Pyrimidines. Part I. The Acylation of 2-Amino-4-Hydroxypyrimidines

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The formation of *O*-acyl and *O*-sulphonyl derivatives of certain 4(6)-hydroxypyrimidines is promoted by the presence of a bulky substituent at the pyrimidine 2-position, and by the use of an acyl or sulphonyl halide having an appreciable steric requirement. 2-Dialkylamino-4-hydroxypyrimidines undergo *O*-acylation and *O*-sulphonylation in good yield regardless of the experimental conditions. 2-Alkylamino-, 2-amino-, and 2-acetylamino-4-hydroxypyrimidines undergo *O*-acylation with pivaloyl chloride and with aroyl halides, and *O*-sulphonylation with arylsulphonyl halides; attempts to prepare *O*-acetyl derivatives of these 4(6)-hydroxy-pyrimidines were unsuccessful, as were attempts to prepare *O*-methanesulphonyl derivatives of 2-amino-4-hydroxypyrimidines. The reaction of 2-dialkylamino-, 2-alkylamino-, 2-amino-, and 2-acetylamino-4-hydroxypyrimidines with phosphorochloridates and phosphorochloridothioates gives *O*-phosphoryl derivatives.

ACYLATION of 2- and 4(6)-hydroxypyrimidines is normally unsuccessful, and it has been generally assumed that only 5-hydroxypyrimidines can be *O*-acylated.[1] The *O*-acetyl derivatives of certain 4-hydroxypyrimidines, for example, 4-acetoxy-6-methyl-2-phenylpyrimidine,[2] and 4-acetoxy-2,6-dibenzyl-5-phenylpyrimidine,[3] have been reported, but no evidence was presented to support these proposed structures and it is possible that the compounds are, in fact, *N*-acetyl derivatives. Some 2- and 4(6)-hydroxypyrimidines are acylated on a ring nitrogen to form an *N*-acyl-oxopyrimidine, readily hydrolysed by water to the parent hydroxy-pyrimidine. Reaction of 4-hydroxypyrimidine with acetic anhydride gives an *N*-acetyl-4-oxopyrimidine different from 4-acetoxypyrimidine prepared by the action of acetic anhydride on pyrimidine-*N*-oxide.[4] Acetylation of uracil or thymine with acetic anhydride yields the 1-acetyl compounds and similarly *N*-acylation has resulted from the action of alkyl chloroformates [5] and alkyl thiochloroformates [6] on uracil. The reaction of cytosine with *p*-nitrobenzenesulphonyl chloride gives the 3-*p*-nitrobenzenesulphonyl derivative.[7] Treatment of 5-methoxyuracil with acyl halides in pyridine gives the corresponding 1,3-diacyl derivatives, while reaction with acetic anhydride gives the 1-acetyl derivative.[8] The reaction of acyl halides in pyridine with 5-methoxy-2-methylthiouracil gives the related 3-acyl compounds.[8] Amino-hydroxy-pyrimidines can generally be selectively acylated on the amino-group, though under forcing conditions acylation can also occur on the ring nitrogen atoms. For example, benzoylation of cytosine at room temperature for 45 minutes gives *N*6-benzoylcytosine, whilst on prolonged benzoylation, 1,3,*N*(6)-tribenzoylcytosine is formed.[9]

Certain anomalous acylations have been reported. Thus, 4-amino-2,6-dihydroxypyrimidine undergoes acylation at the C-5 position with chloroacetyl chloride in dimethylformamide to form 4-amino-5-chloroacetyl-2,6-dihydroxypyrimidine.[10]

In connection with a study of pyrimidines showing fungicidal activity,[11] we have investigated the acylation

[1] D. J. Brown, 'The Pyrimidines,' Interscience, New York, 1962, p. 25, 252.
[2] A. Pinner, *Chem. Ber.*, 1885, **18**, 759.
[3] R. Wache, *J. prakt. Chem.*, 1889, **39**, 245.
[4] H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, 1958, **91**, 2832.
[5] E. Dyer, M. L. Gluntz, and E. J. Tanck, *J. Org. Chem.*, 1962, **27**, 982.
[6] E. Dyer and H. Richmond, *J. Medicin. Chem.*, 1965, **8**, 195.
[7] Y. Nitta, K. Okui, K. Ito, and M. Togo, *Chem. Pharm. Bull. (Japan)*, 1965, **13**, 568.
[8] A. Novacek and I. Hedrlin, *Coll. Czech. Chem. Comm.*, 1967, **32**, 576.
[9] D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 1956, 2384.
[10] C. W. Noell and R. K. Robins, *J. Heterocyclic Chem.*, 1964, **1**, 34.
[11] B.P. application numbers 14266–71/1966; 43133/1966; 30348/1967; 30354/1967.

TABLE 1

6-Pyrimidinyl esters of carboxylic, sulphonic and orthophosphoric acids (I)

