Alkylations of Heterocyclic Ambident Anions. III.[1] 4-Hydroxypyrimidines[2a]

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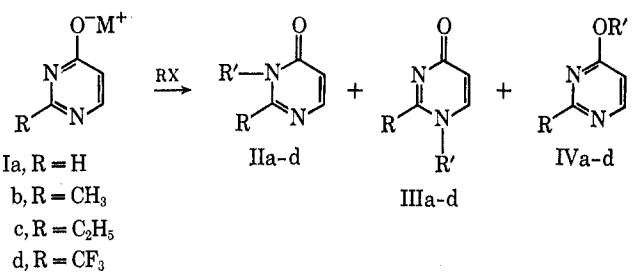
Salts of 4-hydroxypyrimidine and several 2-substituted 4-hydroxypyrimidines were treated with alkyl halides under a variety of reaction conditions. In cation-solvating media, methylation occurred mainly at N-3. Increased N-1 methylation was observed in hydrogen-bonding solvents and solvents of lower dielectric constant. Studies in dimethylformamide revealed significant steric influences. When the alkyl halide was varied from methyl to ethyl to isopropyl or when the group on the 2 position was varied from hydrogen to methyl to ethyl, alkylation at oxygen increased at the expense of alkylation at N-3. 2-Trifluoromethyl-4-hydroxypyrimidine in dimethylformamide reacted with alkyl halides to give mainly 4-alkoxy-2-trifluoromethylpyrimidines.

We have described the effects of alkylating agent, solvent, and cation on the course of alkylation of 2-hydroxypyrimidine[3] and 2-hydroxypyridine salts,[1] and now report on the results of a similar study with 4-hydroxypyrimidine (Ia) and several 2-substituted 4-hydroxypyrimidines (Ib–d).

Reactions of pyrimidines of structure I give both N-alkylation (II + III) and O-alkylation (IV) products. Carbon alkylation of these and related nitrogen heterocycles has not been observed.



Ia, R = H
b, R = CH_3
c, R = C_2H_5
d, R = CF_3

IIa-d

IIIa-d

IVa-d

Results and Discussion

Kornblum has examined the reactions of alkyl halides with silver nitrate and rationalized the changes in product distribution with variation of the alkylating agent by assuming a transition state with both SN1 and SN2 characteristics.[4] In the present study, the sodium salt of 4-hydroxypyrimidine (Ia), 2-methyl-4-hydroxypyrimidine (Ib), and 2-ethyl-4-hydroxypyrimidine (Ic) were alkylated with methyl, ethyl, and isopropyl iodides in methanol. Second-order rate constants were obtained by following the reactions to at least 60% completion (Table I). The rates of alkylation decreased with increasing size of the alkylating agent and of the 2 substituent, also consistent with a bimolecular process.

These observations indicate that, in this series, a changing SN2–SN1 character of the transition state does not play a significant role, and changes in isomer distribution must be due to other factors.

Data in Table II are from studies in dimethylformamide (DMF) and show also that increasing bulk of both the alkylating agent and the substituent in the 2 position favor oxygen alkylation at the expense of N-3. These results are consistent with those obtained under similar circumstances with the salts of 2-pyridones and 2-pyrimidones.[1,3] These results also can be rationalized on the grounds that the rate of nitrogen alkylation is decreased because of steric effects while the rate of oxygen alkylation remains fairly constant, thus leading to exclusive ether formation from the reaction of isopropyl bromide with the sodium salt of 2-ethyl-4-hydroxypyrimidine.

The sodium salt of 2-trifluoromethyl-4-hydroxypyrimidine gives much more O-alkylated product than the other substrates. Electron withdrawal by the trifluoromethyl group would be predicted to reduce the nucleophilicity of the adjacent ring nitrogens to a greater extent than of the "meta" oxygen and, therefore, favors O-alkylation, but steric requirements can-

TABLE I

SECOND-ORDER RATE CONSTANTS[a] FOR ALKYLATIONS OF THE SODIUM SALTS OF 2-SUBSTITUTED 4-HYDROXYPYRIMIDINES (0.45 *M*) IN METHANOL

Alkylating agent	2 substituent H	Me	Et	Temp, °C
MeI	3.34	1.84	1.41	54
EtI	2.28			54
	4.95	3.44	2.61	94
i-PrI	1.70	1.37		94

[a] In l. mol^{-1} sec^{-1} × 10^3.

