[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMID CO.]

Sulfanilamidopyrimidines. I. 4-Sulfanilamidopyrimidines by Heterocyclic Nucleophilic Displacements

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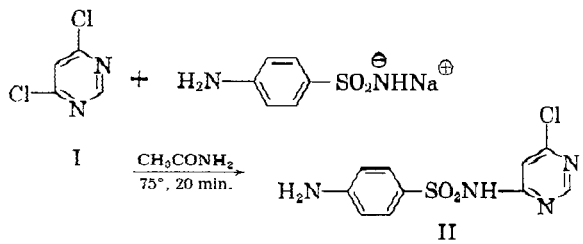
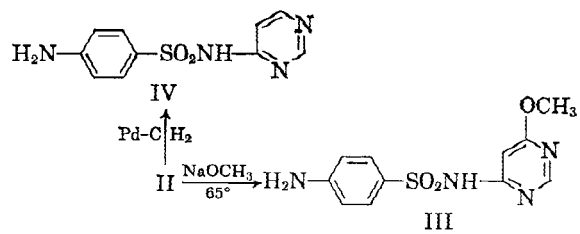
Facile displacement of a methylsulfonyl group by sulfanilamide anion provided a new type of synthesis of the highly antibacterial 4-sulfanilamido-6-methoxypyrimidine. Nucleophilic displacements involving other groups and other sulfonamide anions have been investigated. A new route to 4-sulfanilamidopyrimidine proceeded through the previously unreported 4-sulfanilamido-6-chloropyrimidine.

The recent development of 3-sulfanilamido-6 methoxypyridazine[1,2] as a therapeutically useful[3,4] sulfa drug stimulated our interest in other sulfanilamidomethoxydiazines. In the pyrimidine series three sulfanilamido monomethoxy derivatives have been examined[5] but none has displayed useful chemotherapeutic properties. However, the previously unreported 4-sulfanilamido-6-methoxypyrimidine (III), which was of interest as an analog of the highly soluble 4-sulfanilamidopyrimidine (IV),[6] has been found to have the highest antibacterial activity of any sulfa drug thus far reported.

The very reactive 4,6-dichloropyrimidine (I)[7,8] was chosen as a suitable intermediate for III, and on treatment with sodium sulfanilamide under



extremely mild conditions it yielded 4-sulfanilamido-6-chloropyrimidine (II). Catalytic dehalogenation of this substance (II) provided a new route to 4-sulfanilamidopyrimidine (IV).[6] Replacement of the chlorine in II was effected with sodium methoxide in refluxing methanol to yield



the desired 4-sulfanilamido-6-methoxypyrimidine (III). The reactions leading to II and to III both proceeded under much milder conditions than those required[1,9] for the corresponding reactions of 3,6-dichloropyridazine (140°, thirty minutes) and of 3-sulfanilamido-6-chloropyridazine (120°, fifteen hours).

The reactivities of the dihaloheterocycles with sulfanilamide anion are consistent with a greater activation in the ground state (Va,b,e) toward nucleophilic attack (reagent generalized as Nu^-) and a greater stabilization of the intermediate complex (Vc,d,f)[10] by the pyrimidine ring than by the pyridazine ring. By analogy with effects in dichlorobenzenes,[11] both dichloro compounds would be expected to be more reactive than the monochloro analogs as a result of activation by the additional chlorine. The greater instability (to storage) of 4-chloropyrimidine compared to 4,6-dichloropyrimidine is not inconsistent with this statement since this instability is not a representative nucleophilic displacement. The instability is

(1) J. H. Clark, J. P. English, G. R. Jansen, H. W. Marson, M. M. Rogers, and W. E. Taft, *J. Am. Chem. Soc.*, 80, 980 (1958); J. H. Clark, U. S. Patent 2,712,012 (June 28, 1955); *Chem. Abstr.*, 50, 5777 (1956).

(2) The trademark of the American Cyanamid Co. for this compound is Kynex.

(3) J. T. Litchfield, Jr., 1956, 20th Internat. Physiol. Congress, Brussels, Belgium; R. R. Roepke, T. H. Maren, and E. Mayer, *Ann. N. Y. Acad. Sci.*, 69, 457 (1957).

(4) W. P. Boger, C. S. Strickland, and J. M. Gylfe, *Antibiotic Med. and Clin. Therapy*, 3, 378–387 (1956); D. K. Foerster, W. J. Martin, W. F. McGuckin, and D. R. Nichols, *Proc. Staff Meetings Mayo Clinic*, 31, 678–683 (1956); R. L. Nichols, W. F. Jones, and M. Finland, *Proc. Soc. Exptl. Biol. Med.*, 92, 637–640 (1956).

(5) R. O. Roblin, Jr., P. S. Winnek, and J. P. English, *J. Am. Chem. Soc.*, 64, 567 (1942); H. J. Backer and A. B. Grevenstuk, *Rec. trav. chim.*, 64, 115 (1945).

