Competitive Isomerization and Dealkylation of 2,4-Dialkoxypyrimidines in Aqueous and Nonaqueous Media[1]

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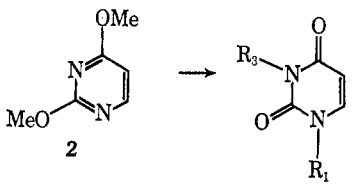
The competitive reactions of lactim–lactam isomerization and dealkylation of several 2,4-dialkoxypryimidines have been observed for the first time in aqueous solutions in the pH range of 1–5. In strong acids or alkali or at a high dilution of the pyrimidine base, dealkylations are singularly important. A rationale is presented for the specific partial hydrolysis of the 2-methoxy group in acid and the 4-methoxy moiety in basic conditions. Isomerizations are favored in nonaqueous media where dealkylations are limited to alkyl oxygen bond cleavage. Aqueous acid treatment of an equimolar mixture of 2,4-dimethoxy- (**2**) and 2,4-diethoxypyrimidine (**6**) confirms the intermolecular nature of the O → N alkyl migration. The alkyl rearrangement cannot be initiated by benzoyl peroxide and the reaction is postulated to proceed *via* alkylation of the free base pyrimidine at N_1 by the conjugate acid. The quaternary intermediate either dealkylates to the *N*-alkyl lactam or catalyzes further rearrangement.

Spectral and X-ray investigations[2] have shown conclusively that uracil (**1**) exists predominantly in the lactam form as pyrimidine-2,4-dione. The preference for the lactam structure is generally true of heterocycles containing an amide moiety.[3] Thus, there exists in 2,4-dimethoxypyrimidine (**2**) which contains two imidate groups a driving force to attain the keto structure by O-demethylation and/or O → N methyl migration to yield products **1**, **3**, **4**, **5**, etc., under appropriate conditions.



2

1, $R_1 = R_3 = H$
3, $R_1 = Me, R_3 = H$
4, $R_1 = H, R_3 = Me$
5, $R_1 = R_3 = Me$

We wish to report the novel finding of the competitive reactions of dealkylation and lactim–lactam isomerization of several 2,4-dialkoxypyrimidines in aqueous and nonaqueous media, and detail the reactivities of the pyrimidine lactim ethers under a variety of conditions. The results are relevant to the synthetic use of heteroaromatic lactim ethers such as in the Hilbert–Johnson procedure for the preparation of pyrimidine nucleosides,[4] and in the isolation of alkylated bases[5] from nucleic acid fractions which require aqueous acid treatments.[6]

Results and Discussion

Analyses of the dealkylation and isomerization products of 2,4-dimethoxy- (**2**), 2,4-diethoxy- (**6**), and 2,4-dimethoxy-5-methylpyrimidine (**7**) were carried out mainly by thin layer and gas–liquid phase chromatography. Major products were identified by actual isolation by preparative tlc and glpc and conventional means. These chromatographic methods in conjunction with uv and nmr spectroscopy for characterization of the isolated products permit an accurate identification and quantitation of the reaction products. A total of 21 mono- and dialkyl derivatives of uracil and thymine were prepared and characterized (*cf.* Experimental Section).

Aqueous Media —The isomerization of heteroaromatic lactim ethers to *N*-alkyl lactams has been effected by heating,[7] the catalytic function of the common alkylated cation,[8] and alkyl halides.[9] Treatment of 2,4-dialkoxypyrimidines with alkyl halide was first discovered by Hilbert and Johnson[10] to yield the isomerized products 1-alkyl-4-alkoxy-2-pyrimidones. Variations of the procedure include the use of Lewis acids[11] such as mercuric salts in aprotic solvents. Mineral acids have not been known to cause isomerization of any heteroaromatic lactim ether, and aqueous hydrochloric and sulfuric acids are routinely employed for the hydrolysis of alkoxypyrimidines.[12,13]

Our present study shows that dealkylation and isomerization of 2,4-dialkoxypyrimidines can occur concurrently under certain aqueous acid conditions. In refluxing 0.1 *N* aqueous hydrochloric acid, the pyrimidine lactim ether **2** at 0.18 *M* concentration and pH 2.7 gave rise to a substantial amount of the *N*-methylated products 1-methyl-4-methoxy-2-pyrimidone (**8**) and 1-

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(2) (a) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952); (b) C. L. Angell, *J. Chem. Soc.*, 504 (1961); (c) G. S. Parry, *Acta Cryst.*, **7**, 313 (1954); (d) K. Hoogsteen, *ibid.*, **13**, 1050 (1960).

(3) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 347, 359, 363 (1963); **2**, 11, 18, 36 (1963).

(4) J. Pliml and M. Prystas, *ibid.*, **8**, 115 (1967), and the pertinent references therein.

(5) There is a sustained interest in the alkylated nucleic acid bases obtained from natural sources: R. H. Hall, *Biochem.*, **3**, 769 (1964). No alkoxypyrimidines or purines have yet been detected which may be due to hydrolysis or isomerization during the isolation of the base constituents from the nucleic acids.

(6) (a) E. Vischer and E. Chargaff, *J. Biol. Chem.*, **176**, 715 (1948); (b) B. Weissman, P. A. Bromberg, and A. B. Gutman, *ibid.*, **224**, 407 (1957).

(7) D. J. Brown and T. C. Lee, *Aust. J. Chem.*, **21**, 243 (1968).

