# Mesoionic Purinone Analogs. VIII. Synthesis and Properties of Mesoionic 5-Substituted-6-methylimidazo[1,2-*c*]pyrimidine-2,7-diones



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Mesoionic imidazo[1,2-*c*]pyrimidine-2,7-diones **1a-c**, analogs of purine-2,8-dione, were prepared from 4-amino-1-methylpyrimidin-6-ones **6a-c**. These mesoionic purinone analogs were found to exist predominantly in the C3-H tautomeric form **1** and to undergo hydrolytic ring-opening reactions to produce 2-(4-imidazolidon-2-ylidenyl)acetamides. Reaction of **1c** with dimethyl acetylene dicarboxylate produced triazacyclopent-[*cd*]indene **25** *via* 1,3-dipolar cycloaddition.

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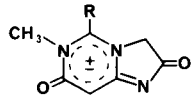
Previous reports in this series have dealt with the formulation, syntheses, and properties of a large class of bicyclic heteroaromatic compounds which possess $\pi$-electron systems isoelectronic with those of the purinones but which cannot be represented by any neutral covalent structure (2-6). A number of mesoionic analogs of xanthine have been reported to exhibit antimicrobial activity (7,8) and to inhibit adenosine cyclic 3′,5′-monophosphate phosphodiesterase (9). This report describes the synthesis and properties of mesoionic imidazo[1,2-*c*]-pyrimidine-2,7-diones (10) **1** which may be viewed as mesoionic analogs of purine 2,8-diones. The tautomerization of



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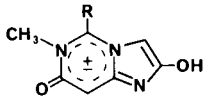
a proton on C-3 could lead to the formation of any of four additional tautomers **2-5** none of which can be represented by any neutral covalent structure.



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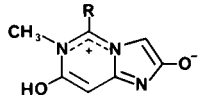

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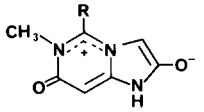

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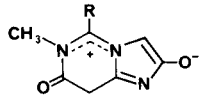

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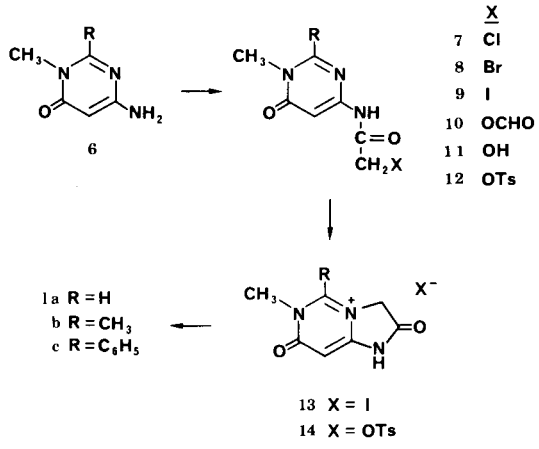
Each tautomer may be represented by a number of dipolar canonical structures: 8 for **1**, 9 for **2**, 5 for **3**, **4**, or **5**. Thus, it was of interest to determine the preferred tautomer, as well as the nature of the reactions of **1** with nucleophiles and dipolarophiles.

Haloacetamide derivatives **7a-c** and **8c** were obtained from 4-amino-1-methylpyrimidine-6-ones **6a-c** by treatment with chloro- and bromoacetic anhydride, respectively. The iodoacetamide **9a** was obtained by halogen exchange from **7a**. Attempted cyclization of these haloacetamides under a wide variety of conditions employing different solvents, catalysts such as bases, iodides, or silver salts, and under pressure in a Paar bomb led to decomposition or recovery of starting materials. Only in the case of **9a**, when heated for 5 hours in refluxing xylene, was spectroscopic evidence obtained indicating *ca.* 40% of **13a** in an inseparable mixture with **9a**.

Scheme I




A successful synthesis of **1** was obtained by the cyclization of the tosylate derivatives **12**. Treatment of **7a-c** with sodium formate in dimethylformamide gave the corresponding formates **10a-c**. Although the amide group in **10** was easily cleaved in aqueous alkali, the alcohols **11a-c** were obtained by use of aqueous sodium bicarbonate in ethanol or by refluxing methanolic solutions of **10a-c**. The tosylates **12a-c** were obtained by addition of the lithium or sodium salts of **11a-c** to an excess of tosyl chloride. Heating tosylates **12a-c** in refluxing xylene or chlorobenzene produced **14a-c** in high yield (80-97%).

Spectroscopic evidence for the structure of **14a** is: the downfield shift of the C2-H resonance from $\delta$ 8.35 in **12a** to $\delta$ 9.35; the upfield shift of C5-H resonance from $\delta$ 6.92 in **12a** to $\delta$ 6.00; and the resonance of C3-H at $\delta$ 4.90 relative to the methylene signal at $\delta$ 4.78 in **12a**. The carbonyl band at 1730 $cm^{-1}$ in **12a** appears to have shifted to

1780 $cm^{-1}$ in **14a**. Similar spectroscopic features, except for the C5-H resonance signal, were observed in **14b** and **14c**. Treatment of **14b** and **14c** with strong base anion exchange resin in methanol gave **1b** and **1c**, respectively, in good yield.