TABLE II

SODIUM SALT ALKYLATIONS OF 4-HYDROXYPYRIMIDINES at 40° AND 0.45 *M* IN DMF[a]

Alkylating agent	2 substituent	Yield, %	Product distribution, % O	N-3	N-1
MeI	H	100		82	18
	Me	96		80	20
	Et	82		81	18
	CF_3	100	60	40	
EtBr	H	91	24	66	10
	Me	90	29	50	21
	Et	100	49	38	13
	CF_3	98	100		
i-PrBr[b]	H	96	55	32	13
	Me	46[c]	100		
	Et	60[c]	100		

[a] Over 80% of pyrimidines accounted for as products and/or starting material. [b] Product analysis of the isopropylation reactions are estimates based on the properties of analogous pyrimidines described in this paper. [c] 4-Hydroxypyrimidine was isolated indicating that dehydrobromination of the alkyl halide had occurred.

(1) Part II: G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **32**, 4040 (1967).

(2) (a) This investigation was supported by the Public Health Service Grants No. CA-02857 and CA-10746 from the National Cancer Institute. (b) Allied Chemical Fellow, 1964–1965.

(3) G. C. Hopkins, J. P. Jonak, H. J. Minnemeyer, and H. Tieckelmann, *ibid.*, **31**, 3969 (1966).

(4) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

not be neglected. Della[5] has found that this group has an equatorial preference as great or greater than that of the ethyl group.

When a good cation solvent was used (*e.g.*, DMF, diglyme, methanol), lithium, sodium, and potassium salts of these 4-hydroxypyrimidines all gave essentially the same product distribution. This is expected since the solvent probably insulates the pyrimidine anion from the cation so the effect of the latter is minimal. Experiments under similar conditions have confirmed this in 2-pyridones and 2-pyrimidones.[1,3] However, in ethyl acetate, where the pyrimidine salts were insoluble, the cation did appear to play a role, but no discernible pattern was evident. Studies in this area are continuing.

The alkylation of silver salts of 4-hydroxy- and 2-methyl-4-hydroxypyrimidine in benzene gave products with oxygen to N-3 alkylation ratios of approximately 5:1, but overall yields were low, 20–30%. If a reaction was quenched after only a short period, it was possible to account for 90% of the starting pyrimidine. However, the products were unstable under reaction conditions. Exclusive of some dialkylated materials, attempts at isolation and identification of decomposition products were unsuccessful. Reactions in which the hydroxypyrimidine and silver carbonate were used gave the same results.

Examples are given in Tables III and IV which show product distribution resulting from reaction of the sodium salt of 2-methyl-4-hydroxypyrimidine with methyl iodide in a variety of solvents. As the ionizing power of the reaction medium decreased, N-1 alkylation increased. Similar results were obtained from methylations and ethylations of the sodium salt of 4-hydroxypyrimidine.

A bench-scale reaction of the sodium salt of 4-hydroxypyrimidine with methyl iodide in DMF gave an 80% yield of 3-methyl-4-pyrimidone. When the methylation was performed in refluxing tetrahydrofuran, 1-methyl-4-pyrimidone was isolated in 54% yield after purification.

Reactions run in dimethyl sulfoxide (DMSO) and in methanol were homogeneous from start to finish, while those in DMF were heterogeneous at the start and became homogeneous as the reaction progressed. Reactions in DMF and in DMSO were essentially complete in 5–10 min at room temperature. Reactions in methanol were complete in 1 hr. Generally, reaction mixtures were examined after considerably longer time. Under the conditions studied, products did not equilibrate.

As the dielectric constant of the solvent decreased, the alkali metal salts became more insoluble and the reactions became slower.

Alkylations in solvents such as isopropyl alcohol, *n*-butyl alcohol, and acetone started heterogeneously and, as the reaction proceeded, homogeneity occurred. Alkylations in ethyl acetate were heterogeneous from start to finish.

Kornblum[6] has shown that homogeneity plays an important role in the alkylation of phenoxides. However, when the sodium salt of 4-hydroxypyrimidine was alkylated with ethyl iodide in isopropyl alcohol the product distribution did not vary within experimental error to 72% completion, even though the reaction was heterogeneous at the start and homogeneous after about 40% completion. Table V summarizes the data.

TABLE III

ETHYLATIONS OF THE SODIUM SALT OF 2-METHYL-4-HYDROXYPYRIMIDINE AT 40° AND 0.45 *M* WITH ETHYL BROMIDE

Solvent	Reaction time, hr	Yield, %	Product distribution, % Ether	N-3	N-1
DMF	17	82	29	50	21
MeOH	13	80	25	59	16
i-PrOH	16	104			
	5	84	17	47	36
EtOAc	24	23[a]	5	5	90

[a] 70% sodium salt of 2-methyl-4-hydroxypyrimidine was recovered.

