Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.40; H, 13.26.

The Isolation of Dicyclohexyl by Preparative Gas Chromatography.—The conditions used for the separation of dicyclohexyl was the same as that used for 2-methylspiro[5.5]undecane, $n^{20.0}D$ 1.4780 (lit.[17] $n^{21.1}D$ 1.4798).

(17) W. Hückel, O. Neunhoeffer, A. Gercke, and E. Frank, *Ann.*, **477**, 99 (1930).

Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.67; H, 13.04.

Vapor Phase Chromatography.—Routine separation and quantitative determinations were carried out on a Yanagimoto Model GCS-100 gas chromatograph. A 2 m × 0.25 in. stainless steel column packed with silicone hivac grease was used. The column temperature was kept at 156° for all dimeric fractions. Hydrogen (70 ml/min) was used as the carrier gas. The retention times in minutes were as follows: 6.5 (A), 9 (B), and 12.5 (C).

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

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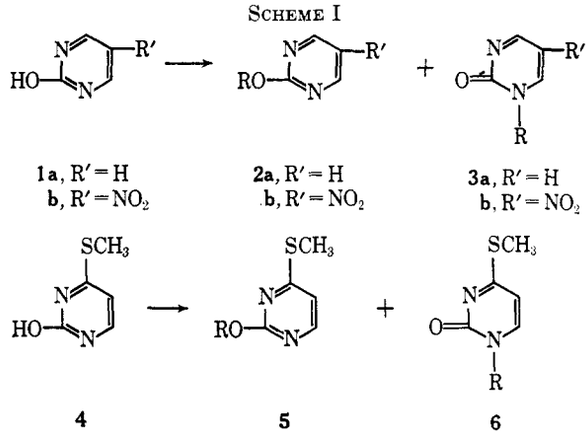
The reaction of salts of 2-hydroxypyrimidine, 2-hydroxy-5-nitropyrimidine, and 2-hydroxy-4-methylthiopyrimidine with alkyl halides and tosylates was investigated. The site of alkylation is primarily a function of the alkylating agent and is insensitive to a variety of experimental and structural variations. Steric factors are proposed to account for the influence of alkylating agent, while insensitivity to other variables is related to the structure of the anions. The preparation, identification, and physical properties of several new alkyl derivatives of the pyrimidines are reported.

We have initiated a study to evaluate the sensitivity of simple monohydroxypyrimidines[2] and related heterocyclic compounds toward factors which are known to influence alkylation sites in other systems such as phenols, enols, and nitroalkanes. We report here the results of an examination of the alkylation of 2-hydroxypyrimidine (**1a**), 2-hydroxy-5-nitropyrimidine (**1b**), and 2-hydroxy-4-methylthiopyrimidine (**4**) with simple alkyl halides, benzyl halides, and tosylates.

Recent alkylation studies,[3] particularly by Kornblum,[4] have been useful in indicating those factors which could be of importance in governing the site of alkylation of heterocyclic ambident anions. Although there have been many investigations and examples of this method of alkylation with hydroxypyrimidines[5a] and related heterocyclic compounds,[5b-g] studies in this area have been limited by technical difficulties associated with the separation and analysis of resulting product mixtures.

Alkali metal and silver salts of **1a**, **1b**, and **4** were treated with alkyl and benzyl halides or tosylates under conditions in which variables such as alkylating agent, solvent, and metal salt were changed systematically. The product distributions resulting from these transformations were conveniently determined by quantitative vapor phase chromatography based on calibrations established with authentic samples of each alkylation product. Although two isomeric nitrogen alkylated products could have formed from the unsymmetrical pyrimidine **4**, 3-alkyl-4-methylthio-2-pyrimidones were not detected. Similarly, no product resulting from carbon alkylation was found. (See Scheme I.)

SCHEME I



Results and Discussion

Pertinent product distribution data are presented either in Tables I–IV or discussed in general terms in the following text and are representative of a larger amount of data actually obtained.

The ratio of nitrogen to oxygen alkylation observed with salts of the 2-hydroxypyrimidines depends primarily on the alkylating agent. Results of representative studies in dimethylformamide at room temperature with sodium salts are summarized in Table I. Oxygen alkylation progressively increases from negligible amounts to as much as 56% when the halides are varied from methyl or benzyl to isopropyl. Treatment of **4** with isopropyl halides gives more oxygen alkylation than does **1a** or **1b**. Since alkylation occurs at only one nitrogen in **4** compared to two in **1a** and **1b**, the increased oxygen alkylation with **4** is attributed to a statistical factor. While models show considerable steric opposition to the formation of 3-

(1) (a) This investigation was supported by Public Health Service Research Grant No. GM-12112 from the National Institute of General Medical Sciences; (b) Allied Chemical Corp. Fellow, 1964–1965.