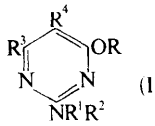
No. of compound*	NR^1R^2	R^3	R^4**	R	Yield (%)	M.p./ (B.p./mm.)	Recryst. from (n_D)	I.r. spectra (cm.$^{-1}$)	Analyses: Found (%) C	H	N	P	S	Formula	Required (%) C	H	N	P	S
2-Dialkylaminopyrimidines																			
1 *a*	NMe_2	Me	Me	$CO{\cdot}C_6H_4{\cdot}NO_2$	53	109°	EtOH	1740	59·0	5·9	16·1			$C_{17}H_{20}N_4O_4$	59·3	5·8	16·3		
2 *b*	NMe_2	Me	Prⁿ	Bz	75	52	EtOH	1740	68·3	7·2	14·0			$C_{17}H_{21}N_3O_2$	68·2	7·1	14·0		
3 *a*	NMe_2	Me	Prⁿ	SO_2Ph	51	72	EtOH	1610, 1560	56·8	6·6	12·3			$C_{16}H_{21}N_3O_2S$	57·3	6·3	12·5		
4 *a*	NMe_2	Me	Prⁿ	SO_2Me	73	71	EtOH	1605, 1555	48·2	7·0	15·3			$C_{11}H_{19}N_3O_2S$	48·3	7·0	15·4		
5 *a*	NMe_2	Me	Prⁿ	$SO_2{\cdot}C_6H_4Me$	49	68	EtOH	1605, 1550	58·7	7·0	12·4			$C_{17}H_{23}N_3O_2S$	58·5	6·6	12·0		
6 *b*	NMe_2	Me	Pen	Bz	80	57	EtOH	1735	69·8	8·0	12·8			$C_{19}H_{25}N_3O_2$	69·7	7·7	12·8		
7 *c*	NMe_2	Me	Pen	SO_2Me	83	69	EtOH	1605, 1555	51·5	7·7	13·8			$C_{13}H_{23}N_3O_2S$	51·6	7·7	14·0		
8 *b*	NMe_2	Me	Bun	Bz	93	59	EtOH–H_2O	1735	69·0	7·7	13·6			$C_{18}H_{23}N_3O_2$	69·0	7·4	13·4		
9 *a*	NMe_2	Me	Bun	SO_2Me	67	162	EtOH	1610, 1560	50·2	7·5	14·3			$C_{12}H_{21}N_3O_2S$	50·1	7·4	14·6		
10 *d*	NMe_2	Me	Prⁿ	$CO{\cdot}C_6H_4Cl$-*m*	70	89	EtOH	1740	61·5	6·1	12·8			$C_{17}H_{20}ClN_3O_3$	61·2	6·0	12·6		
11 *d*	NMe_2	Me	Prⁿ	2-Furoyl	57	91	EtOH	1735	62·6	6·7	15·0			$C_{15}H_{19}N_3O_3$	62·4	6·6	14·6		
12 *d*	Piperidino	Me	H	Bz	82	120	EtOH	1740	68·6	6·5	14·6			$C_{17}H_{18}N_2O_2$	68·7	6·4	14·2		
13 *d*	NMe_2	H	H	SO_2Me	70	76	EtOH	1610, 1555	38·8	5·2	19·6			$C_7H_{11}N_3O_2S$	38·8	5·2	19·4		
14 *a*	NMe_2	Me	H	SO_2Me	72	87	EtOH	1610, 1550	41·4	5·8	18·1			$C_8H_{13}N_3O_2S$	41·7	5·6	18·2		
15 *a*	NMe_2	Me	Et	$P(S)(OEt)_2$	65	(143—148/ 0·02)	(n_D^{26} = 1·5168)	1605, 1540	46·6	7·2	12·9	9·5	9·3	$C_{13}H_{21}N_3O_3PS$	46·9	7·3	12·6	9·3	9·6
16 *c*	NMe_2	Me	Et	$P(O)(OEt)_2$	72	(148—151/ 0·02)	(n_D^{22} = 1·4985)	1605, 1570	48·6	8·4	13·2	9·9		$C_{13}H_{24}N_3O_4P$	49·2	7·7	13·2	9·8	
17 *a*	NMe_2	Me	Pen	$P(S)(OEt)_2$	77		(n_D^{22} = 1·5142)	1605, 1570			11·3	8 3		$C_{16}H_{30}N_3O_3PS$			11·2	8·3	
18 *d*	NMe_2	Me	Bun	$SO_2{\cdot}C_6H_4Br$	68	91	EtOH	1610, 1550	47·4	5·2			7·4†	$C_{17}H_{22}BrN_3O_3S$	47·7	5·2			7·5
19 *a*	NMe_2	Me	Prⁿ	$CO{\cdot}CH{:}CH{\cdot}Ph$	77	88	EtOH	1740, 1642, 1610, 1560	70·2	6·9	12·9			$C_{19}H_{23}N_3O_2$	70·2	7·1	12·9		
20 *d*	NMe_2	Me	Bun	$CO{\cdot}CMe_3$	50	(134—136/ 0·25)	(n_D^{25} = 1·4955)	1770, 1615, 1550	65·2	9·5	14·4			$C_{16}H_{27}N_3O_2$	65·5	9·3	14·3		
21 *d*	NMe_2	Me	Bun	$CO{\cdot}CH{:}CMe_2$	51		(n_D^{24} = 1·5261)	1745, 1640, 1605, 1540	65·9	8·7	14·4			$C_{16}H_{25}N_3O_2$	65·6	8·7	14·5		
22 *d*	NMe_2	Me	Bun	$CO{\cdot}C_6H_4Me$-*p*	80	71	EtOH–H_2O	1745, 1610, 1550	69·6	7·8	12·9			$C_{19}H_{23}N_3O_2$	69·7	7·7	12·8		
23 *c*	NMe_2	Me	Bun	Ac	86	(128—130/ 0·25)	(n_D^{23} = 1·5124)	1780, 1615, 1550	62·1	8·7	16·9			$C_{13}H_{21}N_3O_2$	62·1	8·4	16·7		
24 *d*	NMe_2	Me	Bun	$SO_2{\cdot}C_6H_3Me_2$-2,5	70	77	(60—80) Light petroleum	1610, 1550	60·6	7·3	11·3		8·7	$C_{19}H_{27}N_3O_2S$	60·5	7·2	11·1		8·5
25 *d*	NMe_2	Me	Bun	$SO_2{\cdot}C_6H_4{\cdot}NO_2$-*p*	52	99	MeOH	1610, 1560	51·6	5·5	14·2		8·3	$C_{17}H_{22}N_4O_4S$	51·8	5·6	14·2		8·1
26 *f*	NMe_2	Me	Bun	$SO_2{\cdot}C_6H_4OMe$-*p*	56	85	EtOH	1615, 1550	57·0	6·5	11·4		8·7	$C_{18}H_{25}N_3O_4S$	57·0	6·6	11·1		8·5
2-Alkylaminopyrimidines																			
27 *d*	NHPrⁿ	Me	Bun	$SO_2{\cdot}C_6H_4Br$-*p*	72	58	PriOH	3410, 1610, 1570	48·7	5·2	9·2		7·3‡	$C_{18}H_{24}BrN_3O_3S$	48·9	5·5	9·5		7·3
28 *d*	NHEt	Me	Bun	$SO_2{\cdot}C_6H_4Br$-*p*	84	117	EtOH	3415, 1610, 1560	47·9	5·2	9·8		7·5§	$C_{17}H_{22}BrN_3O_3S$	47·7	5·2	9·8		7·5
29 *d*	NHEt	Me	Bun	Bz	46	69—70	EtOH–H_2O	3260, 1750, 1615, 1550	69·3	7·4	13·4			$C_{18}H_{23}N_3O_2$	69·0	7·4	13·4		
30 *a*	NHBuⁿ	Me	H	$P(S)(OEt)_2$	68		(n_D^{22} = 1·5227)	3280, 1602, 1570			12·4	9·3	9·6	$C_{13}H_{24}N_3O_3PS$			12·6	9·3	9·6
31 *a*	NHEt	Me	Bun	SO_2Me	30	81—82	EtOH	3250, 1610, 1545	50·1	7·6	14·8		11·4	$C_{12}H_{21}N_3O_3S$	50·1	7·4	14·6		11·2
2-Aminopyrimidines																			
32 *d*	NH_2	Me	H	$SO_2{\cdot}C_6H_4Br$-*p*	29	156—157	PriOH	3220, 3190, 1660, 1600, 1575	38·5	2·9	12·2		9·0¶	$C_{11}H_{10}BrN_3O_3S$	38·4	2·9	12·2		9·3
33 *d*	NH_2	Me	Bun	$SO_2{\cdot}C_6H_4Br$-*p*	32	152	EtOH–H_2O	3350, 3190, 1650, 1600, 1570	45·3	4·6	11·1			$C_{18}H_{18}BrN_3O_3S$	45·0	4·5	10·8		
34 *g*	NH_2	Prⁿ	H	$P(S)(OEt)_2$	74	84	(60—80) Light petroleum	3360, 3140, 1660, 1610, 1550	43·3	6·6	13·7	10·0	10·6	$C_{11}H_{20}N_3O_3PS$	43·4	6·6	13·8	10·1	10·5
35 *g*	NH_2	Me	Allyl	$P(S)(OEt)_2$	69	84	Benzene–Light petroleum	3360, 3140, 1660, 1610, 1550			13·3	9·6	10·1	$C_{12}H_{20}N_3O_3PS$			13·2	9·8	10·1
36 *g*	NH_2	Me	H	$P(S)(OMe)_2$	41	106—107	PriOH	3440, 3300, 3160, 1650, 1600 1570			16·7	12·3	12·9	$C_7H_{12}N_3O_3PS$			16·9	12·4	12·9
37 *a*	NH_2	Me	H	$CO{\cdot}CMe_3$	40	105	(60—80) Light petroleum	3440, 3300, 3170, 1760, 1638, 1600, 1560	57·5	7·4	20·2			$C_{10}H_{15}N_3O_2$	57·4	7·2	20·1		
2-Acetylaminopyrimidines																			
38 *d*	NHAc	Me	H	$SO_2{\cdot}C_6H_4Br$-*p*	83	132	EtOH	3210, 3140, 1685, 1609, 1575	40·6	3·0	10·6		8·7‖	$C_{13}H_{12}BrN_3O_4S$	40·4	3·1	10·9		8·3
39 *d*	NHAc	Me	Bun	$SO_2{\cdot}C_6H_4Br$-*p*	62	145—146	EtOH–H_2O	3200, 3140, 1675, 1600, 1575	46·3	4·3	9·5			$C_{17}H_{20}BrN_3O_4S$	46·0	4·5	9·5		
40 *g*	NHAc	Me	H	$P(S)(OEt)_2$	57	74	PriOH	3210, 3140, 1685, 1600, 1560	42·0	6·0	13·0	9·6	10·1	$C_{11}H_{18}N_3O_4PS$	41·4	5·6	13·2		10·0

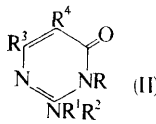
* Method of syntheses: *a* 2, *b* 6, *c* 5, *d* 1, *e* 7, *f* 4, *g* 3. Bromine analyses (%): Found (Required): † 19·1 (18·7); ‡ 18·3 (18·3); § 18·7 (18·7); ¶ 23·4 (23·2); ‖ 20·3 (20·7). ** Pen = Pentyl.

of a number of 2-amino-4-hydroxypyrimidines, and have shown that whereas acylation of 4(6)-hydroxypyrimidines is normally unsuccessful or may occur at a ring nitrogen atom, it is possible to achieve *O*-acylation in those cases where steric factors, *e.g.*, the presence of a bulky substituent at the pyrimidine 2-position and/or the use of a bulky acylating agent, prevent acylation at either of the ring nitrogen atoms.

