explodes!, equivalent weight as oxidizer 67.0, 64.6) thus obtained was 16.0 g.

TABLE II

HALOGENATIONS WITH ALKALI METAL HALIDE $KHSO_5$-$KHSO_4$-K_2SO_4 MIXTURES

Compound	Halide	Procedure	Product	Conversion,[a] %	Yield,[a] %
Toluene	NaCl	19	Benzyl chloride	15[b]	15[b]
Toluene	NaBr	19	Benzyl bromide	21[b]	21[b]
2-Octene	KBr	20	2,3-Dibromooctane (?)	59[c]	59[c]

[a] As defined in Table I. [b] Based on halide. [c] Based on octene.

19. *Benzyl chloride.* An intimate mixture of powdered sodium chloride (11.7 g.), the $KHSO_5$-$KHSO_4$-K_2SO_4 composition (50.5 g.), and toluene was heated under reflux for 15 hr. The solids were removed by filtration and the liquid was distilled through an 18-inch Vigreux column. Four grams of benzyl chloride (b.p. 73–77°/17 mm., m.p. −47° to −45°, n_D^{25} 1.5322) were obtained.

20. *2,3-Dibromooctane.* An aqueous potassium bromide solution (23.8 g. potassium bromide, 50 ml. distilled water) and 2-octene (11.2 g.) were added simultaneously to a stirred solution of 61.4 g. of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture in 250 ml. of distilled water. The addition required about 30 min.; stirring was continued for 2 hr. after the addition was complete. The excess bromine was destroyed by the addition of solid sodium sulfite and the product extracted with methylene chloride (100 ml. in three portions). The extracts were dried over anhydrous magnesium sulfate, filtered, and distilled, first at atmospheric pressure, then under reduced pressure. The major fraction boiled at 105–12°/11 mm. and was identified as a saturated bromoalkane (presumably 2,3-dibromooctane), as it gave a precipitate when treated with alcoholic silver nitrate, but gave negative tests for active unsaturation.

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Synthesis of Pyrimidine-5-carboxaldehydes by the Reimer-Tiemann Reaction

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A study of the structural requirements for the synthesis of pyrimidine-5-carboxaldehydes by the Reimer-Tiemann reaction has shown that the reaction is successful with two methyl and one hydroxyl substituents in the pyrimidine nucleus. The hydroxyl group may be in either the 2- or 4-position. The reaction fails with 4-hydroxypyrimidine and its 6-methyl derivative indicating the necessity for the electron release characteristics of two methyl groups. Monohydroxydimethyl-, di-, and trihydroxypyrimidines give pyrimidine-5-carboxaldehydes. A variety of carbonyl derivatives of the pyrimidine aldehydes are described.

Pyrimidine aldehydes have not been investigated in detail. Their synthesis from acyclic intermediates[1] has not proved to be useful, but a variety of substituted pyrimidines has been converted to aldehydes by standard reactions. Thus, aldehydes have been obtained by ozonolysis of ethylenic groups,[2] by hydrolysis of nitrosomethyl groups,[3] and by suitable conversions of cyano,[4] carboxy,[5] trichlorohydroxyethyl,[6] and hydroxymethyl[7] groups. Formyl groups, or derivatives thereof, have been introduced directly by acylation reactions[8,9,10] and by the Reimer-Tiemann reaction.[6] The last appears to be the most generally useful reaction yet described. Aldehydes have been prepared from 2-amino or alkylamino-4-hydroxy; 2,4-dihydroxy; and 2-piperidinyl or phenyl-4,6-dihydroxy types.[6] Our study was undertaken to extend the Reimer-Tiemann reaction to additional types and to determine minimum structural requirements for activation of the nucleus by electron releasing groups in this reaction.

The pyrimidines converted to aldehydes in the present study are listed in Table I. The aldehydes were prepared, in 13–42% yields, by treating a water-ethanol solution of the pyrimidine with potassium hydroxide and chloroform at 80° for one hour. The potassium salt of the aldehyde

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TABLE I

SUBSTITUTED PYRIMIDINE-5-CARBOXALDEHYDES

No.	Substituent 2-	4-	6-	Yield, %	Recryst. Solvent[a]	M.P.[b]	Nitrogen, % Calcd.	Found
I	OH	OH	OH	42	W	330	17.95	17.92
II	OH	OH	H	18	M; W	304	20.00[f]	19.82
III	CH_3	OH	OH	29	A	300[c]	16.28[g]	16.24
						300	18.18[h]	18.02
IV	OH	OH	CH_3	14[d]	—	—	—	—
V	SH	OH	CH_3	17	W	300	16.46	16.18
VI	SCH_3	OH	CH_3	14	EW	300	15.21[i]	14.99
VII	OH	CH_3	CH_3	26[e]	—	—	—	—
VIII	CH_3	OH	CH_3	13[e]	—	—	—	—