TABLE IV

METHYLATION OF THE SODIUM SALT OF 2-METHYL-4-HYDROXYPYRIMIDINE AT 40° AND 0.45 *M* WITH METHYL IODIDE[a]

Solvent	Reaction time, hr	Yield, %	N-3, %	N-1, %
Formamide[b]	7	86	53	47
Water[b]	2	62	45	55
DMSO	7	76	84	16
DMF	3	96	80	20
MeOH	5	89	66	34
Acetone	11	99	38	62
n-BuOH	8	91	46	54
i-PrOH	8	81	53	47
t-BuOH	60	82	36	64
EtOAc	8	88	12	88
THF	240	47		100

[a] No ether formation was observed. [b] Alkylating agent was insoluble in solvent.

TABLE V

REACTION OF THE SODIUM SALT OF 4-HYDROXYPYRIMIDINE WITH ETHYL IODIDE AT 52° IN ISOPROPYL ALCOHOL

% complete	Product distribution, % Ether	N-3	N-1
10[a]	2	38	60
18[a]	5	42	53
27[a]	4	37	59
33[a]	5	43	52
53[b]	4	42	54
72[b]	4	44	52

[a] Heterogeneous. The first aliquots were difficult to measure accurately because of this heterogeneity. [b] Homogeneous.

The problem of the distribution of negative charge in the 2-pyridone and 2- and 4-pyrimidone anion has not been resolved. On spectroscopic grounds it has been proposed that this charge is located principally on the N-3 or on oxygen.[7–9] Calculations of charge distribution in the 4-pyrimidone anion employing the semiempirical iterative extended Hückel theory[10] are sum-

(5) E. W. Della, *Tetrahedron Lett.*, No. 28, 3347 (1966).

(6) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).

(7) E. Spinner, *J. Chem. Soc.*, 1232 (1960).

(8) Yu. N. Sheinder and Yu. I. Pomerantsev, *Russ. J. Phys. Chem.*, **33**, 174 (1959).

(9) E. Spinner and J. White, *J. Chem. Soc. B*, 966 (1966).

(10) These data were supplied through the courtesy of James Harlos and Dr. George Clarke of our Chemistry Department.

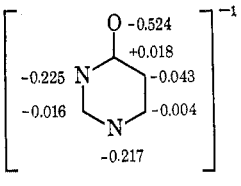
marized in Table VI. The ground-state charge distribution of an isolated ion is shown as structure V. These calculations indicate that approximately 75% of the negative charge in the ion is distributed between the N-3 and the oxygen atom.

TABLE VI

ATOM PARAMETERS USED IN ITERATIVE EXTENDED HÜCKEL TREATMENT OF 4-HYDROXYPYRIMIDINE ANION[11]

	Parameter			
Atom	α_s (eV)	α_p (eV)	$\Delta\alpha$ (eV)	Orbital exponent Z
H	11.6		14.0	1.200
C	25.0	10.0	11.0	1.625
N	30.0	11.5	12.0	1.950
O	33.0	14.0	15.0	2.275

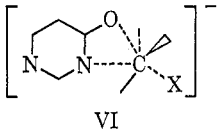
Although the oxygen bears a greater amount of negative charge in the ground state, other factors including the polarizability of the nitrogen atoms must come into play in the transition state to lead to the predominance of nitrogen alkylation (in the absence of steric factors). This is implied by the generalization that alkylating agents carrying little or no charge preferentially form covalent bonds with the more polarizable atom of the ambident systems.[11] Of the atoms under consideration, nitrogen is more polarizable than oxygen, and nitrogen alkylation predominates.



V

In DMF and DMSO, the anion is poorly solvated. It seems reasonable that since approximately 75% of the negative charge is distributed between the N-3 nitrogen and the oxygen atom in the ground state that interaction with the alkylating agent would occur here rather than at N-1. In fact, methylation of the sodium salt of 4-hydroxypyrimidine in DMF leads to 82% N-3 and 17% N-1 isomers.

Brower, Ernst, and Chen[12] have observed in several ambident anion alkylations, including *n*-butylation of the sodium salt of 2-pyridone, that pressure (to 1360 atm) has no effect on product distribution. They concluded from their experiments that "branching of the reactive pathways occurs at or beyond the transition state." By analogy, a transition state as indicated in structure VI involving the "free" pyrimidine anion and



VI

the alkylating agent is consistent with our observations. Since nitrogen is more polarizable, N-C bond formation would be favored.

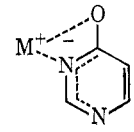
(11) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964).

