buffer solutions at 37° was found to be stable at low and relatively unstable at neutral pH regions.

2) The stability of isonicotinoyl hydrazones was found to decrease with lowering pH. The facile degradation of these compounds in the stomach should be taken into cosideration for oral administration.

3) Isoniazid was absorbed poorly from the stomach, and rapidly from the intestine. Sodium (2-isonicotinoylhydrazino)methanesulfonate was absorbed more slowly from the stomach and the intestine.

4) Intestinal absorption patterns of isonicotinoylhydrazones were divided into two groups; slow and rapid ones. Glucose, lactose, glucuronolactone, and sodium pyruvate isonicotinoylhydrazones were hardly absorbed in intact form whereas furyl methyl ketone isonicotinoylhydrazone was absorbed in intact form to a considerable extent. There was a rough relationship between the degree of absorption of these hydrazones and their lipid/water partition characteristics.

5) The fact that intact hydrazones of slow absorptive group are poorly absorbed was further demonstrated by the urinary excretion study using glucose isonicotinoylhydrazone by humans.

6) Suggestion was obtained to use isonicotinoylhydrazones belonging to rapid absorption group effectively by stabilization of the drug in the gut.

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75. Yoshihiro Nitta, Kiyoshi Okui, and Kiyohiko Ito: Pyrimidine Derivatives. I. Synthesis of a New Series of Sulfanilamides having Dialkylamino Groups in the Pyrimidine Nucleus.*1

(*Research Laboratories, Chugai Pharmaceutical Co., Ltd.**2)

Up to the present time, a large number of sulfanilamidopyrimidines have been prepared in connection with research on new chemotherapeutic agents, and some of them have been used as medicines. Considering the history and development of the sulfanilamides, the authors have been greatly interested in changing the substituentes on the heterocyclic ring. For instance, sulfisomidine having two methyl groups on the pyrimidine ring was found to have stronger and broader antibacterial activities than sulfadiazine having no substituent, and had been used as an excellent sulfa drug in the early stage of the development. However, in 1956, sulfadimethoxine, in which the two methyl groups of sulfisomidine were replaced by two methoxy groups, was presented.[1] This replacement produced more beneficial change in the biological properties. Sulfadimethoxine is well absorbed, maintains prolonged blood concentration, displays a low degree of acetylation, has a low urinary excretion rate, and is less toxic. Consequently, the methoxy group was noted by many investigators as an effective substituent, resulting in the appearance of some valuable compounds such as N^1-(5-methoxy-

*1 Presented at the 83rd annual meeting of the Pharmaceutical Society of Japan (1963).

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1) W. Klötzer: Monatsh. Chem., 87, 131 (1956).

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2-pyrimidyl)sulfanilamide,[2] N^1-(6-methoxy-2-pyrimidyl)sulfanilamide[3] and N^1-(4,6-dimethoxy-2-pyrimidyl)sulfanilamide.[4] The similar history (H→CH_3-Cl-OCH_3) can also be observed in sulfanilamides having other heterocyclic rings.

Considering the facts described above, the authors' attention has been drawn to a dimethylamino group as new substituent: The dimethylamino group is more electron-donating than the methoxy group, and may be assumed to be correlated with antifolic-action.[5] The present investigation was undertaken with a view to studying the preparetion of a new series of sulfanilamides having dialkylamino groups and related compounds in order to lead to new derivatives capable of supplanting older sulfanilamides.

N^1-(2-Alkoxy-6-dimethylamino-4-pyrimidyl)sulfanilamides

Reaction of 2-alkoxy-4-amino-6-chloropyrimidines[6] with dimethylamine in absolute methanol gave 2-alkoxy-4-amino-6-dimethylaminopyrimidines, which were condensed with *p*-acetamidobenzenesulfonyl chloride in pyridine by usual method followed by hydrolysis with aqueous sodium hydroxide solution to give the desired N^1-(2-alkoxy-6-dimethylamino-4-pyrimidyl)sulfanilamides. When 4-amino-6-chloro-2-methoxypyrimidine (I) was allowed to react with dimethylamine in commercial methanol containing some water, the reaction usually did not proceed directly to the desired 4-amino-6-dimethylamino-2-methoxypyrimidine (II), but led to the formation of the undesired pyrimidone (IV)*3 (Chart 1). On the other hand, 4-amino-6-chloro-2-methoxypyrimidine, when treated with acid or alkali, was readily hydrolyzed to the demethylated compounds, 4-amino-6-chloro-2(1*H*)-pyrimidinone (III)*3; this ease of hydrolysis of the methoxy group in the 2-position was also noted with other 2-methoxypyrimidines. An attempt to hydrolyze II under the same condition as used to produce the foregoing demethylated compound (III) was unsuccessful, the unreacted compound being recovered, thus indicating that the methoxy group was stabilized by an electronic effect of the dimethylamino group in the 6-position. However, it was found that III, when treated with dimethylamine in commercial methanol containing some water, gave IV. As described here, the characteristic reactivity of 4-amino-6-chloro-2-methoxypyrimidine are of interest; further studies will be reported in more detail elsewhere.

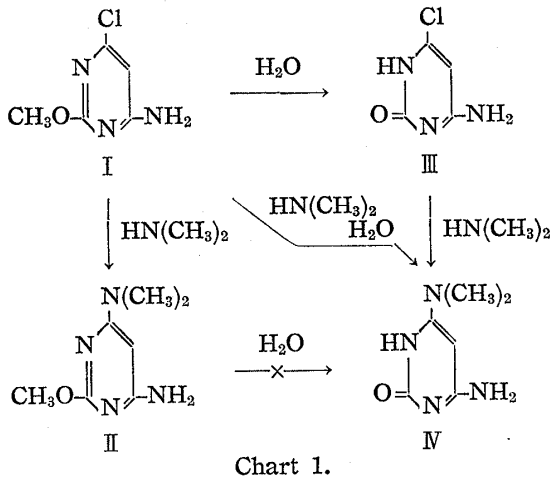

Chart 1.

N^1-(6-Alkoxy(or alkylthio)-2-dimethylamino-4-pyrimidyl)sulfanilamides

6-Alkoxy-4-amino-2-dimethylamino (or alkylthio)pyrimidines (VI or VII) were prepared by reaction of 4-amino-6-chloro-2-dimethylaminopyrimidine[7] (V) with the appropriate sodium alkoxides or sodium thioalkoxides under pressure (Chart 2).