[a] Solvent for recrystallization: W, water; M, methanol; A, acetic acid; EW, aq. ethanol. [b] Uncorrected, with decomposition. [c] The initial product is yellow and analyzes as the monohydrate; on drying it gives the black product which analyzes as the aldehyde. [d] The aldehyde was not isolated from the potassium salt. The yield is based on the yield of the potassium salt. [e] The aldehyde salt did not precipitate. The yield is based on the yield of the phenylhydrazone prepared from the crude solution from which the aldehyde salt has not precipitated. [f] *Anal.* Calcd. for $C_5H_4N_2O_3$: C, 42.86; H, 2.88. Found: C, 42.84; H, 3.00. [g] *Anal.* Calcd. for $C_5H_6O_3N_2H_2O$: C, 41.86; H, 4.68. Found: C, 42.06; H, 4.80. [h] *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92. Found: C, 46.54; H, 4.10. [i] *Anal.* Calcd. for $C_7H_8O_2N_2S$: C, 45.65; H, 4.38. Found: C, 45.92; H, 4.44.

usually precipitates from the reaction mixture, at room temperature or above, or on cooling either to ice or subzero temperatures. The potassium salt is converted to the free aldehyde on neutralization with acetic acid. For those aldehydes having only one hydroxyl substituent, the potassium salt does not precipitate from solution. The formation of the aldehyde in these cases was established by conversion to a derivative which could be isolated. The yields given for such aldehydes are those of the derivatives. This nonprecipitation may be due to an increased solubility of the salt. Insufficient aldehyde is formed to exceed its solubility in the reaction mixture. It may also be attributed to variations in chelating properties of the hydroxy (or thiol) substituted *ortho*-hydroxy aldehyde structure present in the aldehydes which precipitate. A more complete characterization of the chelating properties of these aldehydes may clarify this point and establish more effective procedures for isolation of the aldehydes. In other experiments, a low yield (1.5%) of an aldehyde derivative was obtained in the reaction using 4-hydroxy-6-methylpyrimidine. The product did not have an analysis in accord with the structure of the pyrimidinecarboxaldehyde derivative. No aldehyde or derivative at all was obtained from 4-hydroxypyrimidine. Because the method of isolation used is reasonably sensitive, it is believed that if any aldehyde had been formed, its presence would have been detected.

The available data establish that the Reimer-Tiemann reaction is successful for those pyrimidines having, as a minimum, two methyl groups and one hydroxyl substituent. The hydroxy group can be in either the 2- or 4-position. If it is assumed that this reaction procedes *via* a carbene intermediate[11,12] and that carbenes react as electrophilic reagents,[13] it appears that the pyrimidine nucleus requires activation by the combined electron release characteristics of two methyl groups and one hydroxyl for the success of this reaction. Although this provides only an approximate basis for establishing the reactivity of the pyrimidine nucleus in the Reimer-Tiemann reaction, it does provide data consistent with three currently accepted concepts: first, that there is a definite difference in reactivity between the 6-methyl-4-hydroxy- and 2,6-dimethyl-4-hydroxypyrimidine; second, that the pyrimidine nucleus is definitely less reactive than the benzene nucleus; and third, that the reaction involves an electrophilic attack by the reactive species derived from chloroform.

In addition to a variety of carbonyl derivatives listed in Table II, the oxime of 2,4-dihydroxy-6-methylpyrimidine-5-carboxaldehyde has been converted to the nitrile with acetic anhydride or phosphorus oxychloride and to the 2,4-dichloronitrile by phosphorus oxychloride and dimethylaniline. The ease with which the oxime dehydrates suggests that the hydroxyl and hydrogen atoms of the oxime are in the trans configuration. The 2-chloro, or 4-chloro, group is replaced by ethoxyl on recrystallization of this compound from ethanol.

EXPERIMENTAL[14]

Barbituric acid, uracil, 2-methyl-4,6-dihydroxypyrimidine, 6-methyluracil, and 6-methyl-2-thiouracil were commercial materials. 4-Hydroxy-6-methyl-2-methylmercaptouracil,[15] 2-hydroxy-4,6-dimethylpyrimidine,[16] 4-hydroxy-

