AN ABSTRACT OF THE THESIS OF

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Although 4- and 5-diacetamidopyrimidines have been reported in the literature within the past eleven years, it was not until 1965 that a 2-diacetamidopyrimidine was reported. The current investigation was undertaken to determine whether other 2-diacetamidopyrimidines could be synthesized and what the effect of various nuclear substituents would be on the course of the reaction. The new compounds 2-diacetamido- and 2-diacetamido-4, 6-dimethyl-pyrimidine were synthesized. In the acetylation attempts of 2-amino-4, 6-dihydroxy- and 2-amino-4, 6-dichloro-pyrimidines and 6-aminouracil under identical conditions used for diacetylation of the three 2-aminopyrimidines, no acetylation product at all could be isolated. With 2-methoxy-4-amino- and 6-amino-2, 4-dichloropyrimidine only a monoacetamido derivative was formed and isolated. The former is a new compound. 5-Diacetamido-4, 6-dichloropyrimidine, previously prepared by isopropenyl acetate, was prepared in lower yield under the above

conditions. Therefore, it would seem that m-positioned electron-donating groups (in the 5-aminopyrimidines the ring nitrogens are so positioned) enhance the nucleophilicity of an aminopyrimidine and that similarly positioned electron-withdrawing groups reduce the nucleophilicity of the amine.

The most striking feature that was noticed when the known diacetamido pyrimidines were compared is that almost every one (with the exception of the three 2-diacetamidopyrimidines, which have the ring nitrogens in the ortho position) was substituted in at least one ortho position. That diortho substituents hinder monoacetylation of anilines but greatly enhance the probability and yield of diacetanilides was first observed nearly a century ago. A similar facilitating effect of ortho substitution in the acylation of aminopyridines has also been observed. Since the effect of ortho substituents on an aromatic nucleus in ester or amide hydrolysis is one of hindrance, it was puzzling that steric facilitation seemed to be operative in diacetamide formation. An attempt has been made here to correlate what has been reported regarding the syntheses of N-aryl diacetamides, to make some generalizations regarding the factors necessary for the achievement of diacylation of such compounds, and to draw some conclusions with respect to the probable reasons for the behavior observed.

The infrared and ultraviolet spectra of the diacetamides prepared in this investigation and the behavior of these compounds when chromatographed on silica gel or alumina thin layer plates are described.

An unsuccessful attempt to synthesize 4-amino-2-methyl pyrimidine via reaction between acetamidine hydrochloride and the sodium enolate of cyanoacetaldehyde is reported.

A STUDY OF FACTORS LEADING TO N, N-DIACETYLATION OF AMINOPYRIMIDINES

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A STUDY OF FACTORS LEADING TO N, N-DIACETYLATION OF AMINOPYRIMIDINES

INTRODUCTION

The acetylation of amides has been known since 1857 through the work of Strecker, who reported the preparation of diacetamide from acetamide (1) by heating the latter in the presence of gaseous hydrogen chloride or (2) by refluxing the hydrochloride of acetamide (147). A. W. Hofmann had claimed the synthesis of diacetanilide as early as 1870 from a heated mixture of phenylisothiocyanate and acetic acid, a claim which was later disputed by Bistrzycki and Ulffers (15). Most of the types of synthetic methods for diacylamines and diacetanilides are recorded in Tables I and II. A brief summary of the historical background in the syntheses of diacylamines may be found in the 1956 report of Cadwallader and La Rocca (27). These investigators cited other methods of preparation that had been reported to yield diacylamines: (a) reaction of nitriles with organic acids, including reaction of nitriles with halogenated carboxylic acids under pressure forming mono, di, and trihalo diacylamines; (b) reaction between the mercury salt of acetanilide and an acid chloride; (c) reaction of the sodium salt of benzamide with acid chlorides; (d) acidification of acylbenzimidoethylesters; and (e) reaction of anhydrides with amides in the presence of acid chlorides (51).

Table I. Acetamido derivatives of benzenes

Substituents on benzene 1	2	3	4	5	6	Acylating agent*	Temperature °C	Time in hours	Percent mono-acetyl	Percent di-acetyl	Reference
NH_2						(4)	130			√	67
NH_2						9(1), 1(6)	10	1.5	86		142
NH_2						9(1)	10	1.5	92		142
NH_2						3(1)	10	1.5	89		142
NH_2						3(1), 6(6)	10	1.5	30		142
NH_2						4(1)	R	1	39	53	148
NH_2						large excess(1)	Δ			√	129 131
NH_2						16(1), 100(4)	R	6.5	50		142
NH_2						16(1), 100(4)	R	48	100		142
NH_2						(4)	Δ			√	67
NH_2						1(8)	Δ	"long"		√	31
NHAc						(2)	180	--		√	90
NHAc						1(1)	--	"long"		√	31
NHAc						2(1)	R	1		66	148
NHAc						1.1(5)	15	0.16		√	22
NHAc						16(1), 100(4)	R	96	100		142

*The numbers outside of parentheses refer fo the number of molar equivalents. R = Reflux

Table I Continued.

Substituents on benzene					Acylating agent*	Temperature °C	Time in hours	Percent mono-acetyl	Percent di-acetyl	Reference
1	2	3	4	5	6					
NH_2	CH_3					183	0.5			145
NH_2	CH_3					183	10			145
NH_2	CH_3				4(1)	R	1	7	81	148
NH_2	NO_2				(1)(6)	R	min.		√	16
NH_2		OH			(1), (7)	160	3	81	some	130
NH_2			CH_3		4(1)	R	1	32	60	148
NH_2			Br		(1)	25	-	100		163
NHAc			CH_3		2(1)	R	1	24	72	148
NHAc			CH_3		(2)	180	-		√	90
NHAc	CH_3				(2)	180	-		√	90
NHAc			Br		2(1)	210	8		55	163
NHAc			NO_2		2(1)	200	10		~18	163
NH_2	Br		CH_3		(1)	250	-	100		163
NH_2	Br		Br		(1)	>25	<1	√		163
NH_2	Br		Br		6(1), 195(4)	25	0.08	100		142
NHAc	NO_2		NO_2		(1)	200	10		20	163

* The numbers outside of parentheses refer to the number of molar equivalents R = Reflux

Table I. Continued

Substituents on benzene						Acylating agent*	Temperature °C	Time in hours	Percent mono-acetyl	Percent di-acetyl	Reference
1	2	3	4	5	6						
NH_2	Cl			Cl		(9)	100	1	71		22
NH_2	CH_3		CH_3	CH_3		4(1)	R	1	10	85	148
NH_2	Br		CH_3		Br	(1)	25	sev. days	some		163
NH_2	Br		Br		Br	53(1), (4)	R	2	20		142
NH_2	Br		Br		Br	53(1), (4)	R	6.5	50		142
NH_2	Br		Br		Br	53(1), (4)	R	48	100		142
NH_2	Br		Br		Br	53(1), (4)	R	96	100		142
NH_2	Br		Br		Br	15(1), 1(6), (4)	25	0.16-0.3	91-99		142
NH_2	Br		Br		Br	70(1)	25	2 wks	0	0	142
NH_2	Br		Br		Br	70(1)	75	2 h.	25-30		142
NH_2	Br		Br		Br	70(1)	75	>2 h.		√	142
NH_2	Br		Br		Br	350(1), 0.25(6)	25	0.16	√		142
NH_2	Br		Br		Br	350(1), 0.25(6)	75	1 h.		100	142
NH_2	Br.		Br		Br	350(1), 0.25(6)	25	3	√	√	142
NH_2	Br		Br		Br	350(1), 0.25(6)	25	48		100	142
NH_2	Br		Br		Br	2(1)	138	2		major	163

* The numbers outside of parentheses refer to the number of molar equivalents R = Reflux

Table I. Continued

Substituents on benzene 1	2	3	4	5	6	Acylating agent*	Temperature °C	Time in hours	Percent mono-acetyl	Percent di-acetyl	Reference
NH_2	Br		Br		Br	(1)	Δ	short		√	128
NH_2	Br		Br		Br	(2)	Δ		√		128
NHAc	CH_3		CH_3	CH_3		2(1)	R	1	8	89	148
NHAc	Br		CH_3		Br	2(1)	138	2		~100	163
NHAc	Br		Br		Br	(1)	75	7 h		70	142
NHAc	Br		NO_2		Br	104(1), (6)	25	2		100	142
NHAc	NO_2		CH_3		NO_2	2(1)	200	10		~75	163
NHAc	NO_2		CH_3		Br	2(1)	180	4		major	163

* The numbers outside of parentheses refer to the number of molar equivalents. R = Reflux √ = Reported without yield

(1) acetic anhydride
(2) acetyl chloride
(3) isopropenyl acetate
(4) glacial acetic acid
(5) trifluoroacetic anhydride
(6) sulfuric acid
(7) sodium acetate
(8) benzoyl chloride
(9) N-(trifluoroacetyl)-acetanilide

Table II. Synthetic methods for diacylamines

Substrate	Acylating agent	Solvent or catalyst	Temperature, °C	Time in hours	Diacyl derivative	Yield	Reference
acetamide		HCl(g)	Δ		diacetamide	--	147
acetamide hydrochloride			R		diacetamide	--	147
benzonitrile		fuming H_2SO_4	25		dibenzamide	--	66
aromatic nitriles		1)H_2O 2)H_2SO_4	65		diacylamides *	--	96
acetamide	acetic anhydride		250	6	diacetamide	small	72
acetamide	acetic anhydride		180		diacetamide		55
acetamide	acetic anhydride		R	0.5	diacetamide		72
benzamide	acetic anhydride 1:1 (w/w)	H_2SO_4	140	0.05	N-(acetyl)-benzamide	61	83
benzamide	phenyl acetic anhydride	H_2SO_4	1) fuse 2) 160-180	2)0.017	N-(phenylacetyl)-benzamide	52	83
primary amide	sl. excess acid anhydride or acid chloride		R	0.5-1	N-(acetyl)-propionamide	51	27
primary amide	same		R	0.5-1	dibutyramide	9.3	27
primary amide	same		R	0.5-1	N-(propionyl)-isobutyramide	10.2	27
primary amide	same		R	0.5-1	N-(acetyl)-benzamide	40	27
primary amide	same		R	0.5-1	N-(propionyl)-acetanilide	32	27
N-acetyl-2-naphthyl-amine "addition compound" with s-trinitrobenzene	acetic anhydride		Δ	1	diacet- α -naphthanilide	75	148
β -isomer of above	acetic anhydride		Δ	1	diacet- β -naphthanilide	49	148
amino acid esters	acetic anhydride 10:1	pyridine	R	6.5	N, N-diacylamino acid esters	90	174
amines or amides	acetyl chloride	ether			diacyl amides ***		49
sulfanilide sodium salt	carboxylic acid anhydrides****	dry benzene			acylsulfonylanilides		171
acetamide sodium salt	acetyl chloride	benzene	100		diacetamide **	30-40	158
phenylisocyanate	sl. excess acetic anhydride	dry atmos.	175	11	diacetanilides	72	83
					N,N'-diphenylurea, and acetanilide	trace 6.5	

Table II. Continued

Substrate	Acylating agent	Solvent or catalyst	Temperature °C	Time in hours	Diacetyl derivative	Yield	Reference
phenylisothiocyanate	acetic, propionic, or benzoic anhydrides		175	8-12	diacylanilides		89
phenylisothiocyanate	acetic acid		Δ		diacetanilide		15

*An intermediate imidodiamide was claimed

**An insoluble salt, $(AcNH_2)_2 \cdot HCl$, was also formed. N-Benzyl acetamide would not react with acetyl or benzoyl chlorides under similar conditions. Acetamide and benzoyl chloride gave complex mixtures of acetic anhydride, benzoic acid, acetonitrile, hydrogen chloride, and benzoic anhydride.

***The hydrochlorides and acetyl chlorides of the amines precipitated from the ether while the acetylated compounds remained in solution.

****The anhydrides were reported to act more smoothly than the acid chlorides.

The unusual effect of diortho substitution on the acetylation of anilines was first observed by Remmers in 1874 (128), who found that although acetylation of s-tribromoaniline with acetyl chloride gave the acetanilide, the wholly unexpected diacetanilide resulted if the aniline was heated a short while with acetic anhydride. Remmers also reported that ortho-dinitro-substituted anilines were more difficult to monoacetylate than were ortho-dihalo-substituted anilines.

Bistrzycki and Ulffers in 1894 (15) heated acetanilides with a two-fold excess of acetic anhydride under pressure at 200-205° C for eight to ten hours and reported high yields of diacetanilides. A year later Ulffers and von Janson (163) reported their investigation of acetic anhydride reactions with substituted anilines. These workers concluded that electronegative substituents in the ortho positions (Cl, Br, or NO_2) retarded the formation of the monoacetyl derivatives but that after one acetyl group had been introduced, these ortho substituents facilitated formation of the diacetamido derivative. The monoacetyl derivatives were synthesized by merely mixing the unhindered aniline or an aniline that had only one ortho substituent with cold acetic anhydride. The reaction was usually exothermic if the amine was unhindered and did not proceed at all under these conditions if the amine was diortho-substituted. Diacetanilides could be prepared from the aniline and twice its weight of acetic anhydride if the mixture was heated for two hours at 150-160° C.

Other investigators observed that hindered anilines were difficult, if not impossible, to monoacetylate under ordinary conditions. For example, Paal and Kroschröder (111) in 1896 reported that N-(o-nitrobenzyl)-o-nitroaniline could not be acetylated in contrast to the behavior of the isomeric m- and p-nitroanilines. Paal and Benker later reported the same effect with N-(p-nitrobenzyl)-o-nitroaniline and its nitroaniline isomers (109). Similarly, Paal and Hartel (110) observed that only the hydroxy substituent of N-(o-hydroxybenzyl)-o-nitroaniline was acylated by acetic anhydride in contrast to the m- and p-isomers of nitro aniline, which also formed N-acetyl derivatives.

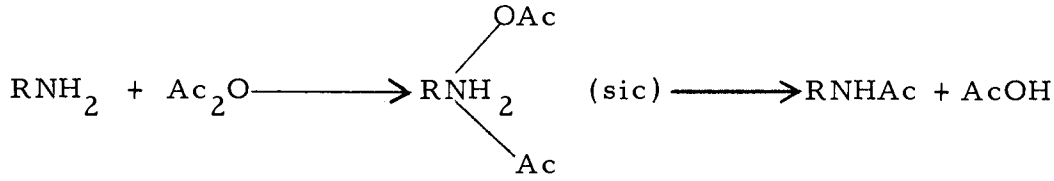
This inhibition to monoacetylation was confirmed by Bischoff in 1897 (145, pp. 428-429) who observed that substituted anilines heated at 100° with acids such as propanoic acid gave yields decreasing from p-, m-, to o-substituted anilides; the ortho nitro group gave the largest inhibition to monoacetylation. Menschutkin (145, pp. 432-433) studied the acetylation of the toluidines at 183° C in the absence of solvent. After 30 minutes the yields were 42.6 percent o-toluide, 58.7 percent m-toluide, and 67.5 percent p-toluide; after ten hours the yields were 65.7, 78.4, and 81.6 percent, respectively.

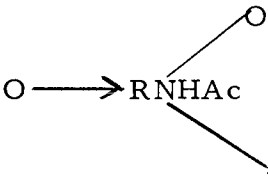
Orton in 1902 (108) reported that diortho-substituted anilines were difficult to monoacetylate with excess acetyl chloride and sodium acetate, expecially if one of the ortho substituents was a nitro

group. In order to effect acetylation with acetyl chloride, the aniline in warm glacial acetic acid was boiled with a slight excess of the reagent, for one-half hour. This procedure was consistently used to obtain monoacetanilides. Diacetanilides were synthesized from the anilines by boiling them for long periods with excess acetic anhydride, ten to one by weight.

In 1901 Sudborough (148) extended the investigation to the acetylations of anilines with electron-donating substituents in one of the ortho positions. His results may be found in Table I. The amides gave from 4 to 13 percent better yields of the diacetyl derivatives than did the free amines. These results indicated that anilines with o-methyl groups gave better yields of diacetanilides than those anilines in which there was no ortho substitution. Sudborough's work along with that of Ulffers and von Janson indicated that an ortho group, regardless of its electronegativity, facilitated diacetylation of anilines. Sudborough was also convinced that his study proved that arylamines were much more readily diacetylated than had been reported previously--even aniline had given a 53 percent yield of diacetanilide.

Sudborough theorized that the process of acetylation of an amine with acetic anhydride involved an "additive compound" between the two which would decompose to yield acetic acid and the monoacetyl derivative:



Then: $RNHAc + Ac_2O \longrightarrow$  $\longrightarrow RNAc_2 + AcOH.$

The ortho substituents, of course, would be expected to retard the reaction. According to Sudborough, the additive compounds would probably vary in stability; and those monoacetyl derivatives whose acetates were the least stable would be the ones most readily diacetylated inasmuch as the diacetyl derivative could form only after the decomposition of the additive compound. In support of this hypothesis was the observation that acetanilide did not form an acetate in recrystallization from glacial acetic acid or from acetic acid-chloroform. Furthermore, p-toluidine treated with an equimolar amount of acetic anhydride in the cold yielded only a monoacetanilide with no evidence of acetate formation.[1]

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[1] Sudborough went on to reason that as substitution of succinic acid facilitates anhydride formation, so might the ortho substituents facilitate removal of acetic acid from the additive compound and thus favor diacetylation. (However, facilitation of anhydride formation has been explained on the basis of steric repulsion of substituents on carbons two and three which forces the carboxyl groups closer together.) Sudborough intended to study this phenomenon in anilines further, but most of his later publications dealt with steric hindrance in the reactions of ortho-substituted acids.

Smith and Orton in 1908 (142) continued the investigation of the acetylation of diortho-substituted anilines by studying the effect of mineral acids. These investigators pointed out that simultaneous acetylation in formation of the diacetylamine was unlikely since the amide is just as readily acetylated. According to Smith and Orton this monoacetyl derivative could always be recognized in the early course of the reaction.

The effect of acid catalysis was dramatic. For example, whereas s-tribromoaniline remained unreacted after treatment with a 70-fold molar excess of acetic anhydride for two weeks at room temperature, monoacetylation was complete within ten minutes under the same conditions if one equivalent concentrated sulfuric acid was added. Without mineral acid monoacetylation proceeded very slowly even at 70 or 100° C and diacetylation occurred at the boiling point. Dilution of the aniline-acetic anhydride mixture with glacial acetic acid insured monoacetylation even in the presence of catalytic amounts of mineral acid. In contrast to the diortho-substituted anilines, those with only one ortho substituent could be monoacetylated quantitatively in minutes at room temperature with a medium excess of acetic anhydride in glacial acetic acid. More surprisingly, mineral acid depressed the reaction rate and yield (see Table I).

Smith and Orton concluded that the amino groups whose diacetylations were acid-catalyzed possessed very little tendency to

combine with acids to form ammonium salts. The speed of acetylation of the more basic anilines was lowered by acids. When the amino group was placed between two electron-withdrawing ortho substituents, its combining power with acids was greatly reduced. The effect could be due, they reasoned, to the electron-withdrawing nature of the substituents and/or to steric hindrance. Therefore, the specific accelerating effect of the acid was not masked by conversion of the amino group into the ammonium salt, thereby removing the acid from the system. Any differences among the effects of various acids might be explained by the hypothesis of mixed anhydride formation (for example: $CH_3CO_2SO_3H$). Orton and Smith also speculated that the acylating species might be an oxonium salt of acetic anhydride.

The speed of acetylation of the diortho-substituted anilines was found to be proportional to the square of the hydrogen ion concentration.

In 1910 Blanksma (16) confirmed that the diacetylation of diortho-substituted anilines or of o-nitroaniline with acetic anhydride was greatly accelerated by mineral acid.

In addition to the effect of ortho substitution on the course of diacetylation, investigators studied other aspects of the chemistry of diacylamines. In 1904 Chattaway (31) reported the thermal

rearrangement of diacetanilides into their corresponding p-acetyl-acetanilides.