(12) K. R. Brower, R. L. Ernst, and J. S. Chen, *J. Phys. Chem.*, **68**, 3814 (1964).

The N-3 and O positions are preferentially blocked by hydrogen-bonding solvents and N-1 alkylation becomes more important. When the sodium salt of 4-hydroxypyrimidine reacted with methyl iodide, the amount of N-3 alkylation decreased from 82 to 68 to 59% (N-1 alkylation increased proportionately) in the solvent series DMF, ethanol, and water.

Several reactions were included to determine the effect of concentration on product ratios. The sodium salt of 4-hydroxypyrimidine was alkylated in isopropyl alcohol (0.45 *M*) with ethyl iodide to give N-3 to N-1 product ratio of 46:54. When the concentration was decreased to 0.03 *M*, this ratio became 56:44.[13] These changes are relatively small but the increased alkylation at the N-3 position with decreasing concentration is consistent with the presence of molecular aggregates or ion pairs in solution. Decreasing concentration favors their dissociation, thereby enhancing alkylation of the initially blocked site. Curtin obtains comparable results in the alkylation of 2,6-dimethylphenoxide.[14]

In solvents of lower solvating ability, observations can be rationalized by assuming that in the aggregate the cation blocks the N-3 nitrogen as in structure VII, and, therefore, the N-1 nitrogen can compete effectively.



VII

Leaving groups did not affect the reaction product distribution in good solvation media such as methanol. Only when reactions were run in ethyl acetate with saturated alkylating agents did the leaving group play an important role. The reaction mixtures were heterogeneous from beginning to end. A detailed study of the effect of heterogeneity was not attempted; however, tosylates gave more alkylation at N-3 than did iodides. The data for methylations are presented in Table VII.

TABLE VII

EFFECT OF LEAVING GROUP ON METHYLATION OF 4-HYDROXYPYRIMIDINE IN ETHYL ACETATE (0.45 *M*[a])

Substrate	Cation	Leaving group	% N-3	% N-1
Ia	Li[b]	I	36	64
Ia		OTs	54	46
Ib		I	43	57
Ib		OTs	53	47
Ia	Na[c]	I		100
Ia		OTs	72	28
Ib		I		100
Ib		OTs	25	75
Ia	K[c]	I	57	43
Ia		OTs	83[d]	13
Ib		I	60	40
Ib		OTs	77[e]	16

[a] At least 80% of pyrimidines were recovered in all experiments. [b] 70°. [c] 40°. [d] 4% of ether was isolated. [e] 7% of ether was isolated.

(13) Alkylation of the sodium salt of 4-hydroxypyrimidine with methyl and ethyl iodide in methanol, a good cation solvent, at concentrations of 0.45 and 0.35 *M* produced no variations in isomer distribution.

(14) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, **80**, 1391 (1958).

Except for decomposition of products at higher temperatures, the variation of temperature (20–90°) had a negligible effect on product distribution. This further supports the premise that branching of the reactive pathway leading to the different isomers occurs after the transition state.

Experimental Section[15]

Methods.—Ultraviolet spectra were determined in aqueous solution on a Perkin-Elmer 202 instrument. Infrared spectra were determined on a Beckman IR-5A spectrophotometer, neat or in a Nujol mull. Nmr spectra were obtained on a Varian A-60 instrument in DMSO-d_6, $CDCl_3$, and D_2O.

Gas chromatograms were obtained on an F & M 720 instrument with column 2 ft in length unless otherwise stated, consisting of 10 or 20% silicon gum rubber on silanized Chromosorb W; the actual pecentage of the silicon gum rubber was not critical. Helium flow rates were 60 ml/min, and runs were programmed from 80–300° at 15°/min. Silica gel was Fisher Certified 100–200 mesh. Alumina was purchased from Woelm and was neutral activity grade I.

General Alkylation Procedure.—The pyrimidine salt alkylating agent[16a] and solvent were sealed in a glass tube and the reaction mixture was maintained at 40 ± 2°. After an appropriate time interval, the reaction mixture was analyzed by gas chromatography to determine the amount of ether, N-3 isomer, and parent hydroxypyrimidine present. Because of its low volatility, the concentration of N-1 isomer was determined by thin layer chromatography on silica gel G containing phosphor G. Separation of all components was accomplished by development with methanol. The pyrimidines were extracted from the silica gel with water. The ultraviolet spectra were determined on the centrifuged supernatant solution. Comparisons with calibrated spectra were reproducible to within ±3%. All compounds were found to be stable under reaction conditions.