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TABLE II

DERIVATIVES OF SUBSTITUTED PYRIMIDINE-5-CARBOXALDEHYDES

Aldehyde[a]	Derivative[b]	M.P.	Prepd.[c] From	Recrys.[d] From	Nitrogen, % Calcd.	Nitrogen, % Found
I	P	271–273	A	A	22.76	22.83
I	DP	301–302	A	DMF/E	25.00	24.79
I	M	283–284	K	M	28.27	28.41
I	O	250[e]	K	W	24.56	24.43
II	S	240[e]	A	RP	32.58[f]	32.69
II	P	298–300	A	DMF	24.34	24.20
II	DP	270–272[g]	A	M	30.76	30.62
II	O	260[e]	K	DMF	27.09	27.05
II	DP	[e]	A	DMF/W	26.25	26.21
II	HO	[e]	K	M	20.80[f]	21.87
III	S	205[e]	A	RP	33.17	32.90
III	P	240[e,h]	A	RP	22.94	23.01
III	M	200[e,h]	A	C	28.56	28.37
III	DP	[e,h]	K	DMF/W	25.15	24.97
IV	M	258–259	K	M	27.30[i]	27.30
IV	HO	320	K	M	21.86	21.72
IV	O	260	K	M	24.84	24.58
V	P	276–277	K	M	21.53	21.41
V	M	232–233	A	M	26.39	26.48
VI	S	263	K	RP	29.04	28.92
VI	P	250–251	K	M	20.43	20.44
VI	DP	283–284	K	DMF	23.07	23.21
VI	M	168–170	K	M	24.76	24.61
VI	O	228–229	A	M	21.09	20.82
VII	P	229–231	S	M	23.13	23.32
VIII	P	277–279	S	M	23.13	23.19
VIII	DP	305	S	DMF	23.99[f]	23.93
					25.30	25.12
VIII	S	265–266	S	RP	33.48	33.22
VIII	M	192–193	S	M	28.85	28.56
VIII	O	238–240	S	M	22.69[f]	22.41

[a] The number refers to the aldehyde number in Table I. [b] M, dimethylhydrazone; O, oxime; S, semicarbazone; P, phenylhydrazone; DP,2,4-dinitrophenylhydrazone; HO, di(2-hydroxyethyl)hydrazone. [c] A, aldehyde; K, potassium salt of aldehyde; S, solution of unisolated aldehyde. [d] A, Acetic acid; DMF, dimethylformamide; E, ethanol; M, methanol; W, water; RP, reprecipitated from alkaline solution; C, ethyl acetate. [e] Changes color at this temperature; melts over 330°. [f] For the 1.5 hydrate. [g] Water of crystallization lost at 240°. [h] Unstable to heat and light. [i] For hemihydrate (0.5 H_2O). The crude reaction mixture was evaporated to dryness; extracted with ethyl acetate to remove unreacted pyrimidine.

2,6-dimethylpyrimidine,[17] 4-hydroxy-6-methylpyrimidine,[18] and 4-hydroxypyrimidine[19] were prepared as previously described.

The substituted pyrimidine-5-carboxaldehydes are described in Table I. Experimental details are given for a typical preparation of an aldehyde (II). Only minor deviations from this procedure were made with other pyrimidines. The potassium salt of barbituric aldehyde (I) precipitated from the hot (80°) solution. Additional salt was obtained on cooling. The 4,6-dihydroxy-2-methyl aldehyde (III) salt precipitated in part at 80°; in part at 50°; and in part on cooling. Acidification of the potassium salt gives a yellow product, m.p. 150–208°, which had an analysis corresponding to the aldehyde (III) monohydrate; thorough drying in vacuum at 100° gives a black solid which analyzes as the aldehyde (III). Its derivatives were prepared from the hydrated material. Neutralization of the potassium salt of 2,4-dihydroxy-6-methyl-(IV), 2-hydroxy-4,6-dimethyl-(VII), and 4-hydroxy-2,6-dimethyl-(VIII) aldehydes did not precipitate the corresponding free aldehydes. Derivatives were prepared using the acidified solution of the salt.

The derivatives of the aldehydes are described in Table II. They were prepared by standard procedures from the free aldehyde or its potassium salt with the appropriate reagent either with or without addition of acetic acid. The di(hydroxyethyl)hydrazine was prepared as elsewhere[20] described and the corresponding hydrazone was isolated by evaporation of the reaction mixture to dryness extraction of the residue with ethyl acetate, and recrystallization of the residue left on evaporation of the ethyl acetate extracts. The dimethylhydrazone of VIII was isolated by evaporating the reaction mixture to dryness, extracting the residue with ethyl acetate, subliming the unchanged pyrimidine from the extracts, and recrystallizing the residue. The oxime of VIII was isolated by evaporating the crude reaction mixture to dryness, extracting the residue with hot ethyl acetate to remove unchanged pyrimidine, and recrystallizing the material insoluble in hot ethyl acetate.