(2) Although generally existing in the lactam structure, the term hydroxypyrimidine will be used to indicate the presence of an ionizable hydrogen and serve to distinguish these compounds from N-alkylated pyrimidones.

(3) A. Brändström, *Arkiv Kemi*, **6**, 155 (1953).

(4) (a) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955); (b) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *ibid.*, **85**, 1141 (1963); (c) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963), and references therein.

(5) Brief accounts of early work in this area and leading references are contained in the following monographs: (a) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp 359–371; (b) H. Meislich, "Pyridine and Its Derivatives," Part III, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp 631–640; (c) R. C. Elderfield, "Heterocyclic Compounds," Vol IV, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp 151–153; (d) W. J. Gensler, 5c, p 435; (e) T. L. Jacobs, "Heterocyclic Compounds," Vol VI, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 121, 122, 132; (f) J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, Inc., New York, N. Y., 1953, p 241; (g) T. A. Williamson, ref 5e, pp 354–356.

TABLE I

EFFECT OF ALKYLATING AGENT ON PRODUCT DISTRIBUTIONS RESULTING FROM ALKYLATION OF SODIUM SALTS IN DIMETHYLFORMAMIDE AT AMBIENT TEMPERATURES

Substrate	Alkyl halide	% complete	Product compn, % N	O	Other
1a	MeI	83	98	2	..
1a	EtI	99	84	16	..
1a	*i*-PrBr	97	67	33	..
1a	*i*-PrI	98	67	33	..
1a	$PhCH_2Cl$	82	98	2[a]	..
1a	$PhCH_2Br$	87	97	3	..
1a	$PhCH_2I$	65	98	2	..
1b	MeI	98	97	3	..
1b	EtI	99	93	7	..
1b	*i*-PrBr	86	69	29	2
1b	*i*-PrI	98	67	31	2
1b	*i*-PrOTs	88	61	39	..
4	MeI	100	93	0	7
4	EtI	102	81	14	5
4	*n*-PrBr	88	75	18	7
4	*i*-PrI	88	40	56	4

[a] Estimated.

TABLE II

EFFECT OF THE CATION ON ALKYLATIONS WITH ETHYL BROMIDE AT AMBIENT TEMPERATURES IN DIMETHYLFORMAMIDE

Substrate	Cation	% complete	Product compn, % N	O	Other
1a	Na	100	80	12	8
1a	Li[a]	88	92	8	..
1a	Ag[b]	78	80	15	5
1a	K_2CO_3	102	90	10	..
1b	Na	96	92	8	..
1b	Ag	97	94	6	..
4	Na	100	81	14	5
4	K	103	86	14	..
4	K_2CO_3	93	80	15	5
4	Ag	99	71	28	1
4	Ag_2CO_3	102	79	21	..

[a] Essentially similar results in 1,2-dimethoxyethane, acetone, and methanol. [b] Essentially similar results in 1,2-dimethoxymethane and methanol.

TABLE III

EFFECT OF EXCESS ALKYLATING AGENT ON YIELDS OBTAINED FROM ALKYLATION OF THE SODIUM SALT OF 2-HYDROXYPYRIMIDINE IN DIMETHYLFORMAMIDE AT AMBIENT TEMPERATURES

Alkylating agent	Excess of theory, %	Yield, % N	O
MeI	0	80	4
MeI	50	41	3
MeI	200	15	3
EtI	50	83	15
EtI	200	55	12
i-PrI	50	66	32
i-PrI	200	70	30

isopropyl-4-methylthio-2-pyrimidone, an analysis of product distributions suggests comparable steric opposition to the formation of corresponding methyl, ethyl, and propyl derivatives.[6,7] 2-Hydroxy-5-nitropyrimidine (**1b**) gives results similar to those obtained from **1a**.[8]

TABLE IV

SOLVENT INFLUENCES ON RATES OF ETHYLATION AT AMBIENT TEMPERATURES WITH SODIUM SALTS[a]