While salts **14a-c** were only soluble in methanol or dimethylsulfoxide, **1b** and **1c** were soluble in acetonitrile and **1c** was soluble in chloroform. Both of the latter compounds were white crystalline substances stable in light and air. The formulas for **1b** and **1c** were determined by elemental analysis and from the parent molecular ion peak in their low resolution mass spectra. Figure 1 shows the $^1H$- and $^{13}C$-nmr chemical shift values for **7b** and **1b**. Of particular note is the large upfield shift of the pyrimidine

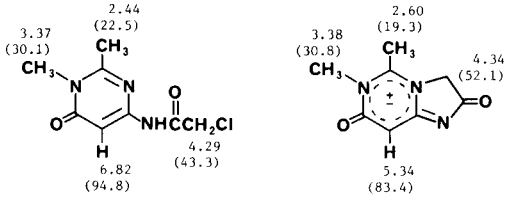
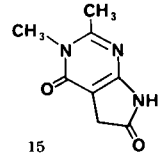



Figure 1. Comparison of pmr and $^{13}C$-nmr (bracketed) chemical shift values ($\delta$) for **7b** and **1b**.

ring proton resonance signal, as well as that of the carbon resonance at this position, indicative of an increase in electron density at this position. It should be noted that structure **15** which may be expected to exhibit similar

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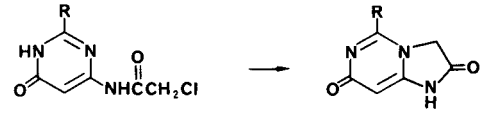
spectroscopic features can be eliminated since the low field $^1H$-nmr signal at $\delta$ 5.34 appears as a sharp singlet with no evidence of nitrogen quadrapole broadening and fails to undergo exchange in deuterium oxide. The singlets at $\delta$ 4.34 and 2.60, however, disappear when deuterium oxide is added to the dimethylsulfoxide solution of **1b** as expected. Since both **1b** and **1c** exhibit a two-proton singlet in their nmr spectra in a variety of deuterated solvents (chloroform, acetonitrile, methanol, and dimethylsulfoxide) the existance of appreciable amounts (>5%) of tautomers **2**, 3, and **4** is unlikely. Also the lack of exchange in deuterium oxide of the proton assigned to the pyrimidine ring in **1b** and **1c** would reduce the likelihood that this signal arises from C3-H in **5b** and **5c**. Thus, **1b** and **1c** appear to be the predominate stable tautomers.

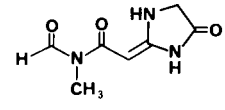
This result is consistent with the tautomerism of related covalent compounds. The related covalent derivatives **17a** and **17b** were prepared from the corresponding chloroacetamidopyrimidones **16** by a modification of the method of Noell and Robins (11). Of the numerous possible tautomeric forms for these compounds (11) only tautomer **17** was observed. The highest frequency carbonyl absorption band in **17a** occurs at 1745 $cm^{-1}$ in comparison to that at 1715 $cm^{-1}$ in **1b**.




16a R = $CH_3$
16b R = $C_6H_5$ 17

Hydrolytic Ring-Opening Reactions.

Treatment of salt **14a** with strong base anion exchange resin or with tertiary amines in dry alcohol led to the recovery of starting material. A product assigned structure **18** was obtained in high yield when **14a** was treated with one equivalent of aqueous sodium hydroxide at 0°. An alternative structure resulting from cleavage of the N6-C5 bond following hydroxide ion attack at C5 appears unlikely due to the lack of splitting observed for the pmr signal assigned to the methyl group in the product.

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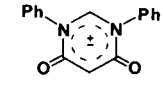


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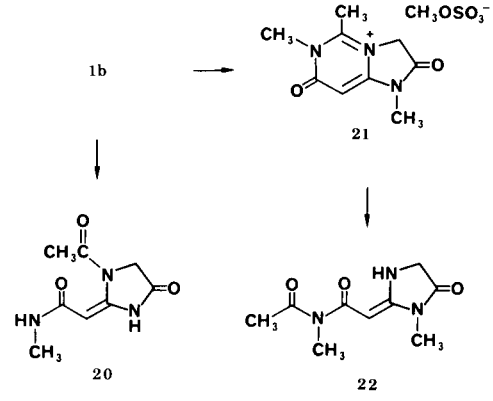
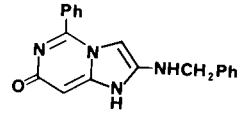
A similar reaction has been reported by Potts and Sorm (12) with the monocyclic mesoionic pyrimidinedione **19**.

The 5-methyl derivative **1b** was stable in water at room temperature but underwent hydrolysis in refluxing aqueous solution or when treated with aqueous sodium hydroxide solution. The hydrolysis product was assigned structure **20** which results from cleavage of the C5-N6 bond following hydroxide ion attack at C5. This assignment of structure is supported by the observation of a doublet attributed to the *N*-methyl group in the pmr spectrum of **20**.



When **1b** was first treated with dimethyl sulfate and the resulting salt **21** was treated with strong base resin, the ring-opened product **22** was obtained. Although the reactions of salts **14a** and **21** to give **18** and **22** appear to proceed by a mechanism different from that of the conversion of **1b** to **20**, acyl group migration following the ring-opening reaction could obscure a common mechanism.

Treatment of **14a** or **1b** with non-anionic nucleophiles such as benzylamine did not yield characterizable products. Phenyl derivative **1c** was stable at room temperature in ethanol containing benzylamine, however, imidazopyrimidone **23** was obtained in good yield upon treatment of **1c** in refluxing ethanol containing a large excess of benzylamine. It would appear that the initial step in this reaction does not involve nucleophilic displacement on the *N*-methyl group because the resulting intermediate **17b** was found to be stable under these reaction conditions.

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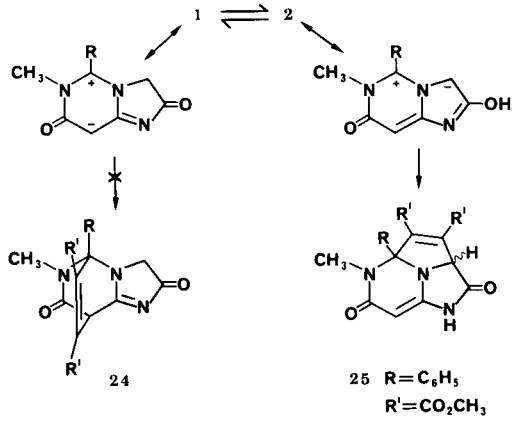
Cycloaddition Reactions.