2-Dialkylamino-4-hydroxypyrimidines.—Monoacyl derivatives were formed in good yield from a series of 2-dialkylamino-4-hydroxypyrimidines and a variety of acyl, sulphonyl, and phosphoryl halides (Table 1). It was found that the reaction was insensitive to alteration of those factors which normally influence the course of the reaction of an ambient nucleophile.[12] Thus, use of the hydroxy-pyrimidine together with an alkali-metal carbonate (Experimental Section, method 1) gave the same product and in similar yield as did the use of the preformed salt (methods 2 and 3), or the use of an organic base such as pyridine (method 4) or triethylamine (method 5). Schotten-Baumann conditions (method 6) could be used satisfactorily provided that an exact equivalent of aqueous sodium hydroxide was used. The nature of the solvent had little effect on the course of the reaction. Solvents used included benzene, toluene, ethyl acetate, methyl ethyl ketone, acetonitrile, dimethylformamide, and water. In certain cases, for example, use of the sodium salt of the pyrimidine in dimethylformamide, acylations were carried out in homogeneous solution, while in others, for example, use of the sodium salt of the pyrimidine in benzene, heterogeneous mixtures were involved. Acylations were carried out at temperatures ranging from room temperature to the boiling-point of toluene; the rate of the reaction was affected by change of temperature, but the final course of the reaction was unaltered. The benzoylation of 5-n-butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine was studied in some detail. It was shown, by thin-layer chromatography, that the same benzoyl derivative was formed as the sole product (yield, 78—96%) under a variety of experimental conditions. Attempted acylation with n-alkanoic acid halides proved unsuccessful, although the use of pivaloyl chloride gave an excellent yield of a pivalate. A monoacetate could, however, be obtained from 5-n-butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine using acetic anhydride under anhydrous conditions. Solutions of the monoacetate in methanol or water were stable for more than 24 hours, but in N-hydrochloric acid the compound was rapidly hydrolysed and within 10 minutes its u.v. absorption spectrum was identical with that of the parent hydroxypyrimidine in N-hydrochloric acid. The monoacetate, a powerful acetylating agent, reacted exothermically with aniline to give acetanilide and the parent hydroxypyrimidine.

The monoacyl derivative of 2-dialkylamino-4-hydroxypyrimidines are considered to be *O*-acyl derivatives (I), rather than *N*-acyl derivatives (II) or (III), on the following evidence.


(I)


(II)


(III)

The i.r. absorption spectrum of the sulphonyl (I; R = SO_2Alk, SO_2Ar; Table 1, compounds 3, 4, 5, 7, 9, 13, 14, 18, 24, 25, and 26) and phosphoryl [I; R = $P(O)(OAlk)_2$, $P(S)(OAlk)_2$; Table 1, compounds 15, 16, and 17] derivatives show no absorption between 1605 and 2000 cm.$^{-1}$. This is consistent only with the structure (I), for compounds having structures (II) or (III) would be expected to show carbonyl absorption at *ca.* 1630—1700 cm.$^{-1}$ due to the 4-pyrimidone carbonyl group. The benzoyl derivatives (I; R = Bz; Table 1, compounds 1, 2, 6, 12, 22 and 29) show only one band in the carbonyl region at *ca.* 1740 cm.$^{-1}$, while the monoacetate (I; R = Ac; Table 1, compound 23) shows one band in the carbonyl region at 1780 cm.$^{-1}$. These values accord with those expected for *O*-benzoyl and *O*-acetyl derivatives (I; R = Bz and I, R = Ac) respectively, but are considerably higher than those expected for the isomeric *N*-benzoyl and *N*-acetyl derivatives (II or III; R = Bz and Ac).

The n.m.r. spectra of representative acyl, sulphonyl, and phosphoryl derivatives of 2-dialkylamino-4-hydroxypyrimidines together with those of a number of 2-dialkylamino-4-alkoxypyrimidines (I; R = Alk) are given in Table 2, together with data for selected hydroxypyrimidines (II; R = H) and 1,6-dihydro-2-amino-1-alkyl-6-oxopyrimidines (II; R = Alk).

The most relevant data of Table 2 may be summarised as follows.

1. For hydroxy-pyrimidines and related compounds having the pyrimidone structure (II): (a) where R^3 = Me; τ *ca.* 7·85; (b) where R^3 = H; τ 2·25—2·40; (c) where R^4 = H; τ 4·27—4·48.

2. For the acyl, sulphonyl, and phosphoryl derivatives of 2-dialkylamino-4-hydroxypyrimidines, and for 4-alkoxy-2-dialkylaminopyrimidines having the pyrimidine structure (I): (a) where R^3 = Me; τ 7·52—7·65; (b) where R^3 = H; τ 1·60—1·94; (c) where R^4 = H; τ 3·75—4·06.

Thus, the absorptions due to the hydrogen atom or methyl group at R^3, and the hydrogen atom at R^4 occur at significantly lower τ values for compounds of the pyrimidine structure (I) than for those of the pyrimidone structure (II), the pyrimidine having appreciably more aromatic character than the pyrimidone system.

The n.m.r. spectrum of 2-dimethylamino-4-methoxypyrimidine (Table 2, example 2) showed absorption in agreement with that found for other pyrimidines of general formula (I). The corresponding spectrum of 1,6-dihydro-2-dimethylamino-1-methyl-6-oxopyrimidine [13] (Table 2, example 33) was anomalous in that the

[12] R. Gompper, *Angew. Chem., Internat. Edn.*, 1964, **3**, 560.

[13] D. J. Brown, *Austral. J. Chem.*, 1965, **18**, 204.

doublet attributed to the C-5 proton was at abnormally low field (τ 3·90) while the signal due to the dimethylamino-group was at abnormally high field (τ 7·13). This suggests that steric interaction between the 1-methyl and the 2-dimethylamino-group forces the latter out of the plane of the pyrimidine ring and limits conjugation between the 2-dimethylamino-group and the pyrimidone ring, thus reducing the normal shielding of the 5-proton by the dimethylamino-substituent.

The u.v. absorption spectra of the acyl, sulphonyl, and phosphoryl derivatives of 2-dialkylamino-4-hydroxypyrimidines (Table 3, examples 6—14), closely resemble the spectra of 4-alkoxy-2-dimethylaminopyrimidines (I; R = Alk; Table 3, examples 1—5), preparrd unambiguously by treating the appropriate chloropyrimidine with an alkoxide anion, but differ considerably from the spectra of 2-dialkylamino-4-hydroxypyrimidines (II; R = H; Table 3, examples 24—27), and from the spectrum of the known 1,6-dihydro-2-dimethylamino-1-methyl-6-oxopyrimidine (II; $R^1 = R^2 = R = Me$; $R^3 = R^4 = H$; Table 3, example 28).[15]

TABLE 2

^{1}H N.m.r. of 2-amino-4-hydroxypyrimidines and related compounds [a]

Example	NR^1R^2	τ	R^3	τ [$J(R^3,R^4)$ c./sec.]	R^4	τ	R	τ
4-Alkoxy-2-dialkylaminopyrimidines (I)								
1	NMe_2	6·85	H	1·93 [5·7]	H	4·00	CH_2Ph	4·63, 2·65 [b]
2	NMe_2	6·72	H	1·94 [6·0]	H	4·06	Me	6·10
7	NMe_2	6·85	H	1·90 [5·8]	H	4·08	Allyl	3·9,[b] 4·7,[b] 4·8,[b] 5·2 [b]
2-Dialkylaminopyrimidines (I)								
4	NMe_2	6·82	Me	7·64	H	3·90	SO_2Me	6·48
5	NMe_2	6·82	H	1·60 [5·7]	H	3·79	SO_2Me	6·48
6	NMe_2	6·85	Me	7·60	Pe^n	7·6,[b] 8·6,[b] 9·1 [b]	SO_2Me	6·58
7	NMe_2	6·82	Me	7·60	Bu^n	7·6,[b] 8·6,[b] 9·1 [b]	SO_2Me	6·43
8	NMe_2	6·99	Me	7·65	Pr^n	7·6,[b] 8·6,[b] 9·1 [b]	$SO_2{\cdot}C_6H_4Me$-*p*	2·3,[c] 7·53
9	Piperidino	6·21	Me	7·65	H	3·77	Bz	1·8, 2·40 [b]
10	NMe_2	6·84	Me	7·58	Pr^n	7·6,[b] 8·7,[b] 9·1 [b]	$CO{\cdot}C_6H_4{\cdot}NO_2$-*p*	2·30 [c]
11	NMe_2	6·90	Me	7·64	Bu^n	7·6,[b] 8·5,[b] 9·1 [b]	Bz	2·15 [b]
12	NMe_2	6·86	Me	7·65	Pr^n	7·6,[b] 8·6,[b] 9·1 [b]	$CO{\cdot}C_6H_4Cl$-*m*	2·26 [b]
13	NMe_2	6·82	Me	7·65	Pe^n	7·6,[b] 8·7,[b] 9·2 [b]	Bz	2·10 [b]
14	NMe_2	6·83	Me	7·62	Allyl	4·6,[b] 7·5 [b]	$CO{\cdot}C_6H_4NO_2$-*p*	1·67 [c]
15	NMe_2	6·85	Me	7·62	Pr^n	7·6,[b] 8·6,[b] 9·1 [b]	2-Furoyl	2·3, 2·64 [b]
16	NMe_2	7·08	Me	7·68	Bu^n	7·6,[b] 8·6,[b] 9·1 [b]	$SO_2{\cdot}C_6H_4Br$	2·20 [c]
17	NMe_2	6·85	Me	7·65	Bu^n	7·6,[b] 8·6,[b] 9·1 [b]	Ac	7·70
18	NMe_2	6·85	H	1·90	Me	8·0	$P(S)(OEt)_2$	5·8,[b] 8·6 [b]
2-Alkylaminopyrimidines (I)								
19	NHEt	6·9,[b] 8·98 [b]	Me	7·69	Bu^n	7·6,[b] 8·6,[b] 9·1 [b]	$SO_2{\cdot}C_6H_4Br$	2·2 [c]
2-Aminopyrimidines (I)								
20	NH_2	4·4	Me	7·68	H	3·75	$P(S)(OEt)_2$	5·7,[b] 8·65 [b]
21	NH_2	4·54	Me	7·68	H	3·74	$SO_2{\cdot}C_6H_4Br$-*p*	2·18 [c]
2-Acetylaminopyrimidines (I)								
22	NHAc	7·52	Me	7·61	H	3·40	$SO_2{\cdot}C_6H_4Br$-*p*	2·14 [c]
23	NHAc	7·40	Me	7·55	H	3·41	$P(S)(OEt)_2$	5·8,[b] 8·6 [b]
23a	NHAc	7·42	Me	7·63	H	3·72	Me	7·63
2-Amino-4-hydroxypyrimidines (II; R = H) and 1,6-dihydro-2-amino-1-alkyl-6-oxopyrimidines (II; R = Alk)								
24	NMe_2	6·82	Me	7·85	H	4·40	H	
25	Morphilino	6·24	Me	7·85	H	4·36	H	
26	NMe_2	6·86	Me	7·85	Bu^n	7·4,[b] 8·6,[b] 9·1 [b]	H	
27	NMe_2	6·85	n-C_6H_{13}	7·5,[b] 8·6,[b] 9·3 [b]	H	4·45	H	
28	NMe_2	6·85	$EtS{\cdot}CH_2$	6·6, 7·4,[d] 8·7 [e]	H	4·27	H	
29	*N*-Methyl piperazinyl	6·25, 7·55,[b] 7·87	H	2·25 [6·0]	H	4·28	H	
30	Morpholino	6·25	H	2·25 [6·0]	H	4·25	H	
31	NMe_2	6·85	H	2·40	Me	8·10	H	
32	Piperidino	6·3, 8·35,	H	2·25 [6·0]	H	4·30	H	
33	NMe_2	7·13	H	2·33 [6·0]	H	3·90	Me	6·55
34	NHAc	7·78	Me	7·78	H	4·21	Me	6·57

