Mesoionic Compounds. XXIII. The *anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium Hydroxide System[1]

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Reaction of 4,6-dimethyl-2-methylaminopyrimidine with carbon suboxide gave *anhydro*-2-hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium hydroxide, a new fused-ring, heteroaromatic betaine containing a "masked" 1,4-dipolar system. With dimethyl acetylenedicarboxylate, dicyanoacetylene, and dibenzoylacetylene, 1,4-dipolar cycloaddition occurred with the formation of the appropriate 8,9-disubstituted pyrido[1,2-*a*]-pyrimidin-6-one system. Olefinic dipolarophiles such as *N*-phenylmaleimide, maleic anhydride, and tetracyanoethylene did not form cycloaddition products with the betaine.

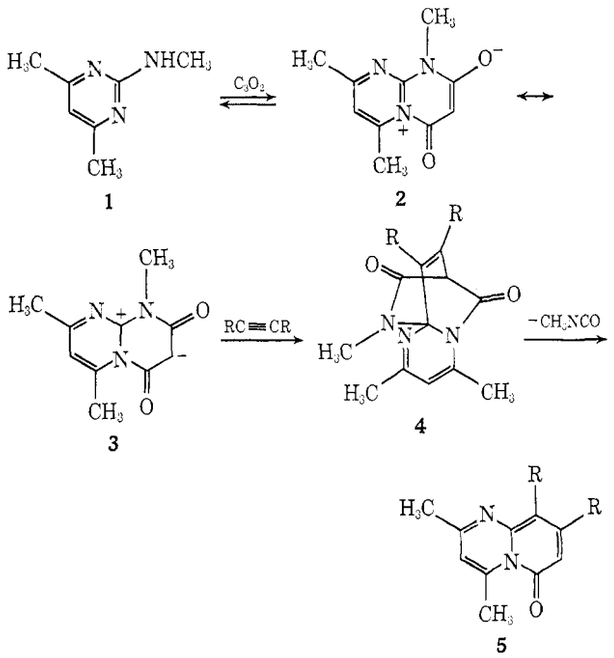
In recent publications it has been shown that N,N'-disubstituted amidines[2] and 2-methylaminopyridines[3] undergo ready reaction with carbon suboxide, forming in excellent yields heteroaromatic betaines such as *anhydro*-4-hydroxy-6-oxo 1,2,3-trisubstituted pyrimidinium hydroxide and *anhydro*-2-hydroxy-4-oxo-1-methylpyrido[1,2-*a*]pyrimidinium hydroxide, respectively. These betaines contain "masked" 1,4 dipoles and undergo cycloaddition with acetylenic dipolarophiles, the former giving substituted 2-pyridones and the latter substituted 4*H*-pyrido[1,2-*a*]pyrid-4-ones. In both cases methyl (or phenyl) isocyanate is eliminated from the initial 1:1 cycloadduct.

Carbon suboxide has also been found to undergo reaction with various N-substituted thioamides[4] with varying degrees of success. In these analogous anhydro 2,3-disubstituted 4-hydroxy-6-oxo-1,3-thiazinium hydroxides sulfur replaces one of the nitrogens of the above pyrimidinium betaines with an accompanying decrease in the stability of the ring system.

These amidines and the thioamides may be represented by a general structural formula RC(=X)ZH, and it is of particular interest to evaluate the scope and limitations of the possible variations of R, X, and Z. Such a series of reactions with carbon suboxide will provide several heteroaromatic betaines anticipated to have interesting chemical properties and, as part of this study, this communication describes the synthesis and characterization of a new fused-ring heteroaromatic betaine, *anhydro*-2-hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium hydroxide (**2**).