(6) R. O. Roblin, Jr., J. H. Williams, P. S. Winnek, and J. P. English, *J. Am. Chem. Soc.*, 62, 2002 (1940).

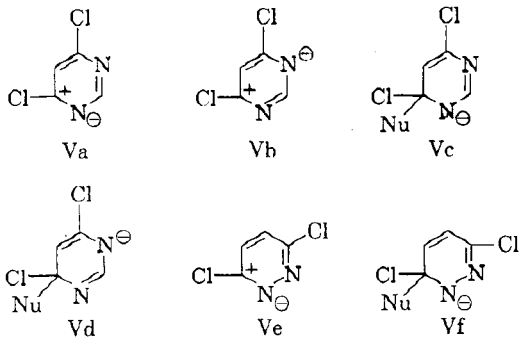
(7) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 575 (1943).

(8) R. Hull, *J. Chem. Soc.*, 2214 (1951).

(9) J. H. Clark, R. G. Shepherd, and W. E. Taft, North Jersey Am. Chem. Soc. Meeting-in-Miniature, Seton Hall University, S. Orange, N. J., Jan. 26, 1959.

(10) J. F. Bunnett and co-workers have discussed (ref. 11, p. 299) and experimentally supported [*J. Am. Chem. Soc.*, 80, 6020 (1958) and earlier papers] the intermediate complex in aromatic nucleophilic displacements; these structures are analogous.

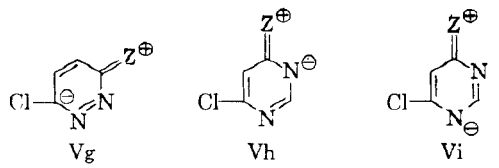
(11) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, 49, 310, 315, 319(1951).



Va Vb Vc

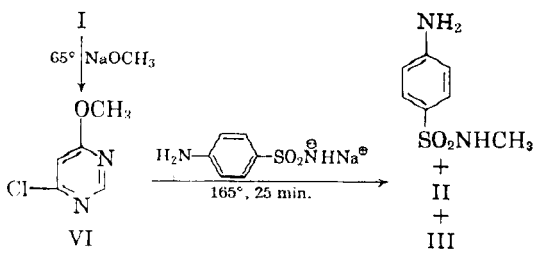
Vd Ve Vf

due to self-quaternization[12] of the former at the 1-position which is sterically hindered in the latter.[13] Greater activation by a *meta* chlorine, as in 4,6-dichloropyrimidine, would be expected than by a *para* chlorine, as in 3,6-dichloropyridazine, where the activating inductive effect of the substituent is opposed by the deactivating mesomeric effect in Vg (Z = Cl). In the pyrimidine derivative, the mesomerism can exert a deactivating effect only indirectly[14] as shown in Vh,i. Although the deactivation resulting from forms Vh and Vi might be more significant here or in



Vg Vh Vi

dichloronitrobenzenes than in dichlorobenzenes, their contribution in certain mono- and dihalo derivatives[15] of 2-chloronitrobenzene is not sufficient to prevent activation or change the relation: activation by *meta chloro* > *para*.



VI II + III

Preparation of III by the reverse sequence, displacement by methoxide ion and then sulfanilamide anion, was less satisfactory. The intermediate 4-chloro-6-methoxypyrimidine[16] was somewhat more difficult to handle and its reaction with sodium sulfanilamide (or with sulfanilamide and potassium carbonate) required a much higher temperature than in the case of the 4,6-dichloro derivative. Paper chromatography of the reaction mixture indicated that the pyrimidine had largely reacted but had yielded a mixture of products. Of the new sulfanilamide derivatives formed, about one third resulted from displacement of the chlorine, about half from nucleophilic attack at the methyl-oxygen link and about one fifth from displacement of the methoxy group. The methyl-oxygen fission led principally to N^1-methylsulfanilamide. Under similar conditions 3-chloro-6-methoxypyridazine with sodium sulfanilamide underwent chlorine displacement and demethylation in roughly equal amounts with very little methoxy displacement.[9] The methylation of sulfonamide anions by heterocyclic methoxy groups seems to be a general reaction[17] which is favored by higher reaction temperatures and by the presence of certain electron-attracting substituents on the ring. A pyrimidone or pyridazone is formed concomitantly with the sulfonamide methylation product.