* Pe^n = Pentyl.

[a] Measured in *ca.* 10% w/v solution in $CDCl_3$ with tetramethylsilane as internal standard. In all cases integrated areas supported the assignments. [b] Multiplet. [c] A_2B_2 multiplet. [d] Quartet. [e] Triplet.

These considerations provide compelling evidence in favour of the general structure [I; R = CO·Alk, CO·Ar, SO_2Alk, SO_2Ar, $P(O)(OAlk)_2$, $P(S)(OAlk)_2$, etc.] for the acyl, sulphonyl, and phosphoryl derivatives of 2-dialkylamino-4-hydroxypyrimidines. We have, in

[14] D. J. Brown, *Austral. J. Chem.*, 1965, **18**, 559.
[15] R. B. Angier and W. V. Curran, *J. Org. Chem.*, 1961, **26**, 1891.

fact, been unable to prepare *N*-acyl, sulphonyl, or phosphoryl derivatives corresponding to formulae (II) or (III), and an examination of models shows that considerable steric hindrance would exist between the 2-dialkylamino-group and a 1- or 3-acyl residue.

of the 2-dimethylamino-group, but we have shown, incidentally, that the alkylation of 2-dimethylamino-4-hydroxypyrimidine is sensitive to the experimental conditions chosen. For example, alkylation with alkyl bromide using potassium carbonate as base and ethyl

TABLE 3

U.v. absorption spectra of 2-amino-4-hydroxypyrimidines and related compounds

					Neutral molecule				Protonated species				
Example	NR^1R^2	R^3	R^4	R	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	Ref.
4-Alkoxy-2-dialkylaminopyrimidines (I)													
1	NMe_2	Me	Bu^n	$[CH_2]\cdot NEt_2$	248	18,900	298	4600					
2	NMe_2	Me	Bu^n	$[CH_2]_2OH$	248	19,100	297	4800					
3	NMe_2	H	H	CH_2Ph	243	16,700	293	5000					
4	NMe_2	H	H	$CH_2\cdot CH{:}CH_2$	243	19,100	294	3700	222	14,800	285	2800 [a]	
5	NMe_2	H	H	Me	241	15,500	294	3310	233	16,200	280	2450 [b]	14
2-Dialkylamino-6-pyrimidinyl esters of sulphonic, carboxylic, and phosphoric acids (I)													
6	NMe_2	Me	H	SO_2Me	246	20,500	307	3600	235	16,600	280	3000 [a]	
7	NMe_2	Me	Pe^n	SO_2Me	247	25,900	313	4100					
8	NMe_2	Me	Pr^n	SO_2Ph	248	19,900	307	4000					
9	NMe_2	Me	Bu^n	Bz	243	29,000	315	4000					
10	NMe_2	Me	Bu^n	$SO_2\cdot C_6H_4Br$-*p*	240	32,700	316	3600					
11	NMe_2	Me	Bu^n	Ac	247	23,600	310	3800					
12	NMe_2	Me	Bu^n	CO·CMe	248	23,600	312	3200					
13	NMe_2	Me	Et	$P(O)(OEt)_2$	247	21,800	308	3900					
14	NMe_2	Me	Et	$P(S)(OEt)_2$	248	21,900	308	4900					
2-Alkylamino-6-pyrimidinyl esters of sulphonic, carboxylic, and phosphoric acids (I)													
15	NHEt	Me	Bu^n	Bz	237	26,300	303	4400					
16	NHEt	Me	Bu^n	$SO_2\cdot C_6H_4Br$-*p*	238	38,300	308	6400					
17	$NHBu^n$	Me	H	$P(S)(OEt)_2$	240	17,600	296	4350					
2-Amino-6-pyrimidinyl esters of sulphonic and phosphoric acids (I)													
18	NH_2	Me	H	$SO_2\cdot C_6H_4Br$-*p*	234	30,200	290	6000					
19	NH_2	Me	Bu^n	$SO_2\cdot C_6H_4Br$-*p*	235	29,700	297	6000					
20	NH_2	Me	H	$P(S)(OMe)_2$	229	14,700	285	4800	221	14,000	287	5200 [b]	
21	NH_2	Pr^n	H	$P(S)(OEt)_2$	230	11,700	286	4400					
4-Alkoxy-2-aminopyrimidines (I)													
22	NH_2	H	H	Me	225	12,600	277	4790 [c]			268	3800 [a]	14
23	NH_2	Me	H	Me	230	9900	275	3700	208	16,300	271	6200 [a]	
2-Dialkylamino-4-hydroxypyrimidines (II; R = H)													
24	NMe_2	Me	Et	H	227	14,200	300	6900					
25	NMe_2	Me	Pr^n	H	228	14,200	304	7000					
26	NMe_2	Me	Bu^n	H	229	15,500	304	7800					
27	NMe_2	H	H	H					222	12,900	265	6310	
28	NMe_2	H	H	Me					235	8910	268	7240	13
1,6-Dihydro-1-alkyl-2-amino-6-oxopyrimidines (II)													
29	NH_2	H	H	Me	225	7240	284	9120 [d]					14
											256	5940 [a]	15
1,4-Dihydro-1-alkyl-2-amino-4-oxopyrimidines (III)													
30	NH_2	H	H	Me			260	5500 [e]	217	9250 [e]	260	7620 [a]	15

* Pe = Pentyl.

Solvents: [a] pH 1·0; [b] pH 0·2; [c] pH 7·8; [d] pH 9·8; [e] 0·1N-NaOH.

The alkylation of 2-dialkylamino-4-hydroxypyrimidines is of interest in this connection. In general, alkylation of 4-hydroxypyrimidines gives predominantly *N*-alkylation.[16] Alkylation of 2-dimethylamino-4-hydroxypyrimidine with methyl iodide under alkaline conditions, on the other hand, gives 2-dimethylamino-4-methoxypyrimidine as the major product together with 1,6-dihydro-2-dimethylamino-1-methyl-6-oxopyrimidine as the minor product.[13] In this case *O*-alkylation is probably favoured by the steric requirements

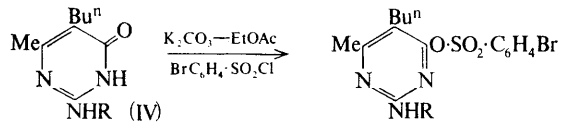
acetate as solvent, conditions known to favour *O*-alkylation in other systems,[17] led to the exclusive formation of 4-allyloxy-2-dimethylaminopyrimidine.