(8) (a) P. Beak, *Tetrahedron Lett.*, 863 (1963); (b) P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Amer. Chem. Soc.*, **90**, 1569 (1968).

(9) (a) L. A. Paquette and N. A. Nelson, *J. Org. Chem.*, **27**, 1085 (1962); (b) H. J. Teague and W. P. Tucker, *ibid.*, **32**, 3144 (1967).

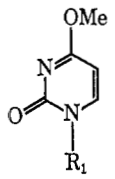
(10) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001 (1930).

(11) D. Tacker and T. L. V. Ulbricht, *J. Chem. Soc. C*, 333 (1968), and previous papers in this series.

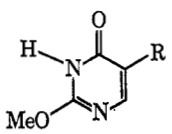
(12) T. L. V. Ulbricht, *Tetrahedron*, **6**, 225 (1959).

(13) R. Daniels, L. T. Grady, and L. Bauer, *J. Amer. Chem. Soc.*, **87**, 1531 (1965).

methyluracil (**3**) in addition to the demethylated compounds 4-methoxy-2-pyrimidone (**9**) and uracil (**1**).



8, R_1 = Me
9, R_1 = H



10, R = H
15, R = Me

In Table I is summarized the concentration effects of the pyrimidine **2** on the course of the two competing

TABLE I

REACTION OF 2,4-DIMETHOXYPYRIMIDINE (2) IN 0.1 *N* AQUEOUS HYDROCHLORIC ACID (100°, 3 HR)

Concn, *M*	pH	Recovered 2, %	Mol % of products 8	3	9	1
0.018	1.1	21.1				100
0.18	2.7	38.8	13.5	16.2	1.4	68.9
0.18[a]	2.8	12.2	8.0	6.8		85.1
1.80	3.8	60.2	67.4	...[b]	...[b]	32.6

[a] Benzoyl peroxide (0.1 equiv) was added. [b] Trace amount detectable by glpc and tlc.

reactions. At 0.18 *M* concentration, the relative rate of O → N methyl migration to hydrolysis is 0.42. The ratio decreases to zero upon tenfold dilution but increases to 2.06 at ten times the original concentration. Since there was no 2-methoxy-4-pyrimidone (**10**) isolated at any stage of an acid treatment, and subjecting 4-methoxy-2-pyrimidone (**9**) to the same acid conditions produced only uracil (**1**), it appears that 1-methyluracil (**3**) does not owe its origin to either **9** or **10**. It is reasonable to assume that **3** was derived from the "Hilbert–Johnson product" **8** for prolonged heating of **2** in acid led to a decrease of **8** with concomitant increase of **3**. Thus, the isomerization products **8** and **3** were derived independent of the hydrolysates **9** and **1** and the reverse must also be true.

The reactivities of 2,4-dimethoxypyrimidine (**2**) and 2,4-dimethoxy-5-methylpyrimidine (**7**) in acids are compared in Table II. The bases were readily soluble

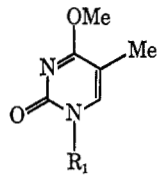
TABLE II

COMPARISON OF THE REACTIONS OF 2,4-DIMETHOXYPYRIMIDINES IN ACIDS

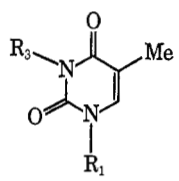
	pH	Pyrimidines recovered, %	Mol % of products			
A. 2,4-Dimethoxypyrimidine (2)			8	3	9	1
...[a]	4.1	25.1		27.5		72.5
...[b]		57.7	50.2	20.9	13.8	15.0
B. 2,4-Dimethoxy-5-methylpyrimidine (7)			11	12	13	14
...[a]	3.7	26.6	5.2	58.2	8.1	28.4
...[b]		21.3	68.7		24.3	7.0

[a] Pyrimidines (0.18 *M*) in 0.01 *N* HCl in 50% aqueous dioxane at 100° for 72 hr. [b] Pyrimidines (0.18 *M*) in 0.1 *N* HCl in anhydrous methanol under reflux for 48 hr.

in 0.01 *N* hydrochloric acid in 50% aqueous dioxane. A 0.18 *M* solution of the pyrimidine ether **7** was allowed to reflux for 72 hr. The isomerization products 1,5-dimethyl-4-methoxy-2-pyrimidone (**11**) and 1-methylthymine (**12**) outweighed the hydrolysis products 4-methoxy-5-methyl-2-pyrimidone (**13**) and thymine (**14**) by a factor of 1.73. The same reaction for the pyrimidine ether **2** gave a much smaller ratio of 0.38.