The low reactivity of 4-chloro-6-methoxypyrimidine and of 3-chloro-6-methoxypyridazine toward sulfanilamide anion occurs also toward trimethylamine, as noted below. In the pyrimidine ring (VI), deactivation by the methoxy group can be effected only indirectly[14] *via* Vh and Vi (Z = OCH_3) which render the ring nitrogens less able to stabilize the negative change present in the intermediate complex (Vc, Vd). However, in the pyridazine ring deactivation toward nucleophilic attack is effected directly as a result of the decreased electron deficiency at the substitution site illustrated in Vg (Z = OCH_3). Deactivation by an anionic sulfonamide substituent, as in the anion of II formed during the synthesis of III, is greater than by methoxy in VI: reaction with methoxide ion at 65° required fifty to seventy hours for the former compared with less than a half hour for the latter. A similar large difference in reactivity toward methoxide ion of the chlorine in anionic 3-sulfanilamido-6-chloropyridazine and in 3-chloro-6-methoxypyridazine has been observed.[1]

The synthesis of III was accomplished also through 4-methoxy-6-pyrimidinyltrimethylammonium chloride (VII) prepared in two ways and generally treated without isolation. 4,6-Dichloropyrimidine and trimethylamine at room temperature readily formed the quaternary salt which was then converted to the methoxy compound. Treatment with sodium sulfanilamide yielded the desired product (III). When the sequence to the quaternary derivative was reversed, the second step was

(12) A. Albert *Heterocyclic Chemistry*, Essential Books, Fair Lawn, N. J., 1959, p. 75.

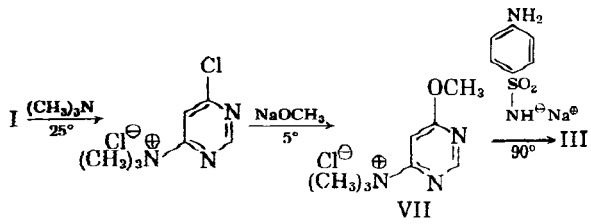
(13) N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 119 (1954).

(14) The "indirect" deactivation of nucleophilic displacements in nitrobenzenes by methyl or methoxy groups is discussed in ref. 11, p. 317, 322, and 354.

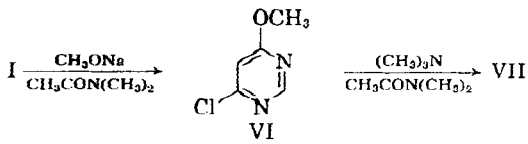
(15) A. F. Holleman, *Rec. trav. chim.*, **35**, 1 (1915); A. F. Holleman and F. E. van Haeften, *Rec. trav. chim.*, **40**, 67 (1921).

(16) D. Isbecque, R. Promel, R. C. Quinaux, and R. H. Martin, *Helv. Chim. Acta*, **42**, 1317 (1959).

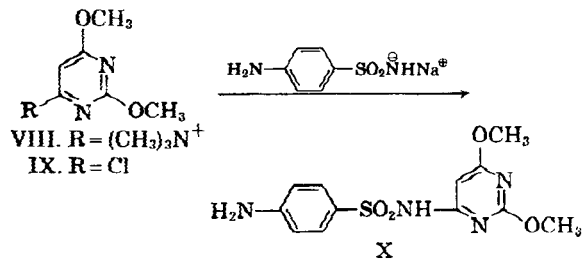
(17) Methylation by methoxy groups in other heterocycles will be discussed in forthcoming papers by the authors. J. T. Thurston, F. C. Schaefer, J. R. Dudley, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2992 (1951) reported methylation of aniline by trimethoxy-s-triazine.



much more sluggish. 3-Chloro 6-methoxypyridazine, the analog of VI, failed to react with trimethylamine under the same conditions.



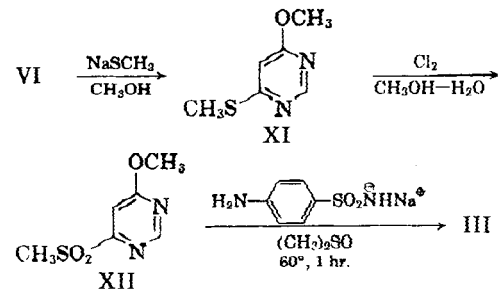
The trimethylammonium group in VII was displaced by sulfanilamide anion more readily than the chlorine in VI. We have confirmed that this high reactivity is true also for 2,4-dimethoxy - 6 - pyrimidinyl - trimethylammonium chloride (VIII)[18,19] which reacted in a few minutes at 90° compared to its 6-chloro analog (IX) which required over two hours at 115–160°. Moreover, the latter underwent almost as much demethylation side-reaction as chlorine displacement.



The displacement of the trimethylammonium group by sulfonamide anions is quite sensitive to changes in nucleophilicity. 4-Nitrobenzenesulfonamide anion gave no appreciable displacement (some demethylation occurred) with 2,4-dimethoxy-6-pyrimidinyltrimethylammonium chloride even after two hours at 100° or a further half hour at 160°. The anion of the acidic N^1-acetylsulfanilamide also gave no displacement although a substantial amount of demethylation occurred.