2-Alkylamino-4-hydroxypyrimidines, and 2-Amino-4-hydroxypyrimidines.—Four possible monoacyl derivatives may be formed from compounds of this type, since, in addition to the oxygen atom or either of the

[16] Ref. 1, p. 25.

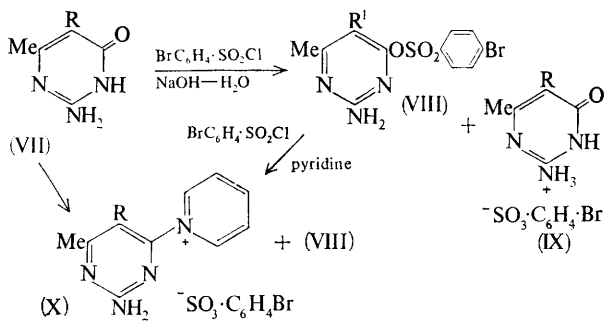
[17] N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269.

ring nitrogen atoms, the 2-alkylamino- or 2-amino-group may itself be acylated. In fact, complex mixtures of products were obtained unless reaction conditions were carefully regulated. With the use of aromatic carboxylic and sulphonic acid halides, and an alkali-metal carbonate to form the salt of the hydroxypyrimidine, it was possible to achieve *O*-acylation in moderate to good yield (Table 1, compounds **27**, **28**, and **29**). For example, 5-n-butyl-2-ethylamino-4-hydroxy-6-methylpyrimidine (IV; R = Et) was converted by



(V; R = Et; 84%)
(VI; R = Pr^n; 72%)

this means to its *O*-bromobenzene-*p*-sulphonate (V; R = Et) 84% yield, and the corresponding derivative of 5-n-butyl-4-hydroxy-6-methyl-2-n-propylaminopyrimidine (VI; R = Pr^n) was obtained in 72% yield. Similarly, 2-amino-4-hydroxy-6-methylpyrimidine (VII; R = H) was converted to its *O*-*p*-bromobenzenesulphonate (VIII; R = H) in 39% yield.



Schotten-Baumann conditions using *p*-bromobenzenesulphonyl chloride led to the formation from 2-amino-4-hydroxy-6-methylpyrimidine (VII; R = H) of the *O*-*p*-bromobenzenesulphonate (VIII; R = H) (73%), together with the *p*-bromobenzenesulphonic acid salt of the starting material (IX; R = H) (13%). Use of triethylamine in dimethylformamide (method 5) in place of aqueous alkali in reactions of this type also gave mixtures of products from which the *O*-*p*-bromobenzenesulphonate [*e.g.* (VIII, R = Bu^n) (56%)], and the *p*-bromobenzenesulphonic acid salt [*e.g.* (IX; R = H) (36%)] could be isolated. The reaction of 2-amino-5-n-butyl-4-hydroxy-6-methylpyrimidine (VII; R = Bu^n) with *p*-bromobenzenesulphonyl chloride in pyridine at room temperature for 4 hours gave the *O*-*p*-bromobenzenesulphonate (VIII; R = Bu^n) (32%), and a second compound, identified as *N*-(2-amino-5-n-butyl-4-methyl-6-pyrimidinyl)pyridinium *p*-bromobenzenesulphonate (X; R = Bu^n) (44%) by analysis, i.r. [$\nu_{max.}$ (Nujol): 3400, 3320, 3210 (NH_2), 3110, 3060 (aromatic C–H), 1650 (NH_2), 1205, 1035, 1005, and 740 cm.$^{-1}$ (sulphonic acid salt)], and n.m.r. spectroscopy [τ 0·75, 1·2, 1·7, multiplet (pyridinium cation); 2·4, A_2B_2 quartet (*p*-disubstituted benzene); 7·45 (4-Me), and 7·8, 8·8, and 9·3 (5-Bu^n)]. Treatment of the *O*-*p*-bromobenzene sulphonate (VIII; R = Bu^n) with pyridine for 6 hours at room temperature gave the pyridinium salt (X; R = Bu^n) (60%) in addition to two further unidentified compounds.

The reaction of 2-alkylamino- and 2-amino-4-hydroxypyrimidines with dialkylphosphorochloridates and dialkylphosphorochloridothioates was relatively straightforward and gave the corresponding *O*-phosphoryl derivatives [I; R = P(O)(OAlk)$_2$; P(S)(OAlk)$_2$; R^1 = H; R^2 = Alk or H] in good yield under a variety of experimental conditions, in agreement with earlier work of Arbusov.[18]

That the acyl, sulphonyl, and phosphoryl derivatives of the 2-amino- and 2-alkylamino-4-hydroxypyrimidines could be represented by the general formula (I), namely that esterification had involved in each case the oxygen atom of the pyrimidine rather than either of the ring nitrogen atoms, was established by spectroscopic methods. The u.v. absorption spectra of sulphonyl (Table 3, examples 18 and 19) and phosphoryl (Table 3, examples 20 and 21) derivatives of 2-amino-4-hydroxypyrimidines closely resemble those of known 4-alkoxy-2-aminopyrimidines (I; R^1 = R^2 = R^4 = H; R^3 = H or Alk; R = Alk; Table 3, examples 22 and 23), but differ from those of known 1,6-dihydro-1-alkyl-2-amino-6-oxopyrimidines (II; R^1 = R^2 = R^4 = H; R = Alk; Table 3, example 29) or 1,4-dihydro-1-alkyl-2-amino-4-oxopyrimidines (III; R^1 = R^2 = R^4 = H; R = Alk; Table 3, example 30). Furthermore, a comparison of the u.v. absorption spectra of corresponding derivatives of 2-amino-, 2-alkylamino-, and 2-dialkylamino-4-hydroxypyrimidines shows a general similarity in shape of the curve, and a bathochromic progression in ascending the series, indicating that the compounds differ only in the extent of substitution of the 2-amino-group (Tables 4 and 5).

The n.m.r. spectra of the acyl, sulphonyl, and phosphoryl derivatives of 2-amino- and 2-alkylamino-4-hydroxypyrimidines (Table 2, examples 19, 20, and 21) closely parallel the spectra of corresponding derivatives of the related 2-dialkylamino-4-hydroxypyrimidines, showing that in all cases, the compounds have the pyrimidine structure (I) rather than either of the pyrimidone structures (II) or (III) (see above). Examination of the i.r. spectra also provides support for the pyrimidine structure (I). Derivatives of 2-amino-4-hydroxypyrimidines show the expected band in their i.r. spectra at 1650—1670 cm.$^{-1}$ (NH_2 deformation), but no absorption due to a pyrimidone carbonyl, and apart from absorption due to N–H bonds, the spectra of corresponding derivatives of 2-amino-, 2-alkylamino-, and 2-dialkylamino-4-hydroxypyrimidines are closely similar (Table 1). The possibility of the formation of *O*-acyl or *O*-sulphonyl derivatives of 2-alkylamino- or

[18] B. A. Arbusov and V. M. Zoroastrova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1958, 1331 (*Chem. Abs.*, **53**, 7182h).

TABLE 4

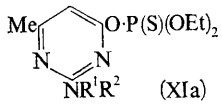
U.v. absorption spectra of pyrimidines (XIa) in methanol

No. of compound	R^1	R^2	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
1	H	H	230	11,600	285	4500
2	H	Bu^n	240	17,600	296	4350
3	Bu^n	Bu^n	249	20,400	305	4700 [19]

TABLE 5

Ultraviolet absorption spectra of pyrimidines (XIIa) in methanol

No. of compound	R^1	R^2	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
1	H	H	235	29,700	297	6000
2	H	Et	238	38,300	308	6400
3	Me	Me	240	32,700	316	3600

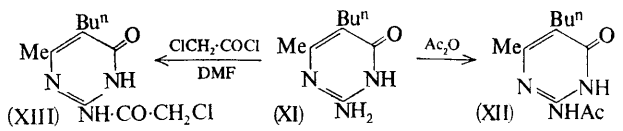


(XIa)

(XIIa)

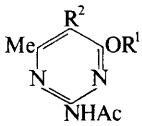
2-amino-4-hydroxypyrimidines is dependent upon the steric requirements of the acylating agent. Thus, while *O*-*p*-bromobenzenesulphonates could be prepared, in good yield, in all cases, *O*-methanesulphonates could be obtained from 2-alkylamino-, but not from 2-amino-4-hydroxypyrimidines. Furthermore, although we could not obtain *O*-acetates of 2-amino- or 2-alkylamino-4-hydroxypyrimidines, an *O*-pivalate could be prepared, from representative 2-amino-4-hydroxy-pyrimidines (*e.g.*, Table 1, compound 37; 40%).