*3 The compound (III) showed ν_{max}^{KBr} (cm^{-1}) 1690s (C=O) but no absorption at 1457s, 1364s (CH_3) and 1052m (C-OCH_3) which were presented in I having a methoxy group. Moreover, this structure may be formulated as shown in Chart 1. because of the known fact (A. R. Katritzky, A. J. Waring: J. Chem. Soc., **1963**, 3046) that cytosine exists predominantly as 4-amino-2-(1*H*)-pyrimidinone. The structure of IV was also formulated tentatively as 2(1*H*)-pyrimidinone from observations similar to III.

2) H. Horstmann, Th. Knott: Arzneimittel-Forsch., **11**, 682 (1961).
3) R. G. Shepherd, W. E. Taff, H. M. Krazinski: J. Org. Chem., **26**, 2764 (1961).
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6) J. Nakazawa, M. Watatani: Takamine Kenkyusho Nempo, **12**, 32 (1961); C. A., **55**, 6491 (1961).
7) W. R. Boon: J. Chem. Soc., **1952**, 1532.

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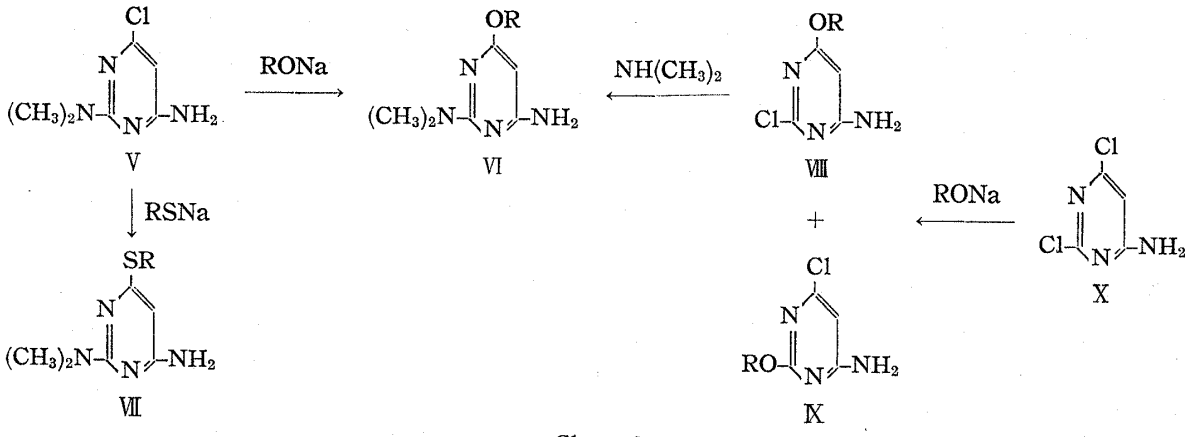

Chart 2.

6-Alkoxy compounds (Ⅵ) were also obtained from the appropriate 6-alkoxy-4-amino-2-chloropyrimidines (Ⅷ) by using the procedure described for 2-alkoxy-4-amino-6-dimethylaminopyrimidine. When 4-amino-2,6-dichloropyrimidine (X) was treated with same equivalent of sodium alkoxides, 6-alkoxy-4-amino-2-chloropyrimidine (Ⅷ) was formed in yields of 5~10%, together with major formation of isomeric 2-alkoxy-4-amino-6-chloropyrimidine (Ⅸ). Chemical proof of the structure of the 6-alkoxy compounds was obtained by the reaction sequence outlined in Chart 3.

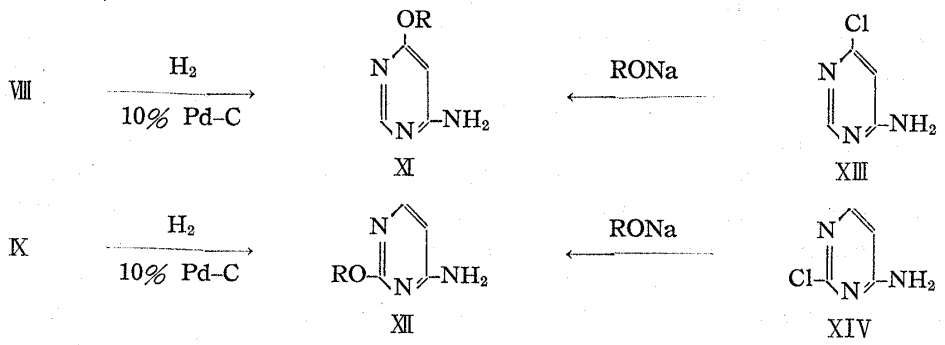

Chart 3.

Hydrogenation of Ⅷ and Ⅸ in the presence of 10% palladium on charcoal gave 6-alkoxy-4-aminopyrimidine (Ⅺ)[8,9] and 2-alkoxy-4-aminopyrimidine (Ⅻ)[10,11] respectively, which were found to be identical with the corresponding compounds obtained by treatment of 4-amino-6-chloropyrimidine (XIII)[12] and 4-amino-2-chloropyrimidine (XIV)[13] with sodium alkoxides, respectively. On the other hand, Ⅷ, when treated with sodium alkoxides or sodium thioalkoxides, afforded the corresponding 2-alkoxy or alkylthio compounds.*4 From the results mentioned above, it was found that Ⅷ*5 is 6-alkoxy-4-amino-2-chloropyrimidine.

*4 Some of these compounds were known (T. Tsuji, *et al.*: This Bulletin, **10**, 9 (1962)). Other unknown compounds were provided to prepare the coresponding sulfanilamides which will be reported elsewhere.

*5 The melting point of Ⅷ (R=C_2H_5) is similar as that of 4-amino-6-chloro-2-ethoxypyrimidine, but the acetylated compound, 4-acetamido-2-chloro-6-ethoxypyrimidine, is sharply distinguished from 4-acetamido-6-chloro-2-ethoxypyrimidine in the melting point.