Several six-membered ring-mesoionic heterocycles have been reported to undergo 1,4-dipolar cycloaddition reactions (4,12,13). Inspection of the dipolar resonance structures of the various tautomers of **1** reveals that reaction with dipolarophiles, such as dimethyl acetylenedicarboxylate might proceed in either a 1,3- or 1,4-dipolar cycloaddition as shown in Scheme II. Based upon the dipolar canonical structures it would appear that; **1** would undergo 1,4-cycloaddition, **3**, **4**, and **5** would favor 1,3-cycloaddition, and **2** might undergo either cycloaddition mode. Reaction of **1c** with dimethyl acetylenedicarboxylate gave 1,3-cycloadduct **25**. This structure was assigned on the basis of the elemental analysis and high resolution mass spectrum, indicating a one to one adduct, and its pmr spectrum which exhibits three one proton singlets, only one of which undergoes exchange in deuterium oxide.

Scheme II




Reaction of **1c** with dimethyl sulfate in dimethylformamide produced the methylsulfate salt **26** of the 1-methyl derivative of **1c**. Evidence supporting the alkylation of the lactam nitrogen rather than the C-3 methylene group is the observation of a two-proton singlet at $\delta$ 5.28 assigned to the C-3 methylene group in **26**. Attempts to prepare the corresponding neutral mesoionic 1-methyl derivative of **1c** by treatment of **26** with various bases led to production of an unstable oil which could not be purified and characterized.

## EXPERIMENTAL

Infrared spectra were obtained on a Perkin-Elmer 727B spectrophotometer or a Nicolet 7199 Fourier Transform spectrophotometer. Pmr spectra were obtained on a Varian T-60A spectrometer, and $^{13}$C-nmr spectra were obtained on a Varian FT-80 spectrometer. Melting points were obtained using a Fisher-Johns hotstage melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlabs, Atlanta, Georgia. Mass spectra were obtained by the Department of Chemistry, Cornell University, Ithaca, New York.

*Mesoionic* 5,6-Dimethyl-3*H*-imidazo[1,2-*c*]pyrimidine-2,7(6*H*)-dione (**1b**).

To a solution of the tosylate salt **14b** (1.7 g, 4.8 mmoles) in methanol (150 ml) was added dry, activated strong base ion exchange resin (Rexyn 201, $OH^-$, 2.5 g, 9.8 meq). The mixture was allowed to stand at room temperature with occasional agitation for 40 minutes. The mixture was filtered and the resin beads washed with additional methanol. The combined filtrate was treated with decolorizing carbon, filtered, and evaporated *in vacuo* to yield 0.61 g (70%) of white needles after recrystallization from methanol, mp 265-270°; ir (potassium bromide): 3450 cm$^{-1}$, 1690 (C=O), 1640 (C=O); pmr (DMSO-$d_6$): $\delta$ 5.34 (s, 1H), 4.34 (s, 2H, exchangeable with deuterium oxide), 3.38 (s, 3H), 2.60 (s, 3H, exchangeable with deuterium oxide); ms: m/e (int), 180 (m + 1, 6.2), 179 (m, 57.6), 55 (100.0), 54 (15.6); uv (water, *p*H 7.0): $\lambda$ ($\epsilon$) 231 (14,300) and 285 (12,900).

*Anal.* Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.66; H, 5.06; N, 23.41.

*Mesoionic* 6-Methyl-5-phenyl-3*H*-imidazo[1,2-*c*]pyrimidine-2,7(6*H*)-dione (**1c**).

Using a procedure identical to that described for **1b**, the tosylate salt **14c** (1.5 g, 3.6 mmoles) in methanol (55 ml) with dry, activated Rexyn 201 (3.0 g 11.7 meq) gave fine white needles, 0.74 g (84%) after recrystallization from methanol, mp 218-218.5°: ir (potassium bromide): 1715 cm$^{-1}$ (C=O), 1630 (C=O), 1490, 1250; pmr (DMSO-$d_6$): $\delta$ 8.03-7.83 (m, 2H), 7.70-7.52 (m, 3H), 6.34 (s, 1H), 4.60 (s, 2H), 4.00 (s, 3H); uv (water, *p*H 7.0): $\lambda$ ($\epsilon$) 229 nm (25,000), 255 (15,200) and 303 (8,900); ms: m/e calcd. for $C_{13}H_{10}N_2O_2$ (m-1); 240.0773. Measured mass: 240.0775.

*Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.69; H, 4.61; N, 17.42.

4-Amino-1,2-dimethylpyrimidin-6-one (**6b**).

Using a procedure identical to that described (14) for **6c**, 4-amino-6-hydroxy-2-methylpyrimidine (20.0 g, 0.16 mole) in dry dimethylformamide (100 ml), sodium hydride (99%, 5.0 g, 0.21 mole) and dimethyl sulfate (22.5 ml, 0.24 mole) gave 10.0 g (44.8%) of **6b**. Recrystallization from methanol produced white needles, mp 251-252°

(lit (15) 242°).

4-Amino-1-methyl-2-phenylpyrimidin-6-one (**6c**).

To a dry 500 ml three-neck flask fitted with addition funnel, overhead stirrer, thermometer, and drying tube (calcium sulfate) was added 4-amino-6-hydroxy-2-phenylpyrimidine (16) (53.2 g, 0.28 mole) and dry dimethylformamide (distilled from calcium hydride, 200 ml). Sodium hydride (99%, 819 g, 0.37 mole) was added in portions with stirring. An ice-water bath was used to moderate the reaction. The mixture was stirred at room temperature until the evolution of gas had ceased (*ca.* 30 minutes). The mixture was cooled to 0-5° and dimethyl sulfate (39.9 ml, 0.41 mole) was added dropwise over 20 minutes. The solution was stirred 25 minutes at room temperature then concentrated *in vacuo* to a viscous oil. The oil was crystallized by stirring in water (100 ml) to yield a white solid, which was collected and dried to yield 41.0 g (72%) of **6c**. An analytical sample was recrystallized from acetone-water (1:1) to yield fine white needles, mp 114.5-116.5°; ir (potassium bromide): 3435 $cm^{-1}$, 1646 (C=O); pmr (DMSO-$d_6$): $\delta$ 8.4-8.2 (m, 2H), 7.5-7.35 (m, 3H), 6.63 (br, 2H, $NH_2$), 5.74 (s, 1H), 3.93 (s, 3H).

*Anal.* Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.72; H, 5.56; N, 20.85.

4-Chloroacetamido-1-methylpyrimidin-6-one (**7a**).