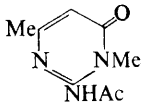
2-Amino-4-hydroxypyrimidines may be selectively acylated on the amino-group by treatment with acetic anhydride [(XI) ⟶ (XII)] [20] or by the use of certain reactive acyl halides in dimethylformamide [(XI) ⟶ (XIII)].



[19] B.P. 1,019,227/1966.
[20] U.S. 2,740,785/1953.
[21] E. G. Antonovich and M. A. Prokof'ev, *Vestnik Mosk. Univ.*, 1955, **10**, No. 3, *Ser. Fiz. Mat. Estestven Nauk*, No. **2**, 55 (*Chem. Abs.*, **49**, 10972f).
[22] B.P. 658,202/1951.
[23] S. Gabriel and J. Colman, *Chem. Ber.*, 1899, **32**, 2921.

2-Acetylamino-4-hydroxypyrimidines.—Representative 2-acetylamino-4-hydroxypyrimidines formed *p*-bromobenzenesulphonates (Table 1, examples 38 and 39) and dialkyl thiophosphates (Table 1, example 40) in good yield under appropriate reaction conditions. These derivatives were shown to be *O*-sulphonyl [(XIV) and (XV)] and *O*-phosphoryl (XVI) derivatives respectively on the basis of their i.r. absorption spectra ($\nu_{max.}$ 1680 $cm.^{-1}$ (NHAc), but no other absorption in the carbonyl region), and n.m.r. spectra (3-proton singlet at τ, 7·55—7·61, attributed to the C-4 methyl of a pyrimidine





(XVIII)

(XIV) $R^1 = SO_2{\cdot}C_6H_4Br\ p$, $R^2 = H$
(XV) $R^1 = SO_2{\cdot}C_6H_4Br\text{-}p$, $R^2 = Bu^n$
(XVI) $R^1 = P(S)(OEt)_2$, $R^2 = H$
XVII) $R^1 = Me$, $R^2 = H$

rather than a pyrimidone; Table 2, examples 22 and 23. Examples 23a (XVII) and 34 (XVIII) give the n.m.r. spectra of appropriate reference compounds). Furthermore, the u.v. absorption spectra of the sulphonyl [(XIV) and (XV)] and phosphoryl (XVI) derivatives closely resemble that of 2-acetylamino-4-methoxy-6-methylpyrimidine (XVII), but differ markedly from that of 2-acetylamino-1,6-dihydro-1,4-dimethyl-6-oxopyrimidine (XVIII) (Table 6).[21]

TABLE 6

U.v. absorption spectra of 2-acetylaminopyrimidines

Example	Compound	R	R^1	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{infl.}$ (mμ)	$\varepsilon_{infl.}$	Solvent
1	(XVIII)			274	9700			MeOH
				262	6800			0·1N-HCl
2	(XVII)	H	Me	239	14,900	260	8300	MeOH
				239	15,000			0·1N-HCl
3	(XVI)	H	$P(S)(OEt)_2$	238	16,000	260	7000	MeOH
4	(XIV)	H	$SO_2{\cdot}C_6H_4Br\text{-}p$	238	31,800	260	8800	MeOH
				237	32,600			0·1N-HCl
5	(XV)	Bu^n	$SO_2{\cdot}C_6H_4Br\text{-}p$	239	30,600	265	8490	MeOH
				239	32,800			0·1N-HCl

EXPERIMENTAL

Microanalyses were by Mr. A. Sarney, and his staff. The following pyrimidines were obtained by known methods: 2-n-butylamino-4-hydroxy-6-methylpyrimidine,[22] 2-amino-4-hydroxy-6-methylpyrimidine,[23] 2-dimethylamino-4-hydroxypyrimidine,[24] 2-dimethylamino-4-hydroxy-6-methylpyrimidine,[25] 4-hydroxy-6-methyl-2-piperidinopyrimidine,[26] 4-hydroxy-2-(*N*-methylpiperazinyl)pyrimidine,[27] 4-hydroxy-2-morpholinopyrimidine,[27] 4-hydroxy-2-piperidinopyrimidine,[27] 2-amino-5-n-butyl-4-hydroxy-6-methypyrimidine,[28] 2-acetylamino-4-hydroxy-6-methylpyrimidine,[29]

[24] D. G. Saunders, *J. Chem. Soc.*, 1956, 3232.
[25] P. B. Russell, G. B. Elion, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1949, **71**, 474.
[26] R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, *J. Chem. Soc.*, 1946, 357.
[27] B. Roth and L. A. Schloemer, *J. Org. Chem.*, 1963, **28**, 2659.
[28] M. Muraoka, A. Takada, and T. Veda, *Keio J. Med.*, 1962, **11**, 95 (*Chem. Abs.*, **57**, 17192c).

2-di-n-butylamino-4-hydroxy-6-methylpyrimidine,[30] 5-allyl-2-amino-4-hydroxy-6-methylpyrimidine,[31] 4-hydroxy-6-methyl-2-morpholinopyrimidine,[27] 2-amino-4,5-dimethyl-6-hydroxypyrimidine.[28]

The following pyrimidines (Table 7) were synthesised by methods analogous to those described by Overberger and Kogan [32] for 2-dimethylamino-4-hydroxy-6-methylpyrimidine (method A), by Sprague [33] for a number of 2-amino-4-hydroxypyrimidines (method B), and by Hull [34] for 2-amino-4-hydroxy-5-methylpyrimidine (method C).

Method 1

5-n-Butyl-2-dimethylamino-4-methyl-6-pyrimidinyl 2,5-Dimethylbenzenesulphonate (*Compound* 24, *Table* 1).—A mixture of 5-n-butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine (10·45 g., 0·05 mole), anhydrous potassium carbonate (6·9 g., 0·05 mole), 2,5-dimethylbenzenesulphonyl chloride (10·23 g., 0·05 mole), and ethyl acetate (200 ml., dry) was stirred and heated under reflux for 7 hr. The reaction mixture was cooled, the solvent was removed under reduced pressure, and the residue taken up in toluene (150 ml.). The toluene was washed with ice-cold 5%-aqueous sodium hydroxide solution, then with water until the washings were neutral, and finally dried ($MgSO_4$). Removal of the toluene under reduced pressure, and recrystallisation of the residue from light petroleum (b.p. 60—80°) gave the 2,5-*dimethylbenzenesulphonate* (13·1 g., 70%), m.p. 77°.

Solvents used satisfactorily in the above reaction included benzene, toluene, acetone, methyl ethyl ketone, and acetonitrile.

Method 2

2-Dimethylamino-4-methyl-5-n-propyl-6-pyrimidinyl p-*Nitrobenzoate* (*Compound* 1, *Table* 1).—2-Dimethylamino-6-hydroxy-4-methyl-5-n-propylpyrimidine (1·95 g., 0·01 mole) was added to a solution of sodium (0·23 g., 0·01 g.-atom) in dry ethanol (25 ml.). The solvent was removed under reduced pressure, and the residue was dried by azeotropic distillation with benzene. To the residue was added dry benzene (25 ml.) and freshly prepared *p*-nitrobenzoyl chloride (2·3 g., 0·012 mole) and the reaction mixture was stirred and heated under reflux for 4 hr. The cooled mixture was shaken with ice-cold 5%-aqueous sodium hydroxide, washed with water until the washings were neutral, and the benzene layer dried ($MgSO_4$). Removal of the benzene, followed by crystallisation of the residue from ethanol gave the p-*nitrobenzoate* (1·8 g., 53%), m.p. 109°.

Method 3

O-*2-Amino-4-methyl-6-pyrimidinyl* OO-*Dimethyl Phosphorothioate* (*Compound* 36, *Table* 1).—2-Amino-4-hydroxy-6-methylpyrimidine (5 g., 0·04 mole) was suspended in dry dimethylformamide (50 ml.), and to the stirred suspension was added, portionwise under nitrogen, sodium hydride (1·92 g., 0·04 g.-mole of 50% dispersion in oil). After 2 min. dimethyl phosphorochloridothioate (6·42 g., 0·04 mole) was added dropwise with stirring. A mild exothermic reaction occurred and the temperature of the reaction mixture rose to 50°. After 1 hr. the reaction mixture was poured onto water (400 ml.). An oil separated which crystallised on standing. The product was filtered off, dried, and recrystallised from isopropyl alcohol (charcoal) to give O-*2-amino-4-methyl-6-pyrimidinyl* OO-*dimethyl phosphorothioate* (3 g., 41%), m.p. 106—107°.