Substrate	Solvent	Time, days	Reaction,[b] %
1a	DMF[c]	2	84[d]
1a	MeOH	5	60
1a	EtOH	5	50
1a	TFE[c]	5	16
1a	Diglyme[c]	5	36
1a	THF[c]	5	6
4	DMF	1	100[d]
4	DMSO	1	96[d]
4	MeOH	5	84
4	EtOH	5	42
4	Diglyme	5	16

[a] All reactions were conducted with 50% excess ethyl bromide. Rate comparisons are only valid within a given substrate. [b] The per cent reaction is based on the starting pyrimidine salt. [c] Abbreviations: DMF = dimethylformamide, DMSO = dimethyl sulfoxide, TFE = 2,2,2-trifluoroethanol, THF = tetrahydrofuran, diglyme = the dimethyl ether of ethylene glycol. [d] The minimum time for complete reaction could be appreciably less than 1 day.

Alkylations with isopropyl bromide under the conditions cited in Table I required 2 days with substrate **4** and 6 days with **1a** and **1b** to reach 50% completion. Corresponding alkylations with the primary alkyl and benzyl bromides and iodides were complete in less than 48 hr. The reactivity sequence with the saturated halides is typical of reactions proceeding by bimolecular nucleophilic substitution.

Product ratios observed with the 2-hydroxypyrimidine salts do not appear related to an SN1–SN2 gradation in mechanism.[3,4] Alkylation of **4** with isopropyl bromide is second order,[9] is slower than methylation and ethylation, and gives good yields, consistent with a bimolecular mechanism.

Alkylation products of the 2-hydroxypyrimidines are stable toward rearrangement and decomposition under the conditions of the reaction and analysis.[10] Thus, observed product ratios do not result from thermodynamic control. The change in product ratios with alkylating agent is attributed to changes in the relative rates of alkylation at nitrogen and oxygen. A study of models of **1a**, **1b**, and **4** suggests that nitrogen alkylations have greater steric requirements than oxygen alkylations.[13] As a consequence, the rate of

(6) The source of the apparent steric interactions arises from interference with both the oxygen atom and the substituent at the 4 position of the pyrimidine with the alkylating agent.

(7) In contrast to the results with salts of **4**, treatment of the potassium salt of 2-hydroxy-4-methylthio-6-methylpyrimidine with methyl iodide or benzyl chloride results in the formation of both N-1- and N-3-alkylated isomers: H. L. Wheeler and D. F. McFarland, *Am. Chem. J.*, **42**, 431 (1909). Such a result is in agreement with the comparable spacial requirements of the methyl and methylthio groups.

(8) An earlier report on the methylation of 2-hydroxy-5-nitropyrimidine [W. J. Hale and H. C. Brill, *J. Am. Chem. Soc.*, **34**, 82 (1912)] has been shown to be in error (L. M. Stempel, G. B. Brown, and J. J. Fox, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963).

(9) G. C. Hopkins, Ph.D. Dissertation, State University of New York at Buffalo, to be published in Feb 1967.

(10) Control experiments ensured that observed product distributions did not result from thermal isomerizations[11] particularly at the vpc injection port. Alkyl halide catalyzed isomerizations of the type described by Hilbert and Johnson[12] were likewise excluded by control experiments.

(11) D. J. Brown and R. V. Foster, *J. Chem. Soc.*, 4911 (1965).

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

(13) Interpretation of comparable results in terms of steric interactions has been rare. Meislich[5b] points out that steric factors do appear to be quite important in the alkylation of hydroxypyridines and that electronic factors "may not be the sole criteria for predicting the course of the alkylation reaction." An interesting review by M. T. Bogart and H. A. Seil [*J. Am. Chem. Soc.*, **29**, 517 (1907)] describes early investigations and contains a number of generalizations which could imply recognition of steric effects. However, the relative importance of steric factors cannot be assessed from existing literature alone because there are insufficient examples that are strictly comparable.

reaction at nitrogen decreases relative to that at oxygen when the alkyl group bulk is increased. The preference of 2-hydroxypyrimidine salts to alkylate at nitrogen in the absence of steric factors is explained by the greater polarizability and charge of the ring nitrogens. Spectral studies in aqueous media have indicated that at least 75% of the charge possessed by the anion of **1a** is localized at nitrogen.[14]

In further experiments not included here, bromides, iodides, and tosylates were compared as leaving groups in a number of methylations, ethylations, and isopropylations of **1a**, **1b**, and **4**.[9] Product distributions changed only slightly toward oxygen alkylation with tosylates compared to bromides and iodides which gave essentially the same results. In a few instances such as the combination of isopropyl tosylate with the sodium salt of **1a** or with silver salts of **1b** or **4**, elimination competed with alkylation. Even in these cases, however, no significant increase in oxygen alkylation was observed.