A mixture of **6a** (17) (625 mg, 5 mmoles) and chloroacetic anhydride (1.71 g, 10 mmoles) in chloroform (30 ml) was heated to reflux for 8 hours. The product was collected by filtration of the cooled mixture and was recrystallized from dioxane to give 400 mg (40%) of **7a**, mp 204-205° dec; ir (nujol): $cm^{-1}$ 3200 (NH), 1700 (C=O); pmr (DMSO-$d_6$): $\delta$ 3.5 (s, 3H), 4.4 (s, 2H), 7.0 (s, 1H), 8.4 (s, 1H); ms: m/e 201.

*Anal.* Calcd. for $C_7H_8ClN_3O_2$: C, 41.70; H, 4.00; N, 20.84. Found: C, 41.78; H, 4.09; N, 20.67.

4-Chloroacetamido-1,2-dimethylpyrimidin-6-one (**7b**).

A mixture of **6b** (1.5 g, 10.7 mmoles) and chloroacetic anhydride (2.6 g 15 mmoles) in chloroform (30 ml) was heated to reflux for 3 days. The precipitate was collected by vacuum filtration and washed with chloroform. Recrystallization from acetone, with charcoal treatment, gave flat, white needles, 1.65 g (72%) of **7b**, mp 191-192°; ir (potassium bromide): 3250 $cm^{-1}$, 1725 (C=O), 1660 (C=O); pmr (DMSO-$d_6$): $\delta$ 10.7 (br, 1H, NH), 6.82 (s, 1H), 4.29 (s, 3H), 3.37 (s, 3H), 2.44 (s, 3H).

*Anal.* Calcd. for $C_8H_{10}ClN_3O_2$: C, 44.56; H, 4.67; N, 19.49; Cl, 16.44. Found: C, 44.55; H, 4.67; N, 19.49; Cl, 16.40.

4-Chloroacetamido-1-methyl-2-phenylpyrimidin-6-one (**7c**).

A solution of **6c** (9.4 g, 47 mmoles) and chloroacetic anhydride (8.2 g, 48 mmoles) in chloroform (200 ml) was heated to reflux for 5 hours. The cooled solution was washed with saturated aqueous sodium bicarbonate solution (2 × 75 ml), dried (magnesium sulfate) and evaporated *in vacuo* to leave a pale yellow solid. Recrystallization from carbon tetrachloride, with charcoal treatment, gave white crystals, 10.7 g, (82%) of **7c**, mp 94.5-95.5°: ir (potassium bromide): 3390 $cm^{-1}$, 1697 (C=O), 1605 (C=O); pmr (deuteriochloroform): $\delta$ 8.82 (br, 1H, NH), 8.5-8.3 (m, 2H), 7.6-7.35 (m, 3H), 7.42 (s, 1H), 4.20 (s, 2H), 4.10 (s, 3H).

*Anal.* Calcd. for $C_{13}H_{12}ClN_3O$: C, 56.23; H, 4.36; N, 15.13; Cl, 12.77. Found: C, 56.18; H, 4.27; N, 15.14; Cl, 12.72.

4-Bromoacetamido-1-methyl-2-phenylpyrimidin-6-one (**8c**).

Using a procedure identical to that described for **7c**, **6c** (4.0 g, 19.9 mmoles) and bromoacetic anhydride (9.0 g, 34.6 mmoles) in chloroform (50 ml) gave white crystals, 4.15 g (68%) of **8c**, mp 116.5-117.5°; ir (potassium bromide): 3309 $cm^{-1}$, 1675 (C=O), 1604 (C=O), pmr (deuteriochloroform): $\delta$ 10.9 (br, 1H, NH), 8.55-8.35 (m, 2H), 7.60-7.45 (m, 3H), 7.50 (s, 1H), 4.12 (s, 3H), 4.05 (s, 2H).

*Anal.* Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.76; N, 13.04; Br, 24.80. Found: C, 48.48; H, 3.76; N, 13.03; Br, 24.89.

4-Iodoacetamido-1-methylpyrimidin-6-one (**9a**).

To **7a** (2.0 g, 10 mmoles) in absolute ethanol (50 ml) was added a solution of potassium iodide (3.2 g, 20 mmoles) in water (2 ml). The mixture was heated at reflux for 5 hours then stirred overnight at room temperature. A white solid was collected and washed with water (2 × 5 ml), ethanol (2 × 5 ml) and ether (3 × 5 ml). Two recrystallizations from methanol produced fine white needles 1.4 g (47%) of **9a**, mp 173-174°; ir (potassium bromide): 3300-2700 $cm^{-1}$, 1710 (C=O), 1660 (C=O); pmr (DMSO-$d_6$): $\delta$ 10.71 (br, 1H, NH), 8.37 (s, 1H), 6.90 (s, 1H), 3.95 (s, 2H), 3.39 (s, 3H).

*Anal.* Calcd. for $C_7H_8IN_3O_2$: C, 28.69; H, 2.75; N, 14.34; I, 43.30. Found: C, 28.67; H, 2.76; N, 14.35; I, 43.25.

4-Hydroxyacetamido-1-methylpyrimidin-6-one (**11a**).

A suspension of **7a** (20.1 g, 0.10 mole) and sodium formate (7.5 g, 0.11 mole) in dry dimethylformamide (100 ml) was warmed on a steam bath for 2 hours, filtered, and the collected solid washed with dimethylformamide. This residue was stirred in water (40 ml), filtered, and washed with water (4 × 10 ml). The dimethylformamide filtrate was concentrated *in vacuo* to give a brown oil which crystallized upon stirring in water (20 ml). These crystals were collected, combined with the previous residue, and were washed with acetone to yield crude ester **10a**, 18.5 g, (88%) which was used without further purification.

