SYNTHESIS AND PROTON NMR SPECTRA OF THE MONOMETHYL- AND DIMETHYLPYRIMIDINE-5-CARBOXYLIC ACIDS. REGIOSELECTIVE COVALENT HYDRATION AT THE 2- AND 4- RING POSITIONS

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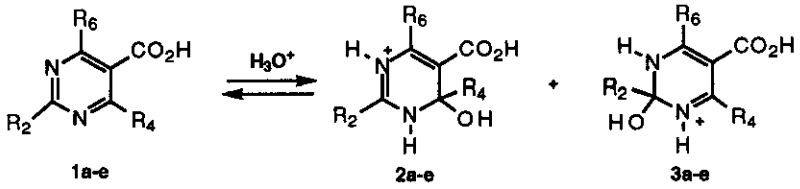
Abstract - Pyrimidine-5-carboxylic acid, its 2-methyl-, 4-methyl, 2,4-dimethyl- and 4,6-dimethyl derivatives have been synthesized and their proton nmr spectra measured in dilute aqueous acid. Pyrimidine-5-carboxylic acid (**1a**, $R_{2,4,6}$=H) was found to afford an equilibrium mixture of covalent hydrates at both the 2- and 4-ring positions (**2a** and **3a**). The 2-methyl derivative (**1b**, R_2=Me, $R_{4,6}$=H) undergoes hydration exclusively at the 4-position (**2b**) while the 4-methyl derivative (**1c**, $R_{2,6}$=H, R_4=Me) hydrates selectively at only the 2-position (**3c**). Covalent hydration was not observable for either the 2,4-dimethyl- (**1d**, $R_{2,4}$=Me, R_6=H), or 4,6-dimethyl- (**1e**, R_2=H, $R_{4,6}$=Me) pyrimidinecarboxylic acids. The synthetic routes to these substances are described and the degree of hydration for each compound was measured.

INTRODUCTION

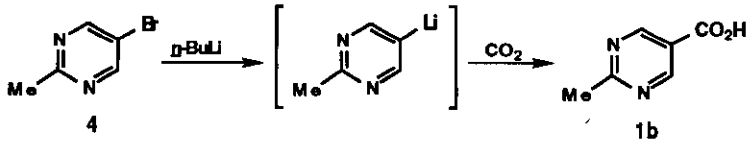
One of the underlying features that in many instances controls the chemistry of pyrimidines in aqueous media is their propensity to undergo the addition of water across the ring carbon-nitrogen double bond .[1] While the observation of these addition products has been largely limited to spectroscopic methods, several groups have been able to isolate covalently bound adducts as stable, crystalline compounds.[2,3] For some time we have been interested in the covalent hydration of simple 5-substituted pyrimidines[4,5] and more recently have observed that pyrimidine-5-carboxylic acid (**1a**, $R_{2,4,6}$=H) undergoes hydration not only at the 4-position but also concurrently at the 2-position[6a,b] (Scheme I). This simultaneous addition to two positions in the pyrimidine ring affording an equilibrium mixture of hydrates appears to be unique and prompted us to synthesize the monomethyl- and dimethylpyrimidine-5-carboxylic acids and determine the extent of hydration in dilute aqueous acid. Of particular interest were the 2- and 4-methyl derivatives since these respective sites would be "blocked" by an alkyl group.[7] Herein, we report the results of this study.



Scheme 1

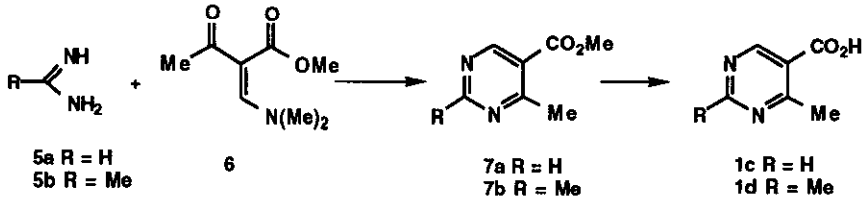
SYNTHESIS

Reaction of 2-methyl-5-bromopyrimidine[8] (**4**) with n-butyllithium followed by carbon dioxide at -95°C gave a smooth conversion to 2-methylpyrimidine-5-carboxylic acid (**1b**, Scheme 2). Interestingly, metal-halogen exchange at that temperature is faster then deprotonation of the 2-methyl group. Product (**1b**) had identical