Silver salts of nitrogen heterocycles often give increased oxygen alkylation when compared to alkali metal salts.[4a] Table II shows a lack of sensitivity of 2-hydroxypyrimidines to the cation.[15] Data from ethylations are used to illustrate the effect of silver ion since alkylations with ethyl halides give some ether even with alkali metal salts. Methylation of the pyrimidines gives almost exclusive nitrogen alkylation regardless of the cation. Isopropylations of silver salts of **1a** and **4** did not permit good contrasts owing to competing elimination reactions. Silver and alkali metal salts of **1b** react with isopropyl iodide to give nearly identical product ratios and yields. Similarly, product ratios from benzylations of **1a** were not altered by a change from silver to alkali metal salts.

Use of the parent compounds together with corresponding metal carbonates gave the same product distributions as the preformed salts, except in alkylations of **1b** where extensive decomposition results using the former procedure. Examples where carbonates were used are shown in Table II.

Excess alkylating agent decreases the yields of methylated pyrimidines. Much greater than stoichiometric quantities of methyl iodide with salts of **1a**, **1b**, and **4** result in greatly decreased yields. Ethylations are influenced to a lesser extent and isopropylations not at all. The magnitude of this effect is illustrated in Table III.[20] Yield reductions with excess methyl iodide are indicated to result from formation of quaternary salts. A precipitate, identified as 1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium iodide from nmr data, was isolated in 55% yield from one run described in Table III. Yields of nitrogen-alkylated isomers are preferentially decreased.

The nature of the solvent had little effect on product distributions in methylations and ethylations although there was a large effect on reaction rates.

Among the solvents included in this study were representative alcohols, ethers and hydrocarbons, dimethylformamide, dimethyl sulfoxide, acetonitrile, acetone, ethyl acetate, and water. The largest effect on product ratios was observed in ethylations of the sodium salt of **1a** where reaction in dimethylformamide produced about 15% more oxygen alkylation than was obtained in methanol. Yields of alkylation products were near theoretical in both solvents. There was only a slight shift toward nitrogen alkylation in solvents capable of strong hydrogen bond formation or of lower dielectric constant. This trend was most pronounced with **1a** and barely perceptible with **1b** and **4**. None of the solvents examined produced higher ratios of oxygen-to-nitrogen alkylation than could be obtained in dimethylformamide (Table I). Solvent studies with isopropylations were attempted, but were generally unsuccessful. Of the solvents examined, isopropylations proceeded at appreciable rates only in dimethylformamide and dimethyl sulfoxide.

Again, alkylations conducted in the various solvents ranged from heterogeneous mixtures to homogeneous solutions, but product distributions did not seem to be affected by this factor. For example, alkylations of the sodium salt of **4** in dimethyl sulfoxide gave product distributions and yields which were identical within experimental error with those obtained in dimethylformamide. Reactions in dimethyl sulfoxide were completely homogeneous, whereas corresponding reactions in dimethylformamide were run as mixtures.

Rates of alkylation, however, are highly solvent dependent and appeared to be primarily a function of ion-solvating properties of the various media. Reactions are fastest in dimethylformamide and dimethyl sulfoxide, intermediate in methanol and ethanol, slow in 1,2-dimethoxyethane and the dimethyl ether of ethylene glycol, and generally do not proceed at all in poor ion-solvating media such as ethyl acetate, acetone, and hydrocarbons. Alkylations did not occur in acetonitrile. The magnitude of solvent effects on rates is illustrated by representative data shown in Table IV.

Variation of temperature, between 25 and 80°, does not influence product distributions although decomposition frequently occurs at the higher temperatures. In solvents where reactions do not proceed at room temperature, heating invariably leads to extensive decomposition. The solvent of choice is

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

(15) Early experiments directed toward synthesis of pyrimidine nucleosides were based on the supposed differential behavior of silver and alkali metal salts toward alkylating agents. It was found that O glycosides were obtained regardless of which salt was treated with a halogenose.[16] The subsequent successful application of pyrimidine mercury salts to nucleoside synthesis[17] is presently understood to proceed by initial O glycosylation followed by a mercury salt catalyzed rearrangement of the sugar moiety to nitrogen.[18] Similar observations with a variety of nitrogen heterocycles have been made by Wagner and his associates.[19] The present data indicate that O glycoside formation would be favored in bimolecular substitution processes because of the bulk of the halogenose.