11, R_1 = Me
13, R_1 = H



12, R_1 = Me; R_3 = H
14, R_1 = R_3 = H

The pyrimidine ethers are practically inert when heated at reflux in 10^{-3} *N* acid (pH of 0.18 *M* solution 7.3) or in 0.1 *N* aqueous sodium hydroxide. In refluxing 5 *N* base prepared in 50% aqueous methanol, hydrolysis of the pyrimidine ethers **2** and **7** took place but no *N*-methylated products were produced. Apparently there is no base-catalyzed isomerization. It is interesting to note that thermal rearrangement (~200°) of 2-[14] and 4-alkoxypyrimidines[15] to 1-alkyl-2-pyrimidones and 3-alkyl-4-pyrimidones, respectively, are accelerated by tertiary bases, whose efficiencies vary according to their basic strengths. Since the aqueous base reactions of **2** and **7** were attempted at much lower temperature, the lack of isomerization may not be unexpected. Thus refluxing **2** for 48 hr in the 5 *N* base led to 68.1% yield of the following pyrimidines: 4-methoxy-2-pyrimidone (**9**) 2.3%, 2-methoxy-4-pyrimidone (**10**) 87.9%, and uracil (**1**) 9.8%. Similarly a 71.5% yield of hydrolysis products was obtained from the 5-methylpyrimidine **7**: 4-methoxy-5-methyl-2-pyrimidone (**13**) 2.3%, and 2-methoxy-5-methyl-4-pyrimidone (**15**) 97.7%. The attack of the hydroxide anion appears to be selective at the 4 position of both **2** and **7**; the 5-methyl group of the latter apparently poses no steric problem to the approaching nucleophile. Further hydrolysis of **10** and **15** to uracil or thymine was very slow indicating the lack of reactivity of the 2-methoxy group in alkaline conditions. Thus, the base treatment of 2,4-dimethoxypyrimidines constitutes a practical preparation of 2-methoxy-4-pyrimidones. The 4-methoxypyrimidines have been shown[16] to be more reactive in aminolysis than the 2-methoxy isomers and explanation has been advanced on the ground that approach of the amine nucleophile is discouraged at the 2 position by electronic repulsion by the two flanking nitrogen atoms. The anionic hydroxide would be expected to meet even more adamant opposition. This greater displaceability of the 4-methoxy group may also be attributed to maximal dispersal of the negative charge in the transition state favoring reaction opposite to rather than adjacent to the activating center.[17]

Nonaqueous Media.—In nonaqueous medium isomerization becomes very competitive. Alcoholic hydrogen chloride has been used[18] in the dealkylation of alkoxypyrimidines in the synthesis of pyrimidine nucleo-

(14) D. J. Brown and R. V. Foster, *J. Chem. Soc.*, 4911 (1965).
(15) D. J. Brown and R. V. Foster, *Aust. J. Chem.*, **19**, 1487 (1966).
(16) D. J. Brown and R. V. Foster, *ibid.*, **19**, 2321 (1966).
(17) R. G. Shepherd and J. L. Fedrick, *Advan. Heterocycl. Chem.*, **4**, 145 (1965).
(18) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 4489 (1930).

TABLE III

REACTION OF 2,4-DIMETHOXYPYRIMIDINE (2) WITH SODIUM IODIDE

Conditions, °C (hr)	Medium[a]	% yield of products	Mol % of products 5	8	3	9	1
100 (15)	2,4-Pentanedione	27.0		46.5	7.1	39.6	6.7
120 (15)	2,5-Hexanedione	45.1	100				
100 (15)	2,5-Hexanedione	40.0	48.0	52.0			
100 (15[b])	2,5-Hexanedione	64.7	8.3	53.8	37.9		

[a] Compound 2 (0.18 *M*) was dissolved. [b] Benzoyl peroxide (0.1 equiv) was added.

TABLE IV

REACTION OF EQUIMOLAR MIXTURE OF 2,4-DIMETHOXY- (2) AND 2,4-DIETHOXYPYRIMIDINE (6)

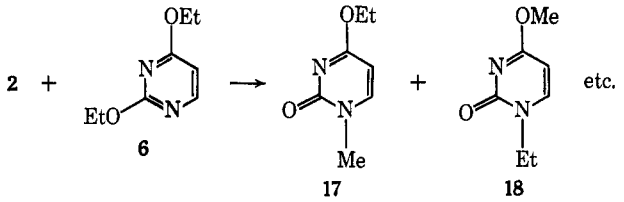
Concn, *M*	Conditions	pH	Mol % of products 8	17	18	19	3	16	9 20	1
0.018	0.05 *N* HCl[a]	1.3								100
0.18	0.05 *N* HCl	2.5					10.8	6.6		82.6
1.80	0.05 *N* HCl	3.6	8.5	11.5	2.3	2.2	17.3	8.9	1.5	47.9
0.36	NaI–2,5-hexanedione[b]		26	56	11	7				

[a] HCl (0.05 *N*) in 50% aqueous dioxane and refluxing for 72 hr. [b] At 100° for 24 hr.

sides. Dealkylation proceeds by alkyl oxygen ether cleavage only since ring substitution by alcohol (SNAr) gives no fruitful products. The former pathway resembles the Pinner cleavage of iminoester hydrochloride into the corresponding amides and alkyl chlorides.[19] This type of SN2 ether cleavage has been shown to be a minor route in the aqueous acid-catalyzed cleavage of 2-methoxypyrimidine.[13] Table II illustrates the reactions of the 2,4-dimethoxypyrimidine 2 and 7 in 0.1 *N* hydrochloric acid in anhydrous methanol under reflux. In both cases, the isomerization products prevail over that of demethylation by more than twofold.

