Sulfanilamidopyrimidines. II.[1] 4-Sulfanilamidopyrimidines and Certain 4,6-Disubstituted Pyrimidines[2]

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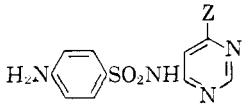
A series of analogs of 6-methoxy-4-sulfanilamido-pyrimidine, a highly potent antibacterial sulfonamide has been prepared and tested. The preparation and nucleophilic displacement reactions of various new 4,6-disubstituted pyrimidines have been investigated.

Recently we reported[1] the preparation of 6-methoxy-4-sulfanil-



amido pyrimidine[3] (I, Z = OCH_3) by various routes. In view of the high antibacterial potency and persistence of this new sulfanilamide derivative the preparation of certain analogs was desirable. Displacement of the moderately reactive chlorine substituent in 6-chloro-4-sulfanilamidopyrimidine (I, Z = Cl) by methylmercaptide or various alkoxide ions at temperatures of 65–100° conveniently yielded the analogs listed in Table I.

Certain differences in relative nucleophilicities of the reagents used for the chlorine displacement reaction were observed. For example, the ethoxylation reaction (78°) was complete in less than 24 hours, whereas the trifluoroethoxylation reaction (73°) required 263 hours to attain 80% completion. Since any steric factor would be slight[4] in this case, the difference in reactivity must be a consequence of the much higher acid strength of trifluoroethanol (K_a = *ca.* 4×10^{-12})[5] compared with ethanol (K_a = *ca.* 3×10^{-16})[6], thus rendering the

(1) Paper I. R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, **26**, 2764 (1961).

(2) Presented before the Division of Medicinal Chemistry at the 140th Meeting of the American Chemical Society, Chicago, Illinois, September 7, 1961.

(3) The generic name of this substance is sulfamonomethoxine.

(4) See L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1960, pp. 226, 228, for comparison of the atomic radii of hydrogen and fluorine.

(5) A. L. Henne and R. L. Pelley, *J. Am. Chem. Soc.*, **74**, 1426 (1952).

(6) P. S. Danner and J. H. Hildebrand, *J. Am. Chem. Soc.*, **44**, 2824 (1922).

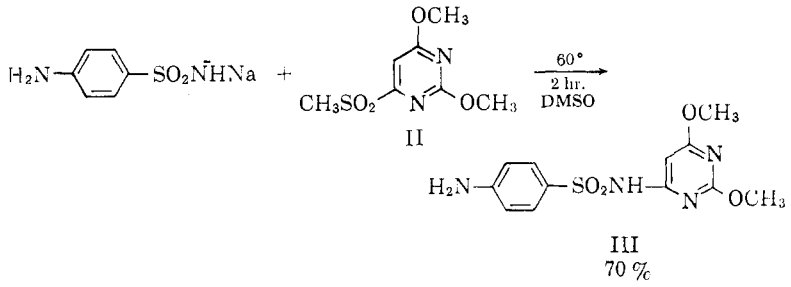
TABLE I: 4-SULFANILAMIDO-6-R-PYRIMIDINES

R	Reaction Temp., °C.	Reaction Time, hr.	Yield, %	Purifn.[a]	M.p., °C. (corr.)	Formula	Analyses, % Calcd. and found C	H	N	S	*Solv.*[b] mg./100 ml. at pH6	Paper[c] chrom. R_f	Relative activity[d] Dosage at −6 hr.	Dosage at +1 hr
CH_3O[e]													5.9	4.0
C_2H_5O	78	24	53	A(30)	193–193.5	$C_{12}H_{14}N_4O_3S$	49.0	4.8	19.0	10.9	11–13	0.35	3.5	1.6
							48.8	5.4	18.8	10.6				
$CH_3OC_2H_4O$	85	96	27	A(25)	198–198.5	$C_{13}H_{16}N_4O_4S$	48.1	5.0	17.3	9.9	8–16	0.24	0.2	0.3
							48.3	5.4	17.0	10.1				
HOC_2H_4O	95	42	26	A(50)	209.5–210.5	$C_{12}H_{14}N_4O_4S$	46.4	4.5	18.0	10.3	40–50	0.15	i[f]	i[f]
							46.3	5.1	18.3	10.7				
CF_3CH_2O	73	284	32	B(20)	192–193	$C_{12}H_{11}F_3N_4O_3S$	41.4	3.2	16.1	9.2	4–8	0.53	2.0	2.0
							41.1	3.6	16.1	9.2				
CH_3S	78	17	28	A(40)	212–213	$C_{11}H_{12}N_4O_2S_2$	44.6	4.1	18.9	21.6	<2	0.33	0.4	0.8
							44.5	4.3	18.8	21.9				
$(CH_3)_2CHO$	82	23	20	B(60)	229–229.5	$C_{13}H_{16}N_4O_3S$	50.6	5.2	18.2	10.4	<5	0.46	2.5	0.8
							50.4	5.0	17.9	10.2				
$CH_3(CH_2)_2O$	97	22	16	B(25)	189–190	$C_{13}H_{16}N_4O_3S$	50.6	5.2	18.2	10.4	<5	0.40	0.8	0.2
							50.5	5.3	18.4	10.3				