8) N. Okuda, I. Kuniyoshi, Y. Oshima, S. Nagasaki: Yakugaku Zasshi, **82**, 1039 (1962).
9) W. Pfleiderer: Ann. Chem., **62**, 163 (1958).
10) S. Gabrial, J. Colman: Ber., **36**, 3382 (1903).
11) S. Spiteller, H. Bertschneider: Monatsh. Chem., **92**, 193 (1961).
12) C.W. Whitehead, J.J. Traverso: J. Am. Chem. Soc., **80**, 2185 (1958).
13) G.H. Hilbert, T.B. Johnson: *Ibid.*, **52**, 1155 (1930).

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Sulfanilamides of 6-alkoxy (or alkylthio)-4-amino-2-dimethylaminopyrimidines were prepared by the usual method. These compounds were identical with those prepared by reaction of 4-amino-6-chloro-2-dimethylaminopyrimidine (V) with *p*-acetamidobenzenesulfonyl chloride followed by hydrolysis with an aqueous sodium hydroxide solution and by treatment with sodium alkoxides or sodium thioalkoxides.

Of sulfanilamides obtained, N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)sulfanilamide showed significant antibacterial activity.

N^1-(6-Chloro-2-dialkylamino-4-pyrimidyl)sulfanilamides

The fact that N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)sulfanilamide was found to possess a strong activity directed the present work to the synthesis of 2-dialkylaminoderivatives, which were obtained from 4-amino-6-chloro-2-dialkylaminopyrimidines formed by reaction of 4-amino-2,6-dichloropyrimidine with secondary amines in a mild condition.

N^1-(2-(or 6)-Dimethylamino-4-pyrimidyl)sulfanilamides and N^1-[2,6-Bis(dimethylamino)-4-pyrimidyl]sulfanilamide

While N^1-(6-dimethylamino-4-pyrimidyl)sulfanilamide was readily prepared by usual method from 4-amino-6-dimethylaminopyrimidine, attempted preparation of N^1-(2-dimethylamino-4-pyrimidyl)sulfanilamide from 4-amino-2-dimethylaminopyrimidine was unsuccessful, starting material being recovered. This synthetic method was found to be unsatisfactory for preparing N^1-(2-dimethylamino-4-pyrimidyl)sulfanilamide. However, the desired compound could be obtained by condensation of 4-amino-2-dimethylaminopyrimidine with *p*-nitrobenzenesulfonyl chloride followed by catalytic reduction of a nitro group in the presence of 10% palladium on charcoal. The compound was identical with the product obtained by elimination of chloro group of N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)sulfamilamide.

4-Amino-2,6-bis(dimethylamino)pyrimidine was obtained by reaction of 4-amino-2,6-dichloropyrimidine with dimethylamine under pressure. N^1-[2,6-Bis(dimethylamino)-4-pyrimidyl]sulfanilamide was prepared in 30% yield by reaction of 4-amino-2,6-bis(dimethylamino)pyrimidine with *p*-acetamidobenzenesulfonyl chloride followed by hydrolysis with methanolic sodium hydroxide. This sulfanilamide has a *pKa* value of 9.25. The higher value of *pKa* of this compound than methoxy compounds may be due to the more strongly electron-releasing property of the dimethylamino group than that of the methoxy group.

Sulfanilamides having a dimethylamino and an alkoxy or alkylthio groups do not show significant antibacterial activities. The dimethylamino group is more electron-donating than the methoxy group. Therefore, these sulfanilamides are much stronger bases (*pKa* ca. 7~8) than sulfadimethoxine (*pKa* 5.93).*[6] However, in contrast to these, N^1-(6-chloro-2-dialkylamino-4-pyrimidyl)sulfanilamides possess favorable activities. This reason is assumed that the electron-attracting property of a chloro group compensates in some degree the electron releasing effect on the pyrimidine ring caused by the dialkylamino group, and resulting adjustment of the *pKa* to the favorable value, 5.95, which show certain optimum distribution of electron density in the molecule to exhibit the biological activities. Particularly, N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)sulfanilamide is less toxic. rapidly absorbed, displays a low degree of acetylation and is well excreted in the urine as an active form. This compound will be effective against systematic infections as well as against urinary infection.*[7]

*[6] The *pKa* values and the antibacterial activities of these sulfanilamides will be reported in the later paper.

*[7] The chemotherapeutic investigation of these drugs was made under the direction of Dr. H. Oya in the department of Microbiology and will be reported in detail elsewhere.

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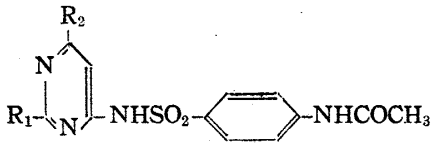
TABLE I. N^1-4-Pyrimidyl-N^4-acetosulfanilamides



R_1	R_2	m.p. (°C)	Yield (%)	Cryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3O	$(CH_3)_2N$	218～220	82	CH_3OH	$C_{15}H_{19}O_4N_5S$	49.31	5.24	19.19	49.56	5.46	19.42
C_2H_5O	〃	220～224	74	〃	$C_{16}H_{21}O_4N_5S$	50.65	5.58	18.46	48.42	5.04	14.30
C_3H_7O	〃	215～216	70	〃	$C_{17}H_{23}O_4N_5S$	51.90	5.89	17.80	52.04	5.80	17.36
iso-C_3H_7O	〃	166～167	74	〃	〃	51.90	5.89	17.80	50.13	6.12	19.70
$(CH_3)_2N$	CH_3O	251～253	69	〃	$C_{15}H_{19}O_4N_5S$	49.31	5.24	19.17	49.52	5.48	19.20
〃	C_2H_5O	223～224	75	〃	$C_{16}H_{21}O_4N_5S$	50.65	5.58	18.46	50.45	5.70	18.17
〃	C_3H_7O	161～162	73	〃	$C_{17}H_{23}O_4N_5S$	51.90	5.89	17.80	51.67	6.21	18.11
〃	C_2H_5S	226～227	81	CH_3OH+H_2O	$C_{16}H_{21}O_3N_5S_2$	48.60	5.53	17.72	45.97	5.66	17.79
〃	C_3H_7S	203～205	75	〃	$C_{17}H_{23}O_3N_5S_2$	49.87	5.66	17.11	50.06	5.73	18.86
〃	iso-C_3H_7S	180～182	86	〃	〃	49.87	5.66	17.11	49.95	5.51	17.33
〃	Cl	261～262	70	CH_3OH	$C_{14}H_{16}O_3N_5SCl$	45.46	4.36	18.93	45.55	4.56	18.95
$(C_2H_5)_2N$	〃	194～195	50	〃	$C_{16}H_{20}O_3N_5SCl$	48.30	5.07	17.60	48.40	5.02	18.46
$(C_3H_5)_2N$	〃	178～179	29	CH_3OH+H_2O	$C_{18}H_{20}O_3N_5SCl$	51.25	4.78	16.61	51.49	4.88	16.70
CH_2-CH_2 | CH_2-CH_2 >N	〃	234～235	81	〃	$C_{16}H_{18}O_3N_5SCl$	48.54	4.58	17.69	47.23	4.51	18.77
O< CH_2-CH_2 CH_2-CH_2 >N	〃	273～274	75	acetone	$C_{16}H_{18}O_4N_5SCl$	46.65	4.40	17.00			
H	$(CH_3)_2N$	296～297	72	CH_3OH	$C_{14}H_{17}O_3N_5S$	50.14	5.11	20.89	48.81	5.19	19.57
$(CH_3)_2N$	〃	210～215[a)]	32								
CH_3S	〃	230～235[b)]	85								

