Pyrimidine Derivatives. IV (1). Synthesis of N^1-(2-Methoxy-4-pyrimidyl)sulfanilamide (2)

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Received March 9, 1972

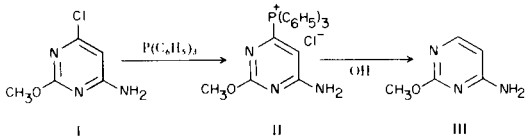
N^1-(2-Methoxy-4-pyrimidyl)sulfanilamide was successfully prepared through three alternative routes. Namely, the above compound was obtained by condensation of 4-amino-2-methoxypyrimidine (III) with *p*-acetaminobenzenesulfonyl chloride and *p*-nitrobenzenesulfonyl chloride and by direct condensation with sulfanilamide.

In the previous paper (4), it was pointed out that the N^1-(2-methoxy-4-pyrimidyl)sulfanilamide prepared by Backer and Grevenstuck (5) should be corrected to be N^1-(2-hydroxy-4-pyrimidyl)sulfanilamide, namely a hydroxy derivative formed by hydrolysis of methoxy group at the 2-position of the former compound. Furthermore, two of the authors reported the synthesis of the title compound in poor yield (4). Since the chemotherapeutic study revealed that N^1-(2-methoxy-4-pyrimidyl)sulfanilamide possessed an equal range of antibacterial activity spectrum with that of sulfadimethoxine or sulfisomezole, the modified synthesis of the title compound was studied. Herein we wish to report these results.

The starting 4-amino-2-methoxypyrimidine (III) was obtained in good yield by catalytic reduction of 4-amino-6-chloro-2-methoxypyrimidine (I) in the presence of palladium charcoal (6). However, in view of the difficulties in the use of palladium charcoal on an industrial scale, some other dechlorination reactions were investigated as follows. Reduction of I with zinc powder (7,8), desulfurization by Raney nickel of the thiol derivative prepared from I by replacement of the chlorine group (9), and reduction of the quarternary ammonium salt prepared from the tertiary amine were all unsuccessful.

Recently Egg and his co-workers (10) reported that chloropyrimidines could be dechlorinated by its conversion, by use of triphenylphosphine, to triphenylphosphonium chloride, followed by hydrolysis with sodium hydroxide.

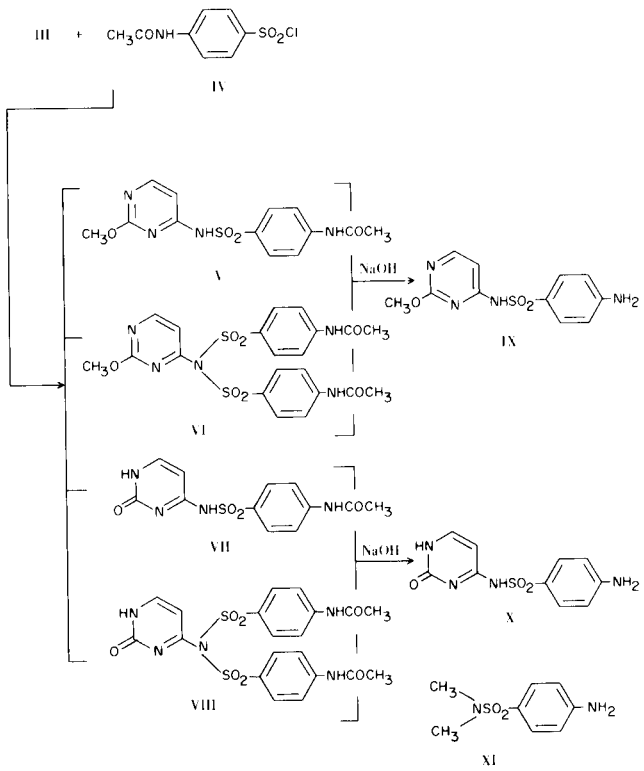
CHART 1



The reaction of I with triphenylphosphine was therefore carried out successfully to give the corresponding triphenylphosphonium chloride (II), which on heating in 5% sodium hydroxide solution afforded 4-amino-2-methoxypyrimidine (III).