4,6-Dimethyl-2-methylaminopyrimidine[5] (**1**), prepared from 4,6-dimethyl-2-pyrimidone[6] *via* the 2-chloro compound[7] and methylamine, underwent ready reaction with carbon suboxide in anhydrous ether, forming **2** in 88% yield. Analytical and mass spectral data showed that a 1:1 adduct had been formed and infrared data indicated the presence of two carbonyl groups (ν_{CO} 1740, 1670 cm^{-1}). The nmr spectrum showed that in addition to the three methyl groups there were only two singlet hydrogens to be considered. Their chemical shifts, τ 5.34 and 2.80, suggested that one was at a center of high electron density. These data are consistent with structure **2** for the adduct. Hydrolysis of **2** with water gave mainly 4,6-dimethyl-2-methylaminopyrimidine (**1**), the use of saturated sodium bicarbonate or 10% sodium hydroxide solution resulting in further degradation of the pyrimidine ring.

The betaine **2** is a resonance-stabilized, heteroaromatic system, structure **2a** representing a 1,4-dipolar contributor to the system. Acetylenic dipolarophiles such as dimethyl acetylenedicarboxylate, dicyanoacetylene, and dibenzoylacetylene underwent ready cycloaddition with **2** in boiling xylene, forming 8,9-disubstituted 2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones (**5**) in good yields. By analogy with



other such cycloadditions, **4** was most likely the intermediate in the reaction, methyl isocyanate being eliminated during the reaction process. The structures of the final products **5** were readily established by analytical and spectral data. Thus in 8,9-dicyano-2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (**5**, R = CN) a molecular ion at *m/e* 224 and analytical data indicated a molecular formula of $C_{12}H_8N_4O$ and infrared data showed the presence of the CN group (ν_{CO}

(1) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.

(2) K. T. Potts and M. Sorm, *J. Org. Chem.*, **37**, 1422 (1972); T. Kappe and W. Lube, *Monatsh. Chem.*, **102**, 781 (1971); T. Kappe and W. Lube, *Angew. Chem., Int. Ed. Engl.*, **10**, 925 (1971).

(3) K. T. Potts and M. Sorm, *J. Org. Chem.*, **36**, 8 (1971).

(4) T. Kappe and W. Gosler, *Synthesis*, 312 (1972); K. T. Potts and M. Nichols, unpublished results.

(5) T. B. Johnson and K. G. Mackenzie, *J. Amer. Chem. Soc.*, **42**, 360 1909).

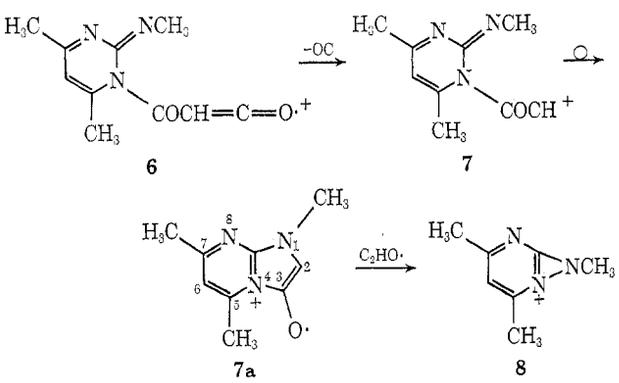
(6) T. Matsukawa and B. Ohta, *J. Pharm. Soc. Jap.*, **69**, 489 (1949); *Chem. Abstr.*, **44**, 3456 (1950).

(7) St. Angesterin, *Ber.*, **34**, 3956 (1901).

1690 cm^{-1}). The presence of two methyl groups was shown by the nmr spectrum (τ 7.50, 7.09), as well as two singlet protons (τ 3.50, 3.37), and the ultraviolet spectrum was consistent with that of 1,2-dicyano-4*H*-quinolizin-4-one.[3]

Ethyl phenylpropiolate, ethyl propiolate, diphenylacetylene, and phenylacetylene did not undergo cycloaddition with **2**, nor was it possible to obtain well-defined products from **2** and olefinic dipolarophiles. *N*-Phenylmaleimide, dimethyl maleate, fumaronitrile, *trans*-1,2-dibenzoylethylene, tetracyanoethylene, acrylonitrile, ethyl azodicarboxylate, and *tert*-butyl azodicarboxylate all failed to undergo reaction with **2**. Despite these shortcomings, this cycloaddition route offers a convenient synthesis of the 6*H*-pyrido[1,2-*a*]pyrimidin-6-one system which is not readily available by other methods, the most direct synthetic route from 2-aminopyridines leading to the isomeric 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.[8]