(16) (a) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914); (b) E. Fischer, *ibid.*, **47**, 1377 (1914); (c) P. A. Levene and H. Sobotka, *J. Biol. Chem.*, **65**, 469 (1925).

(17) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

(18) (a) T. L. V. Ulbricht, *Angew. Chem. Intern. Ed. Engl.*, **1**, 476 (1962); (b) T. L. V. Ulbricht, *Proc. Chem. Soc.*, 298 (1962); T. L. V. Ulbricht and G. T. Rogers, *J. Chem. Soc.*, 6130 (1965).

(19) G. Wagner and H. Pischel, *Naturwissenschaften*, **48**, 454 (1961); H. Pischel and G. Wagner, *Z. Chem.*, **5**, 227 (1965), and leading references therein.

(20) A spot check of 34 pyrimidine alkylations recorded in the literature revealed that in 50% of the cases, excess alkylating agent was used. Since the majority of these employed methyl iodide, reported yields probably do not accurately or even approximately reflect initial product distributions. This is but one illustration why much of the existing literature is of limited value as a source for data pertaining to pyrimidine ambident anions.

TABLE V

PHYSICAL CONSTANTS FOR COMPOUNDS ISOLATED BY GAS CHROMATOGRAPHY

Name	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Ultraviolet, $\lambda_{max}^{methanol}$ mμ
1-Ethyl-4-methylthio-2-pyrimidone	227	$C_7H_{10}N_2OS$	49.38	5.92	16.46	49.49	5.90	16.29	301, shoulder
2-Ethoxy-4-methylthiopyrimidine	Liquid	$C_7H_{10}N_2OS$	49.38	5.92	...	49.87	5.98	...	287, 248
1-Propyl-4-methylthio-2-pyrimidone	101–103	$C_8H_{12}N_2OS$	52.14	6.57	15.21	52.13	6.65	15.08	304, shoulder
2-Propyloxy-4-methylthiopyrimidine	Liquid	$C_8H_{12}N_2OS$	52.14	6.57	15.21	52.07	6.63	15.31	288, 245
1-Isopropyl-4-methylthio-2-pyrimidone	143–145	$C_8H_{12}N_2OS$	52.14	6.57	15.21	52.12	6.40	15.04	302, shoulder
2-Isopropyloxy-4-methylthiopyrimidine	Liquid	$C_8H_{12}N_2OS$	52.14	6.57	...	52.41	7.10	...	288, 249

dimethylformamide where alkylation occurs rapidly and without side reactions.

In summary, the ambident anion chemistry of the hydroxypyrimidines studied here is relatively simple and related to only one of the experimental and structural variations examined. Steric effects are indicated to be the most important single influence on product ratios. The insensitivity of the alkylation site of these salts toward other factors examined can be rationalized in terms of current concepts regarding ambident anion behavior. It is proposed that the observed insensitivity is directly related to the electron-deficient nature of the pyrimidine nucleus. Anions generated from these heterocycles possess a greater negative charge at the ring nitrogens than at oxygen.[14] Since nitrogen is also more polarizable than oxygen, alkylations proceeding by either unimolecular or bimolecular nucleophilic substitution would be predicted to favor reaction at nitrogen.[4] Consequently, the ratio of nitrogen to oxygen alkylation would not be highly influenced by factors which govern the degree to which these mechanisms are operative. The small influence of solvent on product ratios is attributed to similarities between the atoms undergoing substitution. Nitrogen and oxygen are both capable of hydrogen-bond formation and are of comparable electronegativity. Thus, effects due to specific solvation are minimized.

Although 2-hydroxypyrimidines may be unique in their relatively simple ambident anion chemistry, nitrogen *vs.* oxygen alkylation in similar heterocyclic systems might also be less complex than is suggested by the literature.[5] An immediate objective of this continuing investigation is to determine the extent to which the ambident anion chemistry of pyrimidines and related heterocycles follows simple rules.

Experimental Section[21]

Materials.—All solvents and alkylating agents were reagent or spectroscopic grade and were stored over Linde Molecular Sieves (Type 13X) to remove or prevent the absorption of water. Additional purification was carried out by standard procedures when the need was indicated. 2-Hydroxypyrimidine and its derivatives[22] (except for 1-isopropyl-2-pyrimidone), 2-hydroxy-4-methylthiopyrimidine,[23,24] 1-methyl-4-methylthio-2-pyrimidone,[23] and 2-hydroxy-5-nitropyrimidine and its methyl derivatives[25] were prepared by previously described methods. Compounds for which no preparative procedure is given here were collected by vapor phase chromatography after alkylation and are presented in Table V.