a) The melting point is of crude product. Attempt to purify was unsuccessful.
b) The compound was not isolated in pure form, but was utilized in the crude state for the next stage.

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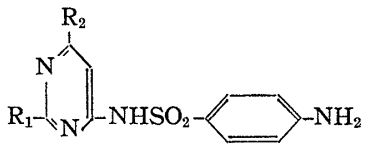
TABLE II. N^1-4-Pyrimidyl-sulfanilamides



R_1	R_2	m.p. (°C)	Method[a]	Yield (%)	Cryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3O	$(CH_3)_2N$	207～208[b]	A	95	CH_3OH	$C_{13}H_{17}O_3N_5S$	48.29	5.30	21.66	48.02	5.42	21.51
C_2H_5O	〃	228～230	〃	87	CH_3OH+H_2O	$C_{14}H_{19}O_3N_5S$	49.84	5.60	20.76	49.52	5.70	20.04
C_3H_7O	〃	182～183	〃	92	〃	$C_{15}H_{21}O_3N_5S$	51.27	6.02	19.93	51.40	6.11	19.96
iso-C_3H_7O	〃		〃	92	〃	〃	51.27	6.02	19.93	50.86	5.88	18.90
$(CH_3)_2N$	CH_3O	218～220	A, B	90 (87)	〃	$C_{13}H_{17}O_3N_5S$	48.29	5.30	21.66	48.11	5.20	21.26
〃	C_2H_5O	185～186	〃	90 (82)	〃	$C_{14}H_{19}O_3N_5S$	49.84	5.68	20.76	49.62	5.65	20.90
〃	C_3H_7O	90～ 91	A	65	acetone+benzene	$C_{15}H_{21}O_3N_5S$	51.27	6.02	19.93	51.05	6.14	20.01
〃	C_2H_5S	139～140	A, B	87 (74)	CH_3OH+H_2O	$C_{14}H_{19}O_2N_5S_2$	47.59	5.42	19.82	47.45	5.58	19.75
〃	C_3H_7S	165～167	A	70	〃	$C_{15}H_{21}O_2N_5S_2$	49.04	5.76	19.07	49.42	5.97	18.86
〃	iso-C_3H_7S	170～171	〃	76	〃	〃	49.04	5.76	49.07	49.58	5.98	19.11
〃	Cl	203～204	〃	92	acetone+H_2O	$C_{12}H_{14}O_2N_5SCl$	43.97	4.33	21.33	44.06	4.55	20.25
$(C_2H_5)_2N$	〃	178～180	〃	93	CH_3OH+H_2O	$C_{14}H_{18}O_2N_5SCl$	47.25	5.10	19.68	47.60	5.28	19.91
$(C_3H_5)_2N$	〃	170～172	〃	98	〃	$C_{16}H_{18}O_2N_5SCl$	50.60	4.75	18.48	50.79	4.67	18.46
CH_2-CH_2 >N CH_2-CH_2	〃	234～235	〃	84	acetone+H_2O	$C_{14}H_{16}O_2N_5SCl$	47.56	4.56	19.83	47.72	4.21	20.09
O< CH_2-CH_2 >N CH_2-CH_2	〃	280～282	〃	89	〃	$C_{14}H_{16}O_3N_5SCl$	45.46	4.36	18.93	45.44	4.47	19.07
H	$(CH_3)_2N$	276～277	〃	64	CH_3OH	$C_{12}H_{15}O_2N_5S$	49.14	5.16	23.88	49.04	5.28	23.88
$(CH_3)_2N$	H	146～147	C	82	CH_3OH+H_2O	〃	49.14	5.16	23.88	49.02	5.40	23.74
〃	$(CH_3)_2N$	221～223	A	56	CH_3OH	$C_{14}H_{20}O_2N_6S$	49.99	5.99	24.99	49.73	5.98	24.60
$(C_2H_5)_2N$	CH_3O	186～188	B	85	CH_3OH+H_2O	$C_{15}H_{21}O_3N_5S$	51.27	6.02	19.93	50.97	6.20	19.63
CH_3S	$(CH_3)_2N$	242～243	A	68	〃	$C_{13}H_{17}O_2N_5S_2$	46.01	5.05	20.64	46.10	5.13	20.43

a) Method A : from N^1-4-pyrimidyl-N^4-acetosulfanilamides
Method B : from N^1-(6-chloro-2-dialkylamino-4-pyrimidyl)-sulfanilamides
Method C : by catalytic hydrogenation of N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)-sulfanilamide
b) H. Bretschneider, J. Dehler, W. Klötzer : Monatsh. Chem., **95**, 207 (1964).

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Experimental*8

Most of all products are characterized in Table I, II, III and IV.

2-Alkoxy-4-amino-6-chloropyrimidines——A solution of 7.1 g. (0.31 mole) of sodium in 300 ml. of the appropriate alcohols was added dropweise to a solution of 50 g. (0.31 mole) of 4-amino-2,6-dichloropyrimidine[14] in 3 L. of the foregoing alcohols in the course of 6 hr. at 50~60° under stirring. After 20 hr., the alcohol was removed *in vacuo*. The resulting residue was washed with water and recrystallized from H_2O or dil. CH_3OH.