Cadwallader and La Rocca (27) were interested in synthesizing diacylamines because of their containing the -CO-NH-CO-group found in several antiepileptic drugs (one such drug is diphenyl hydantoin, the generic name of 5,5-diphenyl-2,4-imidazolidinedione). Diacetanilide and N-methyl-N-acetylphenylacetamide had been reported to have low activities, while N-acetylbenzamide and N-(chloroacetyl) chloroacetamide had exhibited slight antiepileptic activities. Several of their compounds are included in Table II. The yields of the compounds which were derived from branched aliphatic acids were usually less than 12 percent except for the aniline and benzoyl derivatives, whose yields ranged from 30 to 70 percent. N-(acetyl)-isovaleramide, N-(acetyl)-2-phenylbutyramide, and N-(butyryl)-2-phenylbutyramide could not be identified as products from the reaction between the primary amide and the appropriate anhydride at reflux temperatures.

Hurd and Prapas (83) studied the acid-catalyzed synthesis of diacylamines. Some of their results are included in Table II. These workers accepted the proposal of Davidson and Skovronek (46) that the reaction involved initial attack of acyl carbonium ions by the oxygen of the isoimide tautomer of the amide followed by rearrangement to the diacylamine.

Inactivity toward diacetylation often seemed due to the highly electrophilic character of the substituents attached to nitrogen. N-(trifluoroacetyl)-acetanilide was prepared as a syrup from trifluoracetic anhydride and acetanilide as outlined in Table I (22), but trifluoroacetanilide could not be further acylated by trifluoracetic anhydride or by acetic anhydride. Benzanilide also would not yield any isolable product upon treatment with trifluoroacetic anhydride.

The degree of lability of the second acyl group of a diacylamine would seem to vary. The diacetanilide of s-tribromoaniline readily lost one acetyl group when carefully hydrolyzed with sodium hydroxide solution (128). Upon refluxing N-(trifluoroacetyl)acetanilide for 40 minutes in dry methanol, 66 percent acetanilide was recovered (22). Polya and Spotswood (119) refluxed unsymmetrical diacylamines with ethanol on a water bath for two hours and reported significant yields of esters. N-(dichloroacetyl)-dichloroacetamide and N-(dichloroacetyl)-benzamide gave esters in ethanol at lower temperatures.

In 1952 Taschner, Kocor, and Mejer (154) observed that excess diacetamide readily acetylated alcohols in the presence of a small amount of dry hydrogen bromide. They prepared acetates of several sterols in 80 to 93 percent yields. Cholesterol was esterified also by dipropionamide and dibenzamide. Dibenzamide benzoylated primary and secondary alcohols without the use of hydrogen

bromide, but tertiary alcohols were unchanged. Diacetamide and aniline formed acetanilide in 90 percent yield. The reaction conditions usually involved boiling the reactants in toluene.

N-(Trifluoroacetyl)-acetanilide behaved as a trifluoroacetylating agent as observed in its reaction for one hour at 100° with 2,5-dichloroaniline yielding 74 percent acetanilide and 71 percent N-(trifluoroacetyl)-2, 5-dichloroaniline (22).

Dutka, Tudos, and Otvos recently reported that N-alkyldiacetamides exchanged acyl radical with radioactive acetic anhydride, but that N-aryldiacetamides did not (52).

The general solubility characteristics of diacylamines were summarized by Polya and Spotswood (119): soluble in glacial acetic acid, in chloroform, and usually in hot benzene; insoluble in ligroin or low-boiling petroleum ether; some are soluble in ether and can be extracted with it (the ether solution first being treated with dry hydrogen chloride to remove the original amine).

Kraihanzel and Grenda (95) recently reported the preparation of complexes of diacetamide with certain metal (II) perchlorate hydrates. Coordination is believed to occur through the amide oxygens as evidenced by infrared spectroscopy. The colors of the complexes are white or pastel.

2-Diacetamido-4-methylpyrimidine was observed in this laboratory to give no color reaction with a 10 percent solution of ferric

chloride as will 2,4-pentanedione. The only other complexes involving acyclic imides are a 1:1 adduct of N,N-diacetylaniline and tin (II) chloride (50) and bis (dibenzamido) copper (II) (101). Hunter and Reynolds (81) stated that the properties (water-solubility and no true melting point) of these two compounds indicated that they were more likely to be salts rather than coordination compounds. Diacylamines, they concluded, apparently do not possess an imidol tautomer corresponding to the enol form of β-diketones and thus do not give a color test with ferric chloride.

The reaction conditions leading to diacetylation of pyrimidines are listed in Table III. The known diacetamidopyrimidines either have at least one ortho substituent or two ring nitrogens in the ortho position. Every diacetylation required large excesses of acetic anhydride and almost every one was reported to require reflux temperatures. The monoacetylation conditions for many aminopyrimidines may also be found in Table III. Most monoacetylations did not require the high temperatures or the long reaction periods. The high polarity or extremes in pH of the solvents used in recrystallization procedures may also have reduced the likelihood that any diacetylamino derivative could have been isolated.

Brown and Mason (24, p. 327) have found no reports in the literature of any other acyl group capable of the diacylation of an aminopyrimidine. (They have found that most benzoylations reported

Table III. Acetamido derivatives of pyrimidines

Substituent on Pyrimidine					Acylating agent	Temperature °C	Time in hours	Percent Monoacetyl	Percent Diacetyl	Reference
1	2	3	4	5	6						
	NH_2					13(1)	160	2	✓		118
	NH_2					3(1)	120	1	66		25
	NH_2					35(1)	R	2	19	48.6	This lab.
	NH_2		CH_3			35(1)	R	2	10/23	38/67	172/This lab.
	NH_2		OH			13(1)	160	2	✓		118
	NH_2			NO_2		(1), (7)	100	3	80		68
	NH_2			Cl		2.8(1)	Δ	0.5	✓		98
	NH_2			NO_2-PhS		16(1), (7)	R	3	✓		29
	NH_2		CH_3		CH_3	35(1)	R	2	21.2	67	This lab.
	NH_2		CH_3	O	CH_3	1.3(1)	R	0.05	70.8		6
	NH_2		CH_3	CCH_3		8(1)	R	0.03	39		61
	NH_2		CH_3		N⬡	13(1)	160	2	✓		118
	NH_2		NH_2		NH_2	13(1)	160	2	2,4,6 $(NHAc)_3$		118
	NH_2		NH_2		OH	13(1)	160	2	2,4$(NHAc)_2$		118
	NH_2		OH		OH	13(1)	R	2	no isolable product		118
	NH_2		Cl		CH_3	6(1)	R	2	67.3		104
	NH_2		NH_2	CN		15(1)	R	5	72 (2- or 4-NHAc)		79

Table III. Continued

Substituents on Pyrimidine						Acylating agent	Temperature °C	Time in hours	Percent Monoacetyl	Percent Diacetyl	Reference
1	2	3	4	5	6						
	NH_2		NH_2	CN		17(1)	200	4	64 2, 4-(NHAc)		79
	NH_2		NH_2	p-NO_2-Ph	CH_3	16.5(1)	R	0.3	25 (2- and 4-NHAc)		48
	NH_2		CH_3	NH_2	CH_3	1.3(1)	50	--	(5-AcNH)		132
	NH_2		OH	NO_2	CH_3	8(1)	R	1	70		139
			NH_2			3(1)	120	1	77		25
	OH		NH_2					3	/		170
	CH_3O		NH_2			35(1)	R	2	98		This lab.
			NH_2	Ph		11(1), (2)	95	3		48	47
			NH_2	Ph		36(1), (4)	R	2	48		47
			NH_2		NH_2	1(1) dioxane	R	4.5	/		160
			NH_2		CH_3O	6.6(1)	R	0.5	58		114
	CH_3		NH_2	CH_2R*		31(1)		3		17**	168
CH_3	OH		NH_2			(1) pyridine			/		91
	OCH_3		NH_2		OH	2.5(1), 4.2(4)	R	1	95		149
	OCH_3		NH_2		OCH_3	5(1)	R	0.25	78		176
	Cl		NH_2		Cl	38(1)	R	2	70		This lab.
	Cl		NH_2		Cl	15(1)	R	3			99
	$-SCH_3$		NH_2		$N(CH_3)_2$	(1)	100	1	90		9

Table III. Continued

Substituent on Pyrimidine						Acylating agent	Temperature in °C	Time in hours	Percent Monoacetyl	Percent Diacetyl	Reference
1	2	3	4	5	6						
			NH_2	CH_3	OH	4(1)	R	0.5	50		114
		CH_3	NH_2		OH	12(1)	R	0.75	59.5		114
CH_3			NH_2		OH	12(1)	R	0.25	/		114
	SCH_3		NH_2		OCH_3	100(1)	R	0.33	60		114
			NH_2	NH_2 as sulfate	OH	1(1); (4), (7)	R	6	100(5-AcNH)		54
	OH	CH_3	NH_2	CH_3	OH	115(1)	R	3		32.5	117
	OH	CH_3	NH_2	CH_2CH_3	OH	89(1)	R	8		60.1	117
	OH	CH_3	NH_2	n-Pr	OH	62(1)	R	11		65.4	117
	OH	CH_3	NH_2	i-Pr	OH	31(1)	R	7		72.7	117
CH_3	OH	CH_3	NH_2	CH_3	OH	36(1)	R	6		46.8	117
CH_3	OH	CH_3	NH_2	CH_2CH_3	OH	36(1)	R	3		58.2	117
CH_3	OH	CH_3	NH_2	n-Pr/i-R	OH	36(1)	R	8/2.5		66.5/70	117
CH_3	OH		NH_2	CH_3	OH	116(1)	R	2	33.4		117
CH_3	OH	CH_3	NH_2		OH	22(1)	R	1	57.7(5-Ac)		117
CH_3	SCH_3		NH_2		OH	13(1)	R	0.5	43		114
CH_3	SCH_3		NH_2	CH_3	OH	11(1)	R	0.4	0	37.4	114
CH_3			NH_2	CH_3	OH	21(1), Py	R	1		71.4	114
CH_3			NH_2	CH_3	OH	21(1)	R	0.33	43.9		114

Table III. Continued

Substituent on Pyrimidine						Acylating agent	Temperature in °C	Time in hours	Percent Monoacetyl	Percent Diacetyl	Reference
1	2	3	4	5	6						
		CH_3	NH_2	CH_3	OH	10(1)	R	0.5	38.4	26.6	114
CH_3	OH	CH_3	$NHCH_3$		OH	9(1)	R	1	68 & NHAc 5-acetyl)		114
CH_3	OH	CH_3	$N(CH_3)_2$		OH	20(1)	R	3	32.6 5-acetyl		114
CH_3	OH	CH_3	OH		OH	20(1)	R	3	32.6 5-acetyl		114
				NH_2		4(1) benzene	R	2	✓		173
			Cl	NH_2	Cl	11(5)	25	3	✓		157
			Cl	NH_2	Cl	15(3),1(6)	80	0.5		79	157
			Cl	NH_2	Cl	35(1)	R	2		46	This lab.
	CH_3		CH_3	NH_2		(1) py			✓		167
	CH_3		CH_3	NH_2	CH_3	(1) py			✓		167
CH_3	OH	CH_3	CH_3	NH_2	OH	95(1)	R	0.5		67	115
CH_3	OH	CH_3		NH_2	OH	48(1)	80	0.5	47		115
CH_3	OH	CH_3	CH_3	NH_2	OH	95(1)	20	0.5	71		115
CH_3	OH	CH_3	NCH_3Ac	NHAc	OH	57(1)	R	40		100(5-Ac_2N)	57

*R = 4-methyl-5-(2-hydroxyethyl)-4-thiazoline-2-thione

**A-1 The same derivative was prepared by Yoshida & Takasaki in 1959 in almost quantitative yield from the diacetyl derivative of thiothiamine (177)

The number outside of parentheses the molar equivalents of the reactant. R = Reflux py = pyridine

(1) acetic anhydride
(2) acetyl chloride
(3) isopropenyl acetate
(4) glacial acetic acid
(5) trifluoroacetic anhydride
(6) sulfuric acid
(7) sodium acetate

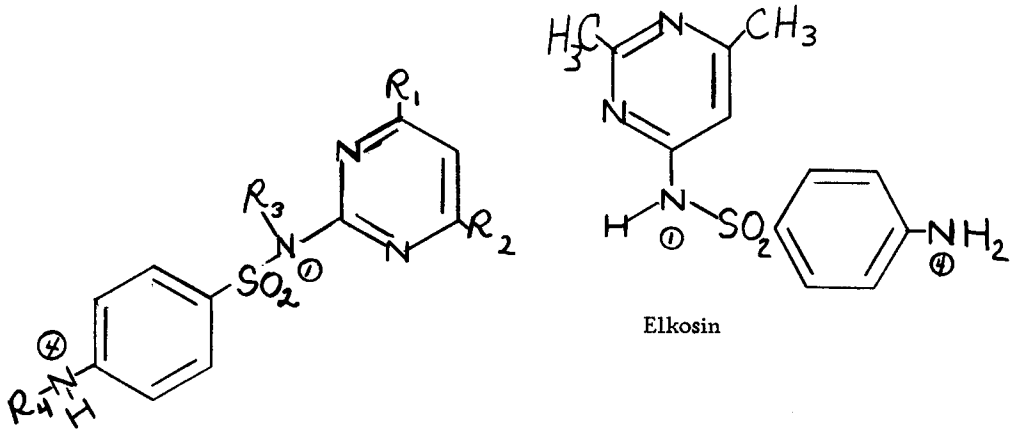
✓ = Reported without yield

involved either Schotten-Baumann conditions with benzoyl chloride or the latter in pyridine.)

Although the 5-amino group was reported by Whittaker (173) to have low nucleophilicity as evinced in its reacting with benzenediazonium chloride only when heated in acetic acid, several workers have cited the preference to acylation exhibited by the 5-amino group. Todd, Bergel, and Karimullah (159) reported that the 5-amino group was selectively acylated with potassium dithioformate in the presence of the 4- and/or 2-amino groups; 2,4-diamino-5-ethylpyrimidine could not be thioformylated. Rose (132) found that the 5-amino group of 2,5-diamino-4,6-dimethylpyrimidine was acylated preferentially by benzoyl chloride. Many other examples could be cited.

A. P. Phillips and J. Mentha in 1954 (118), in assigning the structures of some acetyl derivatives of 2- and 4-aminopyrimidines, demonstrated a parallel between the number of amino groups available and the number of acetyl groups introduced. They believed this to be a strong argument against diacetamido derivatives. Conceding that such compounds are known in the aniline series although not so common, so stable, nor so readily prepared as the monoacetyl derivatives, Phillips and Mentha assumed that the second acetyl group would be so labile as never to allow isolation of diacetamidopyrimidines employing the usual recrystallization procedures. As evidence they cited the report of Tassinari (155; 156) that diacylamino

compounds were easily solvolyzed to the monoacylamino derivative after treatment with ammonia, aniline, alcohol, or acetic acid. Several of their acetylations are reported in Table III. Their products crystallized from the cooling acetic anhydride and were collected, dissolved in 50 milliliters of water, and brought to pH 8 or 9 with dilute ammonium hydroxide, thereby precipitating the monoacetamide, which was usually recrystallized from alcohols or reprecipitated from acid and base. In the light of the current investigation, these procedures seem drastic enough to have destroyed any diacetamidopyrimidine that might have originally formed.



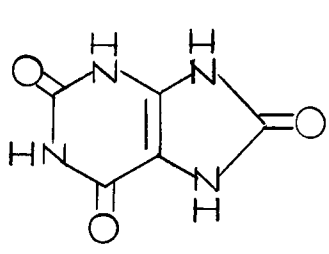
Elkosin

sulfamethazine: $R_1=R_2=CH_3$, $R_3=R_4=H$
sulfadiazine: $R_1=R_2=R_3=R_4=H$
sulfamerazine: $R_1=CH_3$, $R_2=R_3=R_4=H$

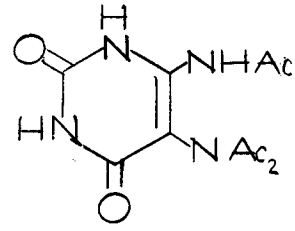
In 1954 Ziegler and Shabica (178) discovered that the N_1 as well as the N_4 of sulfamethazine were acetylated by heating the sulfonamide with an excess of acetic anhydride in pyridine solution.

Only an N_4 monoacetyl derivative resulted, however, when glacial acetic acid replaced pyridine. Sulfadiazine and sulfamerazine gave only N_4 monoacetylation; Elkosin, likewise, gave only an N_4 monoacetyl derivative. The authors proposed that the electron-releasing properties of two C-methyl groups might have aided electrophilic attack by $CH_3\overset{+}{C}{=}O$, but that this effect would be counter balanced in acetic acid by a positively-charged ring nitrogen. They did not attempt to explain what difference the 4-amino position of Elkosin must have from the 2-amino position of sulfamethazine; Elkosin is unsubstituted at position 5.

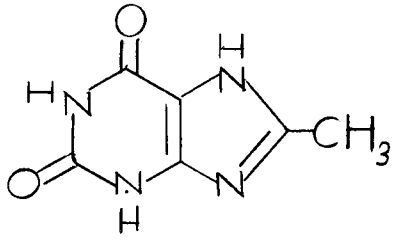
A somewhat unusual preparation of a diacetamidopyrimidine was reported in 1956 by Khmelevskii and Durnitskaya (92; see also 59). 4-Acetamido-5-diacetamidouracil was prepared in 83.5 percent yield by refluxing 106 grams uric acid (0.627 mole) with 5.07 equivalents of acetic anhydride and 100 milliliters of pyridine for five to five and one-half hours. When the product was treated with superheated steam for two hours, 80 percent of the acetyl groups was removed by hydrolysis. The triacetyl derivative could be partially hydrolyzed to 4,5-bis(acetamido) uracil in 86 percent yield by refluxing the former for one-half hour in water. When the triacetyl derivative was refluxed 60 minutes in acetic acid, the 4,5-bis(acetamido) uracil was obtained in 81 percent yield.



uric acid



4-acetamido-5-diacetamidouracil



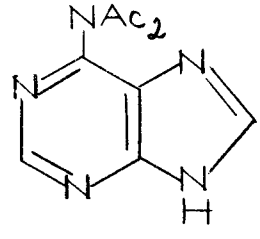
8-methylxanthine

Nearly the same reaction conditions (a seven molar excess of acetic anhydride in pyridine with four and one-half hours' reflux time) were employed by Golovschinskaya in 1959 (58). Rather than the triacetylated product obtained by Khmelevskii and Durnitskaya from uric acid, Golovschinskaya obtained 8-methylxanthine. This product would seem to arise via condensation of a free amino group with the carbonyl of the adjacent N-acetyl group. Golovschinskaya found that these same conditions for acetylation of uric acid when followed by methylation apparently gave the 5-diacetamido-4-acetylmethylamino-1, 3-dimethyluracil previously reported by him (57).

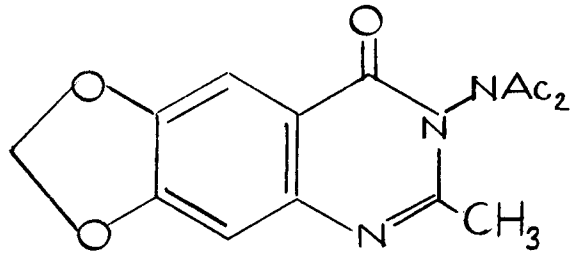
It was mentioned above that Khmelevskii and Durnitskaya had hydrolyzed a 4-diacetamidopyrimidine with superheated steam, boiling water, or boiling acetic acid. Pfleiderer and Strauss removed the second acetyl group of 4-diacetamido-1, 3, 5-trimethyluracil by refluxing 0.0079 mole of the diacetyl compound for eight hours with fifty milliliters of 20 percent acetic acid; 72 percent of the monoacetamido derivative was obtained (117). When stirred with an equivalent

amount of 1.07 normal sodium hydroxide for four hours, 5-diacetamido-4,6-dichloropyrimidine was converted in 44 percent yield to the 5-acetamido derivatative (157). It is somewhat remarkable that this method of preparation of 5-acetamido-4,6-dichloropyrimidine had to be employed. When the corresponding aminopyrimidine was reacted with isopropenyl acetate in the presence of a catalytic amount of sulfuric acid (see Table III), a 79 percent yield of the diacetamidopyrimidine along with recovered aminopyrimidine was obtained! Brown and Mason (24, p. 329) list the commonly used hydrolytic conditions for deacylation of monoacetamidopyrimidines: refluxing with methanolic hydrogen chloride (118), boiling with 6N hydrochloric acid, heating at 50° with aqueous alcoholic hydrochloric acid, heating with concentrated or boiling with dilute sodium hydroxide, and refluxing with sodium methoxide in methanol (91).