In a mildly acidic nonaqueous medium comprised of excess sodium iodide dissolved in 2,4-pentanedione (pK_a 9.16), isomerization and demethylation of the pyrimidine ether 2 are equally facile as shown in Table III. In a neutral medium such as 2,5-hexanedione, sodium iodide catalyzed isomerization of 2 only. One or both of the imidate moieties were reacted depending on the temperature applied. Iodide anion was the catalyst in both cases. The latter result corroborates with the report[20] that 75% yield of 5-bromo-1,3-dimethyluracil was isolated from the treatment of 5-bromo-2,4-dimethoxypyrimidine in the NaI–2,5-hexanedione mixture. Methyl iodide was postulated[20] to be formed *in situ* and is therefore similar to the Hilbert–Johnson reaction.[10]

Intermolecular Reaction —Isomerization of the pyrimidine lactim ethers in aqueous or nonaqueous media increases dramatically over demethylation at increasing concentrations of the base. Since the isomerization of 2 is dependent on the concentration of the pyrimidine, the O → N methyl migration is reminiscent of the Lander rearrangement[21] of alkyl imidates to amides which is intermolecular. The thermal rearrangement of allyl pyrimidyl ethers has been shown[22] to be intramolecular and formally analogous with the ortho-Claisen rearrangement of allyl phenyl ethers, although, in the case of the thermal isomerization of 2-alkoxypyrimidines to 1-alkyl-2-pyrimidones,[14] the intra- or intermolecular nature of the reaction is uncertain. In order to provide evidence to this effect, a crossover experiment employing equimolar amounts of 2,4-dimethoxy- (2) and 2,4-diethoxypyrimidine (6) was run. A solution of 0.18 *M* of the pyrimidine ethers in 0.05 *N* hydrochloric acid in 50% aqueous dioxane was refluxed for 72 hr. The products tabulated in Table IV include uracil (1) as the major product and a considerable amount of 1-ethyluracil (16) as well as 1-methyluracil (3). A tenfold dilution led to uracil only, but, at 1.8 *M* concentration of the mixed pyrimidine ethers, the formation of uracil was suppressed in favor of the isomerization products. All of the possible N_1-alkyl-2-pyrimidones were isolated. The "mixed" isomerization products 1-methyl-4-ethoxy-2-pyrimidine (17) and 1-ethyl-4-methoxy-2-pyrimidone (18) demonstrate the occurrence of intermolecular *N*-alkylation. The N_1-methylpyrimidones 8, 17, and 3 surpassed the N_1-ethyl derivatives, *viz.*, 1-ethyl-4-ethoxy-2-pyrimidone (19), 18, and 16, by a ratio of 4.3. Small



amounts of partial hydrolysis products 4-methoxy-2-pyrimidone (9) and 4-ethoxy-2-pyrimidone (20) were also present. In the NaI–2,5-hexanedione system, the same equimolar mixture of 2 and 6 yielded only the isomerization products 8, 17, 18, and 19 with the N_1-methyl derivatives predominating over the N_1-ethyl derivatives by a factor of 4.6. The preponderance of *N*-methyl products 8 and 17 over the *N*-ethyl ones 18 and 19 is consistent with the greater reactivity[10] of methyl iodide over ethyl iodide, presumably generated *in situ*,[20] in *N*-alkylation.

Ionic Mechanism —The Hilbert–Johnson reaction of 2,4-dialkoxypyrimidines with alkyl halides or sodium iodide has been assumed to proceed *via* a quaternary

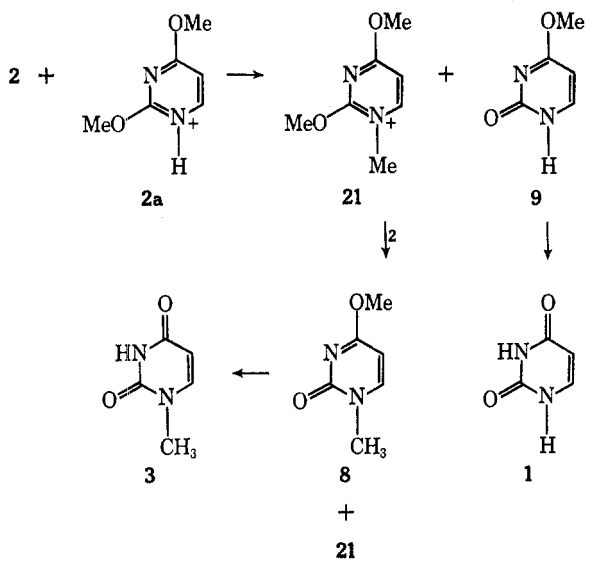
(19) (a) S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, **73**, 2233 (1951); (b) C. L. Stevens, D. Morrow, and J. Lawson, *ibid.*, **77**, 2341 (1955); (c) F. Cramer and H. J. Baldauf, *Chem. Ber.*, **92**, 370 (1959).

(20) T. L. V. Ulbricht, *J. Chem. Soc.*, 3345 (1961).

(21) J. W. Schulenberg and S. Archer, "Organic Reactions," Vol. 14, Wiley, New York, N. Y., 1965, p 24.

(22) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **28**, 1015 (1963).

salt derived from intermolecular *N*-alkylation followed by *O*-dealkylation.[4,10] A recent report[23] on the isolation of the intermediate 1-methyl-2,4-diethoxypyrimidinium salt from a mixture of **6** and methyl iodide in acetonitrile at room temperature lends support to this postulate. It is reasonable to assume that 2,4-dimethoxypyrimidine (**2**) in acid is protonated at the more basic N_1 nitrogen[10,23] to form the active methylating species **2a**. Combination of **2** and **2a** leads to the now established[23] pyrimidinium intermediate **21**, which is the common methylated derivative of the lactim **2** and lactam **8**. The quaternary salt **21** is capable of catalyzing a chain rearrangement of **2** but for the competitive demethylation in aqueous acids. It has been pointed out by Hilbert and Johnson[10] that methyl iodide needs to be present in quantities very much less than molecular proportions of the pyrimidine since the common methylated cation is continually regenerated. This situation is realized in the NaI–2,5-hexanedione system where demethylation was not observed. The following scheme summarizes the events of an acid-catalyzed isomerization of **2**.