Vapor Phase Chromatography.—Vpc analyses were determined on F & M Model 500 or F & M Model 720 gas chromatographs. The column support consisted of 60–70 mesh Chromosorb W which had been washed thoroughly with 10% sodium hydroxide solution, 4 *N* hydrochloric acid, and finally with water. After drying at 110° for 16 hr, the support was treated with hexamethyldisilazane[26] and coated with 10% by weight of silicon gum rubber (SE-30). Two-foot stainless steel columns (0.25-in. o.d.) and flow rates of 60–100 ml/min were used. Analyses were temperature programmed at 15–21°/min between 70 and 300°. All quantitative analyses were by standard procedures employing weighed samples calibrated against peak areas.

Alkylation Procedures.—The pyrimidine (0.500–1.00 mmole) was weighed into a small glass vial and 2.0–5.0 ml of solvent was added. The alkyl halide was added below the solvent surface with a calibrated 50-μl syringe and the stoppered vial was placed on a shaker. After suitable times 10–40-μl samples were withdrawn for vpc analyses.

Sodium Salt of 2-Hydroxy-4-methylthiopyrimidine.—Freshly cut sodium (2.44 g, 0.106 g-atom) in 100 ml of dry methanol was added to a suspension of 2-hydroxy-4-methylthiopyrimidine (15.0 g, 0.10 mole) in 200 ml of dry methanol. After stirring at room temperatue for 3 hr, the solvent was removed at 50° *in vacuo*. The residue was washed with absolute ethanol and dried at 78° *in vacuo* for 12 hr to a white powder (14.8 g, 85%) which melted sharply at 290° with decomposition.

Anal. Calcd for $C_5H_5N_2NaOS$: C, 36.58; H, 3.07, S, 19.53. Found: C, 36.97; H, 3.08; S, 19.11.

Sodium salts of 2-hydroxypyrimidine and 2-hydroxy-5-nitropyrimidine were prepared by an analogous procedure. The lithium salt of 2-hydroxypyrimidine was prepared by the substitution of lithium metal for sodium metal in the illustrative procedure for sodium salts. The composition of the salts was demonstrated by their conversion to the alkylated derivatives.

Potassium Salt of 2-Hydroxy-4-methylthiopyrimidine.—2-Hydroxy-4-methylthiopyrimidine (1.00 g, 7.0 mmoles) in 50 ml of absolute ethanol and 0.48 g of 85% potassium hydroxide (7.3 mmoles) in 45 ml of absolute ethanol were mixed and stirred for 1 hr. The volume of solution was then reduced to 30 ml and filtered to give 0.82 g (65%) of white powder. This was dried at 78° *in vacuo* (0.25 mm) and used in subsequent alkylation reactions. An additional 0.45 g (35%) obtained from the filtrate had an infrared spectrum identical with the first crop.

Anal. Calcd for $C_5H_5KN_2OS$: C, 33.31; H, 2.80. Found: C, 33.22; H, 2.85.

Potassium salts of 2-hydroxypyrimidine and 2-hydroxy-5-nitropyrimidine were prepared by an analogous procedure. The composition of these salts was demonstrated by their conversion to alkylated derivatives.

Silver Salt of 2-Hydroxy-4-methylthiopyrimidine.—A solution of silver nitrate (0.85 g, 5.0 mmoles) in 25 ml of water was added with stirring to a solution of 2-hydroxy-4-methylthiopyrimidine (0.711 g, 5.00 mmoles) in 75 ml of water. The resulting solution was immediately neutralized with concentrated ammonium hydroxide. The gelatinous precipitate was concentrated on a centrifuge and the supernatant liquid was dis-

(21) All melting points are corrected. Ultraviolet spectra were determined in methanol on a Beckman DK-2 instrument and infrared spectra were determined on a Beckman IR-5A spectrophotometer. Microanalyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, and A. Bernhardt, Mülheim, Germany. Where possible, samples were sent for inclusion in the Sadtler collection of infrared spectra.

(22) Preparative procedures for alkylated derivatives of the 2-hydroxypyrimidines have been recently published.[11] We thank Dr. Brown for making this information available to us prior to publication.

(23) Y. Mizuno, M. Ikehara, and K. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **10**, 653 (1962).