Scheme 2

physical properties to a sample prepared in four steps from acetamidine and ethoxymethylenediethylmalonate.[9] Methyl 4-methylpyrimidine-5-carboxylate (**7a**) obtained by reaction of formamidine acetate (**5a**) with methyl 2-acetyl-3-dimethylamino-2-propenoate (**6**) afforded after saponification, the desired 4-methylpyrimidine-5-carboxylic acid (**1c,** Scheme 3) as a white crystalline solid.

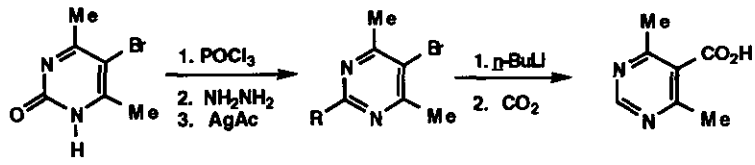


Scheme 3

Condensation of **6** with acetamidine acetate (**5b**) gave an 85% yield of methyl 2,4-dimethyl-5-pyrimidinecarboxylate (**7b**). Treatment of **7b** with hot aqueous base followed by acidification to pH 1 with concentrated hydrochloric acid afforded **1d** (Scheme 3) as fine white needles.

The tetra-substituted pyrimidine intermediate (**8**, Scheme 4), readily available by bromination of the condensation product of urea with 2,4-pentanedione,[10] served as a convenient starting material for 4,6-dimethylpyrimidine-5-carboxylic acid (**1e**). Reaction of **8** with phosphorous oxychloride followed by hydrazine afforded **9b** which on oxidation with silver acetate gave **9c** in 50% overall yield. Subsequent treatment of **9c** with butyllithium/carbon dioxide at -95°C afforded **1e** as a white powder (Scheme 4). It should be noted, as in

the case of **4**, metal-halogen exchange with **9c** is faster than deprotonation of a methyl group.



8 **9a** R = Cl; **9b** R = $NHNH_2$; **9c** R = H **1e**

Scheme 4

RESULTS AND DISCUSSION

Measurement of the proton magnetic spectrum of pyrimidine-5-carboxylic acid (**1a**) in D_2O surprisingly displays only a singlet peak centered at 9.32 ppm for the three aromatic protons. The spectrum of **1a** in 2N DCl/D_2O (Figure 1) displays a similar small singlet at 9.75 ppm in addition to five new upfield singlets. The chemical shifts and ratios (*1:1:1*) of three of the new singlets were similar to those previously observed for a 4-hydrate[4-6] and were consistent with structure (**2a**). The remaining two singlets appear in a 2:1 ratio and thus were reasoned to represent a symmetrical compound. Structure (**3a**) is consistent with these data and would result on the addition of water to the 1,2 C-N bond of **1a**. The postulated structures were confirmed based on the correlation of the proton and carbon chemical shifts obtained by a heteronuclear 2D (^{13}C-^{1}H) nmr experiment (Table 1). Based on integration, the ratio of **1a:2a:3a** in 2N DCl/D_2O is approximately 1:6:3 with the 4-hydrate predominating. The hydrated cation **3a** is the first reported observation of 1,2-hydration in the pyrimidine molecule.

Table 1. ^{13}C Nmr Chemical Shifts of Pyrimidine-5-carboxylic Acid in 2N DCl/D_2O

Position	1a (Parent)	2a (4-Hydrate)	3a (2-Hydrate)
2	155.7	149.5	77.5
4	158.9	68.9	155.0
6	158.9	132.6	155.0
5	126.8	111.9	98.5
carboxyl	166.2	167.0	166.2

Comparison of the spectra of the two monomethylpyrimidine-5-carboxylic acids (**1b**) and (**1c**) between D_2O alone and 2N DCl/D_2O was intriguing (Table 2). The spectrum of 2-methyl derivative (**1b**) in 2N DCl/D_2O was very simple and displayed one peak for the two equivalent aromatic ring protons at 9.61 ppm, two methyl singlets at 2.53 and 3.12 ppm in the ratio of 15:85 respectively and two singlets at 7.69 and 6.03 ppm. The chemical shifts of the hydrated ring protons are similar to those in **2a** and are consistent with formation of only the 4-hydrate (**2b**).