The following compounds were prepared according to established procedures: ethyl tosylate,[17] 2-methyl-4-hydroxypyrimidine,[18] 4-hydroxypyrimidine,[19] 2-trifluoromethyl-4-hydroxypyrimidine,[20] 4-methoxypyrimidine,[21] and 4-chloropyrimidine hydrochloride.[22]

Sodium Salt of Ethyl Formylacetate.—A mixture of 125 g (1.69 mol) of ethyl formate and 125 g (1.42 mol) of ethyl acetate was slowly added to a suspension of sodium hydride (62.7 g, 1.42 mol, from a 54.3% mineral oil dispersion from Metal Hydrides, Inc., which was washed with dry ether) in 500 ml of dry ether. Hydrogen evolution ceased about 2 hr after the ester addition was complete. The yellow precipitate was collected and dried *in vacuo* to give 160 g (49%) of product.

This compound was previously prepared in 35% yield by Gabriel[18] using sodium wire. The procedure described above is much simpler and gives purer product in higher yield.

Salts of 4-Hydroxypyrimidines.—Alkali metal salts were prepared from the 4-hydroxypyrimidines and equivalent amounts of the metal or the hydroxide in ethanol or in methanol and dried over phosphorus pentoxide *in vacuo* after removal of solvent. No impurities were detected in nmr spectra where DMSO-d_6 was used as the solvent.

Sodium salts were prepared from sodium ethoxide and an equivalent amount of the hydroxypyrimidine in ethanol. These salts were dried at 100°.

The lithium salt of 2-methyl-4-hydroxypyrimidine was prepared similarly employing lithium metal dissolved in methanol. After evaporation of the solvent, ether was added and evaporated several times to remove methanol. The product was dried at 100°. Lithium hydroxide in a 1:1 solution of methanol and ethanol was added to the pyrimidine in ethanol to form the **lithium salt of 4-hydroxypyrimidine**, which was dried at 140°. Potassium salts were prepared from 87% potassium hydroxide diluted with ethanol. Solvent was evaporated until precipitation occurred. Addition of ether gave a solid which was washed with ether and dried at 100°.

Silver salts were prepared from silver nitrate and the hydroxypyrimidine in water. After neutralization with ammonium hydroxide the precipitates were collected on a centrifuge and washed with water, methanol, and ether.

1-Methyl-4-pyrimidone.—Methyl iodide (12.1 g, 0.0850 mol) was added to a mixture of the sodium salt of 4-hydroxypyrimidine (10.0 g, 0.0850 mol) and 250 ml of tetrahydrofuran. After the mixture was refluxed for 3 days, the solvent was removed *in vacuo*. An ethyl acetate solution of the residue was applied to a silica gel column, and 5.0 g (54%) of product was eluted with absolute ethanol and with methanol, mp 155–156°. This material was identical with an authentic sample prepared by desulfurization of 1-methyl-2-methylthio-4-pyrimidone,[16b] mp 155–156°.

3-Methyl-4-pyrimidone was obtained from 0.41 g (2.92 mmol) of methyl iodide and 0.345 g (2.92 mmol) of the sodium salt of 4-hydroxypyrimidine in 8 ml of dimethylformamide after 2 hr. Evaporation of the solvent and extraction with chloroform gave 0.3 g (94%) of crude product after removal of chloroform. The analytical sample was recrystallized from chloroform: mp 121–122° (lit.[16b] mp 123–124°); uv max (H_2O) 222 mμ (ε 6990), 272 (4000).

1-Ethyl-4-pyrimidone was obtained as a hygroscopic solid by refluxing 5.0 g (43 mmol) of the sodium salt of 4-hydroxypyrimidine and 7.4 g (47 mmol) of ethyl iodide in 120 ml of isopropyl alcohol for 5 hr. After standing for 12 hr the solvent was removed and the product was purified on a silica gel column by eluting with methanol, methanol–ethyl acetate, and ethyl acetate. The analytical sample (1.6 g, 27%) melted at 64–66° and was obtained by recrystallization from acetone–benzene and then from acetone–petroleum ether: uv max (H_2O) 240 mμ (ε 14,600); nmr δ ($CDCl_3$) 1.5 (t, 3 H), 4.1 (q, 2 H), 6.25 (d, 1 H), 7.8 (d, 1 H), and 8.5 (s, 1 H).

Anal. Calcd for $C_6H_8N_2O$: N, 22.56. Found: N, 22.27.