The crude formate was stirred in absolute methanol at room temperature for 3 days. Solvent was evaporated *in vacuo* and the residue washed once with acetone (30 ml) to yield **11a**, 16.1 g, (88% from **7a**). An analytical sample was recrystallized from water, mp 233-234°; ir (potassium bromide): 3400 $cm^{-1}$ (OH), 1730 (C=O), 1660 (C=O); pmr (DMSO-$d_6$): $\delta$ 9.59 (br, 1H, NH), 8.32 (s, 1H), 6.90 (s, 1H), 5.60 (br t, J = 5 Hz, 1H), 4.00 (d, J = 5 Hz, 2H), 3.33 (s, 3H).

*Anal.* Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.91; H, 4.98; N, 22.87.

1,2-Dimethyl-4-hydroxyacetamidopyrimidin-6-one (**11b**).

Using a procedure identical to that described for **11a** the formoxyacetamide **10b** was prepared from the chloroacetamide **7b** (29.6 g, 0.137 mole) and sodium formate (10.0 g, 0.15 mole) in dimethylformamide (200 ml) in 91.3% yield (28.2 g). The crude formate in absolute methanol was heated at reflux for 5 hours. During this time the solid material dissolved leaving a tan solution. A tan crystallate formed as the solution cooled to room temperature and was collected. Chilling the filtrate at 4° overnight produced a second crop. Recrystallization from methanol gave 18.9 g (71%) of **11b** as fine, white needles, mp 185-186°; ir (potassium bromide): 3500-2700 $cm^{-1}$, 1710 (C=O), 1675 (C=O); pmr (DMSO-$d_6$): $\delta$ 9.40 (br, 1H, NH), 6.83 (s, 1H), 5.65 (br, 1H, OH), 4.05 (s, 2H), 3.40 (s, 3H), 2.47 (s, 3H).

*Anal.* Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.78; H, 5.62; N, 21.27.

4-Hydroxyacetamido-1-methyl-2-phenylpyrimidin-6-one (**11c**).

To a solution of the chloroacetamide **7c** (1.8 g, 6.5 mmoles) in dimethylformamide (7 ml) was added sodium formate (0.48 g, 7.0 mmoles) and the mixture heated on a steam bath for 3.5 hours. The brown mixture was filtered while still warm and the filtrate was concentrated. The oily residue was triturated with ethanol-water (1:1, 10 ml) and the resulting solid collected. After drying overnight the beige solid (2.0 g) was recrystallized from carbon tetrachloride-ligroin (5:1) to yield off-white needles of crude formate **10c**, 1.75 g, (94%), mp 110-112°.

To a mixture of ethanol (95%, 8 ml) and water (10 ml) was added the crude formate **10c** (1.6 g, 5.6 mmoles) followed by saturated aqueous sodium bicarbonate (6 ml). The mixture was heated on a steam bath for 15 minutes, chilled in an ice-water bath, and the resulting crystals collected and washed with cold water to give 1.4 g, (94%) of **11c**. An analytical sample was recrystallized from carbon tetrachloride containing 2-3% methanol to yield fine white needles, mp 176-178°; ir (potassium bromide): 3600-2900 $cm^{-1}$, 1720 (C=O); pmr (DMSO-$d_6$): $\delta$ 8.45-8.20 (m, 3H, integrates for 2H after exchange with deuterium oxide), 7.60-7.30 (m, 4H, integrates for 3H after exchange with deuterium oxide), 7.32 (s, 1H), 4.04 (s, 2H), 3.98 (s, 3H).

*Anal.* Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.07; H, 5.08; N, 16.19.

1-Methyl-4-(4'-methylphenylsulfonyloxyacetamido)pyrimidin-6-one (**12a**).

To a suspension of hydroxyacetamide **11a** (2.7 g, 14.7 mmoles) in dry dimethylformamide (40 ml) was added sodium hydride (99%, 0.50 g, 20.8 mmoles) in a single portion. The mixture was stirred under nitrogen until gas evolution ceased (*ca.* 20 minutes). After stirring an additional 15 minutes the resulting slurry was transferred *via* syringe fitted with a 16 gauge needle to a cold (0-5°), vigorously stirred solution of *p*-toluenesulfonyl chloride (8.5 g, 45 mmoles) in dry tetrahydrofuran (400 ml). The mixture was stirred 30 minutes and filtered. The tan solid was stirred in cold aqueous acetic acid (5%, 10 ml), collected, and washed with cold water (2 × 10 ml) and acetone (2 × 10 ml). The off-white solid was dried to give 3.53 g (71%) of **12a**. An analytical sample was recrystallized once from acetonitrile, mp 159.5-161°; ir (potassium bromide): 3300-2750 $cm^{-1}$, 1730 (C=O), 1670 (C=O); pmr (DMSO-$d_6$): δ 10.14 (br, 1H, NH), 8.35 (s, 1H), 7.82 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 6.82 (s, 1H), 4.78 (s, 2H), 3.38 (s, 3H), 2.38 (s, 3H).

*Anal.* Calcd. for $C_{14}H_{15}N_3O_5S$: C, 49.58; H, 4.48; S, 9.50. Found: C, 49.56; H, 4.58; S, 9.27.

1,2-Dimethyl-4-(4'-methylphenylsulfonyloxyacetamido)pyrimidin-6-one (**12b**).

To a fine suspension of hydroxyacetamide **11b** (2.0 g, 10.1 mmoles) in dry tetrahydrofuran (60 ml) at 0-5° under a nitrogen atmosphere was added *n*-butyllithium (1.6 *M* in hexane, 6.4 ml, 10.2 mmoles). The mixture was stirred 5 minutes then transferred as described for **12a** to a solution of *p*-toluenesulfonyl chloride (6.0 g, 32 mmoles) in tetrahydrofuran (350 ml) at 0-5°. This mixture was stirred at room temperature 45 minutes then worked up as described for **12a** to yield **12b** as a white solid, 2.72 g (76%). An analytical sample was recrystallized from acetonitrile to yield white needles, mp 151-153°; ir (potassium bromide): 3250 $cm^{-1}$, 1730 (C=O), 1670 (C=O); pmr (DMSO-$d_6$): δ 10.4 (br, 1H, NH), 7.80 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 6.74 (s, 1H), 4.77 (s, 2H), 3.39 (s, 3H), 2.42 (s, 6H).