2-Alkoxy-4-amino-6-dimethylaminopyrimidines——2-Alkoxy-4-amino-6-chloropyrimidines (0.125 mole) were dissolved in 20% absolute methanolic dimethylamine solution. The mixture was heated at 120° for 4~6 hr. in a sealed thbe, and concentrated. Addition of water gave yellow product, which was allowed to crystallize. The products were purified by recrystallization from H_2O or benzene.

Hydrolysis of 4-Amino-6-chloro-2-methoxypyrimidine (I)——Sixteen grams (0.1 mole) of 4-amino-6-chloro-2-methoxypyrimidine was added to 200 ml. of 10% aq. NaOH. The resulting mixture was heated on a steam bath for 2 hr. After cooling, the solution was brought to pH 6 with AcOH. The resulting solid was recrystallized from H_2O, giving III, 4-amino-6-chloro-2(1*H*)-pyrimidone, yield 12 g. (82%), m.p. >300°. *Anal.* Calcd. for $C_4H_4ON_3Cl$: C, 33.01; H, 2.77; N, 28.87. Found: C, 33.22; H, 2.76; N, 28.75.

4-Amino-6-dimethylamino-2(1*H*)-pyrimidinone (IV)——a) A solution of 20 g. (0.125 mole) of 4-amino-6-chloro-2-methoxypyrimidine in 200 ml. of 20% methanolic dimethylamine solution was heated at 120° for 6 hr. in a sealed tube. The mixture was concentrated. To the residue was added a 10% aq. NaOH solution, and the solution was filtered. The filtrate was brought to pH 6 with AcOH. The resulting solid was recrystallized from H_2O, giving product (12 g.), m.p. >300°. *Anal.* Calcd. for $C_6H_{10}ON_4$: C, 46.74; H, 6.54; N, 36.34. Found: C, 47.05; H, 6.66; N, 36.10.

b) A solution of 14.5 g. (0.1 mole) of III in 400 ml. of 20% methanolic dimethylamine solution was heated at 140° for 6 hr. in a sealed tube, and then concentrated. IV was obtained by treating the residue as in the above experiment.

4-Amino-6-chloro-2-dialkylaminopyrimidines——Sixty grams (0.66 mole) of 4-amino-2,6-dichloropyrimidine (X) was added to 300 ml. of 20% methanolic dialkylamine solution. The mixture, when stirred at room temperature sometimes with heating, became clear within about 4 hr., and then was concentrated *in vacuo*. The product was recrystallized from benzene or ligroin. Examples of unsuccessful attempts to crystallize the product are given in the following section.

4-Amino-6-chloro-2-diallylaminopyrimidine——A solution containing 3.3 g. (0.02 mole) of 4-amino-2,6-dichloropyrimidine and 2 g. (0.02 mole) of diallylamine in 50 ml. of CH_3OH was heated at 90° for 3 hr. in a sealed tube. The solution was concentrated. To the oily residue was added water, and the solution was extracted with ether. The ether layer was dried over K_2CO_3 and concentrated. The residue was a pale yellow oily substance and attempts to crystallize were unsuccessful.

Acetylation of the oily substance with Ac_2O gave a solid of the desired product. Recrystallization from ligroin gave the crystalline 4-acetamido-6-chloro-2-diallylaminopyrimidine, m.p. 91~93°.

4-Amino-2-chloro-6-methoxypyrimidine (VIII)——A solution of 7.1 g. (0.31 mole) of sodium in 3 ml. of CH_3OH was added dropwise to a solution of 50 g. (0.307 mole) of X in 2.5 L. of CH_3OH in the course of 6 hr. at 50~60° under stirring. After 20 hr., the solution was concentrated to a volume of 300 ml. and diluted with 700 ml. of hot water. After standing over night at room temperature, precipitation, 4-amino-6-chloro-2-methoxypyrimidine (white needles), was removed by filtration. On cooling the filtrate to −10°, a mixture of the foregoing compound and the desired product was obtained. When the mixture was washed with CH_3OH, and recrystallized from CH_3OH, 4-amino-2-chlro-6-methoxypyrimidine was obtained a whith prisms. Yield, 3.5 g.

6-Alkoxy-4-aminopyrimidines (XI)——VIII (0.01 mole) in 100 ml. of 1% methanolic ammonia solution was hydrogenated using 0.2 g. of 10% palladium on charcoal at room temperature and atmospheric pressure. The catalyst was removed and the filtrate was evaporated *in vacuo*. The resulting solid was recrystallized from benzene.

b) These compounds were prepared acording to the method given in the literature.[8]

2-Alkoxy-4-aminopyrimidine (XII)——a) These compounds were prepared from IX under the same conditions used to prepare XI from VIII.

b) These compounds were also obtained from 4-amino-2-chloropyrimidine (XIV)[13] under the same conditions used to prepare XI from 4-amino-6-chloropyrimidine (XIII).

The following derivative is soluble in water in contrast with other derivatives.

4-Amino-2-ethoxypyrimidine——4-Amino-6-chloro-2-ethoxypyrimidine (17.4 g., 0.1 mole) in 500 ml. of 1% methanolic ammonia solution was hydrogenated using 1.5 g. of 10% palladium on charcoal. The

*8 All melting points are uncorrected.

14) V. H. Smith, B. E. Christensen: J. Org. Chem., **20**, 829 (1955).