The pK_a of **2** and **7**, previously unreported, are now determined to be 3.05 ± 0.05 and 3.63 ± 0.04, respectively, by potentiometric titration.[24] Thus, in the pH region of 1–5, significant quantities of both of the pyrimidine ethers and the conjugate acids are present, and intermolecular *N*-methylation will lead to lactim–lactam isomerization. The extremes of the pH spectrum such as in strong acids and bases (>1 *N*) are obviously not conducive to such methyl rearrangement.

An alternative route to the formation of the quaternary intermediate **21** is *via* a free-radical chain reaction. Such has been shown to be the mechanism for the thermal rearrangement of 2-methoxypyridine to 1-methyl-2-pyridone,[25] which can also be catalyzed by benzoyl peroxide. However, addition of 0.1 equiv of benzoyl peroxide to 0.1 *N* hydrochloric acid containing 0.18 *M* of **2** and refluxed led to much smaller ratio of methyl migration to hydrolysis as shown in Table I. Likewise, the presence 0.1 equiv of the peroxide in the NaI–2,5-hexanedione treatment of **2** caused cleavage of the 4-methoxy group yielding considerable amount of 1-methyluracil at the expense of the *N*,*N*-dimethyl derivative (*cf.* Table III). Apparently, O → N methyl migration of the pyrimidine ether cannot be initiated by peroxide, and a radical mechanism seems unlikely.

It has been pointed out earlier[10] that the two lactim configurations within the same pyrimidine molecule of **2** are different in their stability. Alkylation at the more basic 1-nitrogen appears to labilize selectively the 2-alkoxy group. Thus, when the pyrimidine lactim ethers **2**, **6**, and **7** were treated in aqueous acids, both isomerization and dealkylation initially took place at the lactim moiety comprised of 1-nitrogen and the 2-alkoxy group. Attempts to identify 3-methyluracil (**4**), 1,3-dimethyluracil (**5**), 3-methylthymine (**22**), and 1,3-dimethylthymine (**23**) were unsuccessful. There were no 2-methoxy-4-pyrimidones **10**, **15**, or 2-ethoxy-4-pyrimidone (**24**) detected under these conditions. The abundant literature[4] on Hilbert–Johnson type of reactions reflects the same general phenomenon of a greater reactivity of the N_1-lactim function. This provides an interesting contrast to the greater displaceability of the 4-methoxy group in alkaline conditions.

Dealkylation.—In aqueous acids, dealkylations of the pyrimidine lactim ethers probably follow the hydrolysis pathways elucidated[13] for 2-methoxypyrimidine-O^{18}. The cleavage proceeds predominantly *via* an aromatic nucleophilic substitution (SNAr) with a minor contribution (<10%) of the SN2 ether cleavage mechanism. However, the latter mode of ether cleavage is the only one operating in nonaqueous media such as anhydrous methanol and 2,4-pentanedione. A third possibility exists in the presence of benzoyl peroxide, which catalyzed homolytic cleavage of the alkyl oxygen bond in aqueous acid and in NaI–2,5-hexanedione mixture. Demethylations occur in alkaline conditions *via* nucleophilic aromatic substitution exclusively. In the absence of N-protonation, ring substitution is less facile and therefore requires more stringent conditions such as a high normality of the alkali.

Experimental Section

Instrumental.—Glpc analyses were performed on three gas chromatographs: F & M 5750B equipped with a flame-ionization detector, F & M 700 equipped with a thermal conductivity detector, and Perkin-Elmer 800 equipped with a flame ionization detector. All analyses unless otherwise mentioned were done on a 6 ft × 0.125 in. aluminum column packed with 10% Carbowax 20M on Anakrom ABS 60–70 mesh and at 30 cc/min of carrier gas. The more volatile 2,4-dialkoxypyrimidines, **2**, **6**, and **7** were done with T_I = 170°, T_C = 100°, and T_D = 260°. All others were done at T_I = 260°, T_C = 200°, and T_D = 260°. Products were determined by comparing their peak areas (planimeter five times) with those of reproduced peaks (trial and error) of authentic samples. Preparative glpc was performed on the F & M 700 using an aluminum 6 ft × 0.25 in. column packed with 10% UCW 98 on Anakrom ABS 60–70 mesh. Thin layer chromatography was done on silica gel G (Brinkman) with layers of 0.25 mm in thickness. Chloroform and methanol (19:1) was used in all cases as the solvent system unless otherwise noted. Development was accomplished by spraying a 0.5% fluorescein sodium salt solution then exposing to bromine vapor. Preparative thin layer chromatography was done on silica gel G with plates of 20 × 20 cm and 1.0 mm in thickness. No more than 10 mg was placed on the plate at one time. Nmr spectra were run on a Varian A-60A spectrometer with either D_2O as solvent,

(23) T. Ueda and H. Nishino, *J. Amer. Chem. Soc.*, **90**, 1678 (1968).

(24) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, Chapter 2. The pK_a values of **2** and **7** were determined by titrating 0.01 *M* of the base with standardized 0.100 *N* hydrochloric acid under nitrogen atmosphere.

(25) K. B. Wiberg, T. M. Shryne, and R. R. Kintner, *J. Amer. Chem. Soc.*, **79**, 3160 (1957).