1,2-Dimethyl-4-pyrimidone was obtained from 10.2 g (72.5 mmol) of methyl iodide and 1.2 g (9.0 mmol) of the sodium salt of 2-methyl-4-pyrimidone in 24 ml of ethyl acetate after stirring for 4 days at 50°. After evaporation to dryness the residue was taken up in chloroform and applied to a silica gel column. Elution with methanol and with 95% ethyl alcohol gave 0.3 g (26%) of product: mp 180–182°; uv max (H_2O) 240 mμ (ε 12,605).

Anal. Calcd for $C_6H_8N_2O$: N, 22.56. Found: N, 22.54.

2,3-Dimethyl-4-pyrimidone was obtained from 3.2 g (22 mmol) of methyl iodide and 3.0 g (22 mmol) of the sodium salt of 2-methyl-4-pyrimidone in 50 ml of dimethylformamide after a reaction time of 20 hr. After removal of the solvent the residue was extracted with hot ethyl acetate. The solid which precipitated on cooling was sublimed under reduced pressure to give 0.3 g (27%) of product: mp 63–65°; uv max (H_2O) 222 mμ (ε 4920); nmr δ (D_2O) 2.7 (s, 3 H), 3.6 (s, 3 H), 6.5 (d, 1 H), 7.9 (d, 1 H).

Anal. Calcd for $C_6H_8N_2O$: C, 58.06; H, 6.47. Found: C, 58.51; H, 6.68.

2-Methyl-4-methoxypyrimidine was prepared from 2.1 g (0.0926 g-atom) of sodium in 100 ml of methanol and 5.5 g (33 mmol) of 2-methyl-4-chloropyrimidine hydrochloride[17] by stirring overnight. After removal of the sodium chloride the filtrate was evaporated to give an oil which was extracted with ether. The ether extract was washed with water, dried, and evaporated. The residue was dissolved in benzene and applied to an alumina column and eluted with methylene chloride, chloroform, and ethyl acetate to give 2 g (35%) of product: uv max (H_2O) 212, 251 mμ (ε 3740); nmr δ ($CDCl_3$) 2.6 (s, 3 H), 4.0 (s, 3 H), 6.5 (d, 1 H), 8.35 (d, 1 H).

Anal. Calcd for $C_6H_8N_2O$: N, 22.56. Found: N, 22.30.

(15) Melting points were taken on either a Mel-Temp or a Fisher-Johns apparatus and are corrected. Boiling points are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt, Mülheim, Germany.

(16) (a) Initial methylations of the sodium salt of 4-hydroxypyrimidine were conducted with an excess of methyl iodide. Yields were found to be low and a corresponding amount of an unexpected material was isolated from the reaction mixture. The physical and chemical properties of this compound were identical with those reported by Brown, *et al.*,[16b] for 1,3-dimethyl-4-oxopyrimidinium iodide. Hence, all reactions reported in this paper were run with an equivalent amount of alkylating agent. Excess reagent has been shown to be detrimental also for alkylations of 2-hydroxypyridines with methyl iodide.[4] (b) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 211 (1955).

(17) S. Tipson, *J. Org. Chem.*, **21**, 133 (1947).

(18) S. Gabriel, *Ber.*, **37**, 3638 (1904).

(19) D. J. Brown, *J. Soc. Chem. Ind., London*, **69**, 353 (1950).

(20) S. Inoue, A. J. Saggiomo, and E. A. Nodiff, *J. Org. Chem.*, **26**, 4504 (1961).

(21) D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953).

(22) M. Boarland and J. McOmie, *ibid.*, 1218 (1951).

2-Methyl-4-ethoxypyrimidine was prepared from 1.62 g (9.8 mmol) of 2-methyl-4-chloropyrimidine hydrochloride[17] and 0.45 g (20 mg-atom) of sodium in 100 ml of absolute ethanol. After 10 hr the sodium chloride was separated and the solvent was removed. The liquid residue was dissolved in ether and collected by gas chromatography: uv max (H_2O) 212, 251 mμ (ε 4160); nmr δ ($CDCl_3$) 1.45 (t, 3 H), 2.65 (s, 3 H), 4.5 (q, 2 H), 6.6 (d, 1 H), 8.4 (d, 1 H).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30. Found: C, 60.66; H, 7.46.

2-Ethyl-4-ethoxypyrimidine was prepared from 0.36 g (3.3 mmol) of ethyl bromide and 0.50 g (3.4 mmol) of the sodium salt of 2-ethyl-4-pyrimidone in 7.5 ml of DMF. After stirring for 12 hr the liquid product was collected by gas chromatography: uv max (H_2O) 212, 251 mμ; ir (no carbonyl).

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.16; H, 7.89. Found: C, 62.87; H, 8.07.