The reactivity of these trimethylammonium groups illustrates that the relative displaceability of substituents in these pyrimidines differs from the general behavior in benzene analogs.[20] Molecular models[24] of the 4-trimethylammonium pyrimidines indicate steric hindrance to nucleophilic attack, especially by the bulky sulfanilamide anion. It is suggested that the high reactivity relative to the sterically more favorable chlorine substituent is due to electrostatic attraction of the reagent ions and to stabilizationof the resulting intermediates complex by electrostatic interaction of the contiguous negative ring nitrogen and positive ammonium nitrogen. These two effects are analogouto those observed in work on benzene derivatives which has shown the importance of the nature of the reagent[21] and of specific *ortho* interactions[22,23,26] (called "built-in solvation"[23] and intramolecular electrostatic catalysis[26]) in determining relative displaceability. Trimethylamine is a better leaving group than sulfanilamide anion and, judging from the models of the intermediate complex, its loss would give greater steric relief of crowding. The tendency of the sulfonamide formed to lose a proton to trimethylamine by either the sterically-favorable concerted process or a consecutive one effectively prevents reversibility. The resonance-stabilized 4-nitrobenzenesulfonamide and N^1-acetylsulfanilamide anions would be expected to interact less than sulfanilamide anion with the quaternary cation and to form more reversible intermediate complexes.

Sulfanilamide anion displaced the methylsulfonyl substituent in XII more readily than the trimethylammonium group in VII or the chlorine in VI and the reaction proceeded without any of



the demethylation side-reaction. A small amount of by-product is believed to be due to displacement of the methoxy group to give 4-sulfanilamido-6-methylsulfonylpyrimidine. The latter type of product was the predominant one from 3-methoxy-6-methylsulfonylpyridazine.[9]

(18) W. Klötzer, *Monats.*, **87**, 131 (1956).

(19) W. Klötzer and H. Bretschneider, *Monats.*, **87**, 136 (1956).

(20) Ref. 11, p. 332.

(21) Loudon *et al.*, *J. Chem. Soc.*, 902 (1939); 722, 747 (1941); J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, **77**, 5051 (1955).

(22) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954); **80**, 4337 (1958).

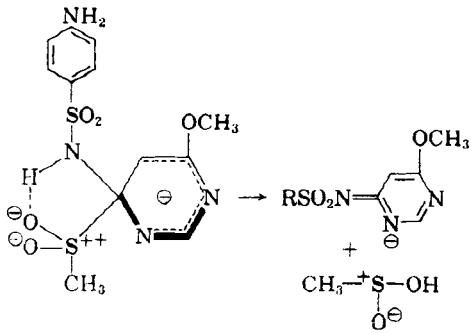
(23) J. F. Bunnett, R. J. Morath, and T. Okamoto, *J. Am. Chem. Soc.*, **77**, 5055 (1955); J. F. Bunnett, *Quart. Revs.*, **12**, 9 (1958); Y. Ogata and M. Tsuchida, *J. Org. Chem.*, **20**, 1631 (1955).

(24) Stuart-Briegleb models of La Pine and Co., Chicago and of Catalin, Ltd., London.

(25) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 6001 (1959); K. J. M. Andrews *et al.*, *J. Chem. Soc.*, 2492 (1949).

(26) M. C. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5388 (1958); M. C. Bender and Y. Chow, *J. Am. Chem. Soc.*, **81**, 3933 (1959).

The reactivity of the heterocyclic methylsulfonyl group in XII is higher than expected from the behavior of benzene analogs[20] and of purine analogs,[25] in spite of the presence of the deactivating methoxy group. Molecular models[24] of the intermediate complex indicate that its stabilization by hydrogen bonding plus electrostatic interaction between the oppositely charged ring nitrogen and sulfur may be important factors in determining the high reactivity toward sulfanilamide anion. This explanation involves a specific reagent effect[21] and an "*ortho*" interaction[22,23,26] which will be amplified by work in various solvents and on additional methylsulfonyl derivatives of heterocycles.



An evaluation of the antibacterial potency of all the sulfa compounds reported above against experimental infections in mice has shown that 4-sulfanilamido-6-methoxypyrimidine has the highest activity on an oral dosage basis. The activity of this compound varies with the microorganism from two to seven times that of sulfadiazine against five infections in mice.[27] On this basis it is the most potent sulfa drug thus far reported.

Rough solubility values of these sulfa compounds are listed in Table I. Although the value for 4-sulfanilamido-6-methoxypyrimidine is low, pharmacological work[28] has shown much higher concentrations (58–213 mg. per 100 ml.) in the urine of dosed animals and has demonstrated a substantial amount of metabolism to a "glucuronide."