In the examination of the preparation of the sulfanilamide (IX), the procedure by Klötzer and his co-worker

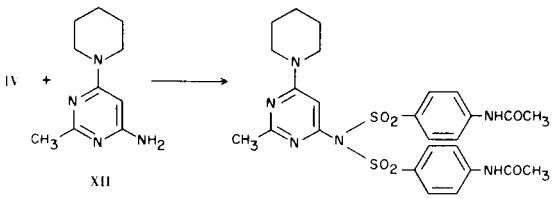
CHART 2



(11) was checked as first. Thus, the reaction of 4-amino-2-methoxypyrimidine (III) with *p*-acetaminobenzenesulfonyl chloride in benzene or dichloromethane was carried out in the presence of trimethylamine to give the following four products: N^1-(2-methoxy-4-pyrimidyl)-N^4-acetylsulfanilamide (V), N^1-(2-methoxy-4-pyrimidyl)-N^1-*p*-acetaminobenzenesulfonyl-N^4-acetylsulfanilamide (VI), 4-*p*-acetaminobenzenesulfonamido-2(1*H*)pyrimidone (VII), and 4-bis-(*p*-acetaminobenzenesulfonyl)amido-2(1*H*)pyrimidone (VIII).

The structures of compounds V and VII were identical with those of the authentic samples prepared previously (4,11). The bis-sulfonylamide derivatives VI and VIII had the molecular formula, $C_{21}H_{21}N_5O_7S_2 \cdot H_2O$ and $C_{20}H_{19}N_5O_7S_2 \cdot H_2O$, respectively, by microanalysis. The infrared spectra of these compounds VI and VIII supported these structures to be correct as Craveri and Zoni (12) had already reported the formation of the bis-sulfonylamide XIII from XII

CHART 3



XII XIII

Compounds V and VI were hydrolyzed individually with 1*N* sodium hydroxide solution to give the expected sulfanilamide (IX), which was identical with an authentic sample (4). In order to obtain pyrimidosulfanilamide (X), hydrolysis of compounds VII and VIII to X was also achieved by the method described above.

In addition to the above products, a trace amount of compound XI, m.p. 175°, was obtained from the mother liquor during hydrolysis. The infrared spectrum of XI showed a strong absorption at 1150 cm^{-1} attributable to SO_2 group. This substance was positive in Ehrlich reagent and easily soluble in 10% hydrochloric acid. These facts and its microanalysis supported the structure of *N*-dimethylsulfanilamide (XI), which was identical with an authentic sample prepared according to the method by Walker (13) by the mixed melting point test. The formation of the compound would be formed by the elimination of methyl chloride during the prolonged reaction of *p*-acetaminobenzenesulfonyl chloride with trimethylamine.

The condition of this reaction was examined from the point of the concentration of trimethylamine, solvent, temperature, reaction time, and condensing agent. After hydrolysis, these results were shown in Table I.

The optimun conditions were found to be as follows: four hours reaction time, 2.5 molar equivalents of trimethylamine to the compound IV, and the temperature between 5° and 10°. Thus the optimal total yield of 71% was attained under the conditions of No. 7, Table I. Pyridine, the solvent generally used in the synthesis of sulfonamides, was not suitable in this case since 4-amino-2-methoxypyrimidine (III) was found to be unstable in basic solvents, especially in pyridine, due to the presence of the methoxy group at the 2-position which is particularly susceptible to hydrolysis. Thus, in the case of the condensation of III with IV in the presence of pyridine, III was demethylated and no sulfonamide V was obtained.