Figure 1. Proton Spectrum of Pyrimidine-5-carboxylic Acid in 2N DCl/D_2O

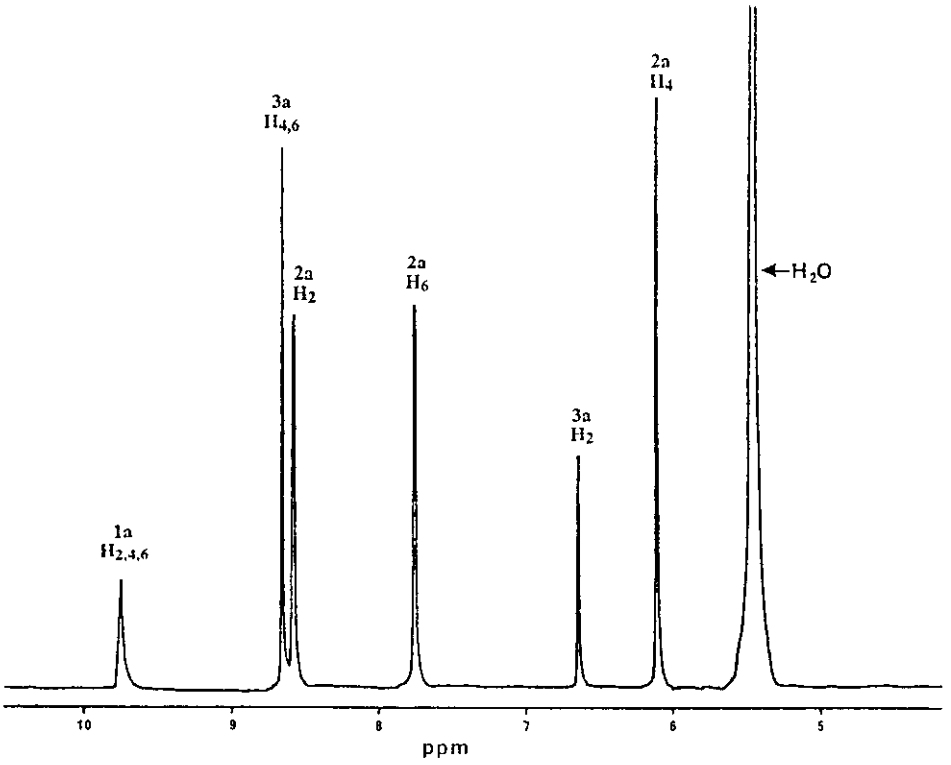


Table 2. ^1H Chemical Shifts of Pyrimidine-5-carboxylic Acids in 2N DCl/D_2O

Cmpd	Substituent			1a-e Parent			2a-e 4-Hydrate			3a-e 2-Hydrate		
	R2	R4	R6	R-2	R-4	R-6	R-2	R-4	R-6	R-2	R-4	R-6
1a	H	H	H	9.75	9.75	9.75	8.58	6.12	7.76	6.65	8.66	8.66
1b	Me	H	H	3.12	9.61	9.61	2.53	6.03	7.69	nd	nd	nd
1c	H	Me	H	9.63	3.10	9.57	nd*	nd	nd	6.50	2.66	8.61
1d	Me	Me	H	3.05	2.99	9.51	nd	nd	nd	nd	nd	nd
1e	H	Me	Me	9.35	2.86	2.86	nd	nd	nd	nd	nd	nd