TABLE I

SOLUBILITIES[a] AND R_f VALUES[b] OF 4-SULFANILAMIDOPYRIMIDINES

4-Sulfanilamido-2-R-6-R'-pyrimidines R	R'	Solubility, Mg./100 Ml.[a]	R_f[b]
H	H	100–200	0.26
H	H, N^4-acetyl	33–50	0.41
H	Cl	40–50	0.40
H	OCH_3	2.5–5.0	0.28
H	OCH_3, N^4-acetyl	8–16	0.39
OCH_3	OCH_3	4–8	0.35
OCH_3	OCH_3, N^4-acetyl	2–4	0.60

[a] At 37° in pH 6 sodium acetate buffer; see Experimental for method. [b] See Experimental for details.

(27) G. S. Redin and M. E. McCoy, Chemotheraphia (Basel), in press, 1961.

(28) H. J. Eisner, personal communication.

EXPERIMENTAL[29]

4-Sulfanilamido-6-chloropyrimidine (II). *Method A.* A total of 62.0 g. (0.420 mole) of powdered 4,6-dichloropyrimidine[7,8] and 170.0 g. (0.880 mole) of powdered sodium sulfanilamide was added quickly to 170.0 g. of acetamide at 60° in a flask with a powerful stirrer. The temperature of the resulting slurry rose to and was maintained at 75° for 20 min. Addition of 750 ml. of water yielded a brown solution which was adjusted to *p*H 8 by the dropwise addition of 1*N* hydrochloric acid with stirring. The mixture was cooled to 5° and the sulfanilamide was removed by filtration. The filtrate was adjusted to *p*H 4 by the dropwise addition of 1*N* hydrochloric acid with stirring and cooling. The yellow precipitate weighed 121 g. (101%); m.p. 185° (capillary inserted at 175°; resolidifies at once). Recrystallization (rapid) from ethanol (14 ml./g.) with charcoal treatment yielded 49.5 g. melting at 188°. A mixture melting point with the product of method B was not depressed. Concentration and cooling of the filtrate yielded additional crops of similar melting point totaling 27.6 g.; yield, 77 g. (64%).

Method B. A powdered mixture of 3.73 g. (0.0250 mole) of 4,6-dichloropyrimidine, 12.9 g. (0.075 mole) of sulfanilamide, and 8.7 g. (0.063 mole) of anhydrous potassium carbonate was added with efficient stirring to 6.0 g. of molten acetamide in a flask. The temperature of the stirred mixture was rapidly raised and was maintained at 135–143° for 30 min. The partially cooled slurry was dissolved in 50 ml. of water. Separation of the sulfanilamide and isolation of the crude product (5.5 g., 77%) was carried out as in the previous experiment. Recrystallization from acetonitrile (30 ml./g.) with charcoal treatment yielded 2.5 g. (42%) of light yellow crystals melting at 187.5° (inserted at 175°).

Anal. Calcd. for $C_{10}H_9ClN_4O_2S$: C, 42.2; H, 3.2; Cl, 12.5; N, 19.7. Found: C, 42.3; H, 3.5; Cl, 12.5; N, 19.7.

4-Sulfanilamidopyrimidine (IV). A solution of 5.96 g. (0.0200 mole) of 4-sulfanilamido-6-chloropyrimidine in 28 ml. of 1.7*N* sodium hydroxide solution was prepared. After addition of 0.96 g. of 10% palladium on charcoal, the mixture was shaken in a Parr hydrogenation apparatus under an initial pressure of 3 atm. till the pressure became constant (73 min.). Filtration of the catalyst and acidification (*p*H 4.5) of the filtrate with 1*N* hydrochloric acid yielded 2.1 g. (44% yield) of product. Recrystallization from acetonitrile (charcoal treatment) and then 70% aqueous acetone (charcoal) yielded 0.92 g. (18%) of product melting at 232–232.5°. This product gave no melting point depression with material which was previously prepared by a different route[5] and which melted at the same temperature.

4-Sulfanilamido-6-methoxypyrimidine (III). *Method A. From* II. 4-Sulfanilamido-6-chloropyrimidine (70.9 g., 0.250 mole) was dissolved in a solution of 15.3 g. (0.670 mole) of sodium in 1000 ml. of anhydrous methanol. Refluxing of the solution for 120 hr. was followed by filtration of the sodium chloride, and concentration of the filtrate to dryness at 50° under vacuum. Examination of the reaction mixture by paper chromatography (*vide infra*) indicated the presence of approximately 2% of starting material after 48 hr. and approximately 0.5% of starting material after 72 hr. There was no detectable starting material after 120 hr.

The residue was dissolved in 675 ml. of water and the *p*H adjusted to 4.5 by the dropwise addition of 6*N* hydrochloric acid at 10° with stirring. The ivory solid weighed 66 g. (94%) and melted at 197–200°. Recrystallization from ethanol (30 ml./g.) with charcoal treatment yielded 47 g. of needles melting at 204.5–206°. The filtrates, on concen-

(29) All melting points are corrected.

tration and charcoal treatment, yielded an additional 12 g.; total 59 g. (84% yield).