(24) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **42**, 30 (1909).

(25) L. M. Stempel, G. B. Brown, and J. J. Fox, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 14-O. The authors acknowledge the kind cooperation of Dr. Fox for supplying details of these preparations prior to publication.

(26) J. Bohemen, S. H. Langer, R. H. Perrett, and J. H. Purnell, *J. Chem. Soc.*, 2444 (1960).

carded. The precipitate was washed twice with 50-ml portions of water, absolute alcohol, and anhydrous ether. The resulting white powder, after drying *in vacuo* in the dark at 135°, weighed 1.26 g (101%).

Anal. Calcd for $C_5H_5AgN_2OS$: C, 24.11; H, 2.02. Found: C, 24.04; H, 2.17.

Silver salts of 2-hydroxypyrimidine and 2-hydroxy-5-nitropyrimidine were prepared by an analogous procedure. The composition of these salts was demonstrated by their conversion to the alkylated derivatives.

1-Benzyl-2-pyrimidone.—Potassium carbonate (1.38 g, 10 mmoles) was added to 2-hydroxypyrimidine (0.96 g, 10 mmoles) dissolved in 25 ml of dimethylformamide. After stirring for 15 min at room temperature, 1.71 g (10 mmoles) of benzyl bromide was added and the reaction was heated at 60° for 18 hr. The dimethylformamide was removed at 60° *in vacuo* and the yellow solids were extracted with chloroform (three 50-ml portions). The chloroform was washed with 25 ml of water, dried over magnesium sulfate, and filtered; the solvent was removed *in vacuo*. The white solid which remained was recrystallized from a mixture of 100 ml of *n*-hexane and 80 ml of acetone. On cooling 0.60 g of white crystals was obtained. An additional 0.36 g of product was obtained as a second crop. The total yield was 53%, mp 137–138°. The combined crops were recrystallized from *n*-hexane–chloroform (3:1) to give 0.74 g (36%) of product, mp 141°, $\lambda_{max}^{methanol}$ 310 mμ.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.41; H, 5.50; N, 15.40.

1-Isopropyl-2-pyrimidone.—Potassium carbonate (2.75 g, 20 mmoles) was added to 2-hydroxypyrimidine (1.92 g, 20 mmoles) dissolved in 50 ml of dimethylformamide. After stirring at room temperature for 30 min, 2.71 g (22 mmoles) of isopropyl iodide was added and the reaction was heated at 65–70° for 6 hr. The dimethylformamide was removed *in vacuo* at 90°. The residue was triturated four times with 50-ml portions of chloroform. The chloroform was then evaporated *in vacuo* at 90°. The yellow semisolid which formed on cooling was extracted repeatedly with 100-ml portions of boiling cyclohexane. White needles were formed on cooling the cyclohexane in an ice bath. After about 20 extractions, 0.73 g (26%) of product was obtained, mp 85–87°, $\lambda_{max}^{methanol}$ 310 mμ (lit.[22] mp 90°, $\lambda_{max}^{methanol}$ 310 mμ).

Product from Treatment of the Sodium Salt of 2-Hydroxypyrimidine with Excess Methyl Iodide.—A stoppered glass vial containing the sodium salt of 2-hydroxypyrimidine (0.059 g, 0.50 mmole) excess methyl iodide (0.213 g, 1.50 mmoles), and 2.0 ml of dimethylformamide was shaken at room temperature for 2 days. Bright yellow needles formed which were collected, washed with chloroform, and dried. The product weighed 0.054 g (42%), was highly soluble in water, and its aqueous solution gave a heavy precipitate on treatment with silver nitrate. The product has been tentatively identified as 1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium iodide: mp 235–237°; $\lambda_{max}^{methanol}$ 314, 225 mμ; nmr spectrum (D_2O), 3.88 (singlet) (area 5.9), 7.11 (triplet) (1.0), 8.92 ppm (doublet) (1.0).

1-Ethyl-5-nitro-2-pyrimidone.—2-Hydroxy-5-nitropyrimidine (1.41 g, 10 mmoles) and 0.66 g of 85% potassium hydroxide (10 mmoles) in 50 ml of dry methanol were stirred at room temperature for 10 min. Ethyl iodide (1.72 g, 11 mmoles) was added and the reaction was stirred at 55–60° for 24 hr. Removal of dimethylformamide *in vacuo* left a light orange-yellow solid, which was extracted with 150 ml of hot benzene. The benzene was removed *in vacuo* and the light yellow residue was recrystallized from 225 ml of cyclohexane–benzene (2:1) to give 0.45 g (27%) of yellow crystals, mp 111–113°, $\lambda_{max}^{methanol}$ 320 mμ.