TABLE V

PHYSICAL PROPERTIES OF ALKYL DERIVATIVES OF URACIL AND THYMINE

Compd no.	Mp, °C	Glpc[k] rrt	uv (H_2O) Ref	pH	λ_{max}	$\epsilon \times 10^{-3}$	Nmr (δ)[l] N_1-R, O_2-R	N_3-R, O_4-R	5-H, 5-CH_3	6-H
1	318[a]		[h]	4–7	259	8.2			5.71	7.60
				12–13	284	6.1				
2	18[b]	(1.00)	[i]	7	258	6.1	4.08[m]	3.97	6.42	8.24
3	233[a]	3.33	[h]	5–7	267	9.7	3.40		5.83	7.68
				12–14	265	7.0				
4	179[a]	6.80	[h]	3–7	258	7.3		3.31	5.96	7.59
				12–14	282	10.7				
5	121–122[a]	1.00	[h]	1–14	266	8.9	3.43	3.37	5.73	7.20
6	19–20[b]	(1.63)	[h]	7	259	6.1	4.23[m]	4.18	6.33	7.50
							1.33	1.33		
7	61[c]	(1.58)		7	264	6.3	4.00[m]	3.97	2.07	8.01
					215	7.9				
8	149–150[b]	1.93	[i]	7	274	5.2	3.42	3.87	6.10	7.82
9	206–208[d]	Dec		7	267	4.9		3.99	6.23	7.85
				11	276	5.4				
10	167–168	Dec		7	256	5.8	3.96		6.11	7.71
				11	263	6.0				
11	144[c]	2.47		5–12	280	5.6	3.51	3.99	1.95	7.47
12	292–293[e]	2.93	[j]	6	273	11.3	3.35		1.87	7.50
				12–13	271	7.9				
13	220–221	Dec		7	274	4.9		4.00	1.97	7.55
				11	283	5.8				
14	340[a]		[h]	4–7	265	7.9			1.83	7.42
				12–13	291	5.4				
15	198–199	Dec		7	260	7.1	3.98		1.94	7.62
					217	6.5				
				11	267	7.4				
16	148[a]	2.80		7	267	9.55	3.87		5.78	7.29
				11	265	7.00	1.33			
17	136[b]	2.00	[h]	7	274	6.1	3.45	4.33	5.71	7.56
								1.30		
18	91–92	1.60		7	272	5.3	3.98	3.99	5.98	7.68
							1.38			
19	88[f]	1.67		7	276	8.4	3.87	4.36	5.73	7.50
							1.30	1.30		
20	167–168[g]	1.64	[h]	4–7	269	5.1		4.25	6.17	7.90
				13	278	6.4		1.40		
22	209–210[e]	5.47	[j]	6	265	8.2		3.28	1.87	7.50
				13	290	11.4				
23	151–153[e]	0.93	[j]	5–12	272	9.8	3.46	3.43	1.83	7.57
24	128–129[g]	1.13	[h]	4–7	259	6.0	4.25		6.25	7.87
				10–13	265	6.7	1.40			

[a] D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, Table XXV–XXVII. [b] T. B. Johnson and G. E. Hilbert, *J. Amer. Chem. Soc.*, **52**, 2001 (1930). [c] T. B. Johnson and G. E. Hilbert, *ibid.*, **52**, 4511 (1930). [d] C. W. Noel and C. C. Cheng, *J. Heterocycl. Chem.*, **5**, 25 (1968). [e] E. Wittenburg, *Chem. Ber.*, **99**, 2380 (1966). [f] J. L. Rabinowitz and S. Gurin, *J. Amer. Chem. Soc.*, **75**, 5758 (1953). [g] G. E. Hilbert and E. J. Jansen, *ibid.*, **57**, 552 (1935). [h] D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952). [i] J. E. Austin, *J. Amer. Chem. Soc.*, **56**, 2141 (1934). [j] E. Wittenburg, *Chem. Ber.*, **99**, 2391 (1966). [k] Detailed conditions for glpc analysis are given in the Experimental Section. Relative retention times (rrt) were determined with a F & M 700 gas chromatograph (thermal couple detector). These values are slightly different from those derived with a Perkin-Elmer 800 equipped with a flame ionization detector, although the order of appearance of the pyrimidines remains unchanged. The three more volatile dialkoxypyrimidines were studied at lower T_C and the rrt are shown in parentheses. [l] Dialkylpyrimidines (*N,N-*; *O,O-*; *N,O-*) were taken in $CDCl_3$ with TMS and all others in D_2O using 3-(trimethylsilyl)propanesulfonic acid sodium salt as the internal standard. In the uracil series, 5-H and 6-H appear as doublets, $J = 7$ Hz, and in the thymine series 5-CH_3 appears as a doublet, $J = 1.5$–2 Hz. Other multiplicities follow normal patterns and are not mentioned. [m] Assignments uncertain.

with 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standard, or with deuteriochloroform, with internal tetramethylsilane as standard. Ultraviolet spectra were obtained on a Cary 14 recording spectrophotometer using water as solvent at known pH. Melting points are uncorrected and microanalyses were performed by M-H-W Laboratories, Garden City, Mich. 48135.

Materials.—The physical properties of the 21 mono- and dialkyl derivatives of uracil and thymine are tabulated in Table V. Preparations of the previous unreported pyrimidines **10**, **13**, **15**, and **18** are shown below.

2-Methoxy-4-pyrimidone (10).—2,4-Dimethoxypyrimidine (**2**) (0.98 g, 7 mmol) was added to 10 ml of 5 *N* sodium hydroxide in 50% aqueous methanol and the solution was refluxed for 72 hr. The solution was neutralized with acetic acid, continuously extracted with chloroform, dried, and evaporated to give 0.74 g of a white solid. Chromatography of the solid on 25 g silica gel (elution with 10% methanol in chloroform) gave 0.25 g (28% yield) of **10**. An analytical sample was prepared by recrystallization from ethanol, and physical properties are shown in Table V.