Anal. Calcd. for $C_{11}H_{12}N_4O_3S$: C, 47.0; H, 4.3; N, 20.0; S, 11.4. Found: C, 47.1; H, 4.6; N, 20.1; S, 11.4.

Method B. From VII. A solution of 0.62 g. (0.0105 mole) of trimethylamine in 4.7 ml. of *N,N*-dimethylacetamide was added dropwise with stirring (drying tube) to 1.49 g. (0.0100 mole) of 4,6-dichloropyrimidine in 5.0 ml. of *N,N*-dimethylacetamide. The thick slurry which formed rapidly was stirred for 10 min. A solution of 0.23 g. (0.010 mole) of sodium in 8.6 ml. of methanol was added to the slurry dropwise with stirring at 5°. After the addition the mixture was stirred for 1 hr. The methanol was removed under an oil pump at room temperature. There was added to the residue 5.0 ml. of *N,N*-dimethylacetamide and 5.83 g. (0.0300 mole) of sodium sulfanilamide. The slurry was stirred at 150–155° for 30 min. during which gas evolution ceased. Addition of 30 ml. of water gave a brown solution which was adjusted to *p*H 8 by the dropwise addition of 6*N* hydrochloric acid with stirring and cooling. The unchanged sulfanilamide was filtered and discarded. Dropwise addition of 1*N* hydrochloric acid to the filtrate to *p*H 4.5 yielded a light tan solid, 0.62 g. (22%) melting at 199–200.5°. The melting point was not depressed on admixture with a sample prepared by the previous method.

Reaction also occurred rapidly at 90° and 120°. No appreciable amount of demethylation of the pyrimidine reagent was evident by paper chromatography.

Method C. From VII. Sodium methoxide (0.14 g., 2.5 mmoles) was added during 2 min. (cooling and stirring) to a solution of 0.38 g. (2.5 mmoles) of 4,6-dichloropyrimidine in 2.0 ml. of *N,N*-dimethylacetamide. The mixture was allowed to warm to room temperature and was stirred for 1 hr. After the sodium chloride had been separated by centrifuging, the liquid portion was treated by the addition, with stirring, of a solution of 0.20 g. (3.4 mmoles) of trimethylamine in 1.52 ml. of *N,N*-dimethylacetamide. The mixture was stirred for 20 hr., at the end of which a moderate amount of precipitate had formed (positive chloride test). Reaction of sodium sulfanilamide (1.46 g., 7.5 mmoles) with the mixture at 90° followed by paper chromatography showed that only partial conversion to the quaternary had occurred.

Method D. From VI. A powdered mixture of 0.43 g. (3.0 mmoles) of 4-chloro-6-methoxypyrimidine, 1.55 g. (9.0 mmoles) of sulfanilamide, and 1.04 g. (7.5 mmoles) of potassium carbonate was added with stirring to 0.36 g. of molten acetamide at 90°. The slurry was heated rapidly with stirring to 160° at which point a vigorous carbon dioxide evolution occurred for about 10 min. After the mixture had been maintained at 160–170° for 10–15 min. it was cooled and dissolved in 10 ml. of 1*N* sodium hydroxide solution. The solution was adjusted to *p*H 8 with dilute hydrochloric acid and the excess sulfanilamide was removed. Acidification of the filtrate to *p*H 4 yielded 0.21 g. (25%) of the desired product. Paper chromatographic examination of the reaction mixture showed N^1-methylsulfanilamide (R_f 0.77), 4-sulfanilamido-6-chloropyrimidine (R_f 0.41) and 4-sulfanilamido-6-methoxypyrimidine in the ratio 5:1:5.

An experiment using sodium sulfanilamide in place of sulfanilamide and potassium carbonate gave, after 25 minutes at 160–170°, the same three products in the ratio 2:1:2 along with some N^1,N^1-dimethylsulfanilamide (R_f 0.87).

Method E. From XII. A solution of 47 mg. (0.25 mmole) of 4-methoxy-6-methylsulfonylpyrimidine and 97 mg. (0.50 mmole) of sodium sulfanilamide in 552 mg. of dimethyl sulfoxide was maintained at 60° for 1 hr. An aliquot (374 mg.) of the reaction mixture was dissolved in 2.5 ml. of water. The solution was adjusted to *p*H 8 (no precipitate) and finally to *p*H 4.5 by the dropwise addition of 1*N* hydrochloric acid with stirring. The white precipitate (18 mg., 48%) melted at 201–203°. This was not depressed on admixture with the product of method A. Paper chromatographic examination of the reaction mixture indicated roughly 75% completion after only 3 min. reaction time. After a reaction time of 1 hr., conversion appeared quantitative except for the formation of about 5% of a by-product of slightly lower R_f value. The latter is believed to be the product 4-sulfanilamido-6-methylsulfonylpyrimidine from displacement of the methoxy group. The reaction mixture was free of N^1-methylsulfanilamide and of 4-sulfanilamido-6-pyrimidone indicating absence of the methylation side-reaction. Reaction for 2 hr. gave the same chromatographic results.