*Anal.* Calcd. for $C_{15}H_{17}N_3O_5S$: C, 51.27; H, 4.88; N, 11.96. Found: C, 51.32; H, 4.92; N, 11.92.

1-Methyl-2-phenyl-4-(4'-methylphenylsulfonyloxy)acetamidopyrimidin-6-one (**12c**).

To a solution of hydroxyacetamide **11c** (2.0 g, 7.7 mmoles) in tetrahydrofuran (40 ml) was added sodium hydride (99%, 0.26 g, 11 mmoles). After gas evolution ceased (*ca.* 15 minutes) the white slurry was transferred in portions *via* syringe to a cold (0-5°) solution of *p*-toluenesulfonyl chloride (4.0 g, 21 mmoles) in tetrahydrofuran (30 ml) over a period of 20 minutes. After stirring, an additional 20 minutes the solvent was evaporated *in vacuo*. The pink residue was stirred in ice-cold 5% aqueous acetic acid (40 ml), collected, washed with ice-cold water (40 ml), and dried. Recrystallization from carbon tetrachloride including treatment with decolorizing carbon gave **12c** as white crystals, 2.4 g (75%), mp 134-135°; ir (potassium bromide): 3450 $cm^{-1}$, 1720 (C=O), 1600; pmr (deuteriochloroform): δ 8.60-8.25 (m, 3H, integrates for 2H after exchange with deuterium oxide), 7.85 (d, J = 8 Hz, 2H), 7.60-7.23 (m, 6H), 4.60 (s, 2H), 4.10 (s, 3H), 2.42 (s, 3H).

*Anal.* Calcd. for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16; S, 7.76. Found: C, 58.11; H, 4.67; N, 10.13; S, 7.72.

6-Methyl-3*H*-imidazo[1,2-*c*]pyrimidinium-2,7(6*H*)-dione *p*-Toluenesulfonate (**14a**).

A suspension of tosyloxyacetamide **12a** (1.75 g, 5.19 mmoles) in chlorobenzene (25 ml) was heated at reflux for 2 hours. The mixture was cooled to room temperature and the white crystalline product was collected and washed with ethyl ether to give **14a** 1.40 g (80%). Recrystallization from acetonitrile produced white needles, mp 195-196°; ir (potassium bromide): 3200-2500 $cm^{-1}$, 1780 (C=O), 1605 (C=O); pmr (DMSO-$d_6$): δ 9.85 (s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 6.00 (s, 1H), 4.90 (s, 2H), 3.50 (s, 3H), 2.38 (s, 3H).

*Anal.* Calcd. for $C_{14}H_{15}N_3O_5S$: C, 49.85; H, 4.48; N, 12.46. Found: C, 49.59; H, 4.54; N, 12.40.

5,6-Dimethyl-3*H*-imidazo[1,2-*c*]pyrimidinium-2,7(6*H*)-dione *p*-Toluenesulfonate (**14b**).

Using a procedure identical to that described for **14a**, tosyloxyacetamide **12b** (21.0 g, 59.8 mmoles) in chlorobenzene (250 ml) gave 20.5 g (97.6%) of **14b**. An analytical sample was obtained by stirring the product in hot acetonitrile, and collecting the solid which was then washed with additional portions of hot acetonitrile, mp 232-233°; ir (potassium bromide): 3300-2300 $cm^{-1}$, 1780 (C=O), 1600; (DMSO-$d_6$): δ 7.45 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 5.95 (s, 1H), 4.95 (s, 2H), 3.55 (s, 3H), 2.80 (s, 3H), 2.30 (s, 3H).

*Anal.* Calcd. for $C_{15}H_{17}N_3O_5S$: C, 51.27; H, 4.88; N, 11.96. Found: C, 51.27; H, 4.91; N, 11.96.

6-Methyl-5-phenyl-3*H*-imidazo[1,2-*c*]pyrimidinium-2,7(6*H*)-dione *p*-Toluenesulfonate (**14c**).

A suspension of tosyloxyacetamide **12c** (0.44 g, 1.1 mmoles) in xylene (12 ml) was heated to reflux whereupon the solid material dissolved. After heating at reflux 2 hours the mixture was cooled to *ca.* 60° and the precipitate was collected and washed with ether to give **14c** as white crystals, 0.38 g (85%), mp 208-210°; ir (potassium bromide): 3150-2300 $cm^{-1}$, 1790 (C=O), 1660 (C=O); pmr (DMSO-$d_6$): δ 8.12-7.80 (m, 2H), 7.80-7.55 (m, 3H), 7.45 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 6.85 (s, 1H), 5.18 (s, 2H), 4.20 (s, 3H), 2.28 (s, 3H).

*Anal.* Calcd. for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16; S, 7.76. Found: C, 58.03; H, 4.65; N, 10.16; S, 7.71.

6-Chloroacetamido-2-methyl-3*H*-pyrimidin-4-one (**16a**).

A mixture of 2-methyl-4-aminopyrimidin-6-one (**14**) (1.75 g, 14.0 mmoles) and chloroacetic anhydride (4.0 g, 23.4 mmoles) in chloroform (50 ml) was heated at reflux for 26 hours. The mixture was cooled, filtered and collected solid was washed with chloroform (3 × 25 ml). Recrystallization from methanol gave 7.3 g (82%) of **16a**, mp 208-210°; ir (potassium bromide): 3300-2400 $cm^{-1}$, 1690 (C=O), 1660 (C=O); pmr (DMSO-$d_6$): δ 12.20 (br, 1H, NH), 10.62 (br, 1H, NH), 6.71 (s, 1H), 4.30 (s, 2H), 2.28 (s, 3H).

*Anal.* Calcd. for $C_7H_8ClN_3O_2$: C, 41.70; H, 4.00; N, 20.84. Found: C, 41.74; H, 4.03; N, 20.79.

6-Chloroacetamido-2-phenyl-3*H*-pyrimidin-4-one (**16b**).