*nd = not detectable

Based on integration of the two methyl groups **1b** prefers to exist almost exclusively (~6:1) as the 4-hydrated cation (**2b**) in aqueous acid medium. The 2-hydrated cation (**3b**) was not detected. Unlike the 2-methyl analog **1b**, the 4-methyl derivative (**1c**) has two unsubstituted ring positions and a priori could form a mixture of both the 4- and 2-hydrates (**2c**) and (**3c**) as in the case of pyrimidine-5-carboxylic acid (**1a**). However, examination of the spectrum of **1c** in 2N DCl/D_2O clearly revealed that we were dealing with only a single hydrate since only three new singlets were observed. One of the singlets at 2.66 ppm was readily assigned as the methyl group of the hydrated cation. The ring proton at 8.61 ppm could be either that of **2c** or **3c**. Based on the previous assignments of the ring protons (Table 2) for the 4-hydrate of **2a** and **2b** (7.69 and 7.76 ppm) and the 2-hydrate of **2a** (8.58 ppm) we have assigned this structure as the 2-hydrated cation(**3c**).The remaining ring proton at 6.50 ppm also corroborated this conclusion in its closer similarity to the 2-hydrate of **3a** (6.65 ppm) than the 4-hydrate of either **2a** or **2b** (6.12 and 6.03 ppm).

The proton spectra of neither **1d** or **1e** in 2N DCl/D_2O displayed any observable peaks for covalent hydration of their respective cations.

CONCLUSIONS

In aqueous acidic media, many 5-substituted pyrimidines prefer to exist as hydrated cations. Pyrimidine-5-carboxylic acid (**1a**) hydrates simultaneously at both the 2- and 4-positions. 2-Methylpyrimidine-5-carboxylic acid (**1b**) hydrates at only the 4-position. 4-Methylpyrimidine-5-carboxylic acid (**1c**) hydrates exclusively at the 2-position. Hydration was not observable by nmr for either the 2,4- or 4,6-dimethylpyrimidine-5-carboxylic acids (**1d** and **1e**).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The mass spectra were determined on a Model 21-110 Consolidated Electrodyne Corp. spectrometer. ^1H and ^{13}C nmr spectra were determined on either a GE QE-300 or a JEOL FX90Q Fourier transform spectrometer. All reactions were performed under a nitrogen atmosphere. Unless specified the proton chemical shifts are relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. Elemental analyses were carried out at Eli Lilly and Company. Pyrimidine-5-carboxylic acid was prepared by a known literature procedure.[11]

2-Methylpyrimidine-5-carboxylic acid (1b). To a solution of **4** (740 mg, 4.3 mmol) in 50 ml of THF at -98°C was added dropwise 3.1 ml of 1.5 M butyllithium (4.7 mmol) over 5 min. The clear orange solution was stirred for 5 min and 5 g of powdered CO_2 was added in one portion. The cooling bath was removed and the mixture was allowed to warm to room temperature. The solvent was removed under vacuum and the residue was dissolved in 29 ml of water resulting in a final pH of 9. After adjusting the pH to 7 with conc. hydrochloric acid the solution was extracted with methylene chloride (3 x 50 ml). The aqueous phase was evaporated to a volume of about 2.5 ml and the pH was lowered to 2.5 with 20% aqueous hydrochloric acid affording a light tan solid. The slurry was stirred at 0-5°C for 2 h and filtered giving after drying 250 mg (42%, mp 197-198°C, lit. value

197-198°C prepared by the method of Yamanaka[9]). Anal. Calcd for $C_6H_6O_2$: C, 52.17, H, 4.38, N, 20.28. Found: C, 52.00; H, 4.46; N, 20.05, uv (EtOH) λ_{max}(log ε) 250(2.33), 215(4.03), m/z 138(100%), ^{1}H nmr 2N DCl/D_2O (Table 2).