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.60; H, 4.17; N, 24.84. Found: C, 42.30; H, 4.11; N, 24.80.

2-Ethoxy-5-nitropyrimidine.—Sodium (28.8 mg, 12.5 mg-atoms) in 10 ml of absolute ethanol was added to a solution of 2.00 g (12.5 mmoles) of 2-chloro-5-nitropyrimidine in 50 ml of absolute ethanol. After heating at reflux for 1.5 hr, the solution was neutral. The solvent was removed *in vacuo* and the solid residue was dissolved in a mixture of water (20 ml) and ether (50 ml). The ether layer was separated; the aqueous phase was extracted again with two 50-ml portions of ether. The combined ether extracts were dried over magnesium sulfate and filtered, and the ether was evaporated. A light-yellow oil remained which crystallized on cooling to 0°. The crude product (1.88 g) was recrystallized from 80 ml of 40% methanol to give 1.60 g (76%) of white crystals, mp 52–54°, $\lambda_{max}^{methanol}$ 273 mμ.

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.60; H, 4.17; N, 24.84. Found: C, 42.93; H, 4.24; N, 24.69.

2-Isopropyloxy-5-nitropyrimidine.—2-Hydroxy-5-nitropyrimidine (2.8 g, 20 mmoles) in 50 ml of dimethylformamide and 1.3 g of 85% potassium hydroxide (20 mmoles) were stirred for 15 min. Isopropyl iodide (5.1 g, 30 mmoles) was added and the solution was then stirred at 60° for 24 hr. Subsequent removal of the solvent *in vacuo* gave an orange gum. Three successive 20-ml portions of perchloroethylene were added and removed *in vacuo*. The residue was triturated with cyclohexane (five 50-ml portions) and the combined extracts were washed with two 20-ml portions of water, and dried over magnesium sulfate. Filtration and removal of the solvent *in vacuo* gave 0.52 g (14%) of a pale yellow oil which crystallized on standing at room temperature, mp 45–47°, $\lambda_{max}^{methanol}$ 275 mμ.

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.89; H, 4.95; N, 22.94. Found: C, 46.12; H, 5.23; N, 22.74.

1-Isopropyl-5-nitro-2-pyrimidone.—The residue from the cyclohexane extraction in the previous experiment was extracted further with 75 ml of acetone followed by 50 ml of chloroform. The combined extracts were filtered and the solvent was removed *in vacuo*. The gum was extracted with two successive 500-ml portions of hot cyclohexane, which on cooling deposited 0.51 g (14%) of white needles. The filtrate was used again (recycled) to extract the residue and gave an additional 0.52 g (14%) of product, mp 109–110°, $\lambda_{max}^{methanol}$ 316 mμ.

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.89; H, 4.95; N, 22.94. Found: C, 45.54; H, 4.95; N, 23.35.

2-Methoxy-4-methylthiopyrimidine. 2-Chloro-4-methylthiopyrimidine[27] (16.1 g, 0.100 mole) was dissolved in 50 ml of dry methanol at 0°. A cold solution of sodum methoxide (5.67 g, 0.105 mole) in 75 ml of dry methanol was added slowly over a period of 12 min with stirring and continued cooling. After warming to room temperature, stirring was maintained for 8 hr. The methanol was removed at 50° *in vacuo;* the residue was triturated with 50 ml of chloroform. The chloroform solution was washed with three 25-ml portions of water and dried. After removal of the chloroform, attempts to purify the resultant oil by fractional distillation were not successful.[28] Purification was effected on a 100–200 mesh silica gel column using chloroform as the eluting solvent. After removal of the solvent, 5.2 g (33%) of chromatographically pure (vpc), 2-methoxy-4-methylthiopyrimidine was obtained: $\lambda_{max}^{methanol}$ 287, 246 mμ.

Anal. Calcd for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.94; S, 20.53. Found: C, 45.96; H, 5.43; N, 17.48; S, 20.05.

(27) T. Ueda and J. J. Fox, *J. Med. Chem.*, **6**, 697 (1963).

(28) Two other components were formed in about 30% yield as determined by vapor phase chromatography. One of these was identified as 2,4-dimethoxypyrimidine on the basis of comparison of its infrared spectrum with an authentic sample.