Using a procedure identical to that described for the preparation of **7c**, 6-amino-2-phenylpyrimidin-4-one (**15**) (1.0 g, 5.3 mmoles) and chloroacetic anhydride (1.5 g, 8.8 mmoles) in chloroform (30 ml) gave 1.31 g (94%), of **16b**. Recrystallization from dimethylformamide gave white needles, mp 226-227°; ir (potassium bromide): 3350-2500 $cm^{-1}$, 1725 (C=O), 1610 (C=O); pmr (DMSO-$d_6$): δ 10.80 (br, 1H, NH), 8.20-8.02 (m, 2H), 7.67-7.42 (m, 3H), 6.94 (s, 1H), 4.40 (s, 2H).

*Anal.* Calcd. for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94; Cl, 13.45. Found: C, 54.63; H, 3.82; N, 15.92; Cl, 13.41.

5-Methyl-3*H*-imidazo[1,2-*c*]pyrimidine-2,7(4*H*)-dione (**17a**).

A mixture of **16a** (0.75 g, 0.37 mmoles) in water (20 ml) was heated to 100° and concentrated aqueous ammonium hydroxide solution (10 ml) was added. The *p*H of the resulting clear solution was adjusted to 6-7 by addition of acetic acid and the solution was chilled overnight at 4°. The white precipitate of **17a** was collected. Two recrystallizations from water gave white crystals, 0.11 g (18%), mp 293-295°; pmr (DMSO-$d_6$): δ 5.35 (s, 1H), 4.61 (s, 2H), 2.31 (s, 3H).

*Anal.* Calcd. for $C_7H_7N_3O_2 \cdot H_2O$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.64; H, 5.18; N, 22.70.

5-Phenyl-3*H*-imidazo[1,2-*c*]pyrimidine-2,7(4*H*)-dione (**17b**).

Chloroacetamide **16b** (1.0 g, 3.8 mmoles) was treated with aqueous ammonium hydroxide (21 ml) as described for **17a**. There resulted 0.41 g (49%) of **17b**, mp >300° after recrystallization from methanol; ir (potassium bromide): 3100 $cm^{-1}$, 3050-2200, 1745 (C=O), 1680 (C=O); pmr (DMSO-$d_6$): δ 7.83-7.34 (m, 6H, integrates for 5H after exchange with deuterium oxide), 5.42 (s, 1H), 4.62 (s, 2H).

*Anal.* Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.24; H, 4.05; N, 18.44.

*N*-Formyl-*N*-methyl-2-(4-imidazolidon-2-ylidenyl)ethanamide (**18**).

To a solution, stirred in an ice-water bath, of **14a** (1.23 g, 3.65 mmoles) in water (25 ml) was added dropwise an aqueous solution of sodium hydroxide (0.2*N*, 18.25 ml, 3.65 mmoles). The resulting white precipitate was collected, washed with ice-cold water (5 ml) and dried to give **18**, 0.55 g, (92%). The product did not exhibit a distinct melting point but gradually decomposed above 160°. An analytical sample was obtained by recrystallization from acetonitrile; ir (potassium bromide): 3380 $cm^{-1}$, 3350-2700, 1735 (C=O), 1660 (C=O); pmr (DMSO-$d_6$): $\delta$ 11.0 (br, 1H, NH), 9.13 (s, 1H), 8.67 (br, 1H, NH), 4.73 (s, 1H), 4.02 (s, 2H), 2.94 (s, 3H).

*Anal.* Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.89; H, 4.98; N, 22.92.

*N*-Methyl-2-(1-acetyl-4-imidazolidon-2-ylidenyl)ethanamide (**20**).

To an aqueous solution of sodium hydroxide (0.2 *N*, 10 ml, 2.0 mmoles) was added **1b** (0.20 g, 1.1 mmoles) and the resulting solution was stirred for 30 minutes. The solution was acidified with glacial acetic acid (0.5 ml) and chilled in an ice-water bath. The resulting off-white crystals were collected, washed with ice-cold water and dried. Recrystallization from methanol produced **20** as white needles, 90 mg (42%), mp 225-226°; ir (potassium bromide): 3350 $cm^{-1}$, 3250, 1780 (C=O), 1690 (C=O), 1610 (C=O); pmr (DMSO-$d_6$): $\delta$ 11.33 (br, 1H, NH), 7.66 (br, q, J = 5 Hz, 1H, NH), 5.90 (s, 1H), 4.26 (s, 2H), 2.54 (d, J = 5 Hz, 3H, collapses to a singlet after exchange with deuterium oxide), 2.05 (s, 3H).

*Anal.* Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.59; H, 5.65; N, 21.22.

*N*-Acetyl-*N*-methyl-2-(3-methyl-4-imidazolidon-2-ylidenyl)ethanamide (**22**).

To a suspension of **1b** (0.20 g, 1.1 mmoles) in dimethylformamide (5 ml) at 90° was added dimethyl sulfate (0.21 ml, 2.2 mmoles). The resulting solution was stirred for 20 minutes then concentrated *in vacuo* to give a brown viscous oil. This oil was dissolved in absolute methanol (15 ml) and dry, activated strong base ion exchange resin (Rexyn 201, $OH^-$, 1.0 g, 3.9 meq) was added. The mixture was allowed to stand for 30 minutes with occasional agitation. The resin beads were removed by filtration and washed with methanol (2 × 5 ml). The filtrate and washings were combined, treated with decolorizing carbon, filtered, and evaporated *in vacuo* leaving an off-white solid residue. Recrystallization from ethyl acetate-methanol (3:1) gave **22** as fine, white needles, 0.14 g (63%), mp 159-161°; ir (potassium bromide): 3300 $cm^{-1}$, 3100, 3500-2500, 1725 (C=O), 1625 (C=O); pmr (DMSO-$d_6$): $\delta$ 10.3 (br, too broad to integrate accurately), 5.05 (s, 1H), 4.03 (s, 2H), 3.12 (s, 3H), 2.95 (s, 3H), 2.28 (s, 3H).

*Anal.* Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.98. Found: C, 51.30; H, 6.27; N, 19.80.

5-Phenyl-2-phenylmethylamino-4*H*-imidazo[1,2-*c*]pyrimidin-7-one (**23**).