Methyl 4-methylpyrimidine-5-carboxylate (7a). To a solution of sodium ethoxide (made from 1.15 g, 0.05 mol of sodium metal) in 100 ml ethanol was added 5.2 g (0.05 mol) of formamidine acetate and 8.55 g (0.05 mol) of **6**. The mixture was refluxed for 18 h, evaporated to an oil and the residue was dissolved in water and extracted with chloroform (3x100 ml). The combined organic layers were dried over magnesium sulfate, filtered and evaporated affording 6.4 g of crude oil which was purified by flash chromatography (1:1 ethyl acetate:toluene/silica gel) to yield 3.8 g (50%) of **7a**, mp 35-37°C. Anal. Calcd for $C_7H_8N_2O_2$: C, 52.17, H, 4.38, N, 20.28. Found: C, 52.00, H, 4.46, N, 20.05, uv (EtOH) λ_{max}(log ε) 247(3.30), 215(3.90), m/z 152(97%), 121(100%, M-OCH_3), ir 1731 cm^{-1} (C=O), ^{1}H nmr ($CDCl_3$/TMS, δ) 9.14(s, 1H, H-2), 9.13(s, 1H, H-6), 3.95(s, 3H, OMe), 2.82(s, 3H, Me).

4-Methylpyrimidine-5-carboxylic acid (1c). A solution of **7a** (3.74 g, 0.25 mmol), 1.47 g (0.36 mol) of sodium hydroxide in 25 ml of water was heated at 80°C for 1 h, cooled to 5°C and the pH was adjusted to 2 with concentrated hydrochloric acid affording a white crystalline solid. The solid was filtered, washed with 5 ml of cold water and dried giving 940 mg (28%) of **1c**, mp 180-181°C. Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17, H, 4.38, N, 20.28. Found: C, 51.90, H, 4.45, N, 20.09, m/z 138(100%), 120(23%), 94(20%), 83(20%), 66(38%). 1H nmr (DMSO/TMS, δ) 9.14(s, 1H, H–2); 9.05(s, 1H, H–6), 2.72(s, 3H, Me), 1H nmr 2N DCl/D_2O (Table 2).

Methyl 2,4-dimethylpyrimidine-5-carboxylate (7b). To a solution of sodium methoxide (made from 1.15 g, 50 mmol of sodium metal) in methanol (100 ml) was added 4.73 g (50 mmol) of acetamidine acetate followed by 8.55 g (50 mmol) of **6** in 50 ml of methanol. The solution was heated at 65°C for 1 h and evaporated to a solid. The solid was dissolved in 75 ml of water and extracted with chloroform (3x100 ml). The combined organic layers were dried over magnesium sulfate, filtered and evaporated giving **7b**, 7.02 g (85%) as a clear yellow oil which crystallized on standing. A portion of **7b** (3.47 g) was purified by flash chromatography (1:1 ethyl acetate:toluene/silica gel) to yield 3.0 g of white needles, mp 33.5-34.5°C, Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82, H, 6.07, N, 16.86. Found: C, 57.93, H, 6.07, N, 16.47, m/z 166(75%), 135(100%, M-OMe), uv (EtOH) λ_{max}(log ε) 222(4.04), ^{1}H nmr ($CDCl_3$/TMS, δ) 9.01(s, 1H, H-6), 3.95(s, 3H, OMe), 2.77(s, 3H, Me), 2.72(s, 3H, Me).

2,4-Dimethylpyrimidine-5-carboxylic acid (1d). A solution of 1.0 g (25 mmol) of sodium hydroxide and 3.32 g (20 mmol) of **7b** in 25 ml of water was stirred at 40°C for 45 min, cooled to 5°C and the pH was adjusted to 1 with concentrated hydrochloric acid giving fine white needles. The solid was filtered, washed with 5 ml of cold water and dried affording 510 mg of **1d**, mp 154-155°C (lit.,[12] 154-155°C prepared from the ethyl ester of **1d**). The aqueous filtrate was evaporated to dryness and the residue was slurried with hot acetonitrile, filtered and dried. Removal of the acetonitrile afforded 1.01 g of additional **1d**. The total yield was 1.52 g (50%). Anal. Calcd

for $C_7H_8N_2O_2$: C, 55.26, H, 5.30, N, 18.41. Found: C, 55.31, H, 5.30, N, 18.27, m/z 152(100%), 111(79), uv (EtOH) λ_{max}(log ε) 250(3.48), 221(3.00), ^{1}H nmr 2N DCl/D_2O (Table 2).