2-Trifluoromethyl-4-ethoxypyrimidine was prepared from 0.380 g (3.49 mmol) of ethyl bromide and 0.38 g (2.08 mmol) of the sodium salt of 2-trifluoromethyl-4-pyrimidone in 4 ml of dimethylformamide. After stirring 5 hr the solvent was removed under a stream of nitrogen and ether was added. After separation of the sodium bromide and evaporation of most of the solvent, the liquid product was collected by gas chromatography using a 10-ft column: uv max (H_2O) 219, 251.5 mμ; ir (no carbonyl).

Anal. Calcd for $C_7H_7F_3N_2O$: C, 43.77; H, 3.64. Found: C, 44.12; H, 3.90.

Using this procedure, 0.52 g (3.69 mmol) of methyl iodide and 0.39 g (2.1 mmol) of the sodium salt of 2-trifluoromethyl-4-pyrimidone in 4 ml of dimethylformamide gave two liquid products when collected by gas chromatography. 2-Trifluoromethyl-4-methoxypyrimidine had the lower retention time; uv max (H_2O) 218, 250 mμ; ir (neat, no carbonyl).

Anal. Calcd for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83. Found: C, 40.16; H, 3.09.

2-Trifluoromethyl-3-methyl-4-pyrimidone: uv max (H_2O) 224, 279 mμ; ir 5.90 μ (C=O).

Anal. Calcd for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83. Found: C, 40.61; H, 2.98.

3-Ethyl-4-pyrimidone was prepared from 0.168 g (1.42 mmol) of the sodium salt of 4-pyrimidone and 0.215 (1.97 mmol) of ethyl bromide in 4 ml of methanol. After 4 days at 40° the mixture was concentrated by evaporation and the product was collected by gas chromatography: uv max (H_2O) 220, 271 mμ, ir 5.99 μ (C=O); δ (D_2O) 1.5 (t, 3 H), 4.2 (q, 2 H), 6.71 (d, 1 H), 8.2 (broad s, 1 H), 8.7 (broad s, 1 H).

Anal. Calcd for $C_6H_8N_2O$: C, 58.10; H, 6.45. Found: C, 58.60; H, 6.75.

This compound was formed in 33% yield from 3.0 g (25 mmol) of the sodium salt and 3.0 g (29 mmol) of ethyl bromide. After 36 hr the hygroscopic solid was recrystallized from benzene and washed with acetone: mp 70.0–71.5°; uv max (H_2O) 222 mμ (ε 7080), 272 (4060).

4-Ethoxypyrimidine.—A solution of sodium ethoxide, prepared from 0.55 g (24 mg-atom) of sodium and 50 ml of absolute ethanol, was added to a mixture of 1.81 g (12.0 mmol) of 4-chloropyrimidine hydrochloride and 50 ml of absolute ethanol. The reaction mixture was stirred overnight at room temperature. Sodium chloride was removed by filtration, and the filtrate was evaporated *in vacuo* to an oil. Water was added and the mixture was extracted several times with ether. The combined extracts were washed with water, dried over magnesium sulfate, and filtered. The solvent was evaporated *in vacuo* to give an oil which was collected by gas chromatography: uv max (H_2O) 250 mμ (ε 3638); ir (no carbonyl).

Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.49. Found: C, 57.94; H, 6.45.

1-Ethyl-2-methyl-4-pyrimidone.—2-Methyl-4-hydroxypyrimidine (5.0 g, 45 mmol) was mixed with 50 ml of absolute ethanol. A solution of 3.31 g (50 mmol) of 85% potassium hydroxide dissolved in 50 ml of ethanol and 5.9 g (54 mmol) of ethyl bromide was added. The reaction mixture was stirred at room temperature for 1 hr, refluxed for 2 hr, and filtered. The filtrate was evaporated to dryness, and the residue was triturated with hot ethyl acetate and applied to a silica gel column. Elution with absolute ethanol gave fractions with uv max at 225 and 268 mμ. Elution with methanol gave a material absorbing at 240 mμ (ε 14,550). The latter fractions were recrystallized from benzene to give 0.10 g (1.5%) of the desired compound: mp 129–130°; ir 6.1 μ (C=O); δ (D_2O) 1.4 (t, 3 H), 2.6 (s, 3 H), 4.1 (q, 2 H), 6.35 (d, 1 H), 7.85 (d, 1 H).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.81; H, 7.23; N, 20.18.