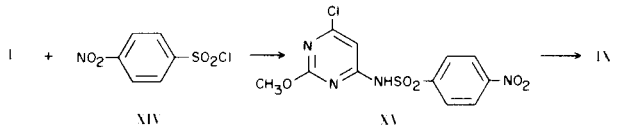
Secondly, 4-amino-6-chloro-2-methoxypyrimidine (I) was condensed with *p*-nitrobenzenesulfonyl chloride (XIV) in pyridine to give 6-chloro-2-methoxy-4-(*p*-nitrobenzenesulfonylamido)pyrimidine (XV), which was then catalytically reduced to give compound IX.

TABLE I

Reaction of 4-Amino-2-methoxypyrimidine (III) (0.02 mole) with *p*-Acetaminobenzenesulfonyl Chloride (IV) (0.024 mole), followed by Hydrolysis of Acetyl Derivatives.

						IX	
No.	Condensation	Reagent (mole)	Solvent	Temp. (°C)	Time (hour)	Yield (g.)	%
1	$N(CH_3)_3$	0.048	CH_2Cl_2	15	8	2.7	47
2	$N(CH_3)_3$	0.044	CH_2Cl_2	15	8	3.5	63
3	$N(CH_3)_3$	0.048	CH_2Cl_2	15	4	3.5	63
4	$N(CH_3)_3$	0.072	CH_2Cl_2	15	4	3.9	69
5	$N(CH_3)_3$	0.096	CH_2Cl_2	15	4	3.9	69
6	$N(CH_3)_3$	0.048	CH_2Cl_2	25	4	2.9	52
7	$N(CH_3)_3$	0.048	CH_2Cl_2	5	4	4.0	71
8	$N(C_2H_5)_3$	0.048	CH_2Cl_2	15	8	1.0	18
9	$N(CH_3)_3$	0.048	CH_3COCH_3	15	4	3.2	57

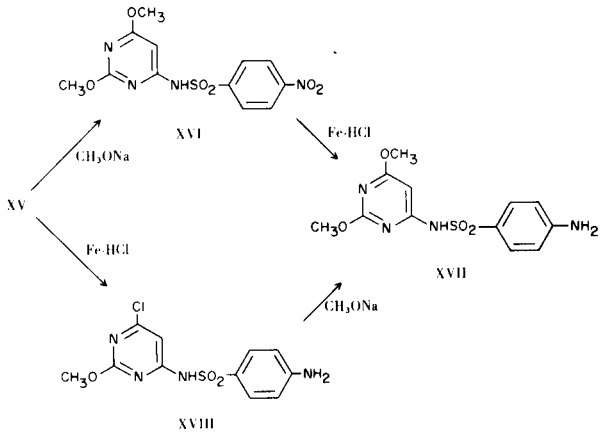
CHART 4



In this case, two by-products, one of which melted at 240° dec. and the other at 243-245° dec., were formed, but their identities remained unclear. In order to determine the structure of XV, this compound was treated with sodium methoxide in methanol to give 2,6-dimethoxy-4-(*p*-nitrobenzenesulfonylamido)pyrimidine (XVI), which was reduced with iron in hydrochloric acid to give the known N^1-(2,6-dimethoxy-4-pyrimidyl)sulfanilamide, namely sulfadimethoxine (XVII).

Furthermore, compound XV was converted in a similar way to N^1-(6-chloro-2-methoxy-4-pyrimidyl)sulfanilamide (XVIII), which was identical with an authentic sample reported in the previous paper (4). Compound XVIII was heated with sodium methoxide in methanol in a sealed tube to give compound XVII.