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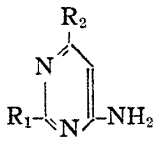
TABLE III. 2,6-Disubstituted-4-aminopyrimidines



R_1	R_2	m.p. (°C)	Method[a]	Yield (%)	Cryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3O	Cl	127~128		72	H_2O	$C_5H_6ON_3Cl$	37.63	3.79	26.33	37.66	3.80	26.16
C_2H_5O	〃	128~129		75	CH_3OH+H_2O	$C_6H_8ON_3Cl$	41.51	4.65	24.21	41.45	4.70	24.00
C_3H_7O	〃	114~115		78	〃	$C_7H_{10}ON_3Cl$	44.81	5.37	22.39	44.97	5.76	22.32
iso-C_3H_7O	〃	134~135		72	〃	〃	44.81	5.37	22.39	44.72	5.40	22.49
CH_3O	$(CH_3)_2N$	158~159		85	H_2O	$C_7H_{12}ON_4$	49.98	7.19	33.31	49.73	6.97	33.25
C_2H_5O	〃	136~137		95	benzene	$C_8H_{14}ON_4$	52.73	7.74	30.75	53.11	7.84	30.45
C_3H_7O	〃	96~ 97		87	ligroin	$C_9H_{16}ON_4$	55.08	8.22	28.55	55.23	8.47	28.51
iso-C_3H_7O	〃	105~106		82	〃	〃	55.08	8.22	28.55	55.26	8.00	28.75
$(CH_3)_2N$	Cl	152~153		73	H_2O	$C_6H_9N_4Cl$	41.74	5.25	32.42	41.69	5.14	33.03
$(C_2H_5)_2N$	〃	124~125		75	benzene	$C_8H_{13}N_4Cl$	47.88	6.53	27.92	47.72	6.22	28.41
$(C_3H_5)_2N$	〃	91~ 93[b]			ligroin	$C_{12}H_{15}N_4Cl$	54.03	5.67	21.01	54.09	5.97	21.11
CH_2-CH_2 >N CH_2-CH_2	〃	184~185		90	CH_3OH+H_2O	$C_8H_{11}N_4Cl$	48.36	5.59	28.18	48.22	5.69	30.00
O<CH_2-CH_2 >N CH_2-CH_2	〃	153~154		84	〃	$C_8H_{11}ON_4Cl$	44.75	5.16	26.10	44.65	5.15	26.10
$(CH_3)_2N$	CH_3O	93~ 94	A	95	ligroin	$C_7H_{12}ON_4$	49.98	7.19	33.31	50.07	6.96	33.23
〃	C_2H_5O	86~ 87	〃	87	CH_3OH+H_2O	$C_8H_{14}ON_4$	52.73	7.74	30.75	52.49	7.61	30.42
Cl	CH_3O	187~188		7.2	CH_3OH	$C_5H_6ON_3Cl$	37.63	3.79	26.33	37.68	3.86	26.44
〃	C_2H_5O	133~134		7	〃	$C_6H_8ON_3Cl$	41.51	4.65	24.21	41.45	4.62	24.40
CH_3O	H	168~169	A	75	H_2O	$C_5H_7ON_3$	47.99	5.64	33.58	47.97	5.47	33.61
C_2H_5O	〃	83~ 86	〃	86	ligroin	$C_6H_9ON_3$	51.78	6.52	30.20	51.64	6.37	30.60
C_3H_7O	〃	77~ 78	〃	86	〃	$C_7H_{11}ON_3$	54.88	7.24	27.43	54.63	7.23	27.75
iso-C_3H_7O	〃	75~ 76	〃	85	〃	〃	54.88	7.24	27.43	54.53	7.20	27.30
H	CH_3O	155~156	〃	88	benzene	$C_5H_7ON_3$	47.99	5.64	33.58	46.91	5.46	33.64
〃	C_2H_5O	151~152	〃	86	〃	$C_6H_9ON_3$	51.78	6.52	30.20	51.84	6.61	30.77
〃	PrO	132~133	B	90	〃	$C_7H_{11}ON_3$	54.88	7.24	27.43	55.14	7.42	27.89
〃	iso-PrO	93~ 94	〃	92	〃	〃	54.88	7.24	27.43	54.25	7.16	28.12
〃	BuO	126~127	〃	85	〃	$C_8H_{13}ON_3$	57.46	7.84	25.13	57.81	7.96	25.21
〃	iso-BuO	132~134	〃	75	〃	〃	57.46	7.84	25.13	57.57	7.83	25.09
〃	*s*-BuO	66~ 67	〃	75	〃	〃	57.46	7.84	25.13	58.21	7.38	25.98
CH_3O	CH_3O	150~151[1]		96	CH_3OH+H_2O	$C_6H_9O_2N_3$						

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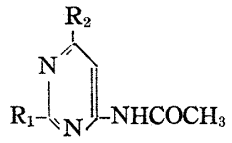
C_2H_5O	〃	144～145[1)]	94	〃	$C_7H_{11}O_2N_3$	49.69	6.55	24.84	49.91	6.38	25.02
iso-C_3H_7O	〃	98～ 99	91	〃	$C_8H_{13}O_2N_3$	52.44	7.15	22.94	52.55	7.00	22.84
CH_3O	C_2H_5O	112～113	95	〃	$C_7H_{11}O_2N_3$	49.69	6.55	24.84	49.55	6.60	24.84
CH_3S	CH_3O	143～144*[4]	94	〃	$C_6H_9ON_3S$	42.10	5.30	24.55	41.94	5.29	24.53
C_2H_5S	〃	116～117	83	〃	$C_7H_{11}ON_3S$	45.40	5.99	22.69	45.38	6.12	22.64
C_3H_7S	〃	99～100	80	〃	$C_8H_{13}ON_3S$	48.23	6.58	21.10	49.89	7.07	21.30
iso-C_3H_7S	〃	116～117	86	〃	〃	48.23	6.58	21.10	48.38	6.69	21.07
CH_3S	C_2H_5O	92～ 93*[4]	93	〃	$C_7H_{11}ON_3S$	45.40	5.99	22.69	45.31	5.84	22.65
iso-C_3H_7S	〃	74～ 75	95	〃	$C_9H_{15}ON_3S$	50.69	7.09	19.71	50.80	7.27	19.92
$(CH_3)_2N$	H	153～155	90	benzene	$C_6H_{10}N_4$	52.15	7.30	40.55	52.42	7.19	40.83
〃	$(CH_3)_2N$	116～117	75	H_2O	$C_8H_{15}N_5$	53.01	8.34	38.64	53.04	8.20	38.88

a) A and B show the a and b method in each compound, respectively, as described in the experiment.
b) The melting point showed of the acetylated compound because attempts to crystallize were unsuccessful.