2-Methyl-3-ethyl-4-pyrimidone.—A mixture of 3.0 g (23 mmol) of the sodium salt of 2-methyl-4-hydroxypyrimidine, 2.13 g (19.5 mmol) of ethyl bromide, and 50 ml of DMF was stirred overnight at room temperature. The solvent was removed *in vacuo* to give 5.7 g of crude product which was chromatographed initially on alumina with methylene chloride and ethyl acetate and then on silica gel with methylene chloride, ethyl acetate, and methanol to give 0.7 g (22%) of hydroscopic product: mp 44–45°; uv max (H_2O) 223, 273 mμ (ε 4685); nmr δ ($CDCl_3$) 1.35 (t, 3 H), 2.6 (s, 3 H), 4.1 (q, 2 H), 6.3 (d, 1 H), 7.75 (d, 1 H).

Anal. Calcd for $C_7H_{10}N_2O$: N, 20.27. Found: N, 19.93.

2-Ethyl-4-hydroxypyrimidine.—The sodium salt of ethyl formylacetate (100 g, 0.725 mol) was dissolved in 500 ml of water. Propionamidine hydrochloride (44.4 g, 0.408 mol) was added to this solution. The reaction mixture was stirred at room temperature for 3 days and then extracted with ether. The solution was neutralized with hydrochloric acid and the solvent was removed under reduced pressure. The product was obtained by continuous extraction of the residue with absolute ethanol. Evaporation of the ethanol and recrystallization from high-boiling petroleum ether gave 25.1 g (36%), mp 118.5–120.5°. The analytical sample was purified further by double sublimation *in vacuo:* uv max (H_2O) 224 mμ (ε 7280); nmr δ (D_2O) 1.3 (t, 3 H), 2.8 (q, 2 H), 6.45 (d, 1 H), 8.0 (d, 1 H).

Anal. Calcd for $C_6H_8N_2O$: C, 58.06; H, 6.45; N, 22.58. Found: C, 57.85; H, 6.64; N, 22.46.

2,3-Diethyl-4-pyrimidone.—Ethyl bromide (3.57 g 32.8 mmol) was added to a mixture of the sodium salt of 2-ethyl-4-hydroxypyrimidine (5.0 g, 34 mmol) and 75 ml of DMF. After 2 days, the solvent was removed under reduced pressure and the residue was triturated with ethyl acetate. The solution was eluted on a silica gel column successively with methylene chloride, chloroform, ethyl acetate, and methanol. The first methanol fractions yielded the desired N-3 compound as an oil. The yield was 2.6 g (52%): uv max (H_2O) 222 mμ (ε 5300), 273 (4582); nmr δ ($CDCl_3$) 1.3 (t, 6 H), 2.85 (q, 2 H), 4.2 (q, 2 H), 6.35 (d, 1 H), 7.85 (d, 1 H).

Anal. Calcd for $C_8H_{12}N_2O$: N, 18.40. Found: N, 18.25.

1,2-Diethyl-4-pyrimidone.—The latter methanol fractions from the preparation of the 2,3-diethyl-4-pyrimidone gave about 0.3 g (27%) of the N-1 isomer: mp 108–111°; uv max (H_2O) 240 mμ (ε 13,580); nmr δ ($CDCl_3$) 1.25 (m, 6 H), 2.6 (q, 2 H), 3.7 (q, 2 H), 6.0 (d, 1 H), 7.0 (d, 1 H).

Anal. Calcd for $C_8H_{12}N_2O$: N, 18.40. Found: N, 18.09.

Registry No.—1-Ethyl-4-pyrimidone, 6146-20-9; 1,2-dimethyl-4-pyrimidone, 24903-63-7; 2,3-dimethyl-4-pyrimidone, 17758-38-2; 2-methyl-4-methoxypyrimidine, 7314-65-0; 2-methyl-4-ethoxypyrimidine, 24903-66-0; 2-ethyl-4-ethoxypyrimidine, 24903-67-1; 2-trifluoromethyl-4-ethoxypyrimidine, 24903-68-2; 2-trifluoromethyl-4-methoxypyrimidine, 24903-69-3; 2-trifluoromethyl-3-methyl-4-pyrimidone, 24903-70-6; 3-ethyl-4-pyrimidone, 6146-22-1; 4-ethoxypyrimidine, 24903-72-8; 1-ethyl-2-methyl-4-pyrimidone, 24903-73-9; 2-methyl-3-ethyl-4-pyrimidone, 24903-74-0; 2-ethyl-4-hydroxypyrimidine, 24903-75-1; 2,3-diethyl-4-pyrimidone, 24903-76-2; 1,2-diethyl-4-pyrimidone, 24903-77-3; 2-methyl-4-hydroxypyrimidine (sodium salt), 24903-78-4; 4-hydroxypyrimidine (sodium salt), 24903-79-5.