There have also been a few reports of diacetylamido derivatives of the pyrimidine moiety of purines and of quinazolines (benzopyrimidines). Birkhofer in 1943 (14) had obtained 6-diacetamidopurine from adenine by heating the latter at the boiling point for several minutes with a 28-fold molar excess of acetic anhydride.

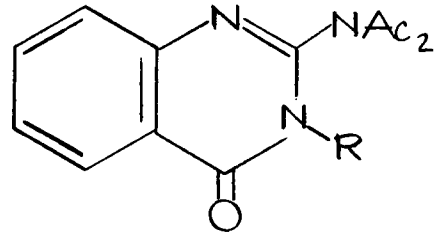


In 1960 Dallacker, Gohlke, and Lipp (43) prepared 2-methyl-3, 3-diacetamido-6, 7-methylenedioxy-8-methoxy-4-quinazolone in 90 percent yield by refluxing the parent amino compound for 30 minutes in an excess of acetic anhydride.



Ac = acetyl

In the same year Grout and Partridge (64) reported their preparation of 2-diacetamido-3-(5-p-toluenesulfonate)-4-quinazolone, 2-diacetamido-3-phenylquinazolone, and 2-diacetamido-3-p-anisyl-4-quinazolone. The acetylation conditions were not given. While monoacetyl derivatives were listed for other aminoquinazolones, none were cited for the precursors of the compounds above.



Here, too, the diacetamido groups are flanked by two ortho groups or one ortho group and a ring nitrogen.

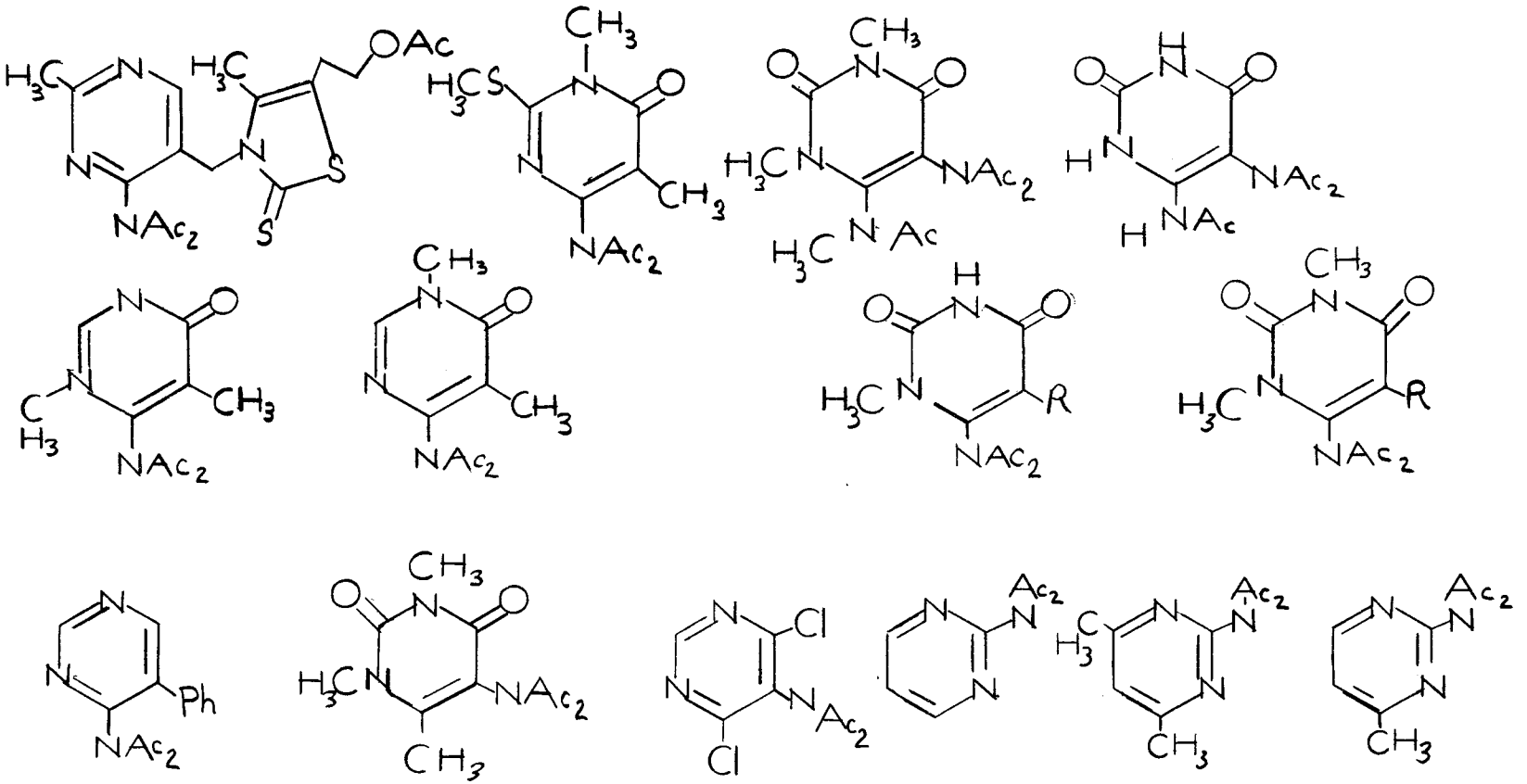


Figure 1. Diacetamidopyrimidines. R = CH_3, C_2H_5, C_3H_7, and i-C_3H_7

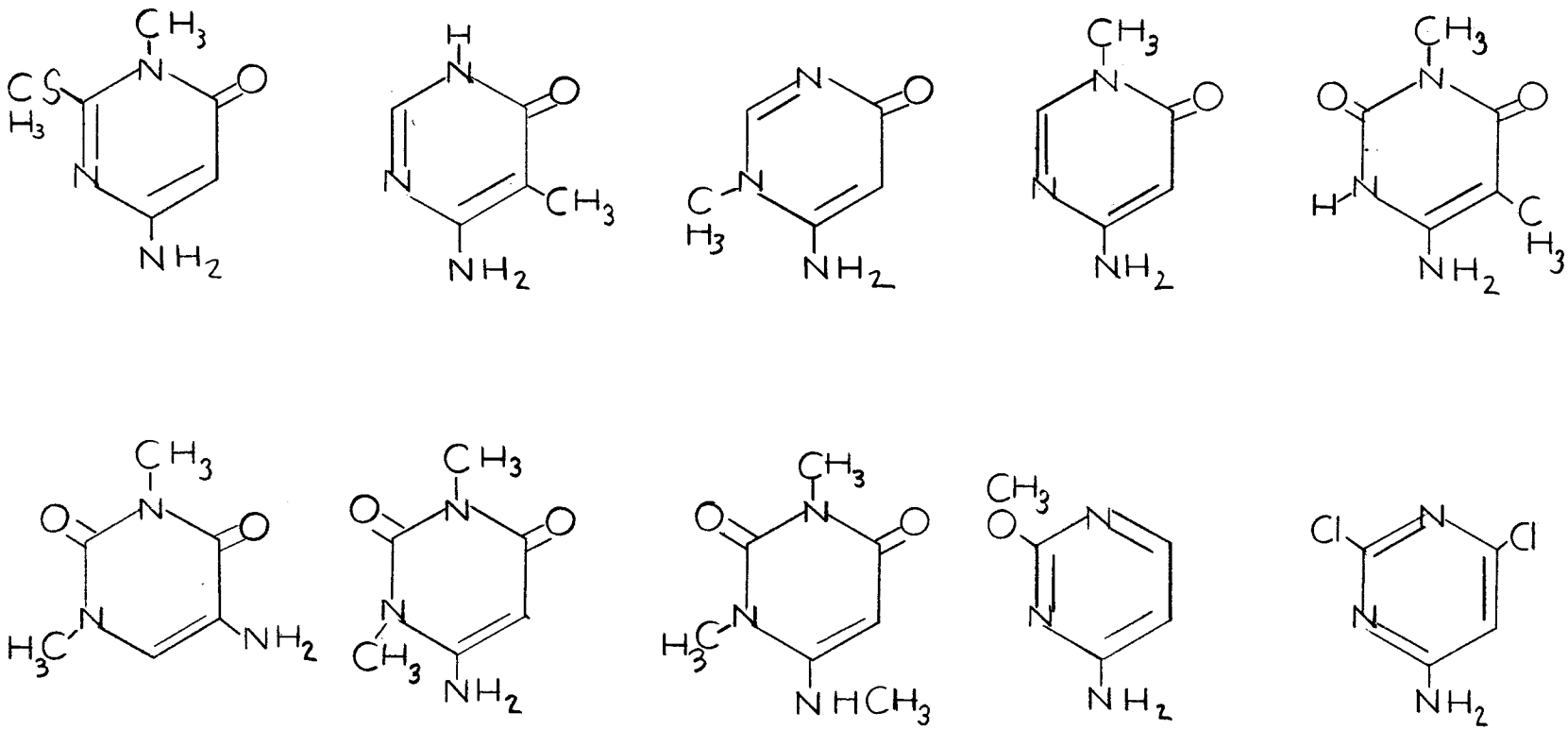


Figure 2. Aminopyrimidines which give only monoacetamidopyrimidines (and/or 5-acyl derivatives for the uracils with the open 5-positions) under extreme acetylation conditions

Many diacetamido derivatives of naphthalene, anthracene, etc., have been described in the literature; it is assumed that the effects observed in the diacetylation of anilines would be similar for these compounds. Moreover a literature search through 1961 revealed nearly 70 heterocyclic diacetamides.

There were 12 compounds in which the diacetamido nitrogen was substituted on the nonheterocyclic ring of the system (for example, 3-diacetamidocarbazole). These compounds, too, might be expected to behave similarly to the anilines. Of the 12 "aniline-type" compounds, nine of the diacetamido groups were flanked by no ortho substituents and three groups were adjacent to only one ortho substituent.

The total of N-heterocyclic diacetamides in which the amide nitrogen was directly attached to a ring having one nitrogen atom was 28. Of these 28, 13 were pyridine and the others were "pyridoaromatics" such as quinoline and acridine. Nine of the compounds possessed amide nitrogens flanked by one ortho substituent; 11 had two substituents ortho to them, three were between the ring N and an ortho substituent; two were adjacent to a ring nitrogen only; and one had neither substituents nor ring nitrogen flanking the amide.

"Pyridine-type" Diacetamides

Number of Compounds	Number of O-substituents
11	2
3	1 + ring N
9	1
2	ring N
1	O

In the pyridine series it was noted by Schickh, Binz, and Schultz in 1936 (136) that one ortho substituent (chloro) greatly facilitated diacetylation of an amino group. Twenty-seven diacetamido compounds had been reported in which the amide nitrogen was substituted on a ring having two or more heteroatoms. The ring types involved were pyrimidine (four in quinazoline and purine); imidazole (five; one in a purine); thiazole (eight); pyrazole (four); triazole (four); isoxazole (one); and furazan (1,2,5-oxadiazole) (one). Of the total 13 imidazole plus thiazole rings, the amide nitrogen was at position 2 in two cases, at position 3 in five instances, and in the remaining six compounds at positions 4 or 5. Two amide nitrogens were at position 2, one at position 4, and the other at position 3 of the pyrimidine rings. There were five ring nitrogen substitutions with diacetamide among the 27.

Diacetamido Heterocyclics (2 or more heteroatoms)

Number of Compounds	Number of ortho-substituents
10	2
13	1 + ring N or S
3	ring N or S
0	1
1	0

It did not seem practical in a work of this scope to investigate further each of these series of heterocyclics so that yields, reaction conditions, and so forth might be tabulated and the compounds which did or did not diacetylate within a series might be compared.

In general diacetylation required reflux temperatures whereas lower temperatures promoted only the monoacetylation. The time requirement for diacetylation varied from a few minutes to several hours; the monoacetylation of a particular compound occurring within a shorter time than its diacetylation. In almost every case acetic anhydride alone or with pyridine or sodium acetate was the acetylating agent. Catalytic amounts of sulfuric acid were reported in a few instances to promote diacetylation. If conclusions may be drawn from the figures cited above, at least one ortho-substituent among the pyridine-type compounds and two (a ring hetero atom may apparently behave as one) among those rings having two or three hetero atoms increases the likelihood of diacetylation.

Table IV. Diacetyl derivatives of amino substituents of all-carbon rings

Formal precursor	Number of ortho-substituents	Reference
3-Aminodibenzofuran	0	138
6-Amino-2-methylchromone	0	127
6-Aminoflavone	0	126
6-Amino-4'-methoxyflavone	0	126
6-Amino-3', 4'-methylenedioxyflavone	0	126
4-Amino-5-oxo-1, 2-dihydrobenz[cd] indole	1	162
N-Benzyl-6-amino-4-nitroindoline	0	93
3-Acetamidocarbazole	0	5
10-Methyl-3-aminophenothiazine	0	137
10-Methyl-3-aminophenoxazine hydrochloride	0	141
10-Acetyl-2-amino-3-acetoxyphenoxazine	1	30
4-Amino-3-methylphthalide	1	169

Table V. Diacetyl derivatives of amino substituents of heterocyclic rings with one nitrogen

Formal precursor	Number of ortho substituents	Reference
3-Amino-4-methylpyridine	1	39; 74
2-Amino-4-ethoxypyridine	1 & ring N	73
3-Amino-5-chloro-4-cyano-3-ethoxymethyl-2-methylpyridine	2	70; 71
3-Amino-4-cyano-3-ethoxymethyl-2-methyl-6-hydroxypyridine	2	70
3-Amino-2, 6-diacetoxy-4-methylpyridine	2	2
2-Amino-3-butylpyridine	1 & ring N	69
3-Amino-2, 6-diacetoxy-5-methylpyridine	1	2
3-Amino-2-chloropyridine	1	136
3-Aminopyridine	1	136
α-Amino-N-methyl anabasine [(2 or 6)-NH_2-3-(2-piperidyl)pyridine]	ring N or 1 & ring N	87
(α'-Amino-N-methyl anabasine gave the α'-dibenzamide derivative)		87
3-Amino-2-hydroxypyridine	1	151
4-Amino-6-methoxyquinoline	1	85

Table V. Continued

Formal precursor	Number of ortho substituents	Reference
4-Amino-2-phenylquinoline	1	7
2-Amino-4-benzyloxyquinoline	ring N	3
3-Amino-4-phenylquinoline	1	107
3-Amino-6, 7-dimethoxyquinoline	0	38
6-Amino-7-chloro-5, 8-quinoline quinone	2	135
3-Amino-4-hydroxyisoquinoline	1 & ring N	84
9-Aminoacridine	2	60
9-Aminotetrahydroacridine	2	113
4-Aminoacridine	1	175
9-Amino-2-chloroacridine	2	175
9-Amino-3-chloroacridine	2	175
9-Amino-4-chloroacridine	2	175
9-Amino-1-methylacridine	2	175
12-Aminoquinindene	2	113

Table VI. Diacetyl derivatives of amino substituents of rings with two or more hetero atoms

Formal precursor	Number of ortho-substituents	Reference
Adenine (6-aminopurine)	1 & ring N	14
2-Amino-3, 4-dihydro-3-phenyl-4-oxoquinazoline	2 ring N's	64
2-Amino-3, 4-dihydro-3-dihydro-(5-p-tosyl)-4-oxoquinazoline	1 & ring N	64
3-Amino-8-methoxy-2-methyl-6, 7-methylenedioxy-4-quinazoline	2 ring N's	43
8-Aminocaffeine	1 & ring N	179
5-Methyl-3-[5-(4-amino)-imidazoyl] 1, 2, 4-oxadiazole	1 & ring N	144
5-Acetylsulfamoyl-4-amino-1-methyl-imidazole	1 & ring N	17
5-Phenylsulfamoyl-4-amino-1-methyl-imidazole	1 & ring N	17
4-Amino-carbamoylimidazole	1 & ring N	144
3-Amino-4-methyl-2-thiothiazole	2	144
2-Amino-4-t-butylthiazole	ring N & S	105
5, 5'-Diamino-4, 4'-diphenyl-2, 2'-dithiazolyl amine	1 & ring S each	12
3-Amino-4-ketothiazolidine-2-thione	1 & ring S	161

Table VI. Continued

Formal precursor	Number of ortho substituents	Reference
3-Amino-4-alkyl-thiazolidine-2-thione	2	134
3-Amino-5-(3-ethyl-2-benzothiazolinyl-idene-ethylidene)-2-thio-thiazolidone	2	150
5-Amino-4-phenyl-2-thiothiazole	1 & ring S	40
3-Amino-4-methyl-4-thiazoline-2-one hydrazone hydrochloride	2	13
3-Amino-4-phenylpyrazole	1 & ring N	4
2-Amino-3, 6-diphenylpyrazine	1 & ring N	106
3-Amino-4-isopropyl-2-methyl-1-phenyl-5-pyrazolone	2	143
4-Amino-5-pentadecyl-2-phenyl-2-pyrazolone	2	125
1-Amino-1, 3, 4-triazole	0	65
4-Amino-5-methyl-1, 2, 4-triazole-3-thione	2	97
4-Amino-3-methyl-5-methylthio-1, 2, 4-triazole	2	97
4-Amino-2, 5-diphenyl-1, 3, 4-triazole	2	62
4-Amino-3-methyl-5-styrylisoxazole	2	122
3-Acetamido-4-phenyl furazan (1, 2, 5-oxadiazole)	1 & ring N	41 42

DISCUSSION

At the inception of this investigation there was no reason to doubt that the diacetamidopyrimidines reported in the literature were, indeed, N,N-diacetyl derivatives. On the basis of these investigations it was judged that high temperatures and large excesses of acetylating agent were necessary to effect diacetylation. It was deemed desirable to study the effects of the position of the amino group on the pyrimidine ring and of other substituents on the ring. It appeared from the literature review that isolation procedures for diacetylamines should not involve protic solvents and extremes in pH since the second acyl group should be very labile in such solutions.

If, as Ziegler and Shabica (178) suggested, the cause for the occurrence or nonoccurrence of diacylation of the same amino group of a pyrimidine were the base strength of that amino group, it might be assumed that the amount of diacetylamino product would decrease in the order 2-amino-4,6-dimethylpyrimidine, basic pK_a = 4.85; 2-amino-4-methylpyrimidine, basic pK_a = 4.15; 2-aminopyrimidine, basic pK_a = 3.54; because of the inductive effect of the 4- and 6-positioned methyl groups (24, pp. 468-472).

In the current study, acetylation of 0.038 mole of 2-amino-4,-6-dimethylpyrimidine with a 35-fold excess of acetic anhydride yielded 21.2 percent 2-acetamido-4,6-dimethylpyrimidine and

67 percent crude 2-diacetamido-4,6-dimethylpyrimidine. The former melted between 118-119° C (lit. m. p. 121°). The latter gave a crop from benzene-petroleum ether that melted between 109-114° and another that melted between 85-95° C, which melted between 102-109° C after one recrystallization. When 2-diacetamido-4,6-dimethylpyrimidine has been purified, preferably by sublimation or by use of dry benzene and reagent grade petroleum ether, it melts between 112-113° C; combination of USP grades of benzene and petroleum ether in the recrystallization caused oiling out, even from cold solutions.