2-Chloro-4,6-dimethyl-5-bromopyrimidine (9a). Compound (**8**)[10] 7.54 g (37 mmol) was treated with 40 ml phosphorous oxychloride and 1 ml dimethylformamide according to the method of Chesterfield[12] giving **9a** 5.77 g (70%) as tan crystals, mp 79-81°C (hexane), m/z 220, 222, 224(100%), ^{1}H nmr ($CDCl_3$/TMS, δ) 2.63 (s, 6H, 4,6-Me), uv (EtOH) λ_{max}(log ε) 365(2.31), 267(3.55), 226(4.01), Anal. Calcd for $C_6H_6N_2BrCl$: C, 32.54, H, 2.73, N, 12.65. Found: C, 32.28, H, 2.74, N, 12.42.

2-Hydrazino-4,6-dimethyl-5-bromopyrimidine (9b). *A solution of* **9a** *4.0 g (18 mmol), 3.8 g (76 mmol) of* hydrazine hydrate in 45 ml of ethanol was heated at reflux for 3 h, cooled to 3-5°C in an ice bath affording a cream colored solid which was filtered, washed with 50 ml of ethanol and dried. The crude product was crystallized from boiling 95% ethanol giving white fine needles 3.25 g (83%) of **9b**, mp 190-191°C, Anal. Calcd for $C_6H_7N_4Br$: C, 33.20, H, 4.18, N, 25.81. Found: C, 33.32, H, 4.19, N, 25.57, m/z 216, 218(100%), 187, 189(62%), uv (EtOH) λ_{max}(log ε) 307(3.46), 244(4.21), ^{1}H nmr (DMSO-d_6/TMS, δ) 8.1, 6.5 (br s, 3H, $NHNH_2$), 2.19 (s, 6H, 4,6-Me).

4,6-Dimethyl-5-bromopyrimidine (9c). A solution of compound (**9b**) 2.17 g (10 mmol) dissolved in a mixture of 2 ml of acetic acid and 250 ml of water was heated to 80°C. To the hot solution was added in 1 g portions 10.0 g (60 mmol) of silver acetate and heating was continued for 2 h. The resulting black slurry was cooled to room temperature and filtered through a 1 inch thick layer of filter aid. The filter aid was washed with chloroform (100 ml) and solid sodium bicarbonate was added to the two phase filtrate until the pH of the aqueous layer was 8-9. The organic phase was separated and the aqueous layer was extracted with chloroform (2x100 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated affording 1.30 g (69%) of pale yellow crystals of **9c**. The crude product was further purified by steam distillation and sublimation affording white crystals, mp 67-69°C, Anal. Calcd for $C_6H_7N_2Br$: C, 38.53, H, 3.77, N, 14.98. Found: C, 38.35, H, 3.72, N, 14.90, m/z 186, 188(100%), uv (EtOH) λ_{max}(log ε) 258(3.53), 220(3.77), ^{1}H nmr ($CDCl_3$/TMS, δ) 8.79 (s, 1H, H-2), 2.61 (s, 6H, 4,6-Me).

4,6-Dimethylpyrimidine-5-carboxylic acid (1e). Compound (**9b**) 1.87 g (10 mmol) was treated with butyllithium/CO_2 in a similar manner to **1b.** The final cold aqueous solution was adjusted to pH 1 with conc. hydrochloric acid whereon **1e** slowly crystallized as a white solid. The crystals were filtered, washed with 5 ml of cold water and dried to give **1e** 630 mg (41%), mp 195-196°C (with effervescence). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26, H, 5.30, N, 18.41. Found: C, 54.98, H, 5.28, N, 18.36, m/z(%) 152(100), uv (EtOH) λ_{max}(log ε) 250(4.00), ir 1717 cm^{-1}, ^{1}H nmr (DMSO-d_6/TMS, δ) 8.85 (s, 1H, H-2), 2,48 (s, 6H, 4,6-Me), 13.90 (br s, 1H, OH), ^{1}H nmr 2N DCl/D_2O (Table 2).

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7. Quinazoline readily undergoes hydration in aqueous acid at the 3,4-carbon nitrogen bond while its 4-methyl and 2,4-dimethyl derivatives do not hydrate. This lack of hydration has been ascribed to "steric blocking" of the 4-position by the methyl group (see ref. 1).
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