CHART 5

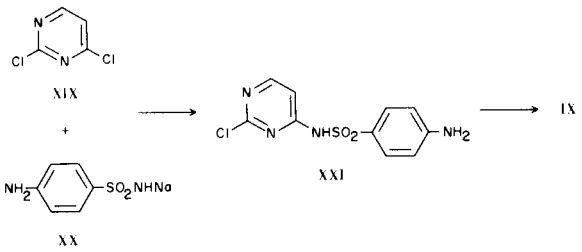


Conversion of XV to IX by hydrogenation of the nitro and chlorine groups at the same time over palladium charcoal catalyst was unexpectedly difficult. The reduction of XV over palladium-barium sulfate or palladium charcoal in the presence of sodium acetate gave the same results. However, the reduction proceeded theoretically over palladium charcoal in the presence of magnesium oxide to give the objective compound IX.

Finally, the condensation of 2,4-dichloropyrimidine (XIX) (14) with sodium sulfanilamide gave N^1-(2-chloro-4-pyrimidyl)sulfanilamide (XXI). The reaction conditions were thoroughly examined and XXI was obtained in 98% yield under the optimal conditions given in the experimental section.

Crystallization of XXI was difficult because of contamination due to a considerable amount of by-products when trimethylamine was used for the condensation agent in this reaction. Dimethylformamide was effective in the selective substitution of the chlorine atom at the 4-position to give XXI. It has been reported that the chlorine atom at the 4-position in 2,4-dichloropyrimidine (XIX) is generally more active than that at the 2-position and that the reaction of XIX with an equimolar amount of sodium methoxide gives 2-chloro-4-methoxypyrimidine in 78% yield (15), but conversion of XXI into IX does not proceed under reflux in methanol. Finally, compound IX was obtained when XXI was heated for 17 hours at 100° in a sealed tube.

CHART 6



EXPERIMENTAL

Melting points are uncorrected.

4-Amino-2-methoxypyrimidine (III).

A mixture of 2.2 g. of 4-amino-6-chloro-2-methoxypyrimidine (I) completely dried over phosphorus pentoxide and 4.0 g. of triphenylphosphine was fused at 160° with stirring. The reaction mixture solidified after 2 hours. The reaction mixture was triturated with 50 ml. of methanol and was filtered to remove an insoluble substance. The filtrate was evaporated and the residue was washed thoroughly with ether. The insoluble brown oil was dissolved in methanol and the solution was treated with charcoal and filtered. The filtrate was evaporated to give 3 g. (52%) of the phosphonium chloride (II), showing one spot in tlc.

A mixture of 3 g. of II in 16.5 ml. of 5% sodium hydroxide was heated on a water-bath for 30 minutes and cooled. The reaction mixture was extracted with ethyl acetate. The extract was again extracted with 24.4 ml. of 2*N* hydrochloric acid. The acidic extract was neutralized with 5% sodium hydroxide and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was extracted with 90 ml. of hot ethanol to remove the precipitate of sodium chloride. The extract was evaporated to half its volume and diluted with ether. The precipitated solid was removed and the filtrate was allowed to stand in a refrigerator to separate III, 81 mg. (9.1%), m.p. 168°. The ir spectrum of this substance was identical with that of an authentic sample (4).

Condensation of 4-Amino-2-methoxypyrimidine (III) with *p*-Acetaminobenzenesulfonyl Chloride (IV) in the Presence of Trimethylamine.

(a) To a suspension of 2.5 g. (0.02 mole) of III and 9.3 g. (0.04 mole) of IV in 18 ml. of dry dichloromethane was added a

20% solution of 2.65 g. (0.04 mole) of trimethylamine in benzene at 15°. The mixture was stirred at 15° for 8 hours after which a pale yellow oil separated. The mixture was allowed to stand at room temperature at 25° overnight. The solvent was removed under reduced pressure and the residue was diluted with water and filtered to give 7 g. of a crystalline product which was then washed with 20 ml. of aqueous sodium carbonate solution five times. The insoluble residue (4.5 g.) was recrystallized from 50% aqueous ethanol to give 4 g. (37%) of VI as colorless needles, m.p. 182° dec.; ir (potassium bromide) ν 3320 (water of crystallization), 1685 (amide CO), 1380 and 1165 (SO_2).