In all the cycloaddition reactions of **2** with the acetylenic dipolarophiles, 4,6-dimethyl-2-methylaminopyridine was found in the reaction. With ethyl phenylpropiolate, phenylacetylene, and diphenylacetylene, the methylamino compound was the sole product obtained. This fragmentation of **2** is in direct contrast to the stability of the *anhydro*-2-hydroxy-4-oxo-1-methylpyrido[1,2-*a*]pyrimidinium hydroxide system[3] and is reflected in the mass spectrum of **2**. In addition to a moderately intense molecular ion at *m/e* 205 (18%), the most intense ion in the spectrum is the M − CO ion at *m/e* 177. Such a ready loss of CO can best be explained in terms of elimination from the valence bond isomer **6** of the molecular ion, a common feature encountered in mesoionic systems.[9] Subsequent rearrangement of **7** into **7a**, the ion anticipated from the unknown *anhydro*-3-hydroxy-1,5,7-trimethylimidazo[1,2-*a*]pyrimidinium hydroxide system, followed by loss of $HC_2O\cdot$, would give **8**, *m/e* 136, which



occurred in the spectrum of **2** to the extent of 20%. This is equivalent to the M − 1 ion observed in the spectrum of 4,6-dimethyl-2-methylaminopyrimidine (32%). It is not unexpected, then, that in the cycloaddition reactions of **2** a competing thermal fragmentation is occurring which becomes the predominant reaction pathway in the presence of moderately reactive acetylenic dipolarophiles. Accordingly it was found that, when **2** was heated in xylene for 14 hr, its precursor **1** was obtained in 25% yield.

(8) C. R. Hansen and M. J. Weiss, *J. Org. Chem.*, **14**, 453 (1949).

(9) K. T. Potts, R. Armbruster, E. Houghton, and J. Kane, *Org. Mass Spectrom.*, **7**, 203 (1973).

Experimental Section[10]

***anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium Hydroxide (2).**—4,6-Dimethyl-2-methylaminopyrimidine (**1**) (2.0 g, 1.35 mmol) in anhydrous ether (100 ml) and a catalytic amount of anhydrous aluminum chloride was added slowly to a stirred ethereal solution (100 ml) of a slight excess of carbon suboxide[11] (1.0 g, 1.48 mmol). After 12-hr reflux the yellow precipitate was collected and recrystallized from acetone, separating as cream prisms: 2.3 g (88%); mp 182° dec; ir (KBr) 3110, 3070 (CH), 1740, 1670 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 228 nm (log ϵ 3.91), 240 (3.95), 322 (3.20); nmr (DMSO-d_6) τ 7.46 (s, 3, C_8 CH_3), 6.72 (s, 3, C_6 CH_3), 6.48 (s, 3, NCH_3), 5.34 (s, 1, C_3 H), 2.80 (s, 1, C_7 H); mass spectrum *m/e* (rel intensity) 205 (18, $M\cdot^+$), 177 (100, M − CO).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.41; H, 5.39; N, 20.41.

Cycloaddition Reactions with Acetylenic Dipolarophiles.—The following illustrates the general procedure used. *anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium hydroxide (**2**) (1.05 g, 3 mmol) and dimethyl acetylenedicarboxylate (0.64 g, 4.5 mmol) in dry xylene (200 ml) were heated under reflux for 3 hr. After evaporation of the solvent the crude residue was chromatographed on silica gel (Florisil F-100) using benzene–ethyl acetate (90:10) as eluent. Dimethyl 2,4-dimethyl-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-8,9-dicarboxylate (**5**, R = $COOCH_3$) crystallized from cyclohexane, and also from methanol, as cream prisms: 0.44 g (51%); mp 126.5–128°; ir (KBr) 3080, 3015, 2970, (CH), 1750, 1685, 1640 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 237 nm (log ϵ 4.16), 268 sh (4.08), 407 (3.82); nmr ($CDCl_3$) τ 7.56 (s, 3, C_2 CH_3), 7.04 (s, 3, C_4 CH_3), 6.20 (s, 3, C_8 $COOCH_3$), 6.12 (s, 3, C_9 $COOCH_3$), 3.40 (s, 1, C_3 H), 3.20 (s, 1, C_7 H); mass spectrum *m/e* (rel intensity) 290 (67, $M\cdot^+$).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.80; H, 4.84; N, 9.68.