Acetylation of 2-amino-4-methylpyrimidine under conditions identical with those for the previous compound (the acetic anhydride being evaporated in the hood) gave 20.6 percent 2-acetamido-4-methylpyrimidine (m. p. 151-152° C) and 66.9 percent 2-diacetamido-4-methylpyrimidine (m. p. 93-95° C). Another acetylation at five and six-tenths scale produced 23 percent of the mono- and 62.5 percent of the diacetylated derivatives (the acetic anhydride had been evaporated in vacuo at 55° C and some red decomposition material had to be removed from the benzene solution of the crude product). It should be noted that the identical reactions and isolation procedures of 2-amino-4,6-dimethylpyrimidine and 2-amino-4-methylpyrimidine produced almost identical amounts of mono- and diacetylated products.

2-Aminopyrimidine upon acetylation gave the expected lower yield of diacetyl derivative. The yield of 2-acetamidopyrimidine (m. p. 145-145.5° C) was 19 percent and that of 2-diacetamidopyrimidine (m. p. about 75°) was 48.6 percent.

Negative results with the iodoform test ruled out the possibility that the diacetyl derivatives were either 4-acetylmethyl or 5-acetyl acetamidopyrimidines.

The infrared absorption spectra of the diacetylamino derivatives possessed no absorption in the N-H stretching region. Acyclic imides possess two carbonyl stretching absorptions at around 5.80 microns and about 5.85 microns, which the compounds in question also exhibited.

Whitlock et al. (172) support the diacetylamino structure for the diacetyl derivative of 2-amino-4-methylpyrimidine with the nuclear magnetic resonance "absorptions (measured in deuterium oxide) at τ = 7.77, 7.45, 5.39 (HOD), 2.50 (doublet, J = 5-6 c. p. s.) and 1.28 (doublet, J = 5-6 c. p. s.) or relative area excluding the HOD line) 6:3:1:1." Furthermore, its isomer, 2-acetamido-5-acetyl-4-methylpyrimidine (61) was known and has a much higher melting point.

The fact that the diacetyl compounds are so readily soluble in benzene (as are many derivatives of diacetamide) should preclude their being acetate salts. Moreover, the diacetylamino structures

are supported by their very much lower melting points compared with those of the starting amino compounds or of the monoacetylamino derivatives, which still have opportunities for hydrogen bonding involving nitrogen.

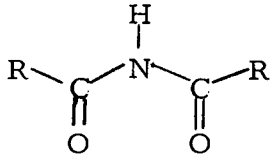
Diacetylamino compounds, being acyclic imides, form hydroxamic acids when treated in the cold with previously mixed methanolic hydroxylamine hydrochloride and methanolic potassium hydroxide. These hydroxamic acids give red to purple complexes when treated with ferric chloride solution. Primary amides must be heated with the hydroxylamine to give the reaction (45). The diacetamido compounds mentioned above give a bright red solution in this test, whereas the amino- and acetamido compounds give the expected precipitate of ferric hydroxide (or the same yellow color if the ferric chloride solution is acidic).

Whitlock et al. (172), regarding their fractional recrystallization of the mono- and diacetylamino derivatives of 2-amino-4-methylpyrimidine from benzene-petroleum ether (b. p. 60-68° C), reported that the first crop (m. p. 147-150° C) gave one spot (R_f = 0.7) on a thin layer chromatogram of silica gel G using 1:4 methanol-chloroform with iodine vapor as indicator, but that the second (m. p. 95-104° C) and third (m. p. 93-128° C) crops and the residue separated into two spots, R_f = 0.7 and 0.8. In this laboratory it has been observed that there is a vast difference in solubility between the two derivatives.

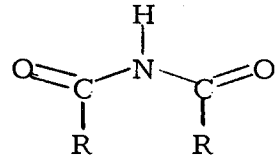
in benzene-petroleum ether (b. p. 30-60° C), 1:1; it seemed puzzling that the second crop, which has been observed to come out of solution only after a great deal of the solvent has been evaporated, should have revealed two components by thin layer chromatography. (The first "crop" is 2-acetamido-4-methylpyrimidine; the second contains the diacetyl derivative.) It was observed in this laboratory that even the purified diacetamido compounds, whose elemental analyses were unequivocal, whose melting points were fairly sharp, and whose ultraviolet and infrared spectra revealed no presence of starting materials nor of monoacetyl derivatives, would separate into two spots of approximately the same size and intensity. One spot would correspond to the monoacetyl derivative, yet both, when scraped from the plate and dissolved in methanol, would have the ultraviolet absorption spectrum of the monoacetyl derivative. The details of this behavior are discussed at length on pages 61-63. On standing from three-fourths to two hours in ethanol, methanol, or 0. 1 N hydrochloric acid solution, 2-diacetamido-4-methylpyrimidine exhibited the ultraviolet spectrum of the monoacetamido compound. It must be concluded that the diacetamido compound was obviously unstable in such media.

In the current investigation the melting point of the purified 2-diacetamido-4-methylpyrimidine was always significantly lower than that reported (94-95° rather than 101. 5-103. 5° C). Diacetamide

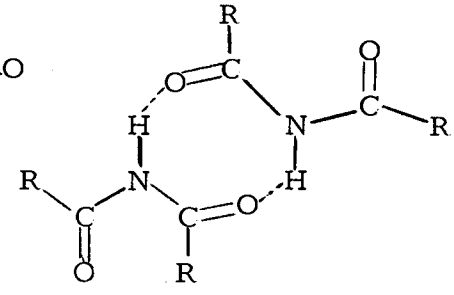
is known to exist in the crystalline state in two modifications (121-2, 3, 4), each with a distinct melting point and infrared spectrum: the trans-trans form is metastable and slowly changes to the cis-trans form in the solid state or changes immediately when dissolved in organic solvents. All higher diacylamines known exist apparently in the trans-trans form. (The cis-trans form of diacetamide exists as a dimer.) There was, however, no significant difference between the infrared amide bands reported for 2-diacetamido-4-methylpyrimidine and for those of the compound prepared in this laboratory.



trans-trans



cis-cis



trans-cis

Acetylation of 2-acetamido-4-methylpyrimidine with a 35-fold excess of refluxing acetic anhydride for two hours afforded 11.5 percent recovery of the starting material and 71 percent of fairly pure 2-diacetamido-4-methylpyrimidine. It would appear that there is very little advantage in acetylation of the amide rather than the amine since the same separation problems are involved. The slightly enhanced yield of diacetamido product obtained in acetylation of the amide rather than the amine would indicate that the amide is an

intermediate in the pathway of the diacetylation.

Catalytic amounts of mineral acid had been reported to facilitate diacetylation of anilines. When a 0.1 molecular proportion of sulfuric acid was used in the acetylation of 2-amino-4-methylpyrimidine under the usual two-hour reflux, greater decomposition occurred as evidenced by a dark red color compared with the usual straw color of the reaction mixture. Some benzene-insoluble sticky, brown residue was also obtained. The yield of diacetylamino derivative was 63 percent while that of the monoacetyl was about 10 percent.

Use of a drop of acetyl chloride as catalyst in the usual acetylation procedure of 2-amino-4-methylpyrimidine involved an inadvertent pyrolysis while vacuum-distilling the acetic anhydride. After the use of charcoal approximately 17 percent of the monoacetyl- and 56 percent of the diacetylpyrimidine could still be recovered. It would appear that acid catalysis at reflux temperature did not facilitate diacetylation.

That diacetylation occurs, when shorter reflux times and much smaller excesses of acetic anhydride are employed, but is not observed because of the lability of the second acetyl group during isolation procedures was disproved for two compounds. Acetylation of 2-aminopyrimidine after the method of Brown and Short (25) (reflux for one hour with a three and two-tenths molar excess of acetic anhydride) gave no imide detectable by Davidson's qualitative test.

Acetylation of ten grams of 2-amino-4, 6-dimethylpyrimidine under the conditions (reflux three minutes with a one and three-tenths molar excess of acetic anhydride) of Asplin, Boyland, Sargent, and Wolf (6) gave 9. 62 grams crude product. Of this, 9. 2 grams melted between 117-123° C (the monoacetyl derivative melts at 123° C). Thin layer chromatography revealed the presence of starting material in the crude product. Davidson's qualitative test for acyclic imide was negative.

Reactions of 5-amino-4, 6-dichloropyrimidine (0. 005-0. 0127 mole) under two hours' reflux with a 35-fold excess of acetic anhydride gave 12 to 29 percent recovery of the crude starting material, melting in the range between 110-140° (after recrystallization 143-144. 5°) and 45-47 percent crude 5-diacetamido-4, 6-dichloropyrimidine melting between 57 and 90° C (70-72° when pure). After removal of the acetic anhydride either by rotary evaporation with a warm water bath or by ordinary evaporation in a hood, the crude product was dissolved in hot benzene and petroleum ether added. Subsequent evaporation of the solvent gave various crops. An analytical sample of the diacetyl derivative (m. p. 70-71. 5° C) was obtained from the last crop. There was not sufficient difference in solubility between the free amine and its diacetyl derivative to effect a clean separation.

In the current investigation acetylations of 4-amino-2-methoxy-

pyrimidine and of 6-amino-2,4-dichloropyrimidine according to the conditions of Whitlock et al. (172) and isolated via their procedure when practical, yielded only the 4-monoacetamido derivatives. Similar acetylations of 2-amino-4,6-dichloro-; 2-amino-4,6-dihydroxy-; and 6-amino-2,4-dihydroxypyrimidines yielded products extremely difficult to isolate if acids and bases were to be avoided in order to prevent hydrolysis of any diacetylamino product.

The acetylation of 1.77 grams (0.014 mole) 4-amino-2-methoxypyrimidine (m.p. 171-172°) produced 0.4 grams of crystals from the cooled acetic anhydride; m.p. 167-170°. The acetic anhydride was evaporated in an open vessel in a hood, leaving 1.88 grams residue insoluble in either hot benzene or hot benzene-petroleum ether, 2:1 or 1:1. Crops from these solvents or from reagent grade ethyl acetate melted at 157-161°. Thin layer chromatography revealed that all of these crops were the same substance, R_f = 0.78-0.80, and not the starting material, R_f = 0.23 (Silica gal G plates developed with butanol-acetic acid-water, 4:1:5, top layer). The sublimed product melted at 165-166° C and turned out to be the monoacetyl derivative. The unsublimed residue, weighing about 50 milligrams, melted at 260° and turned black. On a different set of silica gel plates this residue gave one spot, R_f = 0.35, while the sublimed material gave a spot with R_f = 0.92. Hilbert (75) reported the rearrangement of 4-amino-2-methoxypyrimidine to 3-methylcytosine by

heating the former for five hours at 180°. In that case the yield was only about 5 percent; the rearrangement also occurred, in 75 percent yield, when 4-amino-2-methoxypyrimidine had been refluxed for three hours in 95 percent ethanol. Kenner et al. (91) report the ultraviolet absorptions for N-acetyl-3-methylcytosine as λ_{max}^{EtOH} 215, 246-247, 299-300, which closely correspond to those for the unsublimed material: $\lambda_{max}^{EtOH-H_2O}$ 212, 247, 285, 299-300. Since the sublimation was performed at 0.05 mm Hg with a water-bath temperature of approximately 60° for nearly 48 hours, it seemed probable that the 4-acetamido-2-methoxypyrimidine had rearranged to the extent of about 3 percent to N-acetyl 3-methylcytosine or that the latter had formed in the acetylation but had not been detected by thin layer chromatography.

The acetylation of 0.34 gram (0.00207 mole) 2,4-dichloro-6-aminopyrimidine yielded 0.38 gram crude product, some heat having been employed in the evaporation of the acetic anhydride. Following solution in hot benzene, filtration and dilution with petroleum ether and then slow evaporation, the product gave three crops of crystals melting from 182-186°, whose total weight of 0.30 gram represented a 70 percent yield of 6-acetamido-2,4-dichloropyrimidine (99; m.p. 184-185°). The first crop, 0.12 gram (m.p. 184-186°) was used for the elemental analyses.

A similar acetylation of 2-amino-4,6-dichloropyrimidine, for

which no monoacetylamino derivative has ever been reported in the literature, yielded primarily starting material, as judged by the ultraviolet and infrared analyses of the crops and thin layer chromatography (R_f = 0.9). Roughly a third by weight of the product revealed two spots (R_f's = 0.9 and 0.8) of similar size and intensity by thin layer chromatography. Sublimation and recrystallization from ethanol failed to purify this fraction. It had ultraviolet absorption peaks at 206, 239-240, and 275-280 mμ while the starting material and the majority of the recovered material had peaks at 205, 234-236, and 298 mμ. The infrared spectrum of this material was scarcely different from that of the 2-amino-4, 6-dichloropyrimidine.

Phillips and Mentha (118) tried to acetylate 2-amino-4, 6-dihydroxypyrimidine with a 13.3 molar excess of acetic anhydride refluxed at 160° for two hours. They obtained insoluble material slightly different from the starting material; its C and H values were closer to those of starting material than those for a monoacetyl product. It could not be purified by dissolving in acid and precipitation by base or by the reverse process nor was it soluble to any extent in a variety of solvents. Under the acetylation conditions used commonly in the current investigation, a crude product of nearly 10 grams was obtained from 7.6 grams of 2-amino-4, 6-dihydroxypyrimidine. The crude product in ethanol had peaks in the ultraviolet at 206, 233, and 286 mμ, while in water it had peaks at approximately

215, 235, 260, and 280 mμ. In ethanol the starting material exhibits one peak in the near ultraviolet at 262 mμ. The crude product gave one spot, R_f = 0.55 on a silica gal G thin layer plate and two spots, R_f's = 0.83 and 0.62, on an alumina plate; the starting material did not move. The developing solvent system was the usual mixture of butanol-acetic acid-water. Attempted recrystallization from two liters hot methanol-water; 1:1, was unsuccessful. Material from the attempted recrystallization gave one spot, R_f = 0.65 on a different plate. Its ultraviolet spectra in water had four peaks, the first three of which were of approximately equal intensity and the last much more intense: 266, 256, 240, and 210 mμ.

It was apparent that a reaction had occurred in hot acetic anhydride but it was not possible to isolate the pure acylated products.

Phillips and Mentha also attempted the acetylation of 6-amino-2, 4-dihydroxypyrimidine and reported that no acetylation produce could be isolated (118). Reprecipitating the product several times from dilute acid caused all of the starting material to be recovered. The crude product of the acetylation of the same pyrimidine attempted in this laboratory had absorption peaks in the ultraviolet in ethanol of λ_{max} 266-268 mμ (with a shoulder at approximately 278 mμ) and λ_{max} 206 mμ. The starting material in water has λ_{max} at 264 mμ with no shoulder nor other peaks. Alumina thin layer chromatography of the crude product gave only one spot, R_f = 0.64, while the

starting material on the same plate had one spot at R_f = 0.55. Recrystallization was not successful as judged by inability to isolate pure products from boiling dimethylformamide (5.3 g./ml.), methanol, or methanol-water.

Comparisons among those 4- and 5-aminopyrimidines known to have diacetylated with those that did not indicate that steric hindrance of the amino group is very probably a factor. All of the reported 5-diacetamidopyrimidines have been substituted in both positions ortho to the diacetamido group; so have all of the 4-diacetamidouracils (all reported were methyl substituted at position three). However, not all of the 4-diacetamido-6-oxo-dihydropyrimidines required 3-methyl groups and other 4-diacetamido compounds have been formed in which there was only the one ortho substituent at position 5. Classic examples of steric hindrance to hydrolysis are those aromatic amides which are substituted in one or both ortho positions to the amide group. Possibly one of the reasons why these particular diacetamidopyrimidines can be isolated is that they are not very readily hydrolyzed.

On the other hand, there are cases in the compounds reported by Pfleiderer and coworkers where steric factors seem identical for two compounds yet only one diacetylates. Electronic factors are probably involved as in the findings of Ziegler and Shabica (178) or in the current study wherein 2-aminopyrimidine did not yield so much

diacetamido product as did the corresponding compounds with methyl substituents at positions 4 and 6. The inductive and resonance effects of the 4- and 6-methyls would enhance the negativity of the ring nitrogens to which the former are ortho substituted. The nucleophilicity of the 2-amino group should be enhanced; possibly solvolysis of the 2-diacetamidopyrimidines could be retarded by an electronic repulsion between the free electron pairs of the ring nitrogens and a potential nucleophilic agent. Electron-withdrawing substituents in the 2, 4, and 6 positions, such as chloro or keto groups, have the effect of putting a partial positive charge on the ring nitrogens. Since protonation occurs on the ring nitrogens because of resonance stabilization to the cation afforded by 2- and 4-amino groups, such electron-withdrawing substituents do lower the basic pKa's of the parent aminopyrimidines. For example, the basic pKa of 4-aminopyrimidine is 5.71, while that of 4-amino-6-chloropyrimidine is 2.10 (24, p. 469). This may explain some of the difficulties encountered in the acetylations of 2-amino-4, 6-dichloropyrimidine, of 6-amino-2, 4-dihydroxypyrimidine, and of 2-amino-4, 6-dihydroxypyrimidine and why only monoacetylation was obtained with 6-amino-2, 4-dichloropyrimidine and with 4-amino-2-methoxypyrimidine (a methoxy group positioned meta to the amino group could reduce its nucleophilicity by its electron-withdrawing field effect).

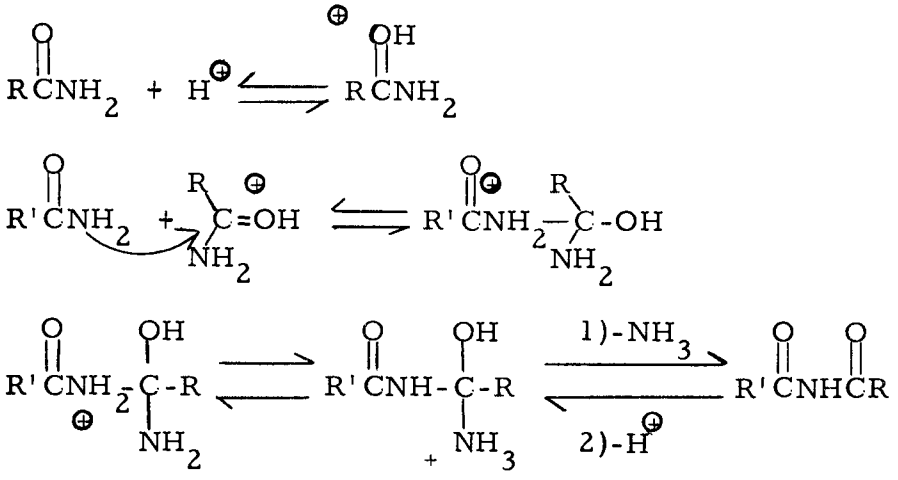
In summary, the diacetylation of an aminopyrimidine if

properly substituted can be effected with large excesses of acetic anhydride at high temperatures. A 2-aminopyrimidine may be unsubstituted or be substituted with electron-donating groups. Of the acetylations of 5-aminopyrimidines reported only diortho substituted 5-aminopyrimidines have been observed to diacetylate. 4-Aminopyrimidines have been observed to diacetylate if the ring is substituted at the 5 position and, as an empirical rule, if the ring nitrogen at position 3 cannot protonate by tautomerization.

Sidgwick (140, p. 140-145) has stated that, "The effect of substitution is solely on the energy of activation" in the benzoylations of anilines with benzoyl chloride. Possibly part of the explanation as to why a diortho substituted aromatic amine is difficult to monoacetylate and yet, when once the primary amide has formed, very readily diacetylates could lie in the hindered amine's having a high energy of activation which is only slightly lower than (or possibly, equal to) the energy of activation for diacetylation. Once sufficient energy has been provided for monoacetylation, the amide would not be too far from possessing the necessary energy to acetylate once more. In the case of the acetylation of 5-amino-4, 6-dichloropyrimidine, only starting amine and 5-diacetamido-4, 6-dichloropyrimidine were isolated. Possibly the rate of diacetylation was equal to or faster than the rate of monoacetylation, which would account for this behavior.