Anal. Calcd. for $C_{21}H_{21}N_5O_7S_2 \cdot H_2O$: C, 46.92; H, 4.34; N, 13.03. Found: C, 47.27; H, 4.50; N, 12.94.

The former aqueous filtrate was acidified with acetic acid to give 2.5 g. of an insoluble product and the latter aqueous sodium carbonate washings were acidified with 5*N*-hydrochloric acid to give 1.6 g. of a crystalline product. Both products were combined and refluxed in 300 ml. of 50% ethanol and filtered. The insoluble material was washed with ethanol to give VIII (1.8 g., 16%) as colorless fine needles, m.p. 200° dec.; ir (potassium bromide) ν 3320 (water of crystallization), 1740 (CO), 1670 (amide CO), 1376 and 1155 (SO_2).

Anal. Calcd. for $C_{20}H_{19}N_5O_7S_2 \cdot 2H_2O$: C, 44.35; H, 4.78; N, 12.93. Found: C, 44.19; H, 4.35; N, 12.96.

The ethanolic filtrate was concentrated and the residue was allowed to stand to give 2 g. of crude crystals, which were recrystallized from dilute ethanol to give 1.4 g. (22%) of V as colorless prisms, m.p. 230°; ir (potassium bromide) 3320 (NH), 1660 (CO), 1357 and 1145 (SO_2).

Anal. Calcd. for $C_{13}H_{14}N_4O_4S$: C, 48.44; H, 4.38; N, 17.38. Found: C, 48.17; H, 4.48; N, 17.18.

(b) To a suspension of 12.5 g. (0.1 mole) of III and 28 g. (0.12 mole) of IV in 85 ml. of dry dichloromethane was added dropwise with stirring a 20% solution of 13.2 g. (0.22 mole) of trimethylamine in benzene at 15° and the stirring was continued at 15° for 8 hours. The mixture was then allowed to stand at room temperature at 25° overnight, and diluted with 10 ml. of water and concentrated under reduced pressure. The residue was diluted with 100 ml. of water and collection by filtration gave 21 g. of crude crystals (V). The filtrate was acidified with acetic acid and collected to give 13 g. of an additional product. The acidic filtrate was allowed to stand to separate 0.1 g. of VII, m.p. 270° dec., which was recrystallized from a 6-fold volume of 60% aqueous methanol to give colorless prisms, m.p. 271° dec., the ir spectrum of which was identical with that of an authentic sample (4).

In addition, the combined crude products from above were placed in 340 ml. of 1*N* sodium hydroxide aqueous solution and heated at 95° on a steam bath for 2 hours. The reaction mixture was cooled and filtered to remove an insoluble material. Carbon dioxide gas was then introduced into the filtrate. The separated crystals were collected by filtration to give 8.5 g. of IX. Acidification of the filtrate with acetic acid gave 12 g. of an additional amount of IX. The combined crude product was recrystallized from 70% aqueous methanol to give 13.3 g. (47%) of IX, m.p. 187°. The mother liquor left after acidification and crystallization was further acidified to afford 0.4 g. (1.5%) of X, m.p. 270°, which was identical with an authentic sample X (4). The acidic mother liquor was then concentrated and allowed to stand at room temperature overnight to give a crude solid XI, which was recrystallized from 50% aqueous methanol to give 0.2 g. of colorless plates, m.p. 175°, which were identical with an authentic sample prepared by treatment of IV with dimethylamine, followed by deacetylation with 1*N* sodium hydroxide (12).

N^1-(2-Methoxy-4-pyrimidyl)sulfanilamide (IX).

(a) A mixture of 1.1 g. (3.4 mmoles) of V and 12 ml. of 1*N* sodium hydroxide was heated at 95° for 3 hours, cooled and neutralized with acetic acid, the precipitated crystals were collected by filtration, washed with water and dried to give 0.9 g. of a solid, the recrystallization of which from 30 ml. of 50% aqueous methanol afforded 0.7 g. (73%) of IX as colorless fine needles, m.p. 187-188° [lit. (4) m.p. 187-188°]. This product was identical with that of an authentic sample prepared previously (4).