2,4-Dihydroxypyrimidine-5-carboxaldehyde. A mixture of 24 ml. (0.333 mole) of chloroform and 56 g. of potassium hydroxide in 60 ml. of water was added to a solution of 22.4 g. (0.2 mole) of 2,4-dihydroxypyrimidine and 11.2 g. of potassium hydroxide in 100 ml. of water and 80 ml. of ethanol at 80° during 20 min. and with stirring. The mixture was refluxed 1 hr., cooled to room temperature, and filtered to separate the precipitated potassium chloride. The filtrate was stored 10 hr. at room temperature to precipitate the crude potassium salt of the aldehyde. This salt was suspended in water and neutralized with acetic acid to precipi-

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tate the crude aldehyde. Recrystallization from methanol gave 2.4 g. (8.6%) of the product as yellow crystals. Addition of phenylhydrazine to the filtrate from which the potassium salt of the aldehyde had precipitated gave an additional 4.3 g. (9.4%) of the phenylhydrazone of the aldehyde.

2,4-Dihydroxy-5-cyano-6-methylpyrimidine. A solution of 0.5 g. of the aldoxime and 10 ml. of acetic anhydride were heated under reflux for 30 min. The hot solution was filtered and cooled to room temperature to precipitate 0.15 g. of crystals, m.p. over 330°; ultraviolet, λ_{max} 273 mμ.

Anal. Calcd. for $C_6H_5N_3O_2$: N, 27.80. Found: N, 27.81. The same product was obtained by refluxing 0.5 g. of the aldoxime with 4.5 ml. phosphoryl chloride. The cooled reaction mixture was poured onto ice-water and the precipitate collected and recrystallized from ethanol to give 0.25 g. (56%) of product.

2,4-Dichloro-5-cyano-6-methylpyrimidine. Dimethylaniline (3 ml.) was added slowly and with cooling to a solution of 0.7 g. of 2,4-dihydroxy-6-methylpyrimidine-5-aldoxime in 6 ml. of phosphoryl chloride. The mixture was refluxed 0.5 hr., cooled, and poured onto ice water. The mixture was extracted with ether and the ether extracts washed with bicarbonate, dried, and evaporated to give a yellow crystalline residue. Recrystallization from petroleum ether (b.p. 60–80°) gave 0.45 g. (57%) of the product, m.p. 93–94°.

Anal. Calcd. for $C_6H_3N_3Cl_2$: N, 22.35. Found: N, 22.54.

2(4?)-Chloro-5-cyano-4(2?)-ethoxy-5-methylpyrimidine. On recrystallization of the 2,4-dichloro compound from ethanol, the 2(4?)-ethoxy compound was obtained as yellow plates, m.p. 134–136°.

Anal. Calcd. for $C_8H_8N_3OCl$: N, 21.27. Found: N, 21.20, 21.42.

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Syntheses of Some Arylamino- and Arylguanidinopyrimidines

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A number of 6-hydroxy-5-unsubstituted pyrimidines having variously substituted arylamino, or arylguanidino groups at C-2 and/or C-4 positions were synthesized. It has been shown that the condensation of arylamines with 2-methylthio-4-amino-6-hydroxypyrimidine under mild condition yields 2-arylamino-4-amino-6-hydroxypyrimidines and under drastic conditions 2,4-bis(arylamino)-6-hydroxypyrimidines.

Curd and Rose[1] demonstrated that 5-unsubstituted 6-alkyl pyrimidines with amino or substituted amino groups at C-2 and C-4 positions were active as antimalarials. Hitchings,[2] *et al.* showed further that if 2,4-diamino-6-alkylpyrimidines have bulky substituents (for example phenyl, phenoxy, etc.) at the C-5 position, they prove to be strong antagonists of folic acid and some of them possess marked antimalarial[3] and antileukemic[4] properties. In connection with our studies of pyrimidines of potential chemotherapeutic value, it was considered of interest to investigate the biological properties of pyrimidines having hydroxyl group in the 6-position and which had variously substituted amino groups at C-2 and C-4 positions, while C-5 position was kept free. The synthesis of some arylamino- and arylguanidinopyrimidines of this type having various substituents at the *para* position of the benzene ring (I to IV) is being reported here. The pronounced inhibitory effects of some of these compounds on bacterial growth have already been reported in preliminary communications.[5,6]

The pyrimidines of type I were synthesized by the reaction of 2-methylthio-4-amino-6-hydroxypyrimidine[7] (V) with the appropriate arylamines according to the method of Wheeler.[8] The reaction takes place with the elimination of methylthiol when an intimate mixture of equimolecular quantities of V and the corresponding arylamine is heated in an inert atmosphere at a temperature necessary for the mixture to go into solution. This type of displacement was not possible with the compound (VI) in which the C-4 and C-6 positions of pyrimidine ring were occupied by methyl groups (*Cf.* ref. 1). The lability of the methylthio group in compound V may be due to the possibility of tautomerism between V and Va as suggested by Curd and Rose.[1] Apparently this type of reaction does

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