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.6; H, 4.8; N, 22.2. Found: C, 47.7; H, 4.8; N, 22.2.

4-Methoxy-5-methyl-2-pyrimidone (13).—A mixture of 0.925 g (6 mmol) of 2,4-dimethoxy-5-methylpyrimidine (**7**) and 10 ml of freshly distilled acetyl chloride was stirred at 50° protected from moisture for 24 hr. The volatiles were evaporated and the residue washed with ether giving 0.7 g (68%) of 1-acetyl-4-methoxy-5-methyl-2-pyrimidone: mp 107°; nmr ($CDCl_3$) δ 1.95 (d,

3, J = 1.5 Hz), 2.75 (s, 3), 4.00 (s, 3), and 8.02 (m, 1, J = 1.5 Hz). The N_1-acetyl derivative (0.7 g, 4.1 mmol) was added to 5 ml of 5% sodium bicarbonate solution, stirred at room temperature for 3 hr, and extracted continuously with chloroform, dried, and evaporated to give 0.52 g of solid. Chromatography of the solid on 20 g of silica gel (elution with 10% methanol in chloroform) yielded 0.4 g (70%) of **13**, and physical properties are shown in Table V.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.1; H, 5.9; N, 20.1.

2-Methoxy-5-methyl-4-pyrimidone (15).—To 10 ml of 5 N sodium hydroxide in 50% aqueous methanol was added 0.308 g (2 mmol) of 2,4-dimethoxy-5-methylpyrimidine (**7**) and the solution was heated at reflux for 48 hr. The solution was neutralized with acetic acid, continuously extracted with chloroform, dried, evaporated to a solid, and recrystallized from ethanol to yield 0.19 g (69%) of **15**, and physical properties are shown in Table V.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.2; H, 5.9; N, 20.1.

1-Ethyl-4-methoxy-2-pyrimidone (18).—A mixture of 0.5 g (3.6 mmol) of 2,4-dimethoxypyrimidine (**2**) in 5 ml of freshly distilled ethyl iodide was stirred in the dark at room temperature for 1 week. The ethyl iodide and unreacted **2** were evaporated off and the residue was washed with petroleum ether to give 0.27 g of brown solid. Chromatography of the solid on a 12 g silica gel column with 10% acetone in ethyl acetate as eluents yielded 0.15 g (27%) of **18**. Sublimation (50°, 0.05 mm) gave pure sample, and physical properties are shown in Table V.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2. Found: C, 54.7; H, 6.6; N, 18.0.

Reaction of 2,4-Dimethoxypyrimidine (2) in 0.1 N Aqueous Hydrochloric Acid.—A mixture of 25.2 mg (0.18 mmol) of **2** in 1.0 ml of 0.1 N aqueous hydrochloric acid was refluxed for 3 hr. The reaction was stopped by addition of saturated sodium bicarbonate solution. The reaction mixture was continuously extracted with chloroform for 14 hr, dried, and evaporated. Preparative tlc revealed the presence of 2,4-dimethoxypyrimidine (**2**), 1-methyl-4-methoxy-2-pyrimidone (**8**), 1-methyluracil (**3**), and 4-methoxy-2-pyrimidone (**9**) (relative R_f 4.5, 2.5, 2.0, and 1.0, respectively). To quantitate the pyrimidines, the experiment was repeated and the chloroform extracts diluted to 1.0 ml volumetrically. Analyses by glpc by comparing their peak areas with those of the authentic samples and normalized gave the following yields (mg, 10^{-2} mmol); **2**, (9.79, 6.98); **8**, (1.14, 0.82) **3**, (1.43, 1.13). Since 4-methoxy-2-pyrimidone (**9**) decomposed on the column under the conditions used, the chloroform extracts were evaporated to dryness and the residue silylated with 200 μl of *O,N*-bis(trimethylsilyl)acetamide and 600 μl of acetonitrile in a sealed tube at 150° for 1 hr.[26] A 1.0 ml solution of the acetonitrile was made up and chromatographed on a 6 ft × 0.125 in. column packed with 10% UCW 98 on Chromosorb W, 80–100 mesh: T_I = 210°, T_C = 150°, T_D = 260°, and 20 cc/min of nitrogen. The yield of **9**, determined in the usual manner, was 0.11 mg (0.087 × 10^{-2} mmol). The average results of four glpc analyses of these components are reported below (10^{-2} mmol): **2**, 6.98; **8**, 0.98; **3**, 1.18; and **9**, 0.098. The aqueous layer after continuous extraction with chloroform was diluted to 1000 ml volumetrically for ultraviolet assay of uracil (**1**) present: $OD_{259\ nm}$ = 0.41, and, using ϵ = 8200, yield of **1** was calculated to be 5.6 mg (5.00 × 10^{-2} mmol). The mole percentages of the products are shown in Table I, and 14.24 × 10^{-2} mmol (79%) of the starting material **2** was accounted for.