Method 4

5-n-Butyl-2-dimethylamino-4-methyl-6-pyrimidinyl p-*Methoxybenzenesulphonate* (*Compound* 26, *Table* 1).—A mixture of 5-n-butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine (10·45 g., 0·05 mole), *p*-methoxybenzenesulphonyl chloride (10·33 g., 0·05 mole), and dry pyridine (125 ml.) was stirred at room temperature for 24 hr. Pyridine was removed under reduced pressure, and the residue was dissolved in a mixture of water (200 ml.) and methylene chloride (200 ml.). The methylene chloride layer was washed with water (3 × 100 ml.), ice-cold 5% aqueous sodium hydroxide solution (100 ml.), then with water until the washings were neutral, and finally dried ($MgSO_4$). Removal of the solvent, and crystallisation of the residue from aqueous methanol gave the p-*methoxybenzene sulphonate* (9·8 g., 56%), m.p. 85°.

Method 5

5-n-Pentyl-2-dimethylamino-4-methyl-6-pyrimidinyl Methanesulphonate (*Compound* 7, *Table* 1).—To a stirred solution

TABLE 7

4-Hydroxypyrimidines (II; R = H)

No. of compound	NR^1R^2	R^3	R^4	M.p.	Method of synthesis	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
1	NMe_2	Me	Et	143°	A	59·5	8·3	23·4		$C_9H_{15}N_3O$	59·7	8·3	23·2	
2	NMe_2	Me	Pr^n	120	A	61·5	8·8	21·1		$C_{10}H_{17}N_3O$	61·5	8·7	21·5	
3	NMe_2	Me	Bu^n	102	A	63·0	9·3	20·3		$C_{11}H_{19}N_3O$	63·5	9·2	20·5	
4	NMe_2	Me	n-C_5H_{11}	84	A	64·7	9·6	18·9		$C_{12}H_{21}N_3O$	64·6	9·5	18·8	
5	NMe_2	Me	$CH_2{\cdot}CH{:}CH_2$	96	A	61·9	7·9	22·1		$C_{10}H_{15}N_3O$	62·2	7·8	21·8	
6	NMe_2	n-C_6H_{13}	H	80	A	64·6	9·3	18·6		$C_{12}H_{21}N_3O$	64·6	9·5	18·8	
7	NMe_2	Et·S·CH_2	H	118	A	51·1	7·5	20·2	15·3	$C_9H_{15}N_3OS$	50·7	7·4	19·5	15·5
8	NMe_2	Pr^n	Et	103	A	63·3	9·1	20·1		$C_{11}H_{19}N_3O$	63·2	9·2	20·1	
9	NHEt	Me	Bu^n	159	A	63·2	9·1	20·2		$C_{11}H_{19}N_3O$	63·2	9·2	20·1	
10	$NHPr^n$	Me	Bu^n	154	A	64·3	9·6	19·0		$C_{12}H_{21}N_3O$	64·6	9·5	18·8	
11	NH_2	Pr^n	H	209	B	54·9	7·2	27·4		$C_7H_{11}N_3O$	55·0	7·2	27·4	
12	NMe_2	H	Me	186—187	C	55·0	7·0	27·5		$C_7H_{11}N_3O$	55·0	7·2	27·4	

[29] I. T. Matsukawa and K. Shirakawa, *J. Pharm. Soc. Japan*, 1952, **72**, 909 (*Chem. Abs.*, **47**, 6425h).
[30] B.P. 741,667/1955.
[31] V. Hach, *Chem. Listy*, 1951, **45**, 459 (*Chem. Abs.*, **46**, 7573b).
[32] C. G. Overberger and I. C. Kogon, *J. Amer. Chem. Soc.*, 1954, **76**, 1879.
[33] J. M. Sprague, L. W. Kissinger, and R. M. Lincoln, *J. Amer. Chem. Soc.*, 1941, **63**, 3028.
[34] R. Hull, B. J. Lovell, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 1947, 41.

of 5-n-pentyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine (5·58 g., 0·025 mole) in dry dimethylformamide (25 ml.) was added, all at once, methanesulphonyl chloride (2 ml., 0·025 mole). To the stirred mixture was added dropwise triethylamine (2·53 g., 0·025 mole). The temperature of the reaction mixture rose to 42°. After 2 hr. the mixture was poured onto water (200 ml.), and the precipitated material was filtered off, washed with a little cold water, and dried. Recrystallisation from ethanol gave the *methanesulphonate* (6·24 g., 83%), m.p. 69°.

Method 6

(*5-n-Butyl-2-dimethylamino-4-methyl-6-pyrimidinyl*) *Benzoate* (*Compound* 8, *Table* 1).—5-n-Butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine (4·18 g., 0·02 mole) was added to a solution of sodium hydroxide (0·8 g., 0·02 mole) in water (50 ml.), and the mixture was stirred for a few minutes at room temperature to obtain a clear solution. Benzoyl chloride (2·81 g., 0·02 mole) was added, and the mixture was stirred vigorously for 6 hr. The precipitate was filtered off, washed with water, dried, and recrystallised from aqueous ethanol to give the *benzoate* (5·8 g., 93%), m.p. 59°.

The synthesis of 5-n-butyl-2-dimethylamino-4-methyl-6-pyrimidinyl benzoate was studied using a variety of experimental conditions, with the following results, *viz:* [method, solvent, yield (%)]; (2, ethyl acetate, 96; 2, acetonitrile, 78; 2, methyl ethyl ketone, 83; 1, ethyl acetate, 83; 1, methyl ethyl ketone, 81; 6, water, 93).

Method 7

5-n-Butyl-2-dimethylamino-4-methyl-6-pyrimidinyl Acetate (*Compound* 23, *Table* 1).—A mixture of 5-n-butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine (10·45 g., 0·05 mole) and acetic anhydride (100 ml.) was heated at 120—130° (oil-bath temperature) for 4 hr. Distillation gave the *acetate* (10·8 g., 86%), b.p. 128—130°/0·25 mm.

The reaction of 5-n-Butyl-2-dimethylamino-4-methyl-6-pyrimidinyl Acetate with Aniline.—Aniline (250 mg.) was mixed with 5-n-butyl-2-dimethylamino-4-methyl-6-pyrimidinyl acetate (250 mg.). An exothermic reaction occurred, and the mixture set solid. The solid was filtered on a glass sinter, drained dry, and dissolved in a mixture of N-aqueous sodium hydroxide (10 ml.) and ether (10 ml.). From the ether layer was obtained acetanilide (140 mg.), and from the aqueous alkaline layer was obtained 5-n-butyl-2-dimethylamine-4-hydroxy-6-methylpyrimidine (150 mg.).

5-n-Butyl-4-chloro-2-dimethylamino-6-methylpyrimidine.—A mixture of 5-n-butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine (0·1 mole, 20·9 g.) and freshly distilled phosphorus oxychloride (50 ml.) was heated under reflux for 2 hr. The excess of phosphorus oxychloride was removed by distillation under reduced pressure, and the reaction mixture was poured onto ice–water (200 ml.), and allowed to stand until all reaction had ceased. The solution was neutralised carefully with ammonia (*c* 0·88) with the temperature below 10°. The product was obtained by extraction with ether (5 × 200 ml.), the ether was dried (Na_2SO_4), and the product was obtained by distillation, b.p. 96—97°/0·1 mm (22 g., 96%) (Found: C, 15·8; N, 18·3. $C_{11}H_{18}ClN_3$ requires C, 15·6; N, 18·4%).

5-n-Butyl-2-dimethylamino-4-(2-diethylaminoethoxy)-4-methylpyrimidine.—Sodium (0·46 g., 0·02 g.-atom) was dissolved in 2-diethylaminoethanol (30 g.). To the solution was added 5-n-butyl-4-chloro-2-dimethylamino-6-methylpyrimidine (4·56 g., 0·02 mole), and the reaction mixture was stirred at 130—140° for 3 hr. The excess of 2-diethylaminoethanol was removed under reduced pressure, and the residue was dissolved in a mixture of methylene chloride and water. The methylene chloride layer was dried (Na_2SO_4), and the solvent was removed. The product was purified by distillation, b.p. 126°/0·23 mm., $n_D^{23} = 1·5046$ (Yield 3·2 g., 53%) (Found: C, 66·0; H, 10·6; N, 17·8. $C_{17}H_{34}N_4O$ requires C, 66·2; H, 10·4; N, 18·2%).

In a similar manner was prepared 5-n-butyl-2-dimethylamino-4-(2-hydroxyethoxy)-4-methylpyrimidine, b.p. 126—128°/0·4 mm., $n_D^{20} = 1·5250$ (Yield 2·2 g., 44%) (Found: C, 62·0; H, 9·2; N, 16·8. $C_{13}H_{23}N_3O_2$ requires. C, 61·7; H, 9·1; N, 16·6%).