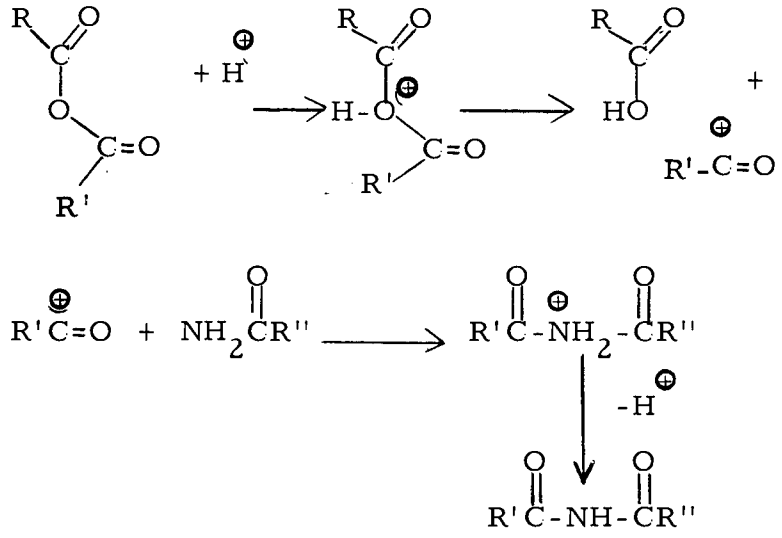
Polya and Spotswood (119) have shed some light on the acid

catalyzed syntheses of diacylamines from amides. As Strecker (147) had shown, heating amides in the presence of mineral acid yielded diacylamines and ammonia. A reasonable mechanism for such a transformation would be (1):

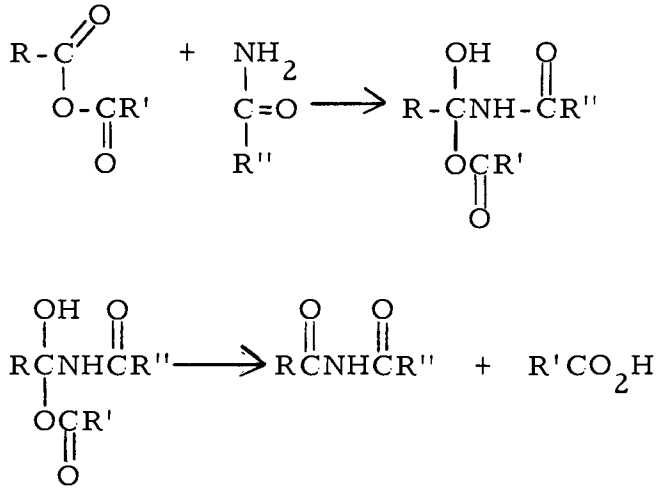


(In these mechanisms $R\overset{O}{\overset{\|}{C}}OH$ will be a stronger acid than $R'\overset{O}{\overset{\|}{C}}OH$.) Such a mechanism would explain the high percentage where possible of unsymmetrical diacylamine formed. For example a solution of acetamide and dichloroacetamide with a trace of hydrogen chloride gave 44 percent unsymmetrical imide and negligible traces of symmetrical imides. Benzamide and dichloroacetamide gave 48.5 percent unsymmetrical imides.

In the presence of acid and anhydride, the following mechanism (2a) is probably operative:



It has been suggested that the following pathway (2b) may be traversed in absence of acid.



Alcoholysis to form the amide and an ester would be likely to follow such a pathway in reverse.

If mechanism (2a) is followed, the acyl group from the weaker acid of an unsymmetrical anhydride would be more likely to add to the amide, whereas the reaction of the acyl group of the stronger acid

with the amide would favor pathway (2b). According to the data of Polya and Spotswood below for acylation of amides with chloroacetyl acetic anhydride, both mechanisms are apparently operable with or without acid.

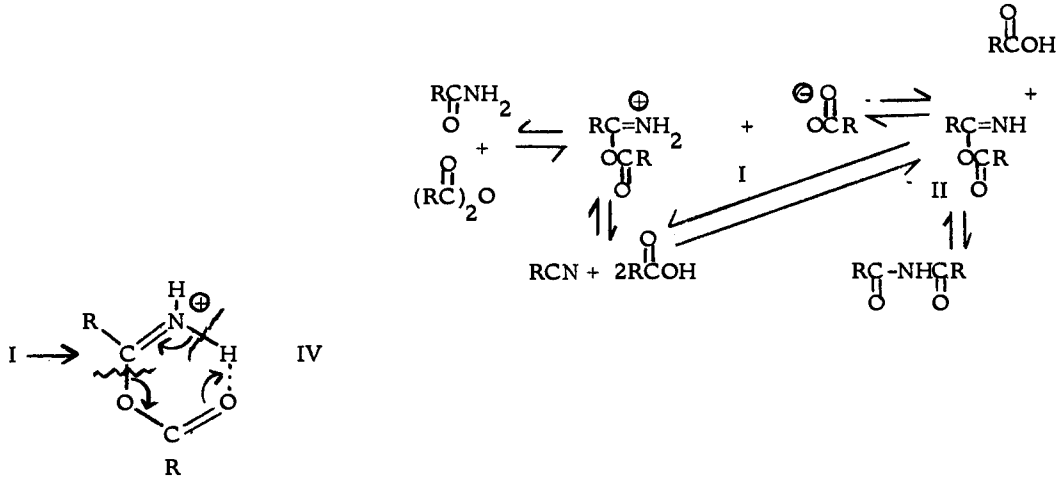
Table VII. Acylation of amides with chloroacetyl acetic anhydride

Amide	Product	Yield in presence of 0.1-1% HCl	Path indicated	Yield in absence of HCl
CH_3CNH_2	$(CH_3C)_2NH$	19%	2a	9%
	$(ClCH_2C)_2NH$	13%	2b	12%
$CH_3CH_2CNH_2$	$CH_3CNCCEt$ (H)	20%	2a	6%
	$ClCH_2CN\text{-}CCEt$ (H)	15%	2b	12%
$PhCNH_2$	$CH_3C\text{-}N\text{-}CPh$ (H)	16%	2a	8%
	$ClCH_2C\text{-}N\text{-}CPh$ (H)	9%	2b	10%

Davidson and Skovronek (46) have proposed a mechanism for the acylation of acid amides with the corresponding acid anhydride. The proposal satisfactorily explains the occasional production of nitriles rather than imides. It may also be extended to explain reports

that small amounts of acid chloride increased the yield of imide (119) or others in which the yield of imide was reduced (51). The proposal explains why pyrolyses of imides may yield nitrile and acid (82) or amide and anhydride (46). As will be shown, the pathway that leads to nitrile may just lead back to starting amide with N-substituted amides and anhydrides.

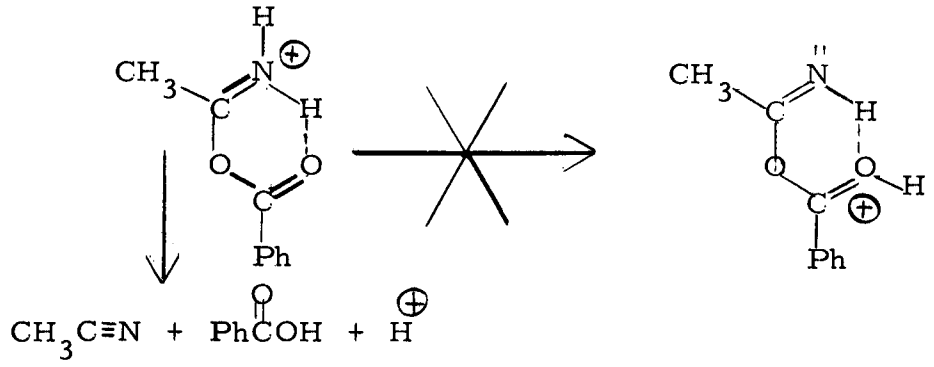
The primary attack of an electrophilic species upon an amide would be expected to occur at the amide oxygen. The amide oxygen of acetamide is a million times more basic than the amide nitrogen (112, pp. 207-208). The product would be the isomidinium carboxylate(I), which may either decompose into nitrile and acid or rearrange into imide. Davidson and Skovronek state that the decomposition should occur much faster than the uncatalyzed rearrangement. Since the decomposition involves a six-center intermediate (IV), acid catalysis should not affect its rate; but it should be expected to affect the intramolecular acylation, that is, the rearrangement to imide.



(That there is equilibrium among these reactions was demonstrated in the system of benzamide--benzoic anhydride, which attains equilibrium after refluxing [200° C] for one hour with 2.7 percent imide and 90 percent nitrile. Equilibrium was also attainable after one hour's reflux time with benzonitrile and twice as much benzoic acid.)

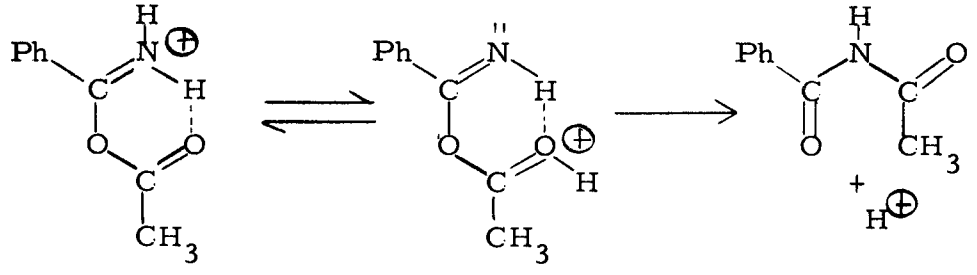
Under ordinary conditions enough of the intermediate base II should be present to account for formation of imide at a moderate rate. Very small amounts (0.002-0.01 equivalents) of acid would probably be insufficient to catalyze the rearrangement, but might suppress II. Under such conditions, the yield of nitrile is indeed increased while that of the imide is decreased. Strong acid may activate the carbonyl group of the isoimidinium ion (in I), which would more than compensate for decreased concentration of II.

An intermediate like IV would explain why acetamide-benzoyl chloride produces acetonitrile and no imide, while benzamide-acetyl chloride gives no nitrile but does give a high yield of imide. In the first system, the opposed inductive effects of methyl and phenyl in the isoimidinium ion inhibit proton migration from the nitrogen to the carbonyl oxygen so that the six-center decomposition to nitrile is the predominant one.



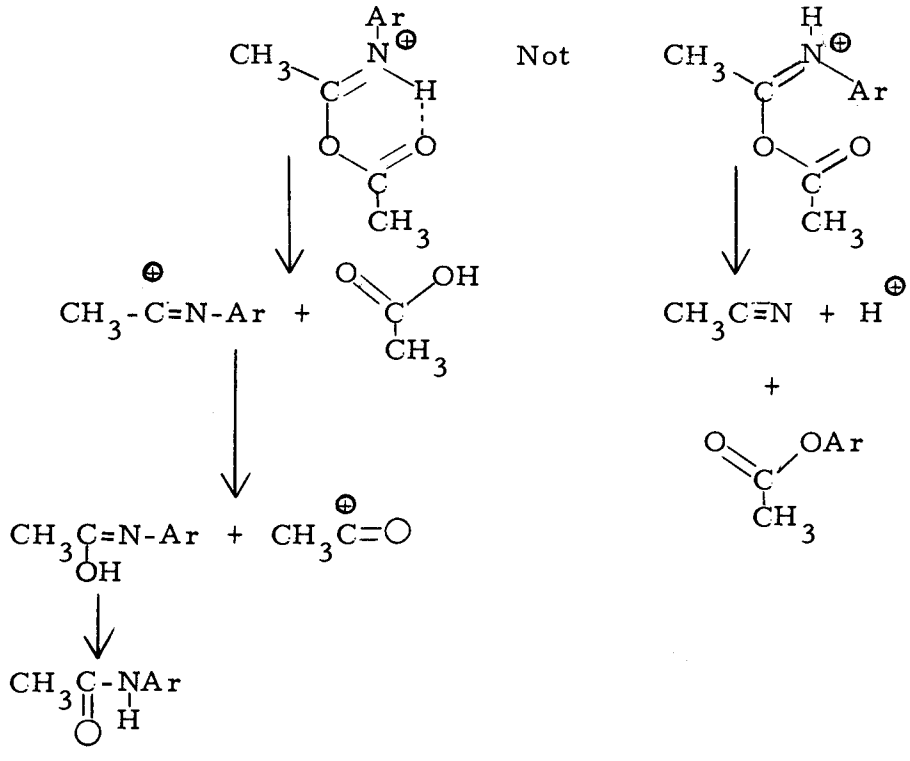
Benzoyl chloride-acetamide system

In the second system, the inductive effects of the interchanged methyl and phenyl groups promote proton transfer, yielding the intermediate which leads to imide.

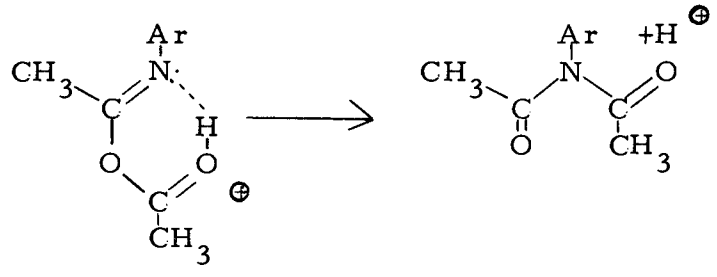


Acetyl chloride-benzamide system

If this mechanism is tenable for the acylation of N-aryl substituted amides, the products to be expected are the imide (still favored by strong acid) or the starting amide. For example:



When the proton is transferred to the carbonyl oxygen, a new six-center intermediate is possible:

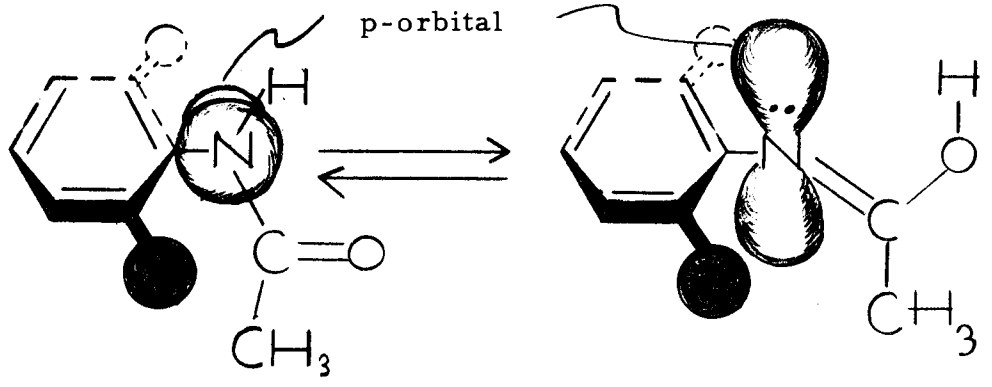


The following explanation for the behavior of diorthosubstituted aromatic (including the heterocyclic) amines can be offered.

If the amino group of a diortho-substituted aromatic amine lies relative to the ring so that the nitrogen's free pair of electrons would be relatively unencumbered for nucleophilic attack on an anhydride

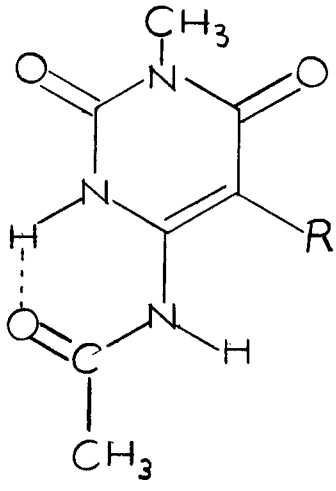
or acylium ion, these pi electrons are then in a position to be delocalized into the aromatic system thereby reducing the nucleophilicity of the nitrogen. If resonance is avoided by rotating the pi cloud at right angles to the ring, steric hindrance to nucleophilic attack due to the ortho groups or electronic repulsions due to the pi cloud of ring hetero atoms comes into play. The extremes of excess anhydride and reflux temperatures will finally effect acylation in the aniline or aminopyrimidine series. Possibly the rate enhancement due to mineral acid involves reduction in size of the electrophilic species from anhydride to acylium ion or to  . Once monoacylation is effected under these extreme conditions, formation of the imide is very fast. An ordinary aromatic amide would have little tendency to adopt the imidol form because the pi electrons of the nitrogen can resonate with the ring. Ortho substituents would favor the localization of the nitrogen's pi cloud at right angles to the ring (steric interaction between the acyl group and the ortho-substituents would be worse than that between the latter and the pi electrons of the amino nitrogen). Now the amide may tautomerize to the imidol, which may now be acylated. Since nucleophilicity of the free amine is obviously retarded by steric hindrance, the primary nucleophilic attack by the imidol oxygen is especially attractive in these cases. The steric hindrance of the ortho substituents would restrict the conformations of the isoimidinium ion to the desired intermediate for imide

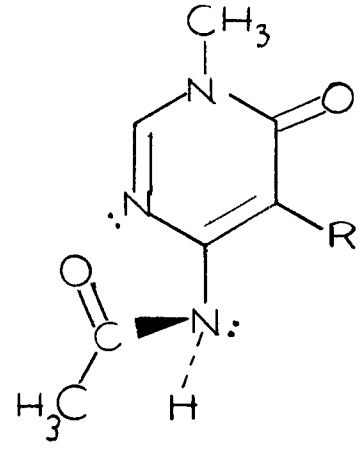
formation. Once the imide has been formed, ortho groups should hinder solvolysis of the imide to the amide and should enhance the former's isolability.



The facilitating effect of ring heteroatoms ortho to the amine in diacetylation might be explained as follows: In 2-monoacetamido-pyrimidines, where there are no ortho substituents, and in 4-acetamido-1-methyl-5-substituted-6-oxo-pyrimidines, wherein there is no possibility for tautomerization as there would be either in the presence of a 2-oxo group or in the absence of the 1-methyl substituent, the N-acetyl group is not hindered from lying in the plane of the ring (thereby adding resonance stabilization to the compound) except by whatever electronic repulsion is operative between the free electrons of the hetero atom and those of the carbonyl oxygen. This repulsion might be sufficient to cause the acyl group to lie above or below the plane of the ring; this facilitates its access to the second acetyl group. On the other hand, if the ring nitrogen can bear a

hydrogen, the tendency of the acetyl group to lie in the plane of the ring could be enhanced by hydrogen bonding. The compound would then be rendered resistant to diacetylation.





The elemental analyses of the diacetamidopyrimidines were in good agreement with the calculated values. The similar ultraviolet spectra of 2-amino, - 2-amino-4-methyl, -and 2-amino-4, 6-dimethylpyrimidine were distinctly different from the spectra of their corresponding 2-amino- or 2-acetamido compounds. Yet, in several instances a diacetamido compound would give two spots, one corresponding reasonably well with that of the monoacetamidopyrimidine, the other different from it or that of the starting material. Apparently a cleavage had occurred on the activated plate during development.

The spots were scraped from the silica gel plate developed by dioxane and water, dissolved in a little methanol, and their ultraviolet spectra observed. The single spots from the 2-amino-4-methyl

and 2-monoacetamido-4-methylpyrimidine gave their characteristic spectra, but both spots from 2-diacetamido-4-methylpyrimidine possessed spectra very similar to that of the monoacetamido compound. The normal ultraviolet spectra of 2-diacetamido-4-methylpyrimidine in methanol is a peak at 242 mμ, which is almost a shoulder to strong end absorption (around 200 mμ; this is also present in a spectrum of a water solution of the compound). After standing 18 days, this same solution possessed the spectrum of the monoacetamido derivative.