Reaction of 2,4-Dimethoxypyrimidine (2) in 0.1 N Methanolic Hydrogen Chloride.—A solution of 25.3 mg (0.181 mmol) of **2** in 1.0 ml of 0.1 N methanolic hydrogen chloride was allowed to reflux for 48 hr. The reaction was stopped by the addition of sodium bicarbonate, filtered and diluted to 1.0 ml volumetrically with methanol. Glpc analysis of the solution gave (mg, 10^{-2} mmol): 2,4-dimethoxypyrimidine (**2**) (14.29, 10.21); 1-methyl-4-methoxy-2-pyrimidone (**8**) (5.48, 3.91); 1-methyluracil (**3**) (2.12, 1.68). The average results of four glpc analyses are as follows (10^{-2} mmol): **2** 10.48, **8**, 4.04; **3**, 1.69. The methanol solution was evaporated followed by addition of water and continuous extraction with chloroform. The chloroform layer was dried, evaporated, and the residue chromatographed on a preparative silica gel plate. The band corresponding to 4-methoxy-2-pyrimidone (**9**) was eluted with methanol, diluted to 100 ml volumetrically, and assayed by ultraviolet absorption spectroscopy: $OD_{267\ nm}$ = 0.545, equivalent to 1.40 mg (1.11 × 10^{-2} mmol). The aqueous layer was made up to 1000 ml and uv determination showed 1.36 mg (1.21 × 10^{-2} mmol) of uracil (**1**). The pyrimidines analyzed totaled 18.5 × 10^{-2} mmol representing quantitative material balance. The mole percentages of the products are shown in Table II.

Reaction of 2,4-Dimethoxypyrimidine (2) with Sodium Iodide in 2,4-Pentanedione.—To a mixture of 1.0 ml of 2,4-pentanedione and 100 mg of sodium iodide was added 25.3 mg of **2** (0.181 mmol) and the mixture was heated at 100° for 24 hr, cooled, and evaporated. The reaction products were analyzed by the techniques elaborated above: glpc analyses gave 1-methyl-4-methoxy-2-pyrimidone (**8**), 3.11 mg (2.22 × 10^{-2} mmol), and 1-methyluracil (**3**), 0.43 mg (0.34 × 10^{-2} mmol); preparative tlc yielded 4-methoxy-2-pyrimidone (**9**), 2.38 mg (1.89 × 10^{-2} mmol), and uv analysis of the aqueous layer gave uracil (**1**), 0.36 mg (0.32 × 10^{-2} mmol). Total amounts of pyrimidines isolated were 4.77 × 10^{-2} mmol (27%); unreacted **2** was evaporated with 2,4-pentanedione. The mole percentages of the products are shown in Table III.

Reaction of Equimolar Mixture of 2,4-Dimethoxy- (2) and 2,4-Diethoxypyrimidine (6) in Aqueous Hydrochloric Acid.—A mixture of 125.4 mg (0.896 mmol) of **2** and 150.9 mg (0.898 mmol) of **6** in 1.0 ml of 0.05 N hydrochloric acid in 50% aqueous dioxane was heated at reflux for 72 hr. The solution was neutralized with saturated sodium bicarbonate solution, continuously extracted with chloroform for 15 hr, dried, and evaporated. The residue was taken up in 1.0 ml of methanol volumetrically. Glpc analyses gave the following yields (mg, 10^{-2} mmol): for 2,4-diethoxypyrimidine (**6**) (111.9, 66.56); 2,4-dimethoxypyrimidine (**2**) (69.3, 49.50); 1-ethyluracil (**16**) (3.39, 3.29); 1-methyluracil (**3**) (8.26, 6.55). The average results of four glpc analyses are as follows (10^{-2} mmol): **6**, 66.89; **2**, 49.95; **16**, 3.29; **3**, 6.36. The Hilbert-Johnson products **8**, **17**, **18**, and **19** gave an ill-resolved four-component trace, and analysis was achieved by matching it with a synthetic chromatogram prepared by trial and error mixing of authentic samples (mg, 10^{-2} mmol): 1-methyl-4-methoxy-2-pyrimidone (**8**) (4.36, 3.12); 1-methyl-4-ethoxy-2-pyrimidone (**17**) (6.50, 4.22); 1-ethyl-4-methoxy-2-pyrimidone (**18**) (1.33, 0.86); 1-ethyl-4-ethoxy-2-pyrimidone (**19**) (1.33, 0.79). Ultraviolet determination of the aqueous layer gave 19.7 mg (17.6 × 10^{-2} mmol) of uracil (**1**). Since 4-methoxy-2-pyrimidone (**9**) and 4-ethoxy-2-pyrimidone (**20**) cannot be effectively separated by either glpc or tlc, they were determined together as uracil by treating the chloroform extract in hot concentrated hydrochloric acid and isolating the uracil formed by preparative tlc to yield 0.604 mg, equivalent to 0.54 × 10^{-2} mmol of **9** and **20**. Total amounts of pyrimidines isolated were 156.37 × 10^{-2} mmol (87.2%), and the mole percentages of the products are shown in Table IV.

Registry No—**1**, 66-22-8; **2**, 3551-55-1; **3**, 615-77-0; **4**, 608-34-4; **5**, 874-14-6; **6**, 20461-60-3; **7**, 5151-34-8; **8**, 7152-66-1; **9**, 18002-25-0; **10**, 25902-86-7; **11**, 25902-87-8; **12**, 4160-72-9; **13**, 25902-89-0; **14**, 65-71-4; **15**, 25902-91-4; **16**, 6490-42-2; **17**, 6220-46-8; **18**, 25902-94-7; **19**, 25902-95-8; **20**, 6220-43-5; **22**, 4160-77-4; **23**, 4401-71-2; **24**, 25957-58-8.

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