4-Benzyloxy-2-dimethylaminopyrimidine.— 4-Chloro-2-dimethylaminopyrimidine (1·5 g., 0·095 mole) [35] was added to sodium (0·25 g., 0·011 g.-atom) in benzyl alcohol (7·5 ml.) and the mixture was heated at 180° for 3 hr., cooled, poured onto water (100 ml.), and extracted with ether (3 × 100 ml.). The ether was dried ($MgSO_4$). Fractional distillation gave *4-benzyloxy-2-dimethylaminopyrimidine* b.p. 118—120°/0·1 mm.; $n_D^{22} = 1·5602$ (Found: C, 68·0; H, 6·9; N, 18·2. $C_{13}H_{15}N_3O$ requires C, 68·2; H, 6·7; N, 18·3%).

4-Allyloxy-2-dimethylaminopyrimidine.—A mixture of 2-dimethylamino-4-hydroxypyrimidine (6·90 g., 0·05 mole), anhydrous potassium carbonate (6·91 g., 0·05 mole), and dry benzene (100 ml.) was stirred and heated under reflux with azeotropic removal of water (Dean and Stark trap) for 2 hr. To the cooled mixture was added allyl bromide (6·0 g., 0·05 mole) and the reaction mixture was stirred and heated under reflux for 4 hr. The cooled mixture was washed with ice-cold 5%-aqueous sodium hydroxide, then with water until the washings were neutral, dried ($MgSO_4$), and the solvent removed. Distillation gave *4-allyloxy-2-dimethylaminopyrimidine*, b.p. 63—65°/0·1 mm. (8 g., 89%), $n_D^{22} = 1·5305$ (Found: C, 60·7; H, 7·4; N, 23·4. $C_9H_{13}N_3O$ requires C, 60·3; H, 7·3; N, 23·4%); V.p.c. (10% silicone on Celite, 210°, helium as carrier gas at 5 lb./sq. in.) showed the product to be homogeneous.

2-Amino-4-methyl-6-pyrimidinyl p-Bromobenzene Sulphonate (*Compound* 32, *Table* 1).—2-Amino-4-hydroxy-6-methylpyrimidine (2·5 g., 0·02 mole) was added to a solution of sodium hydroxide (0·8 g., 0·02 mole) in water (50 ml.), and the mixture was stirred for a few minutes to obtain a clear solution. Finely powdered *p*-bromobenzenesulphonyl chloride (5·12 g., 0·02 mole) was added, and the mixture was stirred vigorously at room temperature for 2 hr. The precipitated material was filtered off, washed with a little cold water, and dried. Recrystallisation from isopropyl alcohol gave the *p-bromobenzene sulphonate* (5 g., 73%), m.p. 156—157°. From the mother-liquor was obtained a second compound, the *p*-bromobenzene sulphonate salt (IX) of 2-amino-4-hydroxy-6-methylpyrimidine, m.p. 227° (EtOH) (900 mg., 13%) $\nu_{max.}$ (Nujol) 3360, 3120 (NH_2), 1690—1660 (CONH), 1165, 1038, 1005, and 745 (RSO_3^-) (Found: C, 36·0; H, 3·1; N, 11·5. $C_{11}H_{12}BrN_3S$ requires C, 36·5; H, 3·3; N, 11·6%).

Neutralisation of an aqueous solution of this compound with sodium hydroxide solution gave 2-amino-4-hydroxy-6-methylpyrimidine, from which the above salt (IX) could be remade by mixing hot ethanolic solutions containing equimolar quantities of 2-amino-4-hydroxy-6-methylpyrimidine and *p*-bromobenzenesulphonic acid.

[35] C. G. Overberger and I. C. Kogon, *J. Amer. Chem. Soc.*, 1954, **76**, 1065.

The Reaction of 2-*Amino*-5-*n*-*butyl*-4-*hydroxy*-6-*methylpyrimidine with* p-*Bromobenzenesulphonyl chloride in Pyridine*.—(a) *Isolation of* 2-*amino*-5-*butyl*-4-*methyl*-6-*pyrimidinyl p-bromobenzenesulphonate*. A mixture of 2-amnio-5-n-butyl-4-hydroxy-6-methylpyrimidine (0·9 g., 0·005 mole) and *p*-bromobenzenesulphonyl chloride (1·3 g., 0·005 mole) in dry pyridine (10 ml.) was stirred at room temperature for 1½ hr., and then poured into ice–water (100 ml.). Liquid was decanted off, and the residue was washed with water. Recrystallisation from aqueous ethanol gave the p-*bromobenzenesulphonate* (0·65 g., 32%), m.p. 151—152°.

(b) *Isolation of* 2-*amino*-5-*n*-*butyl*-4-*methyl*-6-*pyrimidinyl-pyridinium* p-*bromobenzenesulphonate* X, R = Bu^n). 2-Amino-5-n-butyl-4-hydroxy-6-methylpyrimidine (7·25 g., 0·04 mole) was suspended in dry pyridine (50 ml.) and *p*-bromobenzenesulphonyl chloride (10·24 g., 0·04 mole) was added in portions. The solution was stirred at room temperature for 4 hr., filtered, and the filtrate diluted with benzene (250 ml.). The crystalline material which formed was filtered off, washed with a little cold benzene, and dried. Recrystallisation from isopropyl alcohol gave *N*-2-amino-5-n-butyl-4-methyl-6-pyrimidinylpyridinium *p*-bromobenzenesulphonate, m.p. 215° (8·5 g., 44%) (Found: C, 50·3; H, 4·7; Br, 16·9; N, 11·8; S, 6·8%. $C_{20}OH_{23}BrN_3O_3S$ requires C, 50·1, H, 4·8; Br, 16·7; N, 11·7; S, 6·7%) $\nu_{max.}$ (Nujol): 1205, 1035, 1005, and 740 ($R{\cdot}SO_3^-$); τ values for protons (*ca.* 10% w/v in $CDCl_3$) 0·75, 1·2, 1·7 (5-proton multiplet; pyridinium salt); 2·42 (4-proton A_2B_2 multiplet; *p*-disubstd. benzene); 7·45 (3-proton singlet; C-4, Me); 7·8, 8·8, 9·3 (9 proton multiplet; C-5, Bu^n).

2-*Acetylamino*-5-*n*-*butyl*-4-*hydroxy*-6-*methylpyrimidine* (XV).— 2-Amino-5-n-butyl-4-hydroxy-6-methylpyrimidine (15 g.), was heated under reflux with acetic anhydride (60 ml.) for 30 min. The excess of acetic anhydride was re-removed under reduced pressure, and the residue was crystallised from aqueous ethanol to give 2-acetylamino-5-n-butyl-4-hydroxy-6-methylpyrimidine, m.p. 151—153° (14·7 g., 80%) (Found: C, 58·3; H, 7·4; N, 18·7. $C_{11}H_{17}N_3O_2$ requires C, 58·4; H, 7·6; N, 18·8%), $\lambda_{max.}$ 244 mμ (ε 9500), $\lambda_{max.}$ 292 mμ (ε 7900).

5-*n*-*Butyl*-2-*chloroacetylamino*-4-*hydroxy*-6-*methylpyrimidine* (XVI).—To a stirred suspension of 2-amino-5-n-butyl-4-hydroxy-6-methylpyrimidine (1·81 g., 0·01 mole) in dry dimethylformamide (10 ml.) was added, dropwise with stirring under nitrogen, chloroacetyl chloride (1·13 g., 0·01 mole). After 2 hr. the reaction mixture was poured into water. The precipitated material was filtered off, washed with a little cold water, dried, and crystallised from a little ethanol to give 5-n-butyl-2-chloroacetylamino-4-hydroxy-6-methylpyrimidine (1·8 g., 70%), m.p. 156° (Found: C, 51·4; H, 6·3; Cl, 13·7; N, 16·0. $C_{11}H_{16}ClN_3O_2$ requires C, 51·3; H, 6·3; Cl, 13·8; N, 16·3%), $\lambda_{max.}$ 246 (ε 9000) and 291 mμ (ε 9000).

2-*Acetylamino*-4-*methoxy*-6-*methylpyrimidine* (XIX).—2-Amino-4-methoxy-6-methylpyrimidine [36] (2 g.) was heated under reflux with acetic anhydride (10 ml.) for 1 hr. The excess of acetic anhydride was removed under reduced pressure, and the residue was crystallised from ethanol to give 2-acetylamino-4-methoxy-6-methylpyrimidine (2 g., 95%), m.p. 98—99°, $\nu_{max.}$ (Nujol): 3220, 3140 (NH), 1665 (NHAc), 1600, and 1565 (ring C:C, C:N) cm.$^{-1}$ (Found: C, 53·2; H, 6·2; N, 23·5. $C_8H_{11}N_3O_2$ requires C, 53·0; H, 6·1; N, 23·2%).

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[36] W. Baker, E. J. Pribyl, J. T. Sheehan, E. R. Spitzmiller, and W. A. Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 3072.