Table VIII. Thin layer chromatography of the aminopyrimidines and their acetyl derivatives

Spot	MeOH λ_{max} mμ	R_f of spot
2-Amino-4-methylpyrimidine	229 292	0.57
2-Acetamido-4-methylpyrimidine	234 ~ 263 sh [1]	0.59
Sublimed 2-diacetamido-4-methylpyrimidine	233 271 [2]	0.64
Recrystallized 2-diacetamido-4-methylpyrimidine	231 ~ 270	0.66 [3]
	234 ~ 270 sh	0.60
2-Diacetamido-4-methylpyrimidine treated with ammonium hydroxide	234 ~ 265 sh	0.60 [4]
2-Diacetamido-4-methylpyrimidine after recrystallization from hot water with activated charcoal	233 ~ 262 sh	0.60
	264 and sh	0.66
2-Diacetamidopyrimidine	233 270	0.64

[1] sh = shoulder [2] a definite peak [3] smaller spot [4] gave two spots on plate 2

The two-spot phenomenon occurred with developing solvents such as ethyl acetate-methanol, 106:1, or with dioxane-water, 9:1, and as the methanol solution for the normal ultraviolet spectra stood very little longer than the methanol solutions above of the spots scraped from the plates, it might appear that the silica gel or the residual traces of acid catalyzed the hydrolysis; see Tables IX-XI. Some support for this hypothesis may be found in the report of Rabini and Vita (124) that activated alumina has remarkable catalytic ability in acylation of hydrazines with acids. Nearly quantitative and exclusive yields of the monoacyl product (ordinarily polyacyl hydrazines and tetrazines are also formed) were obtained at much lowered temperatures. However, a usual acetylation of 2-amino pyrimidine in the presence of one-seventh equivalent of "Aluminum Oxide G for Thin Layer Chromatography" did not alter the usually obtained product ratio.

Whitlock et al. (172) reported in 1965 that the reaction of 2-diacetamido-4-methylpyrimidine with N-bromosuccinimide gave a low yield of 2-diacetamido-4-dibromoethylpyrimidine, m.p. 109-111°, rather than 2-diacetamido-4-bromomethylpyrimidine. Attempted brominations in this laboratory (according to the method of Whitlock et al.*) were unsuccessful. The only compound recovered and identified from the reaction mixture was the starting material.

*Unpublished research

Table IX. Silica gel thin layer chromatography of the amino-pyrimidines and their acetyl derivatives

Pyrimidine	R_f VALUES Plate 1[1,2,3]	Plate 2[1,3,4]	Plate 3[3,4,5]	Plate 4[4,5,6]
2-Acetamido-	0.49	0.44		
2-Diacetamido-	0.64	0.58	0.52	0.53 0.36
2-Mono + 2-diacetamido-	0.64 0.52			
2-Amino-4-methyl-	0.57	0.52		
2-Acetamido-4-methyl-	0.59	0.50		
2-Diacetamido-4-methyl- (sublimed)	0.64	0.60 0.50 (tail)	0.57	0.53
2-Diacetamido-4-methyl- (recrystallized)	0.66 0.60	0.58 0.49	0.57 0.50	0.50
2-Diacetamido-4-methyl- (after dissolution in ammonium hydroxide)	0.60	0.57 0.50		
2-Diacetamido-4-methyl- (after dissolution in water with charcoal)	0.65 0.59	0.58 0.50		
2-Amino-4-methyl- + 2- diacetamido-4-methyl-			0.60 0.52	0.51
2-Acetamido-4-methyl- + 2-diacetamido-4-methyl-		0.58 0.48	0.57 0.46	0.50
2-Diacetamido-4, 6-dimethyl-				0.53

[1] Activated silica gel plate

[2] Dioxane/water 9:1 as developing solvent

[3] Spots detected by ultraviolet lamp 254 mμ

[4] Butanol/acetic acid/water 4:1:5 (top layer)

[5] Deactivated silica gel plate

[6] Spots detected by iodine vapor

[7] There was also a higher, unidentified colorless streak

Table X. Alumina thin layer chromatography with solvents indicated

Pyrimidine	Methanol and pyridine 1:1	R_f Values (Detected by I_2 Vapor) Dry methanol	Ethyl acetate and methanol, 106:1	Dioxane and water 9:1	Butanol, acetic acid and water 4:1:5 (bottom layer)
1) 2-amino-4-methyl	~0.8	0.71		0.74	0.86
2) 2-acetamido-4-methyl	~0.8	0.75		0.70	0.82
3) 2-diacetamido-4-methyl	~0.8	0.75		0.73[1]	0.81 0.87
Mixture of 1), 2), & 3)		0.68		0.71[1]	
4) 2-amino-4, 6-dimethyl			0.88	0.77[1]	0.90
5) 2-acetamido-4, 6-dimethyl			0.86	0.77	0.88
6) 2-diacetamido-4, 6-dimethyl			0.87[2] 0.93	0.78[1]	0.87 0.91
Mixture of 4), 5), & 6)			0.87 0.94	0.73[1]	
7) 2-amino-pyrimidine hydrochloride			0.72		0.89
8) 2-acetamido-			0.61	0.72	0.81
9) 2-diacetamido			0.57	0.71	0.82 0.90 faint
Mixture of 7), 8), & 9)			0.62 0.72		

[1]There was also a colorless spot slightly above the origin

[2]The spots were not cleanly separated

Table XI. Thin layer chromatography of the unidentified acetylation products of the dihydroxyaminopyrimidines

Compound	$\lambda_{max}^{H_2O}$ in mμ	R_f [a]
2-amino-4, 6-dihydroxy-pyrimidine	262	0
Crude acetylation product of the former	233, [b] 286	0.83 0.62
6-aminouracil	264	0.55
Crude acetylation product of 6-aminouracil	267	0.64

[a] Alumina plate; butanol/acetic acid/water, 4:1:5, as developing solvent; spots detected by iodine vapor

[b] Spectrum observed in 95 percent ethanol

In the current work it was deemed of interest to attempt a simpler preparation of 2-methyl-4-aminopyrimidine than had as yet appeared in the literature. The usual synthesis involved condensation to provide an oxypyrimidine which was chlorinated and finally treated with ammonia to produce the desired amino compound.

For example, Gabriel (56) had prepared 2-methyl-4-aminopyrimidine by reacting 2-methyl-4-chloropyrimidine with ammonia at 100° C. Budĕsinsky (26) prepared 2-methyl-4-aminopyrimidine in several steps following an original condensation of mucobromic acid with acetamidine hydrochloride. Cairn's et al. prepared 4-amino-2, 6-dimethylpyrimidine by a high pressure tautomerization of acetonitrile.

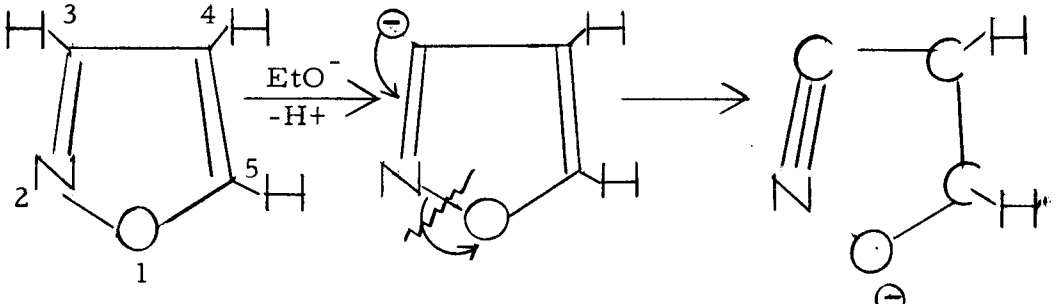
An earlier synthesis of 4-amino-2, 6-dimethylpyrimidine (78, pp. 71-72) required much prior purification of the reactants.

A condensation of acetamidine with cyanoacetaldehyde to give the desired 2-methyl-4-aminopyrimidine was considered. There are few literature references to cyanoacetaldehyde. Chautard in 1889 (33) described its preparation in 10 percent yield from silver cyanide and iodoacetaldehyde.

A British patent for preparation of the free aldehyde via a Wittig reaction appeared in 1958 (10), but it was later admitted that the yield reported was ten times that obtained and that the authors had been unable to repeat their original synthesis.

Quilico et al. in their 1962 monograph (123, p. 45) state that the only practical route to cyanoacetaldehyde is the reaction of isoxazole with sodium ethoxide, which gives the sodium enolate "which can be used as such for further synthetic purposes."

In 1891 Claisen (34) had reported the isomerization to cyano-ketones of 5-monosubstituted isoxazoles at ordinary temperatures with alkali metal alkoxides. For example 5-phenyl-isoxazole treated with sodium ethoxide gave formylacetophenone (37) and 5-methyl-isoxazole with sodium methoxide gave the sodium salt of cyanoacetone, which polymerized explosively when boiled (35). Streitwolf reported to Claisen (36) that isoxazole itself treated in ethanol with sodium or calcium ethoxide gave the sodium enolate of cyano-acetaldehyde.



isoxazole

No yields or experimental data were given. Quilico and Freri (121) reported that reaction of some 5-alkyl isoxazoles gave the cyanoketone quantitatively after treatment with sodium ethoxide.

On the other hand, Brignell et al. (23) in 1963, after having searched the literature for a suitable derivative of cyanoacetaldehyde, used the method of Borsche and Manteuffel (21) to obtain in fair yield the potassium salt of the desired aldehyde. Borsche and Manteuffel had prepared this salt by reacting potassium, acetonitrile, and ethyl formate in an ethanol-ether solution cooled to sub-zero temperatures. The sodium enolate was prepared similarly. Brignell et al. synthesized a substituted pyridine from the potassium enolate of cyanoacetaldehyde. This seems to represent the only use of such a derivative of cyanoacetaldehyde "for further synthetic purposes." [Ku and Tsah, however, condensed the monopotassium salt of α-chloromalonaldehyde with guanidine successfully, yielding 2-amino-5-chloropyrimidine (98)].

The following derivatives (enol ethers, acetals, or aminomethylene derivatives) of cyanoacetaldehyde have been employed successfully in the synthesis of aminopyrimidines: 2-ethoxymethylenemalonitrile (63; 32); alkyl derivatives of the former (80); the enol ether of 2-phenyl-cyanoacetaldehyde (101); 2-(methoxymethylene)-3-ethoxypropionitrile (100); β-ethoxyacrylonitrile (prepared from isoxazole) (153); and cyanoacetal (11; 77). Takamizawa (152) in 1959 summarized the use of aldehydonitrile derivatives in pyrimidine syntheses and showed that two different reaction pathways give rise to the products obtained.

Others have reported difficulties in pyrimidine synthesis with compounds similar to derivatives of cyanoacetaldehyde. While

formamidine hydrochloride reacted with malononitrile producing 4-amino-5-cyanopyrimidine via a presumed intermediate aminomethyleneenitrile, formamidine would not condense with ethyl α-cyanoacetate (8). In order for acetamidine hydrochloride to react successfully with ethyl α - cyanoacetate, four equivalents of sodium methoxide were required; one equivalent of sodium methoxide gave ethyl 2-cyano-3-amino-2-butenoate accompanied by loss of ammonia (103). Condensations between sodium α-nitromalonaldehyde and aryl amidines were successful, but those with alkyl amidines were not; the alkyl amidines apparently decomposed faster than condensation could take place. The decomposition yielded ammonia which reacted with the aldehyde, giving a dark amorphous product, whose elemental analysis and spectra shed no light on its identity. A brown-black resin was also obtained when the salt of the aldehyde was treated with concentrated aqueous ammonia, ammonium chloride, ammonium acetate, or acetamide in the presence of Triton B.

Isoxazole, prepared by the method of Justoni and Pessina (86), was reacted with sodium ethoxide in ethanol employing the method of Quilico and Freri (121) for a similar reaction with 5-acetylisoxazole. The weight of the yellowish-tan product indicated a 55 percent yield of the sodium enolate. Its elemental analysis revealed it to be impure; and if it was contaminated only with sodium ethoxide, it may have been a 1: 1.17 molar ratio of the enolate and sodium ethoxide.

Its infrared spectra revealed a nitrile band and trans vinyl protons. The solid material gave an enol reaction (purple color) with acidified ferric chloride, but it gave only a tiny amount of the phenylhydrazone derivative (36).

The following attempted condensations with the above material were attempted before the results of the elemental analysis were known.

Equimolar amounts of the supposed sodium enolate and acetamidine hydrochloride were suspended in absolute ethanol and were refluxed for three to four hours with stirring. Ammonia was evolved. Both the solid and oily liquid residue obtained upon evaporation of the ethanol absorbed in the ultraviolet with a λ_{max} of 310 mμ. The original solid product melted from 150-155° C * and gave dark red-brown solutions when dissolved in fresh, hot ethanol. These could not be decolorized with charcoal. Recovered material from the recrystallization was brownish and melted 250-260° with decomposition. Cold ethanol rinsings of the original solid (mp 150-155°) were evaporated in vacuo at 100° giving dark oils, which gave some crystals on standing. These crystals were separated from the oil and rinsed, but turned orange on exposure to air. The oils were soluble in water or

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* Borsche and Manteuffel reported that when the sodium or potassium enolate of cyanoacetaldehyde was introduced into a solution of aniline in 2N formic acid, prussic acid was evolved; a yellow oil was obtained which turned red-brown and deposited brown feathery prisms after two days. The solid was recrystallized from ethanol and melted 153° C. It was assumed to be anil.

ethanol, but not in diethyl ether or petroleum ether. Other cold ethanol rinsings of the original solid material (mp 150-155°) were evaporated at lower temperatures and material melting between 130-160° C was recovered. This material also had a λ_{max} 310 mμ. Its n. m. r. analysis revealed 3-4 aromatic hydrogens and trans vinylic hydrogens of a substituted acrylonitrile. There were no methyl hydrogens; this was not, therefore, a condensation product with acetamidine. (The ultraviolet absorption of the desired 2-CH_3-4-NH_2-pyrimidine $\lambda_{max}^{H_2O}$, 236 and 267; ref. 23)

The condensation was no more successful if the acetamidine hydrochloride and impure sodium enolate were neutralized prior to mixing. If kept at 0° C, the reaction mixture had strong absorption in the ultraviolet at 250 mμ; if allowed to warm up to room temperature, a peak appeared at 310 mμ, which became dominant if the mixture was refluxed. (Basification of the solution would cause a $\lambda_{max}^{H_2O}$ 253 mμ at the expense of the 310 mμ peak.)

When the reactants were refluxed in acid solution, the solution revealed many weak peaks in the ultraviolet with a slightly stronger one at about 237 mμ and with very strong end absorption.

Another attempt involved dropwise addition of a cold ammonium chloride-sodium enolate suspension in ethanol to the acetamidine hydrochloride preneutralized with sodium ethoxide in ethanol. Ultraviolet spectra of the cold ammonium chloride-sodium enolate

suspension and of the reaction mixture after 40 minutes both possessed λ_{max} in 95 percent EtOH in the 250-255 mμ region. Thin layer chromatography on silica gel plates with the usual butanol-acetic acid water developing solvent revealed the following:

	R_f*
Cold water solution of impure sodium enolate and ammonium chloride	0.68 0.12
Water solution of material on which n.m.r. was run	0.69
Impure sodium enolate in water	0.69 (plus a higher spot if allowed to stand at room temperature)
Ethanol solution from last-mentioned reaction	0.86 0.68 (yellow without I_2) 0.57 and several others less well separated.

*Spots detected by iodine.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman model DB spectrophotometer or with a Cary model 15 spectrophotometer; the latter spectra were taken by S. Vachananda. The infrared spectra were taken with a Perkin-Elmer model IR 8 infrared spectrophotometer using a sodium chloride prism with samples in the form of Nujol mulls. (The Nujol produces the two strong absorptions at approximately 2920 and 2860 cm^{-1} and the weaker ones at about 1460 and 1375 cm^{-1}.) The nuclear magnetic resonance spectrum was taken by Dr. Gerald Caple on a Varian model A-60 NMR Spectrometer. Elemental analyses were performed by Frank Lehmkuhl.

2-Aminopyrimidine

2-Aminopyrimidine was synthesized after the manner of Protopopova and Skoldinov (120). To a stirred solution containing 10 grams guanidine hydrochloride, 40 grams water, and 25 ml. concentrated hydrochloric acid was added dropwise 22 grams tetraethoxypropane over one and one-half hours. The mixture was stirred an additional two hours, and was then allowed to stand for another 18 hours. The mixture was evaporated to dryness under reduced

pressure (rotary evaporator) using a warm water bath of 50° for heat. The residue was then treated with 40 percent aqueous sodium hydroxide. The solid material was removed by filtration and dried in vacuum desiccator over calcium chloride. The solid was extracted several times with benzene at room temperature. Protopopova and Skoldinov reported the 2-aminopyrimidine, m. p. 123-124°C from benzene, was obtained in 82 percent yield (7. 2 grams on this scale). About five grams of crude product was obtained from the extractions. One recrystallization from hot benzene or acetone gave lemon yellow crystals. The product was dissolved in warm benzene with decolorizing charcoal and filtered. The benzene was evaporated under reduced pressure until crystals began to form; the solution was then set in a refrigerator to allow time for crystal formation, then filtered and dried overnight in vacuo to yield 4. 67 grams (49 percent yield) pure 2-aminopyrimidine.

2-Amino-4, 6-dimethylpyrimidine

The abstract of the patented procedure of Amazu and Inoue (1) provided adequate directions for the synthesis of 2-amino-4, 6-dimethylpyrimidine. A solution containing 100 gm. (one mole) 2, 4-pentadione in 500 ml. of 95 percent ethanol to which was added 100 gm. pulverized guanidine carbonate (about 0. 83 mole) was refluxed for five hours and then immediately filtered while hot. The filtrate

was concentrated in vacuo to approximately 60 ml. and the pyrimidine product was allowed to crystallize. A second crop was also obtained by evaporating the remainder of the ethanol from the mother liquor using reduced pressure and slight warming. The total weight of crude, dried product was 83.9 grams or 68.2 percent yield. (Amazu and Inoue reported a yield of 91.5 percent m.p. 150°.) One further recrystallization from hot ethanol gave material melting 152-153° subsequent to drying in a vacuum desiccator over calcium chloride for 17 hours.

2-Amino-4-methoxy- and 4-amino-2-methoxypyrimidines

The procedure of Hilbert and Johnson (76) as modified by Boarland and McOmie (18) was used in the synthesis of 2, 4-dichloropyrimidine. In this procedure uracil is converted to the desired product by phosphorus oxychloride in the presence of dimethylaniline.

Hilbert and Johnson's method (76) for the synthesis of a mixture of 2-amino-4-chloro- and 4-amino-2-chloropyrimidines was employed. Ten grams pulverized 2, 4-dichloropyrimidine was dissolved in 75 ml. of absolute alcohol that had been saturated with ammonia gas. The reaction mixture, stored in a ground-glass-stoppered Erlenmeyer flask, became warm within one-half hour and then cooled. After 18 hours the solid material which separated was removed by filtration. This precipitate was rinsed with small

portions of very cold water followed by rinsing with diethyl ether. The dried product weighed 6.23 grams (71.8 percent yield; Hilbert and Johnson reported a yield of 95 percent).

The preparation of 2-amino-4-methoxy- and 4-amino-2-methoxypyrimidines from the corresponding amino-chloropyrimidines mixture was carried out according to the direction of Hilbert and Johnson (76). To a solution containing 6.23 grams (0.048 mole) of the isomeric pyrimidine mixture and 76.5 ml. reagent methanol was added 1.31 grams finely divided, clean sodium metal (0.057 mole)* in 24 ml. reagent methanol. The mixture was then maintained under reflux for six hours. After cooling, the solution was filtered to remove sodium chloride. The volume of solution was then reduced in vacuo to 20 ml. The 1.40 grams of dried product which had crystallized from the concentrated solution melted 179-180° (Hilbert and Johnson report 173°).

The methanolic filtrate was evaporated to dryness. The 4.43

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*Apparently it is highly desirable to use a generous excess of sodium metal. Observations very similar to those of Hilbert were noted in an experiment in which there seemed to be an insufficient excess. The product which was expected to be 4-amino-2-methoxypyrimidine was not homogeneous. Hilbert reported (75, p. 192):

> On crystallization various fractions were obtained which individually melted rather sharply somewhere in the range of 176-210°; the different fractions gave tests for halogen and were solid solutions of 4-NH_2-2-Cl- with 4-NH_2-2-MeO-pyrimidine as on further treatment with sodium methoxide pure 4-NH_2-2-MeO-pyrimidine was obtained.

grams residue was rinsed with cold dioxane instead of being dissolved in hot water, treated with Norite, and cooled to give more of the above isomer as Hilbert and Johnson's procedure suggested. The dioxane treatment was recommended by Karlinskaya and Khromov-Borisov (94) as an improvement upon the method of the former workers.