TABLE IV. 2,6-Disubstituted-4-acetamidopyrimidines



R_1	R_2	m.p. (°C)	Yield (%)	Cryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3O	Cl	195～196	94	CH_3OH	$C_7H_8O_2N_3Cl$	41.70	3.99	20.84	41.64	4.02	20.86
C_2H_5O	〃	194～196	94	〃	$C_8H_{10}O_2N_3Cl$	44.41	4.99	19.84	44.72	4.83	19.30
Cl	CH_3O	216～217	93	〃	$C_7H_8O_2N_3Cl$	41.70	3.99	20.84	41.70	4.12	20.88
〃	C_2H_5O	215～216	90	〃	$C_8H_{10}O_2N_3Cl$	44.41	4.99	19.42	44.45	4.70	19.56
H	CH_3O	138～139	94	〃	$C_7H_9O_2N_3$	50.27	5.43	25.14	49.90	5.42	25.14
〃	C_2H_5O	130～131	95	〃	$C_8H_{11}O_2N_3$	53.03	6.12	23.19	52.89	6.16	23.18
〃	PrO	135～136	74	〃	$C_9H_{13}O_2N_3$	55.37	6.71	21.53	55.46	6.71	21.72
〃	iso-PrO	105～106	70	〃	〃	55.37	6.71	21.53	55.12	6.62	21.66
〃	BuO	95～ 96	63	〃	$C_{10}H_{15}O_2N_3$	57.40	7.23	20.08	57.56	7.25	20.13
$(CH_3)_2N$	CH_3O	187～188	90	CH_3OH+H_2O	$C_9H_{14}O_2N_4$	51.42	6.71	26.65	51.63	6.82	27.00
〃	C_2H_5O	166～167	92	〃	$C_{10}H_{16}O_2N_4$	53.55	7.19	24.99	53.50	7.41	24.91
〃	PrO	165～167	84	〃	$C_{11}H_{18}O_2N_4$	55.44	7.61	23.52	55.45	7.42	23.79
〃	iso-PrO	156～157	87	〃	〃	55.44	7.61	23.52	55.23	7.72	23.73
〃	C_2H_5S	155～156	83	〃	$C_{10}H_{16}ON_4S$	49.99	6.71	23.32	49.50	6.70	23.37
〃	PrS	165～167	94	〃	$C_{11}H_{18}ON_4S$	51.95	7.14	22.03	51.69	7.51	21.77
〃	iso-Prs	186～187	90	〃	〃	51.95	7.14	22.03	52.46	7.99	21.19

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product which is soluble in water was purified by sublimation. The yield of sublimed product was 12 g. (86%), m.p. 84°. Spraque, *et al.*[15] reported that the melting point of this compound was 152°. However, our result was agreement with that by Klötzer.[16] One gram of this product was dissolved in 2 ml. of 35% HCl, and the solution was chilled in an ice bath, 0.7 g. of colorless needles (m.p. 168°) appeared. The hydrochloride is insoluble in water in contrast of the free base. *Anal.* Calcd. for $C_6H_9ON_3 \cdot \frac{1}{2}HCl$: C, 45.78; H, 6.08; N, 26.70; Cl, 11.26. Found: C, 45.56; H, 6.04; N, 27.35; Cl, 10.42.

4-Amino-2,6-dialkoxypyrimidines——These compounds were obtained from Ⅷ by using the appropriate alcohols and NaOH. The products were recrystallized from dil. CH_3OH.

6-Alkoxy-2-alkylthio-4-aminopyrimidines——Ⅷ (0.01 mole) and sodium thioalkoxids (0.015 mole) were dissolved in 50 ml. of the appropriate alcoholes. The mixture was heated on a steam bath for 3 hr. The solvent was removed by evaporation. The resulting residue was diluted with H_2O. The precipitate was recrystallized from dil. CH_3OH.

6-Alkoxy-4-amino-2-dimethylaminopyrimidines (VI)——a) Ⅷ (0.01 mole) was added to 200 ml. of 10% methanolic dimethylamine solution. The mixture was heated at 100° for 5hr. in a sealed tube and concentrated. The residual oil was allowed to cool. The solidified product was recrystallized from benzene or ligroin.

b) To 10 g. (0.058 mole) of Ⅴ in absolute appropriate alcohol was added 2 g. of sodium. The mixture was heated at 100° for 5 hr. in a sealed tube and concentrated. The resulting residue was diluted with benzene. The precipitate was recrystallized from benzene or ligroin.

Propoxy and iso-propoxy compounds were oily substance and attempts to crystallize were unsuccessful. However acetylation of the oily substance with Ac_2O gave the crystalline product.

6-Alkylthio-4-amino-2-dimethylaminopyrimidines (VII)——These derivatives wereprepared by the reaction of the corresponding 6-chloropyrimidines (Ⅴ) with sodium thioalkoxides in a sealed tube at 100° for 5 hr. The products were oily substance and attempts to crystallize were unsuccessful. Acetates of Ⅶ were obtained as crystals.

4-Amino-2-dimethylaminopyrimidine——This compound was prepared from 4-Amino-2-chloropyrimidine (XIV) and dimethylamine in CH_3OH under the similar method used to prepare Ⅵ from Ⅷ. On the other hand, this compound was also prepared from Ⅴ by hydrogenation with 10% palladium on charcoal in CH_3OH at room temperature and atmospheric pressure.

4-Amino-2,6-bis(dimethylamino)pyrimidine (XXXI)——Thirty grams (0.183 mole) of Ⅹ was dissolved in 200 ml. of 20% methanolic dimethylamine solution. The solution was heated at 120~130° for 6 hr. in a sealed tube, concentrated and diluted with 100 ml. of 10% aq. NaOH. The solution was chilled in an ice bath, whereupon crystals appeared. Recrystallization from H_2O gave pale yellow needle-like crystals, yield 25 g.

N^1-(4-Pyrimdyl)-N^4-acetylsulfanilamides——4-Aminopyrimidines and *p*-acetamidobenzenesulfonyl chloride (1~1.2 mole) were dissolved in pyridine (1 ml. of pyridine per gram of the chloride). The mixture was allowed to stand for 12 hr. at room temperature, added to 100 ml. of H_2O, and then allowed to stand in a cold room for 2 or 3 days. Filtration gave crude product, which was deacetylated without further purification. The product, after a odor of pyridine disappeared completely, was dissolved in hot CH_3OH. When the solution was decolorized with charcoal and concentrated to 1/3 volume, crystals precipitated. One recrystallization from CH_3OH usually gave product of high purity in yields of 29~86%.