(b) A solution of 1 g. (2.9 mmole) of XV in 50 ml. of methanol was hydrogenated catalytically in the presence of 0.2 g. of 10% palladium on charcoal and 1 g. of magnesium oxide at atmospheric pressure and room temperature. The theoretical amount of hydrogen was absorbed within about 0.5 hour. After filtration, the filtrate was concentrated to one-fifth of its volume. The resulting mixture was adjusted to *p*H 7 and further concentrated under reduced pressure to separate crystals, which were collected, washed with water and recrystallized from dilute methanol to give 0.75 g. (92%) of IX as colorless fine needles, m.p. 187-188°, identical with the above sample.

(c) To a solution of 5.7 g. (0.02 mole) of XXI in 100 ml. of methanol was added 1.2 g. (0.05 mole) of metallic sodium. The solution was heated in a sealed tube at 100° for 5 hours. The reaction mixture was concentrated and the residue was diluted with 40 ml. of water. After decolorization by treatment with active charcoal, the resulting solution was adjusted to *p*H 1 and filtered. The filtrate was again adjusted to *p*H 4.5 with 10% sodium hydroxide aqueous solution. The separated crystals were collected to give 4.0 g. (71.5%) of IX as a solid, m.p. 182-184°, which on recrystallization from dilute methanol gave colorless needles, m.p. 187-188°, identical with the above sample.

6-Chloro-2-methoxy-4-(*p*-nitrobenzenesulfonamido)pyrimidine (XV).

To a solution of 3.2 g. (0.02 mole) of I in 5 ml. of dry pyridine was added 4.4 g. (0.02 mole) of XIV. The resulting reddish-orange solution was allowed to stand at room temperature for 15 hours to give a reddish brown viscous oil, which was diluted with water and allowed to stand to separate crystals. The crystals were collected by filtration, washed with water and dried to give 5.6 g. of a solid, m.p. 85-105°, which was extracted with 50 ml. of hot ethanol to remove an insoluble material. The extract was concentrated and the residue was acidified with 50 ml. of concentrated hydrochloric acid and heated at 70-80° for a few minutes. After cooling, the separated crystals were collected and recrystallized from dilute ethanol to give 1.8 g. (28%) of XV as pale yellow fine needles, m.p. 174-175°, ir (potassium bromide) 1535 (NO_2), 1374 and 1135 (SO_2).

Anal. Calcd. for $C_{11}H_9ClN_4O_5S$: C, 38.32; H, 2.68; N, 16.25. Found: C, 38.43; H, 2.70; N, 16.20.

The above insoluble material was recrystallized from 70% aqueous ethanol to give 1 g. of the compound (A) as yellow prisms, m.p. 240° dec. On the other hand, the former aqueous filtrate was then concentrated under reduced pressure and the residue was treated with 10 ml. of water. The precipitate was collected and recrystallized from water to give 2 g. of the compound (B) as pale yellow needles, m.p. 243-245° dec. The structure of both compounds (A) and (B) remained unclear, but its elucidation is under investigation.

2,6-Dimethoxy-4-(*p*-nitrobenzenesulfonamido)pyrimidine (XVI).

A solution of 0.83 g. (2.4 mmoles) of XV and 0.144 g. (6.3

mmoles) of metallic sodium in 30 ml. of dry methanol was heated in a sealed tube at 100° for 15 hours. The reaction mixture was filtered to remove an insoluble product. The filtrate was evaporated under reduced pressure. The residue was diluted with 15 ml. of water and adjusted to *p*H 4 with 5% hydrochloric acid solution. The precipitate was collected and recrystallized from ethanol to give 0.53 g. (65%) of XVI as pale yellow fine needles, m.p. 158°, ir (potassium bromide) 1530 (NO_2), 1350 and 1143 (SO_2).