The 2-amino-4-methoxypyrimidine is more soluble in cold dioxane and can be recovered by removing the dioxane via distillation or by evaporation under reduced pressure. The latter isomer oiled out when recrystallization was attempted from hot water. Warm water and activated charcoal treatment proved fairly satisfactory for purification. Material was obtained which melted 121-123° C (lit. 125° with decomposition to an oil).

6-Acetamido-2, 4-dichloropyrimidine

To 0. 34 grams 6-amino-2, 4-dichloropyrimidine (0. 00207 mole), melting point with decomposition 256. 5° [lit. 270-271° C (99)], was added 7. 5 milliliters acetic anhydride and the mixture was refluxed for two hours. A waterbath temperature of 60° C with rotary evaporation gave very slow evaporation; so the acetic anhydride was removed by evaporation from a 600 milliliter breaker set in a well-ventilated hood. The residue which weighed 0. 38 gm. was dissolved in 30 milliliters of hot dry benzene and a brown insoluble material

was removed by filtration. Then ten milliliters reagent petroleum ether was added and as there was no immediate crystallization, some solvent was removed in vacuo. This led to some crystallization giving a first crop (0.12 gm.) m.p. 184-186°. 6-Acetamido-2,4-dichloropyrimidine is reported in the literature to melt 184-185° (114); total yield 70 percent.

Anal. Calc'd for $C_6H_5Cl_2N_3O$: C, 35.0; H, 2.43; N, 20.4

Found: C, 35.2; H, 2.58; N, 20.5

4-Acetamido-2-methoxypyrimidine

A solution of 1.77 grams (0.014 mole) 4-amino-2-methoxypyrimidine, prepared and purified as described above, m.p. 171-172° C, together with 47 ml. acetic anhydride was refluxed for two hours and the acetic anhydride removed by evaporation from a large open vessel in a well-ventilated hood. About 0.4 gram of material crystallized and was removed by filtration from the acetic anhydride when it had cooled. After complete evaporation of the anhydride, the remaining material weighed 1.88 grams and would not dissolve appreciably in hot benzene-petroleum ether solution, 1:1 or 2:1 by volume. The material was more soluble in reagent ethyl acetate or in dry benzene alone and gave crops melting 157-161° from these solvents. A slight (0.17 gram) brownish residue was insoluble and

removed by filtration. The material which had crystallized from the cooling acetic anhydride melted 169-173° C. The latter gave an R_f value of 0.79 on a silica gel plate developed with the top layer of a butanol-acetic acid-water mixture, 4:1:5 by volume. The bulk of the material gave an R_f value of 0.78. There appeared, therefore, to have been only one product for this reaction. The qualitative test for imide was negative. The product was sublimed to give material melting 165-166° for elemental analyses. The crude yield of 4-acetamido-2-methoxypyrimidine calculated as the 2.11 grams recovered was 89 percent. This compound apparently has not been described in the literature.

Anal. Calc'd for $C_7H_9N_3O_2$: N, 25.15

Found: N, 25.15

Appriximately one-tenth gram of brownish residue was recovered from the sublimation; it was not observed to sublime. This material melted and turned black around 260° C. Kenner (91) reported that N-acetyl-1-methylcytosine, m.p. 268° from ethanol, possessed an ultraviolet spectrum λ_{max}^{EtOH} 215 mμ (4.30), 246-7 mμ (4.6), and 299-300 mμ (3.83). A crude spectrum of the material melting at 260° gave peaks of $\lambda_{max}^{50 \text{ percent EtOH}}$ 212, 247, 285, and 299-300 of the same relative intensities as Kenner reported.

2-Diacetamidopyrimidine and 2-acetamidopyrimidine

A solution of 3.61 grams (0.038 mole) 2-aminopyrimidine and 125 ml. acetic anhydride was refluxed for two to two and one-half hours. The acetic anhydride was removed by use of a rotary evaporator under water aspirator pressure (45 mm. Hg). Maintaining the temperature of the bath at 50° C for three hours did not materially affect the rate of evaporation. However two hours at nearly 65° C were sufficient to evaporate to near dryness. Some decomposition, represented by tacky, red-black tar, had occurred as usual during the evaporation at the higher temperature. The material was dissolved in 200 ml. hot benzene and decolorized twice with activated charcoal. Addition of approximately 100 ml. petroleum ether to the clear filtrate produced cloudiness. The cooled mixture was placed in a refrigerator to effect crystallization then filtered to give the monoacetylated product. This material was dried over calcium chloride and weighed 0.99 grams, m.p. 145-145.5°, and represented an 18.9 percent yield of 2-acetamidopyrimidine (lit. m.p. 145-146.5°, ref. 18). The mother liquor was concentrated further under reduced pressure. The second crop weighed 1.82 grams and melted 74-75°; further concentration gave crop three, weight 1.49 grams m.p. 72-74.5°. The residue weighed 0.14 grams. The second was apparently contaminated with monoacylated pyrimidine since the m.p. range was

increased on recrystallization to 72.5-75.5°C and 73.5-79°C. These last crops gave a positive qualitative test for imide. The product was therefore assumed to be 2-diacetamidopyrimidine (crude yield 50.8 percent). This was confirmed by analysis.

Anal. Calc'd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46

Found: C, 53.1; H, 4.82; N, 23.7

2-Diacetamido-4, 6-dimethyl- and 2-acetamido-4, 6-dimethylpyrimidines

A solution of 4.67 grams (0.038 mole) of 2-amino-4, 6-dimethylpyrimidine and 125 milliliters acetic anhydride was boiled under reflux conditions for two hours. The acetic anhydride was removed by evaporation using a large open container in a well-ventilated hood. The products were dissolved in dried benzene and filtered to remove a slight amount of insoluble material. An equal volume of reagent petroleum ether was added and the solution set aside to crystallize. The first two crops weighed 1.33 grams (crude yield 21.2 percent) and after being dried in vacuo over night above calcium chloride melted between 118-119°. This product was identical as judged by thin layer chromatography and ultraviolet spectroscopy to the 2-acetamido-4-methylpyrimidine, (m.p. 124°), prepared according to Asplin (4). [In this procedure a mixture of ten grams (0.0813 mole) with ten milliliters acetic anhydride boiled under reflux for three

minutes. The product was recrystallized from water and gave the same 70 percent yield reported by Asplin.]

After the mother liquor had been in the refrigerator for several hours, huge, thick needles formed. When filtered, rinsed with two or three small portions of cold reagent petroleum ether, collected and dried, this crop weighed 1.75 grams and melted 109-114°. The residue from evaporation of the remaining mother liquor gave 3.51 grams, which melted between 85-100° when dried. One more fractional recrystallization from benzene-petroleum ether gave 2.14 grams, melting between 102-109°. These last crops taken to be crude diacetyl derivative represent a 67 percent yield. Further recrystallizations from 95 percent EtOH gave a m.p. 112-113°C. Elemental analyses confirmed the synthesis of a diacetyl derivative. The qualitative test for imide was positive for this material. The crude reaction product from the three minutes' reflux gave a negative test for imide with hydroxylamine.

Anal. Calc'd for $C_8H_9N_3O_2$: C, 58.0; H, 6.28; N, 20.3

Found: C, 57.6; H, 6.33; N, 20.4

5-Diacetamido-4, 6-dichloropyrimidine

A mixture of 2.08 grams (0.0127 mole) 5-amino-4, 6-dichloropyrimidine was refluxed in a solution containing 35 molecular

proportions (42 ml) acetic anhydride for two hours. The acetic anhydride was removed using a rotary evaporator and a hot water bath. The product was then dissolved in 25 ml. hot benzene to which an equal volume of petroleum ether was added. The first crop of material was small (0.03 g.) and discolored. Evaporation of the benzene-petroleum ether solution was attempted with a rotary evaporator and a hot water bath. Decomposition ensued, and 0.01 g. of solid was removed by filtration. Even a bath temperature of 45° with the reduced pressure evaporation lead to oiling out of some product. The various crops obtained with their dry weights and melting point ranges were as follow.

	yield	m.p. range
Crop 2	0.20 g.	125-134°C
Crop 3	0.05 g.	119-134°C
Crop 4	0.59 g.	60-90 °C
Crop 5	0.26 g.	57-90 °C
residue	0.63 g.	70-72 °C

The ultraviolet and infrared spectrum of crops 2 and 3 were significantly different from that of crops 4 and 5 and the residue. Recrystallization from benzene-petroleum ether improved the melting point range of crops 2 and 3 to 143-144.5° and that of crops 4 and 5 to 61.0-64.5°. The residue was analyzed for its nitrogen content. These results confirmed the opinion that the residue was the diacetyl derivative of the starting aminopyrimidine, while the recrystallized crops 2 and 3 proved to be the unreacted aminopyrimidine (crude

yield 12 percent; m.p. 144). The last crops and residue gave a positive test for acyclic imide.

A repetition of the acetylation using 0.82 g. 5-amino-4, 6-dichloropyrimidine with 16.5 acetic anhydride followed by evaporation of the acetic anhydride from an open 400 ml. beaker placed in a well ventilated hood gave needles of the starting material as the solution cooled. The product was dissolved in dry benzene at room temperature and the solution was filtered. Some of the excess benzene was removed under reduced pressure; petroleum ether was added and the crystals removed. The procedures of evaporation, addition of more petroleum ether, and filtration to remove the crops was repeated several times. The combined crops weighed 0.80 g. The various crops showed less clean separation between the starting material and the diacetylamino derivative:

	weight	m.p. range
Crop 1	0.03 g.	128-134°
Crop 2	0.10 g.	135-140°
Crop 3	0.04 g.	110-125° fast
Crop 4	0.56 g.	began-60°
Residue	0.07 g.	125-140°
Total	0.80 g.	

If crops 1-3 and the residue are starting material, this would represent a 29 percent recovery whereas crop 4, as the diacetyl product would be a 45 percent yield. This is comparable to its 47 percent yield in the first attempt. The procedure for separation of the

diacetyl material could obviously be improved. The procedure of Temple (157) was reported to produce nearly pure 5-diacetamido-4, 6-dichloropyrimidine in 79 percent yield. Also as the starting material was in scant supply and is difficult to prepare, it did not seem justifiable to improve this procedure at this time.

Anal. Calc'd for $C_8H_7Cl_2N_3O_2$: C, 38.71; H, 2.82; N, 16.94

Found: C, 38.7; H, 3.11; N, 17.17

Anal. Calc'd for $C_4H_3Cl_2N_3$: N, 25.61

Found: N, 25.02

2-Diacetamido-4-methylpyrimidine and
2-acetamido-4-methylpyrimidine

A procedure similar to that of Whitlock et al. (172) was employed. A solution of 4.40 grams (0.0404 mole) 2-amino-4-methylpyrimidine (m.p. 161°C from acetone) was dissolved in 130 ml. (1.38 mole) acetic anhydride using an apparatus consisting of a 250 ml. round-bottomed flask provided with ground-glass fittings and a water-cooled condenser. This mixture was refluxed for two and one-fourth hours. (It had been observed in this laboratory that removal of the acetic anhydride under reduced pressure by use of a rotatary evaporator required the use of a bath whose temperature had to be maintained around 50-60°C. Furthermore, at this temperature some decomposition usually accompanied the isolation of the product. On

the other hand, such decomposition could be avoided by evaporation of the acetic anhydride from the product mixture in a large open container at room temperature in a well-ventilated hood.) The yellow residue isolated by the latter procedure was then dissolved in a four to one mixture of dry benzene and petroleum ether. The yield of the material which crystallized first was 1. 33 grams (20. 6 percent). This product was dried overnight in a vacuum desiccator over calcium chloride. Its melting point range 151-152° C was close to that reported for 2-acetamido-4-methylpyrimidine, 152-154° C. Further recrystallizations from ethanol improved the purity of this product. The petroleum ether-benzene solution was evaporated under reduced pressure to near dryness. The combined dried crops weighed 5. 21 grams (66. 9 percent yield) and melted between 93-95° C. The recorded value for the melting point range of 2-diacetamido-4-methylpyrimidine is 101. 5-103. 5° C. Subsequent recrystallizations or sublimations gave no higher a melting point range though the range was narrowed to 94-95° C.

Anal. Calc'd for $C_7H_9N_3O$:	C, 55. 61;	H, 6. 00;	N, 27. 80
Calc'd for $C_9H_{11}N_3O_2$:	C, 55. 94;	H, 5. 74;	N, 21. 74
Found:	C, 56. 0;	H, 5. 6;	N, 21. 9

When the acetylation was carried out using 23. 56 grams (0. 216 mole) 2-amino-4-methylpyrimidine and 701 ml. of acetic anhydride maintained at reflux conditions for four hours with the acetic

anhydride then being removed with a rotary evaporator and a water-bath temperature of 55° C (some decomposition occurring), the yield of monoacetylamino derivative was 23 percent and that of the diacetylamino was 62.5 percent. The ultraviolet spectrum of a water solution of the diacetamido product agreed well with that reported by Whitlock et al. However, at pH 1 a solution of the diacetamido product if allowed to stand for a period as short as 45 minutes would show the ultraviolet-absorption peaks characteristic of the monoacetamido product. The infrared absorption data for the two compounds compared well with those reported.

An acetylation of 4.2 grams (0.038 mole) 2-amino-4-methylpyrimidine with 125 ml. acetic anhydride was allowed to proceed at reflux temperature for two and one-half hours. The acetic anhydride was removed by means of the rotary evaporator accompanied by warming no higher than 50° C. The product had a slight yellow coloration, which was usual if no decomposition had occurred. The dried crude product was dissolved in 50 ml. hot (but not boiling) distilled water. No crystals formed on cooling even when the solution was kept in the refrigerator several hours. The water was removed by evaporation from the solution under reduced pressure at temperatures 30 to 40° above room temperature. The approximately five grams yield of material was dissolved in 80 ml. warm acetone. About 1.3 grams (22 percent) crude 2-acetamido-4-methylpyrimidine

crystallized on cooling. Evaporating the acetone with the rotary evaporator followed by washing the residue with petroleum ether yielded 3.84 grams (52 percent) crude 2-diacetamido-4-methylpyrimidine, m.p. about 95° C.

A solution of 2.87 grams (0.019 mole) 2-acetamido-4-methylpyrimidine, m.p. 149-151° C, in 63 ml. (0.668 mole) acetic anhydride was refluxed for two hours. The acetic anhydride was evaporated from a large open vessel in a well-ventilated hood. The crude product was then dissolved in a one-to-one mixture of benzene petroleum ether and 0.33 grams (11.5 percent) crude 2-acetamido-4-methylpyrimidine, m.p. 140-150° C was recovered. Evaporation under reduced pressure of the rest of the solvent gave a second crop, 1.45 grams, m.p. 94-98° C; the third crop weighed 1.16 grams, m.p. 93-98° C; and 0.05 gram residue of crude 2-diacetamido-4-methylpyrimidine remained. These combined fractions represent a 71 percent yield based on the 2.87 grams of the starting material, 2-acetamido-4-methylpyrimidine.

Isoxazole

The directions for the synthesis of isoxazole by Justoni and Pessina (86) were followed. A two-phase mixture of 242 milliliter tetraethoxy propane and 80 grams hydroxylamine hydrochloride in 1000 ml. water were placed in a two-liter round-bottomed flask

provided with a ground-glass joint and a condenser. This mixture was heated cautiously with a Glass-col heating mantle (the initial boiling is so extremely vigorous and exothemic that some of it boiled up and out of the condenser) to boiling. As the mixture boiled, it changed colors from yellow to orange-red to cherry-red to a dark maroon within 15 minutes. The mixture was refluxed for one-half hour, and after the flask had been provided with a Claisen head, was distilled. The fraction boiling 77 and 88. 5° C (no forerun) was collected and treated with 274 grams cadmium chloride dihydrate in 170 ml. water. The mixture was kept overnight in the refrigerator. The directions suggested washing the isoxazole cadmium chloride addition compound with cold saturated aqueous $CdCl_2$ and ice water. (The addition compound is so fine that it is not practicable to carry out this washing accompanied by vacuum filtration.) The addition compound was suspended in 500 ml. water and distilled. The fraction distilling between 80-90° was allowed to stand overnight; it separated into two phases. The lower phase was isoxazole saturated with water; the upper was water saturated with isoxazole. The layers were saturated with ammonium sulfate. The top layer of wet isoxazole was separated and the lower salt water solution was distilled to recover some isoxazole (fraction collected that distilled between 76-89°). The isoxazole layer was dried over calcium chloride, filtered from it, and the calcium chloride was distilled to recover more

isoxazole. The yield obtained was only 23 grams, whereas Justoni and Pessina (86) obtained 62 grams working on the same scale. The isoxazole was fractionally distilled through a Podbelniak column packed with Heli-Grid. The major part of the liquid boiled at 95° C.

Reaction of Isoxazole with Sodium Ethoxide

Six and nine-tenths gram (0. 1 mole) of isoxazole was added dropwise with stirring to a cooled solution of 5. 52 grams 0. 24 grams (0. 24 mole) sodium metal in 50 ml. absolute ethanol (i. e. at temperatures just under boiling point not all of the sodium ethoxide was in solution). The alcohol was then boiled for 30 minutes. According to Quilico and Freri the sodium enolate crystallized from solution. In the present case sodium ethoxide was already undissolved in the ethanol. The hot mixture was filtered and the solid rinsed with ethanol. After drying in vacuo, the 5 grams of material represented a yield of 55 percent had it been pure sodium enolate of cyanoacetaldehyde.

Anal. Calc'd for C_3H_2ONNa: N, 15. 38; Found: N, 8. 25

This might represent a 1:1. 17 mixture of the enolate with sodium ethoxide.

The Reaction of N-bromosuccinimide with 2-diacetamido-4-methylpyrimidine

Two crystals of benzoyl peroxide and 2.52 grams (0.0144 mole) N-bromosuccinimide were added to a solution of 2.76 grams 2-diacetamido-4-methylpyrimidine in 120 ml. carbon tetrachloride. A heat lamp was used to maintain the mixture at reflux temperature for four hours. The solid residue was removed by filtration and discarded. The filtrate was washed with a saturated solution of sodium bisulfite and dried over anhydrous sodium sulfate. The solvent was removed by means of a rotary evaporator and the residue was dissolved in hot carbon tetrachloride and allowed to crystallize. The material obtained from the first recrystallization weighed 0.43 gram and the mother liquor yielded an additional 0.17 gram. Upon further recrystallizations from carbon tetrachloride the material had the melting point range of the 2-diacetamido-4-methylpyrimidine and was identical with it as judged by thin layer chromatography. Elemental analysis confirmed their identity.

Anal. Calc'd for $C_9H_9N_3O_2Br_2$: C, 30.6; H, 3.12

Calc'd for $C_9H_{11}N_3O_2$: C, 55.9; H, 5.74

Found: C, 55.3; H, 5.61

Qualitative Test for Acyclic Imides

When one-tenth gram of a primary amide is boiled for a few minutes with normal hydroxylamine hydrochloride in methanol, cooled, and a drop of 10 percent ferric chloride is added, red to violet colored salts of the hydroxamic acids are formed (44).

$$R\overset{\overset{O}{\|}}{C}NH_2 + NH_2OH \cdot HCl \xrightarrow{\text{boil}} R\overset{\overset{O}{\|}}{C}NHOH + NH_4Cl$$

The hydroxamic acid can be produced from acyclic secondary amides (that is, diacylamines or imides) in the cold if the hydroxylamine hydrochloride solution is previously mixed with a methanolic potassium hydroxide solution.