4-(N⁴-Acetylsulfanilamido)-6-methoxypyrimidine. Acetic anhydride (10.8 g., 0.105 mole) was added quickly to a vigorously stirred suspension of 5.0 g. (0.018 mole) of 4-sulfanilamido-6-methoxypyrimidine in 35 ml. of glacial acetic acid. Solution became almost complete followed by rapid precipitation of a fine white solid. After the mixture had been stirred for 1 hr. it was filtered and the white precipitate was washed with acetic acid followed by water. The product (4.5 g., 80%) melted at 227–228°. Recrystallization from methanol (50 ml./g.) yielded 2.3 g. (41%) of white solid melting at 228–228.5°. Concentration of the filtrate yielded an additional 0.95 g. melting at 227–228°.

Anal. Calcd. for $C_{13}H_{14}N_4O_4S$: N, 17.4. Found: N, 17.6.

4-(N⁴-Acetylsulfanilamido)pyrimidine. The method was similar to that used in the previous experiment. The product was recrystallized from methanol and melted at 215.5–217.5°; yield, 46%.

Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: N, 19.2. Found: N, 19.2.

4-Chloro-6-methoxypyrimidine (VI). A solution of 1.15 g. (0.050 mole) of sodium in 20 ml. of methanol, was added dropwise with stirring at 20–25° to a solution of 7.45 g. (0.0500 mole) of 4,6-dichloropyrimidine in 50 ml. of methanol. After refluxing for 30 min., the sodium chloride was filtered and the filtrate was diluted wth 1.6 volumes of water and was chilled at 5° for 20 hr. The resulting solid was filtered, washed, and sublimed at 28° (0.1 mm.). The sublimate (0.75 g., 10%) melted at 34.5–35°, lit.,[16] m.p. 31–32°. This substance showed appreciable volatility even at room temperature

A superior work-up involved removal of the methanol followed by distillation of the residue at 60° (50 mm.) to give the product in a yield of 80%.

4,6-Dimethoxypyrimidine.[30] A solution of 9.35 g. (0.063 g. mole) of 4,6-dichloropyrimidine in 60 ml. of methanol was added dropwise with stirring to a solution of 7.64 g. (0.32 g.-atom) of sodium in 150 ml. of dry methanol. Precipitation of the sodium chloride with spontaneous warming to 40° occurred. After completing the addition at this temperature, the reaction was largely complete (negative Beilstein test). After refluxing for 1 hr. and filtration of the sodium chloride (theoretical amount), the filtrate was concentrated under vacuum to a white residue which was stirred with 75 ml. of water, then saturated with sodium chloride and extracted with two 100-ml. portions of benzene. The extract was dried (Drierite) and concentrated under vacuum to about 5 g. of white, semicrystalline solid. Sublimation at 0.5 mm. and 30–40° yielded 4.9 g. (55% yield) of white, crystalline solid, melting at 30–31°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.6; H, 6.0; N, 20.3.

4-Methoxy-6-methylthiopyrimidine (XI). A solution of 4.47 g. (0.194 mole) of sodium in 100 ml. of methanol was saturated with methyl mercaptan at 5°. This solution was added dropwise with stirring at 35° to a solution of 28.1 g. (0.194 mole) of 4-chloro-6-methoxypyrimidine in 50 ml. of methanol. On completion of the addition (copious white precipitate) the mixture was refluxed for 30 min. After removal of the methanol under vacuum the residue was stirred with 100 ml. of hexane and the salt was filtered off. Concentration of the filtrate under vacuum to a pale yellow residue, and distillation at 51–65° (0.06–0.07 mm.) yielded 20.0 g.

(30) Recently reported as a liquid by D. J. Brown and J. J. Harper, *J. Chem. Soc.*, 1303 (1961).

of water-white material which was converted to the methylsulfonyl derivative without further purification.

4-Methoxy-6-methylsulfonylpyrimidine (XII). The above 4-methoxy-6-methylthiopyrimidine (1.56 g.) was dissolved in 10 ml. of 70% methanol. Chlorine was passed into the solution in an ice bath for 1.5 hr., a white precipitate appearing after 1 hr. The precipitate was sublimed at 70–80° and 0.02 mm. to yield 0.44 g. (23%) of white sublimate melting at 98.5–99.5°. Further material could be obtained from the mother liquor.

Anal. Calcd. for $C_6H_8N_2O_3S$: C, 38.3; H, 4.3; N, 14.9; S, 17.0. Found: C, 38.6; H, 4.4; N, 14.6; S, 17.1.

