data lines to a CYBER 170-855 (NOS operating system) where all computations are performed. The final R value was 0.316 for 723 unique reflections [F > 3.00 (F)].

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