N^1-(4-Pyrimidyl)sulfanilamides——The foregoing acetosulfanilamides were dissolved in approximately 10 volumes of 10% aq. NaOH. The mixture was heated at 100° for 1 hr. on a steam bath. After cooling, the solution was neutratilzed with AcOH. The resulting precipitate was recrystallized from dilute CH_3OH or acetone. Yield, 64~98%.

N^1-(6-Chloro-2-dimethylamino-4-pyrimidyl)sulfanilamide——Thirty two grams (0.186 mole) of Ⅴ and 56 g. (0.24 mole) of *p*-acetamidobenzenesulfonyl chloride were dissolved in 50 ml. of pyridine. The mixture was allowed to stand at room temperature for 12 hr. and then diluted with H_2O. Recrystallization of the resulting precipitate from dil. CH_3OH gave a pale yellow crystalline N^4-acetylsulfanilamide compound, yield, 48.3 g.

The N^1-(4-pyrimidyl)-N^4-acetylsulfanilamide (37 g.) was dissolved in 370 ml. of 10% NaOH. The solution was heated at 100° for 1 hr., and then neutralized with AcOH. The resulting oily substance solidified while being kept in an ice bath. The solid was filtered and recrystallized from dil. acetone giving 30 g. of pale yellow prisms.

N^1-(2-Dimethylamino-6-methoxy-4-pyrimidyl)sulfanilamide——To a solution of 0.5 g. (0.022 mole) of sodium in 100 ml. of absolute CH_3OH was added 3.3 g. (0.011 mole) of N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)sulfanilamide. The solution was heated at 130° for 5 hr. in a sealed tube, and the solvent was then removed. The residue was dissolved in H_2O and neutralized with AcOH to precipitate. The precipitate was filtered and recrystallized from dil. CH_3OH giving 2.5 g. (77%) of white crystals (m.p. 220~221°).

15) J.M. Spraque, R.M. Lincoln, L.W. Kissinger: J. Am. Chem. Soc., **63**, 3028 (1941).
16) W. Klötzer, J. Schantl: Monatsh. Chem., **94**, 1178 (1963).

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Identity of this product with the compound from 4-amino-2-dimethylamino-6-methoxypyrimidine and *p*-acetamidobenzenesulfonyl chloride was demonstrated by comparision of IR absorption spectra and an undepressed mixed melting point.

N-(2-Dimethylamino-4-pyrimidyl)-*p*-nitrobenzenesulfonamide——A solution of 1.4 g. (0.01 mole) of 4-amino-2-dimethylaminopyrimidine and 2.2 g. (0.01 mole) of *p*-nitrobenzenesulfonyl chloride in 2.5 ml. of pyridine was allowed to stand at room temperature for 12 hr., and then diluted with 30 ml. of H_2O. The resulting solid was washed well with CH_3OH, and dissolved in 10% aq. NaOH. To the solution was added a small amount of CH_3OH. The solution was acidified with dil. AcOH, which resulted in the precipitation of yellow product. Recrystallization from dil. CH_3OH gave 1.6 g. (49%) of pale yellow needles, m.p. 236~237°. *Anal.* Calcd. for $C_{12}H_{13}O_4N_5S$: C, 44.58; H, 4.05; N, 21.67. Found: C, 44.72; H, 4.13; N, 21.81.

N^1-(2-Dimethylamino-4-pyrimidyl)sulfanilamide——a) To a solution of 1.6 g. (0.005 mole) of N-(2-dimethylamino-4-pyrimidyl)-*p*-nitrobenzenesulfonamide in 50 ml. of CH_3CH and 4 ml. (0.01 mole) of 10% aq. NaOH, 0.2 g. of 10% palladium on charcoal was added and the mixture was shaken with hydrogen at room temperature and atmosphoric pressure. At the end of reaction the catalyst was removed and the filtrate was concentrated at 40~50°. The residue was diluted with H_2O, and the solution was brought to pH 6.5 giving 0.6 g. of a crystalline precipitate (m.p. 165°). The structure of this product remained unestablished. The filtrate was evaporated to dryness. The residue was dissolved in CH_3OH. The solution was treated with charcoal, concentrated to its half volume, and allowed to stand in a cold room. An oily substance was separated. The methanol layer was diluted with a small amount of H_2O to separate pale yellow crystals. Recrystallization from dil. CH_3OH gave 0.6 g. (41%) of the desired product, m.p. 145~147 (decomp.).

b) To a solution of 3.3 g. (0.01 mole) of N^1-(6-chloro-2-dimethylamino-4-pyrimidyl)sulfanilamide of CH_3OH and 8 ml. (0.02 mole) of 10% aq. NaOH, 0.5 g. of 10% palladium on charcoal was added, and the mixture was shaken with hydrogen at room temperature and atmospheric pressure.

The catalyst was removed and the filtrate was concentrated at 40°. The residue was diluted with H_2O, and the solution was brought to pH 6.5 giving a precipitate. Recrystallization from dil. CH_3OH gave the desired product, yield, 2.6 g. Identity of the product with compound prepared by the foregoing method a) was demonstrated by IR comparision and an undepressed mixture melting point.

N^1-[2,6-Bis(dimethylamino)-4-pyrimidyl]sulfanilamide——A solution of 18 g. (0.1 mole) of 4-amino-2,6-bis(dimethylamino)pyrimidine and 23 g. (0.1 mole) of *p*-acetamidobenzenesulfonyl chloride in 23 ml. of pyridine was allowed to stand at room temperature for 12 hr., and then poured into 500 ml. of H_2O. The resulting oily substance soon solidified. The solid, was difficult to recrystallize m.p. 215°, yield, 12 g. (32%). A solution of 12 g. (0.0317 mole) of the solid in 100 ml. of 10% aq. NaOH and 30 ml. of CH_3OH was heated for 2 hr. on a steam bath, and then neutralized with AcOH to precipitate pale yellow needles, which were filtered and dissolved in a solution of NaOH in CH_3OH. The solution was then decolorized with charcoal. Neutralization of the solution with AcOH resulted in the precipitation 6 g. (56%) of the desired product. Upon addition of this product to 10% aq. NaOH, all of it dissolved temporarily, then its sodium salt began to precipitate slowly.

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Summary

The synthesis of a number of sulfonamides having dialkylamino groups in the pyrimidine nucleus was described. Among these new compounds, N^1-(6-chloro-2-dialkylamino-4-pyrimidyl)sulfanilamide were found to possess notable antibacterial activities.

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