Anal. Calcd. for $C_{12}H_{12}N_4O_6S$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.51; H, 3.65; N, 16.71.

N^1-(6-Chloro-2-methoxy-4-pyrimidyl)sulfanilamide (XVIII).

To a solution of 1 g. (2.7 mmoles) of XV in 20 ml. of 50% ethanol was added 0.2 ml. of concentrated hydrochloric acid and 1.4 g. of iron powder. The mixture was refluxed for 2 hours and then filtered. The filtrate was concentrated. The residue was made alkaline with 5% sodium hydroxide, and the solution was decolorized with active charcoal and the *p*H was adjusted to 5.5 with 5% hydrochloric acid. The separated crystals were recrystallized from dilute ethanol to give 0.51 g. (56%) of XVIII as pale yellow fine needles, m.p. 169-170° dec., which were identical with an authentic sample (4) by the mixed melting point test and infrared spectral comparison.

N^1-(2,6-Dimethoxy-4-pyrimidyl)sulfanilamide (XVII).

(a) To a solution of 1 g. (2.9 mmoles) of XVI in 20 ml. of 5% aqueous ethanol was added 0.2 ml. of concentrated hydrochloric acid and 1.4 g. of iron powder. The mixture was refluxed for 2 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was made alkaline with 5% sodium hydroxide, decolorized with active charcoal and adjusted to *p*H 6 with 5% hydrochloric acid. The precipitate was collected and recrystallized from dilute ethanol to give 0.62 g. (68%) of XVII as colorless flakes, m.p. 201°; ir (potassium bromide) 1353 and 1145 (SO_2), identical with an authentic sample by the mixed melting point test and infrared spectral comparison.

(b) A solution of 1 g. (3.2 mmoles) of XVIII and 184 mg. (8 mmoles) of metallic sodium in 50 ml. of dry methanol was heated in a sealed tube at 100° for 15 hours. The reaction mixture was filtered to remove an insoluble material. The filtrate was concentrated under reduced pressure. The residue was diluted with 15 ml. of water and the resulting solution was acidified with acetic acid. The precipitate was collected and recrystallized from dilute ethanol to give 0.65 g. (66%) of XVII, m.p. 201°.

N^1-(2-Chloro-4-pyrimidyl)sulfanilamide (XXI).

To a suspension of 23.3 g. (0.12 mole) of sodium sulfanilamide (XX) in 60 ml. of purified dimethylformamide was added 7.5 g. (0.05 mole) of 2,4-dichloropyrimidine (XIX) (14) in small portions. The mixture was heated at 60° for a few hours and the stirring was continued for an additional 10 hours. The solvent was removed under reduced pressure. The residue was diluted with 70 ml. of water and adjusted to *p*H 7~8 by an introduction of carbon dioxide gas. The precipitated sulfanilamide was removed by filtration. The filtrate was adjusted to *p*H 4 with 5% hydrochloric acid. The separated oil solidified on standing in a refrigerator. The crude compound XXI (14 g.), m.p. 230°, was recrystallized from 40 ml. of 50% aqueous methanol to give 7.9 g. (56%) of XXI as pale yellow fine needles, m.p. 240-250°, which were very labile in solvents and changeable during recrystallization.

Anal. Calcd. for $C_{10}H_9ClN_4O_2S$: N, 19.69. Found: N, 19.67.

This compound was proved to be correct by methoxylation, leading to the formation of XI.

Acknowledgment.

We are grateful to President K. Ueno and Director H. Sano of the Chugai Pharmaceutical Co. Ltd., for their encouragement. We also thank Dr. Y. Imai and Dr. M. Koizumi for their helpful discussion and encouragement.

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(3) Communications concerning this paper should be directed to Professor Tetsuji Kametani.

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