The presence of diacetylamines was checked using a procedure similar to that of Davidson (44). One-half milliliter of a concentrated methanol solution (that is, just sufficient methanol to effect solution) of the pyrimidine was added to the supernatant liquid resulting from premixture of one molar methanol solutions of hydroxylamine hydrochloride and potassium hydroxide. The diacetylamino pyrimidines gave clear red solutions upon the addition of a 10 percent water solution of ferric chloride; no precipitate of ferric hydroxide appears. An exception to this behavior was observed with the material melting around 70° from the acetylation of 5-amino-4, 6-dichloropyrimidine, which was later purified and identified with the known

5-diacetamido-4, 6-dichloropyrimidine. This material gave black to purple coloration after standing a few hours at room temperature; at first some ferric hydroxide had precipitated. Tea-colored solutions with precipitates of ferric hydroxide were observed with crude products which apparently were still not completely free from acetic anhydride, although other similarly crude reaction products definitely gave negative results. The material recovered after allowing 2-diacetamido-4-methylpyrimidine to stand in solution of ammonium hydroxide gave negative results with the test. The same compound after attempted recrystallization from water with charcoal produced a brownish-red solution after treatment with the test reagents. When 2-diacetamido-4-methylpyrimidine had stood in solution with butanol-acetic acid-water, 4:1:5, and alumina, the material melted about the same as before and gave a positive red color in the qualitative test for imide.

The monoacetylated amines gave the red color when no potassium hydroxide had been used, but only after they had been boiled with the hydroxylamine solution.

Preparation of the Thin Layer Chromatography Samples for Ultraviolet Spectral Analysis

The spots detected by fluorescence in ultraviolet light on the thin layer chromatography silica gel plate were carefully removed.

Each sample was placed in a separate test tube to which was added a few milliliters of reagent methanol. The test tubes were shaken and centrifuged to assist extraction and the solution was removed by decantation. Repetition of this process once or twice gave approximately enough solution of sufficient concentration to fill the cells and to give reasonable absorption in the ultraviolet. A reference solution was prepared in the same manner from some silica gel removed from the plate where there had been no evidence of spots.

Table XII. Ultraviolet spectra

Pyrimidine	λ_{max} in 0.1N HCl	ϵ	log ϵ	Lit. ref.	λ_{max} 95%EtOH	ϵ	log ϵ	Lit. ref.
2-NH_2-	221	14,800		24,p.	227		4.22	19
	302-3	4,000		492	297		3.59	
2-NHAc-	228	14,760	4.17					
	282	3,890	3.59					
2-NAc_2-*	203	12,000	4.08		203	17,500	4.24	
	229	4,120	3.62		230	7,340	3.87	
2-NH_2-4-Me-	b) 222	13,200	4.12					
	b) 298	4,650	3.67					
					204	5,600	3 75	
2-NHAc-4-Me-	230	15,200	4.18		233	19,350	4.29	
	276	5,040	3.70		265	4,660	3.67	
	231	17,000	4.23	125				
	275	5,000	3.70					
2-NAc_2-4-Me**	231	4,780	3.68		204	13,600	4.13	
	(246 no peak	3,520)	3.55		238	5,950	3.78	
	275	1,100	3.04					
	246	3,500	3.54	172				

*Solution less than two hours old

**Solution two hours old

b) Run on Beckman DB

Table XII. Continued

Pyrimidine	λ_{max} in 0.1N HCl		ϵ	log ϵ	Lit. ref.	λ_{max} 95% EtOH	ϵ	log ϵ	Lit. ref.
2-NH_2-4, 6-$(Me)_2$	b)	222	11,600	4.06		228	7,240	3.86	20
	b)	296	6,210	3.79		290	18,600	4.27	
						201	6,660	3.82	
2-NHAc-4, 6-$(Me)_2$		232	13,400	4,13		234.5	5,170	3.71	
		279	6,960	3.84		265 sh	17,600	4.25	
2-NAc_2-4, 6-$(Me)_2$**		203	14,200	4.15		203	17,500	4.24	
		246	4,060	3.60		~230	7,340	3.87	
2-NH_2-4, 6-$(Cl)_2$	b)	234	11,800	4.07		202.5	15,900	4.20	
		296	4,860	3.69		234	18,700	4.27	
						295	5,110	3.71	
						236	15,500	4.19	20
						298.5	4,570	3.66	
2-NH_2-4, 6-$(OH)_2$	b)	256	1,680	3.23					
4-NH_2-2-MeO at pH 2		229.5		3.95	146				
		260.5		3.98					
4-AcNH-2MeO		203	9,650	3.98		204.5	24,320	4.39	
		227	8,320	3.92		230	14,400	4.16	
		258	9,080	3.96		275	13,500	4.13	

**Solution two hours old

sh = shoulder

b)Run on Beckman DB

Table XII. Continued

Pyrimidine	λ_{max} in 0.1 N HCl			Lit. ref.	λ_{max} 95% EtOH			Lit. ref.
6-NH_2-2,4-$(Cl)_2$	232	11,000	4.04		202	18,430	4.27	
	290	4,410	3.64		234.5	17,470	4.24	
					292-3	4,490	3.65	
6-NHAc-2,4-$(Cl)_2$	207.5	37,500	4.57		210.5	29,400	4.47	
	238	9,670	3.99		235.5	13,500	4.13	
	275	4,230	3.63		269.5	10,900	4.04	
					200	8,930	3.95	
6-NH_2-2,4-$(OH)_2$ b)	257	650	2.81		220.5	6,200	3.79	
					263	23,340	4.37	
					203	10,100	4.00	
5-NH_2-4,6-$(Cl)_2$	246	7,230	3.86		248	6,820	3.98	
	308	2,960	3.47		310	4,270	3.63	
5-NHAc-4,6-$(Cl)_2$	255	44,500	4.65	157				
5-NAc_2-4,6-$(Cl)_2$**	204	22,300	4.35		202	49,000		
	255.5	3,970	3.60		254	4,660	3.67	

**Solution two hours old

b)Run on Beckman DB

Table XIII. Infrared absorption spectra

2-Diacetamido-pyrimidine cm^{-1}		2-Diacetamido-4-methylpyrimidine cm^{-1}		2-Diacetamido-4, 6-dimethylpyrimidine cm^{-1}	
1720	s	1732	s	1720	s
1700	s				
		1650	m, sh	1680	s
1577	m	1593	s	1590	s
1552	w	1548	m	1540	vw
1518	vw			1520-1500	w
1451	m				
1429	m				
1410	s				
1303	m	1312	m	1360	s
1270	s	1272	s	1340	m
1240	s, sh	1250	s	1330	m
		1239-1228	s	1260	s
				1236-1228	s
1087	w			1110	vw
1049	m	1051	m	1050	vw
1040	w			1030	vw
1000	w	1006	mw	1020	vw
962	w	965	w	1000	vw
				962-953	vw
923	w	943	w	939-934	vw
				893	vw, sh
834	w	843	mw		
802	vw	789	w		
		650	ms		
		632-628	ms		

s - strong
m - medium
w - weak
v - very
sh - shoulder
brd - broad

Table XIII. Continued

5-Diacetamido-4, 6-dichloropyrimidine cm^{-1}		4-Acetamido-2-methoxypyrimidine 3/45 cm^{-1}	
1728	s	1710	s
1691	s, sh		
1531	m	1590	s
1506	s, sh	1520	s
1405	s		
		1336	s
1247	w	1242	s
1235	m		
1211	s		
1159	m	1110	m
1040	vw	1068-1049	m
1026	vw	1017	m, sh, brd
1010	m	985	w
958	vw		
943	w		
897	w	820-788	vw, brd
807	ms		
773	m		
769	m		
662	w, brd	666	vw, brd

s - strong
m - medium
w - weak
v - very
sh - shoulder
brd - broad

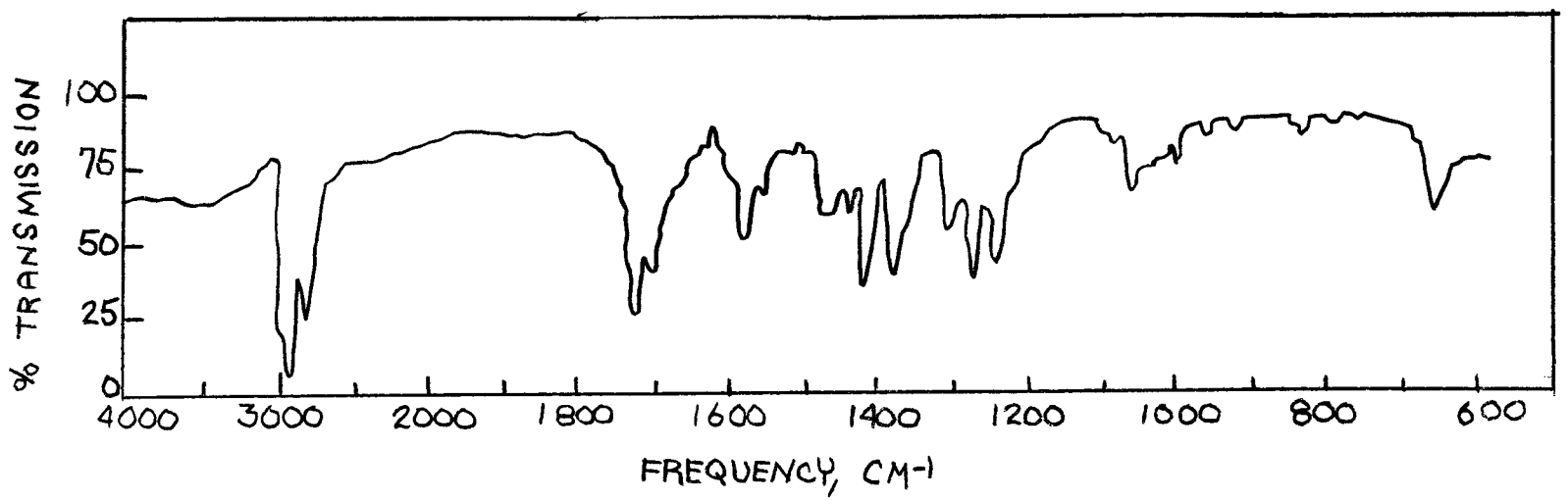

Figure 3. Infrared spectrum of 2-Diacetamidopyrimidine

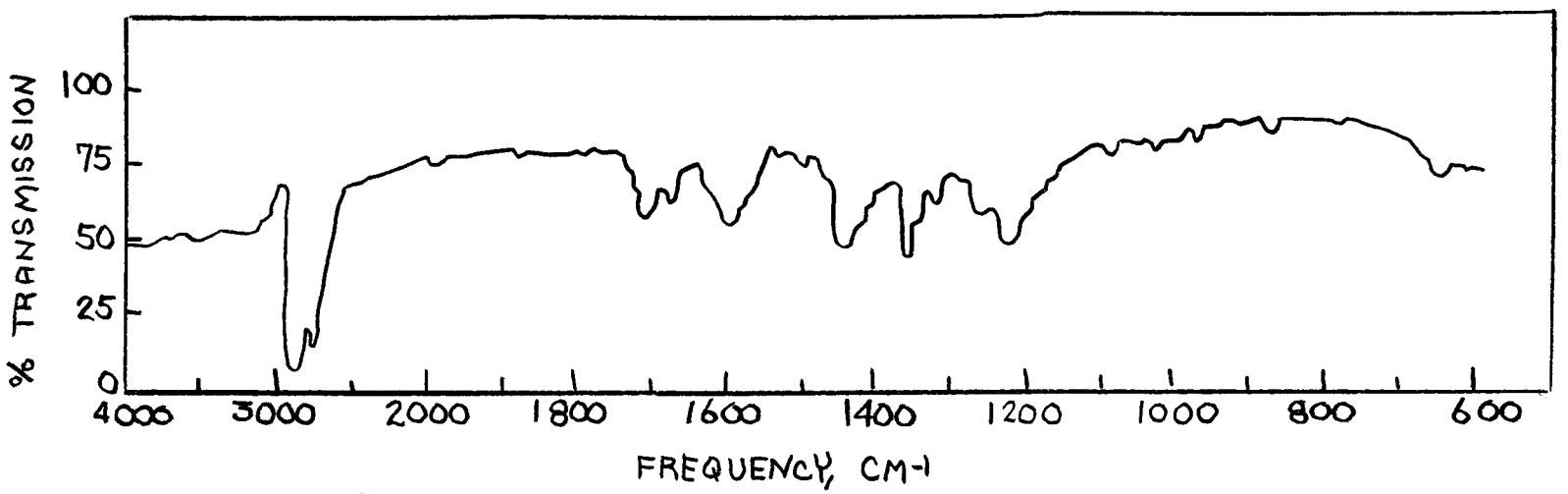

Figure 4. Infrared spectrum of 2-Diacetamido-4, 6-dimethyl-pyrimidine

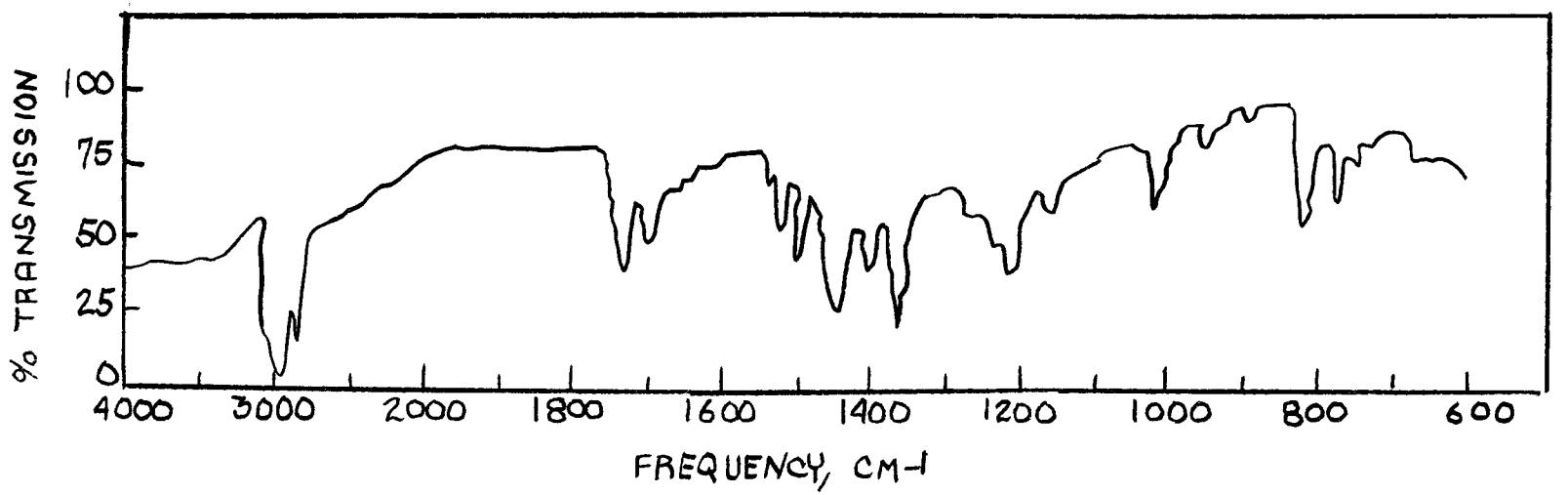

Figure 5. Infrared spectrum of 5-Diacetamido-4, 6-chloropyrimidine

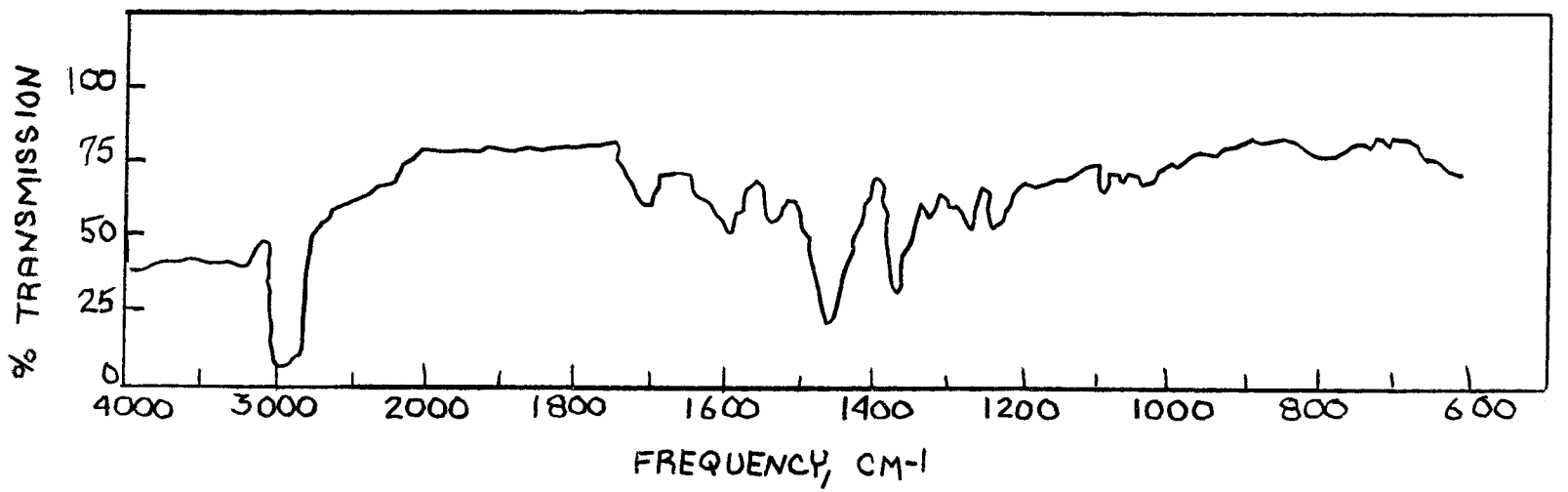

Figure 6. Infrared spectrum of 4-acetamido-2-methoxypyrimidine

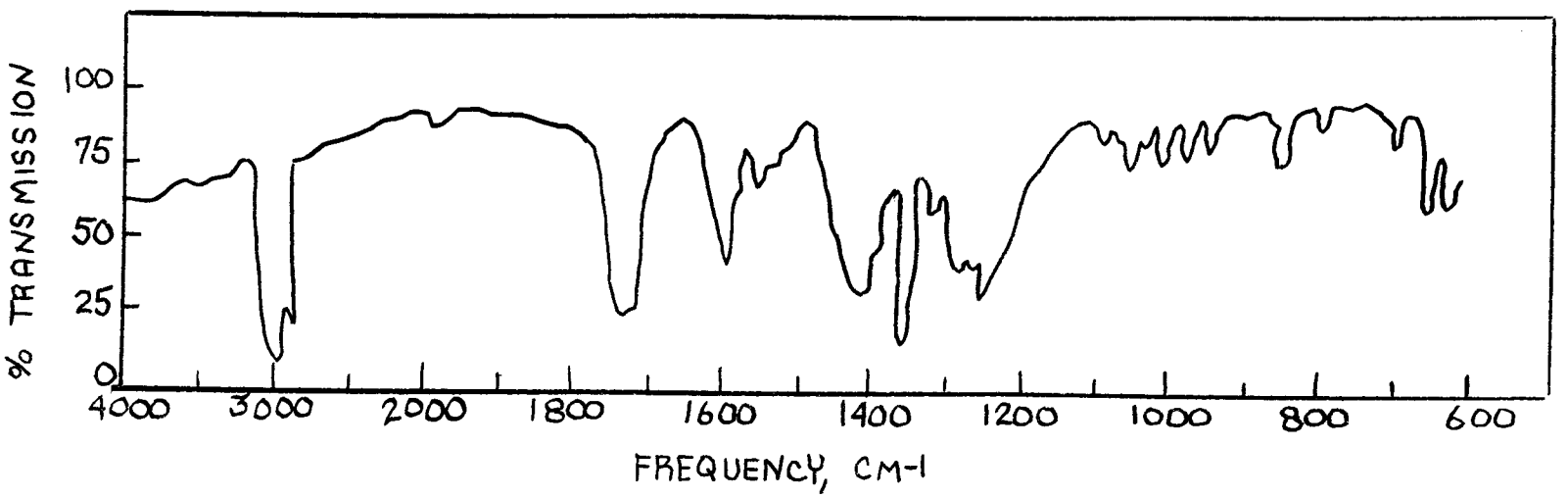

Figure 7. Infrared spectrum of 2-Diacetamido-4-methylpyrimidine

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