Similarly **8,9-dicyano-2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one** (**5**, **R = CN**) crystallized from benzene–cyclohexane as yellow prisms: mp 220–221°; ir (KBr) 3070 (CH), 2230 (CN), 1690 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 239 nm (log ϵ 4.34), 274 (3.80), 399 (4.02), 418 (4.03); nmr ($CDCl_3$) τ 7.50 (s, 3, C_2 CH_3), 7.09 (s, 3, C_4 CH_3), 3.50 (s, 1, C_3 H), 3.37 (s, 1, C_7 H); mass spectrum *m/e* (rel intensity) 224 (39, $M\cdot^+$).

Anal. Calcd for $C_{12}H_8N_4O$: C, 64.29; H, 3.60; N, 24.99. Found: C, 64.19; H, 3.60; N, 24.93.

8,9-Dibenzoyl-2,4-dimethyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (**5**, **R = COPh**) crystallized from methanol as yellow prisms: 47%; mp 208–209°; ir (KBr) 3070, 2940 (CH), 1690, 1680, 1650 cm^{-1} (CO); $\lambda_{max}^{CH_3OH}$ 237 nm (log ϵ 4.35), 252 (4.41), 391 (3.94); nmr ($CDCl_3$) τ 7.82 (s, 3, C_4 CH_3), 6.94 (s, 3, C_4 CH_3), 3.55 (s, 1, C_3 H), 3.54 (s, 1, C_7 H), 2.7–2.0 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) 382 (100, $M\cdot^+$).

Anal. Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.29; H, 4.74; N, 7.14.

4,6-Dimethyl-2-methylaminopyrimidine (**1**).—2-Chloro-4,6-dimethylpyrimidine (9.0 g, 6.33 mol) and methylamine (15 ml of 40% solution) were heated in a bomb for 16 hr (oil bath temperature 100°). After cooling the colorless solid was collected, washed with water, and recrystallized from hexanes, forming colorless needles, 7.38 g (90%), mp 99° (lit.[5] mp 99°).

Hydrolysis of *anhydro*-2-Hydroxy-4-oxo-1,6,8-trimethylpyrimido[1,2-*a*]pyrimidinium Hydroxide.—The betaine (0.8 g) was refluxed in water (50 ml) for 2 hr. After cooling, the aqueous solution was extracted with chloroform and the organic phase was evaporated to dryness leaving a pale yellow oil. The oil was chromatographed on Florisil F-100 using ethyl acetate–chloroform as eluent. The product was recrystallized from hexanes giving colorless needles as described for **1** above.

Registry No.—**1**, 15231-64-8; **2**, 41108-47-8; **5** (R = $COOCH_3$), 41108-48-9; **5** (R = CN), 41108-49-0; **5** (R = COPh), 41108-50-3; dimethyl acetylenedicarboxylate, 762-42-5; 2-chloro-4,6-dimethylpyrimidine, 4472-44-0; methylamine, 74-89-5.

(10) Spectral characterizations were carried out with the following instrumentation: ir, Perkin-Elmer Model 337 infrared spectrophotometer, uv, Cary Model 14 spectrophotometer; nmr, Varian T-60 spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV using the direct insertion probe at a temperature of *ca.* 150°. Evaporations were done under reduced pressure using a rotatory evaporator and melting points were determined in capillaries. Microanalyses are by Instranal Laboratories Inc., Rensselaer, N. Y.

(11) A. Stock and H. Stolzenberg, *Ber.*, **50**, 498 (1917).