4-Sulfanilamido-2,6-dimethoxypyrimidine (X). *Method A. From* VIII. A mixture of 8.74 g. (0.0450 mole) of sodium sulfanilamide and 8.74 g. of acetamide was heated to 155° to dissolve, then cooled to 90°. 2,4-Dimethoxy-6-pyrimidinyltrimethylammonium chloride[18,19] (3.5 g., 0.015 mole) was added in small portions with vigorous stirring. A moderate gas evolution occurred during five minutes after which a sample was removed for chromatographic examination. After the temperature had been maintained at 100° for an additional 5 min. another sample was removed. The reaction mixture was dissolved in 15 ml. of water and the solution was adjusted to *p*H 8 with dilute hydrochloric acid. After the mixture had been cooled, the unchanged sulfanilamide was removed. The filtrate was adjusted to *p*H 5 and the mixture was heated to 70° to effect crystallization of the resulting gum. The product was filtered at 40° to give 2.3 g. (43%), melting at 190–194°. Recrystallization from ethanol (40 ml./g.) with charcoal treatment gave a 69% recovery of product melting at 199.5–200.5°; lit.[19] m.p. 201–203°.

Examination of the reaction mixture after 5 and 10 min. by paper chromatography indicated complete reaction in both with the formation of a small amount of N^1-methyl sulfanilamide (R_f 0.78) along with a trace of by-product with R_f 0.16 (probably the 4-sulfanilamido-2 or 6-methoxy-6 or 2-pyrimidone).

When sodium *p*-nitrobenzenesulfonamide was substituted for sodium sulfanilamide in the above reaction, no amine evolution occurred during two hours at 100° or a subsequent half hour at 160°. Samples for paper chromatography taken after the first half hour and at the end revealed only *p*-nitrobenzenesulfonamide (R_f 0.70) plus a substantial amount of its N^1-methyl derivative (R_f 0.88).

In a third experiment, the use of sodium sulfacetamide at 90° for 40 min., then at 140° for 20 min yielded no 4-sulfanilamido-2,6-dimethoxypyrimidine nor derivative, the major product being N^1-methylsulfanilamide.

Method B. From (IX). A powdered mixture of 0.20 g. (1.2 mmoles) of 4-chloro-2,6-dimethoxypyrimidine[31] and 0.67 g. (3.5 mmoles) of sodium sulfanilamide was added to 0.68 g. of acetamide at 90°. Samples of the stirred reaction slurry were withdrawn for paper chromatographic examination after 40 min. at 115°, 80 min. at 115°, and after an additional 50 min. at 130–160°. The approximate amounts of N^1-methylsulfanilamide (R_f 0.78), N^1,N^1-dimethylsulfanilamide (R_f 0.86), 4-sulfanilamido-2,6-dimethoxypyrimidine (R_f 0.34), and of sulfanilamidomethoxypyrimidone (R_f 0.14) were as follows: for sample 1 = 25, 5, 15, and 5%; for sample 2 = 30, 8, 18, and 8%; and for sample 3 = 40, 10, 25, and 20%. These results indicate that the total amount of chlorine displacement (20, 26, 45%) increased with time and temperature, that the amount of demethylation of desired product increased especially with temperature and that methylation resulted largely from the 4-chloro-2,6-dimethoxypyrimidine reagent.

Chromatography. Paper partition chromatography was used throughout this work to follow the progress of reactions and as a criterion of product purity. The chromatograms were run on Whatman #1 paper in descending fashion using for development the top layer of a 9:1:8 butanol–ammonium hydroxide–water mixture. The dried sheets were examined under an ultraviolet lamp for any quenching (characteristic of free sulfanilamides and nitrobenzenesulfonamides) or fluorescence (characteristic of N^4-acetylsulfanilamides). The sheet was sprayed with a butanol–acetic acid-butyl nitrite (5:1:6) solution followed (2 min. later) by a 0.1% solution of *N*-(1-naphthyl)ethylenediamine dihydrochloride in butanol. The presence of a primary arylamino group is indicated by a red color which is visible for 5×10^{-9} mole of arylamine. The method is easily adaptable to quantitative work.[32]

Solubility determinations. The solubilities of these compounds were determined by a rough, visual method in *p*H 6 sodium acetate buffer. The buffer was prepared from 0.1*N* acetic acid by adjusting with 2*N* sodium hydroxide. A typical determination follows: 20 mg. of finely powdered 4-sulfanilamidopyrimidine was suspended in 10 ml. of the sodium acetate buffer. The suspension was shaken in a machine for 16 hr. at 37°. At the end of this time a moderate amount remained undissolved. An additional 10 ml. of buffer was added and the shaking was repeated. A clear solution resulted and the solubility was recorded as 100–200 mg./100 ml. buffer.

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PEARL RIVER, N. Y.

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(32) R. G. Shepherd, *Proc. Sci. Med. Confs. Am. Pharm. Mfrs. Assoc.*, Feb. 1949, p. 30–35. For various qualitative methods, see E. Lederer and M. Lederer, *Chromatography*, Elsevier Publ. Co., Amsterdam, 1957, p. 223.