A mixture of **1c** (0.25 g, 1.0 mmole) in absolute ethanol (20 ml) and benzylamine (1.0 g, 10 mmoles) was heated at reflux for 20 hours. The mixture was concentrated *in vacuo* to a yellow oil which crystallized upon trituration with ether (15 ml). Recrystallization from ethanol gave 0.28 g (85%) of **23**, mp 270° dec; ir (potassium bromide): 3280 $cm^{-1}$, 3175, 1600 (C=O); pmr (DMSO-$d_6$): $\delta$ 8.43 (br, 1H, NH), 7.93-7.70 (m, 2H), 7.70-7.40 (m, 3H), 7.32 (s, 5H), 5.77 (br, 1H, NH), 4.70-4.40 (br, 2H), 4.38 (s, 2H); ms: m/e (int) 316 (M+, 34.8), 315 (m-1, 100.0), 91 (41.8), 79 (7.14), 77 (3.52).

*Anal.* Calcd. for $C_{19}H_{16}N_4O$: C, 72.19; H, 5.10; N, 17.71. Found: C, 72.08; H, 5.19; N, 17.70.

Dimethyl 1,2,2a,4a,5,6-hexahydro-5-methyl-2,6-dioxo-4a-phenyl-1,5,7b-triazacyclopent[*cd*]indene-3,4-dicarboxylate (**25**).

To a solution of **1c** (0.11 g, 0.46 mmole) in chloroform (8 ml) was added dimethyl acetylenedicarboxylate (60 ml, 0.50 mmole). The resulting yellow solution was stirred for 2 days at room temperature. The solution was concentrated *in vacuo* to a red brown oil which was taken-up in ethyl acetate (1.5 ml) and placed on a column of 7.5 g of silica gel. Elution with ethyl acetate gave 65 mg of a yellow semi-solid which was further purified *via* thick-layer chromatography on a silica gel plate (5 × 20 cm, 1 mm) developed in ethyl acetate-methanol 9:1 to give, after recrystallization from ethyl acetate, 37 mg (21%) of **25**, mp 183-184°; ir (potassium bromide): 1730 $cm^{-1}$ (C=O), 1715 (C=O), 1620 (C=O), 1605 (C=O); pmr (deuteriochloroform): $\delta$ 7.68-7.32 (m, 5H), 7.10 (s, 1H, NH), 6.57 (s, 1H), 6.33 (s, 1H), 4.03 (s, 3H), 3.80 (s, 3H), 3.60 (s, 3H); ms: m/e calcd. for $C_{19}H_{16}N_3O_6$ (m-1); 382.1039. Found: 382.1051.

*Anal.* Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47. Found: C, 59.49; H, 4.49.

1,6-Dimethyl-5-phenyl-3*H*-imidazo[1,2-*c*]pyrimidinium-2,7(6*H*)-dione Methylsulfate (**26**).

Dimethyl sulfate (0.22 ml, 2.5 mmoles) was added to a suspension of **1c** (0.64 g 1.7 mmoles) in dimethylformamide (5 ml) heated to 75°. The resulting orange-red solution was stirred for 5 minutes then concentrated *in vacuo* and the residual oil was triturated with chloroform-ether (1:1, 10 ml) to give a pale orange solid. This solid was collected, washed with ether (2 × 5 ml), and recrystallized from isopropanol to give 0.41 g (68%) of **26** as white needles, mp 157-159°; ir (potassium bromide): 3100 $cm^{-1}$, 3025, 1785 (C=O), 1685 (C=O); pmr (DMSO-$d_6$): $\delta$ 8.14-7.86 (m, 2H), 7.83-7.60 (m, 3H), 7.30 (s, 1H), 5.28 (s, 2H), 3.24 and 3.22 (two singlets unresolved, >6H due to water peak), (acetonitrile-$d_3$): 8.06-7.55 (m, 5H), 6.78 (s, 1H), 5.05 (s, 2H), 4.20 (s, 3H), 3.37 (s, 3H), 3.27 (s, 3H).

*Anal.* Calcd. for $C_{15}H_{17}N_3O_6S$: C, 49.04; H, 4.66; N, 11.44; S, 8.73. Found: C, 49.13; H, 4.70; N, 11.37; S, 8.67.

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## REFERENCES AND NOTES

(1) Taken in part from the dissertation submitted by M. D. Taylor to the Graduate School, State University of New York at Buffalo, in partial fulfillment of the requirements for the Ph.D. degree.

(2) R. A. Coburn, *J. Heterocyclic Chem.*, **8**, 881 (1971).

(3) R. A. Coburn, R. A. Carapellotti, and R. A. Glennon, *ibid.*, **10**, 479 (1973).

(4) R. A. Coburn and R. A. Glennon, *ibid.*, **10**, 487 (1973).

(5) R. A. Coburn and B. Bhooshan, *J. Org. Chem.*, **38**, 3868 (1973).

(6) R. A. Coburn and R. A. Carapellotti, *Tetrahedron Letters*, 663 (1974).

(7) R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.*, **62**, 1785 (1973).

(8) R. A. Coburn, R. A. Glennon, and Z. F. Chmielewicz, *J. Med. Chem.*, **17**, 1025 (1974).

(9) R. A. Glennon, M. E. Rogers, J. D. Smith, M. K. El-Said, and J. L. Egle, *ibid.*, **24**, 658 (1981).

(10) *Anhydro*-2-hydroxyimidazo[1,2-*c*]pyrimidinium-7-one hydroxide.

(11) C. W. Noell and R. K. Robbins, *J. Heterocyclic Chem.*, **1**, 34 (1963).

(12) K. T. Potts and M. Sorm, *J. Org. Chem.*, **37**, 1422 (1972).

(13) T. Kappe and W. Lube, *Angew. Chem., Int. Ed. Engl.*, **10**, 925 (1971).

(14) A. Maggiollo, A. P. Phillips, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 106 (1951).

(15) H. Hiramo, Y. Yomainoto, *J. Pharm. Soc. Japan*, **76**, 237 (1956).

(16) F. Bergman, *J. Chem. Soc.*, 3729 (1963).

(17) W. Pfleiderer and E. Liedek, *Ann. Chem.*, **612**, 163 (1958).