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

Thomas J. Kress

Chemical Process Research and Development Division
The Lilly Research Laboratories, A Division of Eli Lilly and Company,
Lilly Corporate Center, Indianapolis, Indiana 46285, U.S.A.

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, R2,4,6=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, R2=Me, R4,6=H) undergoes hydration exclusively at the 4-position (2b) while the 4-methyl derivative (1c, R2,6=H, R4=Me) hydrates selectively at only the 2-position (3c). Covalent hydration was not observable for either the 2,4-dimethyl- (1d, R2,4=Me, R6=H), or 4,6-dimethyl- (1e, R2=H, R4,6=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 pyrimidines⁴,⁵ and more recently have observed that pyrimidine-5-carboxylic acid (1a, R2,4,6=H) undergoes hydration not only at the 4-position but also concurrently at the 2-position⁶a,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.
SYNTHESIS

Reaction of 2-methyl-5-bromopyrimidine (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 than deprotonation of the 2-methyl group. Product (1b) had identical physical properties to a sample prepared in four steps from acetamidine and ethoxymethylene diethylmalonate.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.

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.

![Scheme 4]

**RESULTS AND DISCUSSION**

Measurement of the proton magnetic spectrum of pyrimidine-5-carboxylic acid (1a) in D$_2$O surprisingly displays only a singlet peak centered at 9.32 ppm for the three aromatic protons. The spectrum of 1a in 2N DCI/D$_2$O (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 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-1H) nmr experiment (Table 1). Based on integration, the ratio of 1a:2a:3a in 2N DCI/D$_2$O is approximately 1:6:3 with the hydrated cation 3a is the first reported observation of 1,2-hydration in the pyrimidine molecule.

<table>
<thead>
<tr>
<th>Position</th>
<th>1a (Parent)</th>
<th>2a (4-Hydrate)</th>
<th>3a (2-Hydrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>155.7</td>
<td>149.5</td>
<td>77.5</td>
</tr>
<tr>
<td>4</td>
<td>158.9</td>
<td>68.9</td>
<td>155.0</td>
</tr>
<tr>
<td>6</td>
<td>158.9</td>
<td>132.6</td>
<td>155.0</td>
</tr>
<tr>
<td>5</td>
<td>126.8</td>
<td>111.9</td>
<td>98.5</td>
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<tr>
<td>carboxyl</td>
<td>166.2</td>
<td>167.0</td>
<td>166.2</td>
</tr>
</tbody>
</table>

Comparison of the spectra of the two monomethylpyrimidine-5-carboxylic acids (1b) and (1e) between D$_2$O alone and 2N DCI/D$_2$O was intriguing (Table 2). The spectrum of 2-methyl derivative (1b) in 2N DCI/D$_2$O 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/D2O

Table 2. $^1$H Chemical Shifts of Pyrimidine-5-carboxylic Acids in 2N DCl/D2O

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

*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/D2O 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/D2O 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 13C 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 CO2 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
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 of 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 (3×100 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 C7HgN2O2: C, 52.17, H, 4.38, N, 20.28. Found: C, 52.00, H, 4.46, N, 20.05, uv (EtOH) 247(3.30), 215(3.90), m/z 152(97%), 121(100%, M-OMe). ir 1731 cm⁻¹ (C=O), 1H nmr (CDCl₃/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) in 25 ml of water was heated at 80°C for 1 h, cooled to 50°C and the pH was adjusted to 2 with concentrated hydrochloric acid giving 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 C₇H₄N₂O₂: 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), 1.91(s, 3H, OMe), 2.72(s, 3H, Me).

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 solution was heated at 165°C for 1 h and evaporated to a solid. The solid was dissolved in 75 ml of water and extracted with chloroform (3×100 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 C₈H₁₀N₂O₂: 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) 222(4.04), 1H nmr (CDCl₃/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 C7H8N2O2: 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), (EtOH) λ_max(log e) 250(3.48), 221(3.00), 1H nmr 2N DCl/D2O (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 Chesterfield12 giving 9a 5.77 g (70%) as tan crystals, mp 79-81°C (hexane), m/z 220, 222, 224(100%), 1H nmr (CDCl3/TMS, δ) 2.63 (s, 6H, 4,6-Me), uv (EtOH) λ_max(log e) 365(2.31), 267(3.55), 226(4.01), Anal. Calcd for C6H12BrCl: 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 C6H7N4Br: 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 e) 307(3.46), 244(4.21), 1H nmr (DMSO-d6/TMS, δ) 8.1, 6.5 (br s, 3H, NHNHz), 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 C6H7N2Br: 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 e) 258(3.53), 220(3.77), 1H nmr (CDCl3/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/CO2 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 C7H8N2O2: 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 e) 250(4.00), ir 1717 cm-1, 1H nmr (DMSO-d6/TMS, δ) 8.85 (s, 1H, H-2), 2.48 (s, 6H, 4,6-Me), 13.90 (br s, 1H, OH), 1H nmr 2N DCl/D2O (Table 2).
ACKNOWLEDGMENT

The author would like to thank Mr. Thomas Elzey of the Physical Chemistry Department of the Lilly Research Laboratories who performed the heteronuclear 2D \((^{13}\text{C}-^{1}\text{H})\) nmr experiment on 1a.

REFERENCES

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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