Pyrazolo[3,4-*b*]pyridines. I. Xanthine and Isoguanine Analogs Derived from 1-Methylpyrazolo[3,4-*b*]pyridine

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The synthesis of 4,6-dihydroxy-1-methylpyrazolo[3,4-*b*]pyridine (**2**) and 4-amino-6-hydroxy-1-methylpyrazolo[3,4-*b*]pyridine (**3**) as analogs of xanthine and isoguanine has been accomplished from ethyl 5-amino-1-methylpyrazole-4-carboxylate (**4**) and 5-amino-1-methylpyrazole-4-carbonitrile (**6**), respectively.

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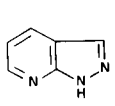
Structural variations of the natural purines have produced new chemical entities possessing potent biological properties. One such modification in which the N-7 and C-8 atoms of the purine nucleus have been interchanged has resulted in biologically interesting derivatives of the pyrazolo[3,4-*d*]pyrimidine ring system (1). As part of our study into deaza derivatives of such *iso*-purines (*i.e.*, based on **1**) the synthesis of the xanthine and isoguanine related molecules (**2** and **3**, respectively) was necessary.

Thus, reaction of ethyl 5-amino-1-methylpyrazole-4-carboxylate (**4**) (2) with diethyl malonate in ethanol containing sodium ethoxide led to ethyl 4,6-dihydroxy-1-methylpyrazolo[3,4-*b*]pyridine-5-carboxylate (**5**) which, upon saponification, produced compound **2**. Following an analogous approach, **3** was prepared from 5-amino-1-methylpyrazole-4-carbonitrile (**6**) (3) and diethyl malonate with subsequent saponification of the resultant ethyl 4-



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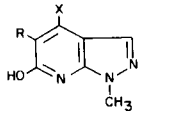
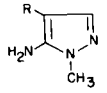


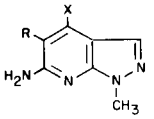
2, X = OH, R = H
3, X = NH_2, R = H
5, X = OH, R = CO_2Et
7, X = NH_2, R = CO_2Et
9, X = NH_2, R = CN



4, R = CO_2Et
6, R = CN
8, R = H

amino-6-hydroxy-1-methylpyrazolo[3,4-*b*]pyridine-5-carboxylate (**7**). Compound **2** was alternatively obtained from the reaction of 5-amino-1-methylpyrazole (**8**) (4) and diethyl malonate in diphenyl ether. On the other hand, **3** could not be synthesized in this way from **8** and ethyl cyanoacetate.

In hopes of extending this scheme to other 1-methylpyrazolo[3,4-*b*]pyridines, treatment of **6** with ethyl cyanoacetate produced 4-amino-6-hydroxy-1-methylpyrazolo-[3,4-*b*]pyridine-5-carbonitrile (**9**) with no indication of the other possible product (*i.e.*, **10**) being formed. All



10, X = NH_2, R = CO_2Et
11, X = OH, R = CN
12, X = NH_2, R = CN

attempts at reacting the malononitrile anion with **4** or **6** with plans of achieving **11** or **12** were unsuccessful, leading to recovery of starting material.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman AccuLab 3 spectrophotometer. Pmr spectra were obtained on a Varian EM-360 spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard. The pmr spin multiplicities are indicated by the symbols s (singlet), t (triplet), and q (quartet). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Ethyl 4,6-Dihydroxy-1-methylpyrazolo[3,4-*b*]pyridine-5-carboxylate (**5**).

After stirring 3.4 g. (21.3 mmoles) of diethyl malonate in 20 ml. of absolute ethanol in which 0.6 g. (0.026 g.-atom) of sodium had been dissolved at room temperature for 10 minutes, 1.5 g. (8.8 mmoles) of ethyl 5-amino-1-methylpyrazole-4-carboxylate (**4**) (2) was added slowly and the resulting solution refluxed for 4 hours. During the reflux period, a white solid began to form and at the completion of the reflux time there was a large amount of this material. The solution was then evaporated to dryness on a rotary evaporator and the residue dissolved in a minimum amount of water. Upon acidification (*p*H 2) of the aqueous solution with concentrated hydrochloric acid, the resulting precipitate was obtained by filtration and recrystallized from acetic acid-water as white crystals of **5** (0.45 g., 21.6%), m.p. 358° dec.; ir (potassium bromide): 3100-2300 (broad OH), 1700 (C=O), 1660 (C=C) cm^{-1}; pmr (trifluoroacetic acid): δ 1.60 (t, 3 H, J = 7 Hz, CH_3 of ester), 4.22 (s, 3 H, N-CH_3), 4.80 (q, 2 H, J = 7 Hz, CH_2), 8.49 (s, 1 H, H-3).

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.64; H, 4.67; N, 17.72. Found: C, 50.44; H, 4.69; N, 17.63.

4,6-Dihydroxy-1-methylpyrazolo[3,4-*b*]pyridine (**2**).

Method A.

After dissolving 0.4 g. (1.68 mmoles) of **5** in 10 ml. of 15% sodium hydroxide solution, the resulting solution was refluxed for 5.5 hours and then cooled to room temperature and placed in an ice bath. Upon acidification to *p*H 3 with concentrated hydrochloric acid, the precipitate which resulted was isolated by filtration and recrystallized from water (0.22 g., 79%) as white crystals of **2**, m.p. 335-337° dec.; ir (potassium bromide): 3290 (NH), 3110-2540 (broad OH), 1650 (C=C) cm^{-1}; pmr (trifluoroacetic acid): δ 4.20 (s, 3 H, CH_3), 6.41 (s, 1 H, H-5), 8.48 (s, 1 H, H-3).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.45. Found: C, 50.74; H, 4.20; N, 25.36.

Method B.

Diethyl malonate (0.85 g., 5.3 mmoles) and 0.46 g. (4.75 mmoles) of **8** (4) were placed in 5 ml. of diphenyl ether and the solution heated at 145° for 15 minutes in an oil bath and then under reflux for 2 hours. A precipitate began to form in the

yellowish solution during this time. Following the reflux period, the solution was cooled and 20 ml. of diethyl ether added to produce a small additional amount of product which was isolated by filtration. The material thus obtained (0.26 g., 33.2%) was recrystallized from water and found to be identical (by ir, pmr, and m.p. comparisons) to **2** obtained by Method A.

Ethyl 4-Amino-6-hydroxy-1-methylpyrazolo[3,4-*b*]pyridine-5-carboxylate (**7**).

In a manner analogous to that for preparing **5**, 2.14 g. (17.5 mmoles) of **6** was added to a 50 ml. ethanolic solution in which 1.2 g. (0.052 g.-atom) of sodium was originally added followed by 6.8 g. (42.5 mmoles) of diethyl malonate and this solution refluxed for 4 hours. After cooling the mixture (a precipitate was present) to room temperature, the ethanol was removed to dryness on a rotary evaporator and the residue dissolved in 25 ml. of water. Within seconds, a precipitate formed in the aqueous solution and it was isolated by filtration. Recrystallization of this material from acetic acid produced 0.62 g. (15%) of **7** as white crystals, m.p. 253°; ir (potassium bromide): 3480 (NH), 3310 (NH), 3200-2760 (broad OH), 1625 (hydrogen bonded C=O) cm^{-1}; pmr (hexadeuteriodimethylsulfoxide): δ 1.22 (t, 3 H, J = 7 Hz, CH_3 of ester), 3.40 (broad s, 1 H, exchangeable with deuterium oxide, OH), 3.70 (s, 3 H, N-CH_3), 4.17 (q, 2 H, J = 7 Hz, CH_2), 7.94 (s, 1 H, H-3), 8.18 (broad s, 2 H, exchangeable with deuterium oxide, NH_2).

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.85; H, 5.11; N, 23.72. Found: C, 50.60; H, 5.20; N, 23.57.

Acidification of the filtrate remaining after isolation of **7** produced no additional product formation.

4-Amino-6-hydroxy-1-methylpyrazolo[3,4-*b*]pyridine (**3**).

A mixture of 0.9 g. (3.8 mmoles) of **7** in 20 ml. of 15% sodium hydroxide solution was heated under reflux for 6 hours during which time the mixture became homogeneous. Upon cooling the solution overnight in a refrigerator, long white needles precipitated and were isolated by filtration and dissolved in a minimum amount of water. Acidification of this solution with the dropwise addition of concentrated hydrochloric acid produced a voluminous white precipitate which was obtained by filtration and recrystallized from water as white crystals of **3** (0.62 g., 100%), m.p. > 330°; ir (potassium bromide): 3380 (NH), 3200 (NH), 3100-2380 (broad OH), 1625 (C=C) cm^{-1}; pmr (hexadeuteriodimethylsulfoxide): δ 3.83 (s, 3 H, CH_3), 5.48 (s, 1 H, H-5), 6.35 (broad s, 3 H, exchangeable with deuterium oxide, NH_2, OH), 7.99 (s, 1 H, H-3).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.22; H, 4.91; N, 34.13. Found: C, 51.06; H, 4.97; N, 34.03.

4-Amino-6-hydroxy-1-methylpyrazolo[3,4-*b*]pyridine-5-carbonitrile (**9**).

To a stirred solution of 1.2 g. (0.052 g.-atom) of sodium dissolved in 50 ml. of absolute ethanol was added 4.8 g. (42.5 mmoles) of ethyl cyanoacetate followed, 10 minutes later, by 2.14 g. (17.5 mmoles) of **6**. This mixture was refluxed for 4 hours and the resulting precipitate, which appeared during the reflux and upon cooling the reaction flask, was isolated by filtration and dissolved in a minimum amount of water. Acidification of the aqueous solution to *p*H 2 with concentrated hydrochloric acid followed by filtration of the resulting voluminous solid produced **9** which was recrystallized from water as white flakes (1.2 g., 36.3%), m.p. > 360°; ir (potassium bromide): 3340 (NH), 3140-2760 (broad OH), 2205 (C≡N), 1650 (C=C) cm^{-1}; pmr (hexadeuteriodimethylsulfoxide): δ 3.76 (s, 3 H, CH_3), 7.75 (broad s, 2 H, exchangeable with deuterium oxide, NH_2), 7.91 (s, 1 H, H-3).

Anal. Calcd. for $C_8H_7N_5O$: C, 50.80; H, 3.73; N, 37.02. Found: C, 50.68; H, 3.83; N, 37.12.

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