[a] Recrystallized from A (ethanol) or B (50% ethanol); the figures in parentheses represent ml. of solvent per g. of solute. [b] See ref. 1 for details; solubility in pH 6 acetate buffer. [c] Chromatographic solvent, 9:1:8 1-butanol; concd. ammonia:water. [d] We wish to thank G. S. Redin and M. E. McCoy for these data. Dosage before infection (−6 hr.) and after infection (+1 hr.) gives an over-all measure of persistence relative to sulfadiazine. About 5 times the amount of sulfadiazine is required at −6 hr. as at +1 hr. for the same therapeutic effect. Such a dosage schedule in conjunction with this rapidly fatal (average survival time 20–26 hr.) infection makes the therapeutic effect very sensitive to the drug concentration in the blood during the first few hr. after infection. In this test the slowly excreted 6-methoxy-3-sulfanilamido-pyridazine is reproducibly more persistent than sulfadiazine; furthermore, the rapidly excreted 3,4-dimethyl-5-sulfanilamidoisoxazole is less persistent. In these and many other instances, confirmatory blood level studies have been carried out; see G. S. Redin and M. E. McCoy, *Chemotherapia*, **4**, 386 (1962). [e] Ref. 1. [f] Inactive at highest dose tested.

trifluoroethoxide ion a weaker nucleophile than ethoxide ion. Displacement by methylmercaptide ion in ethanol was complete in less than 17 hours, and no ethoxy byproduct was detectable (< 5%) on a paper chromatogram.[1]

Displacement of a 4-pyrimidinyl methylsulfonyl group by sulfanilamide anion, which we previously reported[1] for 6-methoxy-4-methylsulfonylpyrimidine, was extended to the preparation of 2,6-dimethoxy-4-sulfanilamidopyrimidine (III)[7,8] through 2,6-dimethoxy-4-methylsulfonylpyrimidine (II).[9] This reaction was very facile



(40% complete at 60° in 3 minutes) in dimethylsulfoxide or dimethylformamide, even at room temperature. In contrast, reaction of the 4-chloro analog of II at 60° for 2 hours gave the sulfanilamido derivative in less than 5% yield, together with a 5–10% yield of N^1-methylsulfanilamide. The superior reactivity of the methylsulfonyl group over the chlorine atom in this reaction is most striking and was discussed in the earlier paper.[1] Previously the methylsulfonyl group has been regarded as inferior[10] or roughly equivalent[11] to the chlorine atom in ease of aromatic nucleophilic displacement.

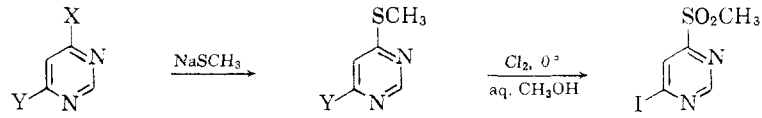
Treatment of 4,6-dimethoxypyrimidine with sodium sulfanilamide in refluxing methanol for 25 hours gave no detectable reaction. Use of a higher temperature (155–160°, 2 hours in acetamide) led mainly to demethylation (*ca.* 40% N^1-methylsulfanilamide) and to little (<2%) methoxy displacement. The N-oxide function in 4,6-dimethoxypyrimidine-1-oxide enhanced the methoxy reactivity, displacement (product R_f 0.23) and demethylation each occurring to the extent of about 30% in 18 hours in refluxing methanol.

(7) W. Klötzer and H. Bretschneider, *Monatsh.*, **87**, 136 (1956).
(8) H. Bretschneider and W. Klötzer, U. S. Patent 2,703,800, March 8, 1955.
(9) S. B. Greenbaum, *J. Am. Chem. Soc.*, **76**, 6052 (1954); supplied by Cyclo Chemical Co., Los Angeles 1, California.
(10) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 332 (1951).
(11) See, *e.g.*, C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

4,6-Bis(methylthio)pyrimidine (VII)[12] was more reactive than the dimethoxy analog; sodium sulfanilamide at 140–200° in acetamide for 2 hours gave 6-methylthio-4-sulfanilamidopyrimidine in 50% yield together with N^1-methylsulfanilamide (10%). In 60 minutes at 100° the amount of reaction was insignificant. The increased amount of displacement in this case compared with that in the case of 4,6-dimethoxypyrimidine illustrates the indirect deactivating effect discussed by Bunnett and Zahler.[13] Although the leaving groups are different in these two cases, their mobilities would appear to be approximately equal.[14] The principal difference, then, is the effect of the remaining substituent on the reaction site. In contrast to the sulfur 3p orbitals, the 2p orbitals of oxygen can effectively form π-bonds with the heteroaromatic ring.[15] Such π-bond participation decreases the activating effect of the ring nitrogen atoms by increasing their electron density in the ground state, in the transition states and in the intermediate complex.

Attempted preparation of 6-iodo-4-sulfanilamidopyrimidine through reaction of sodium sulfanilamide at 60° with either 4,6-diiodopyrimidine or 4-iodo-6-methylsulfonylpyrimidine resulted in formation of complex mixtures.

The 4,6-disubstituted pyrimidines required for these reactions were readily accessible (Fig. 1) from the highly reactive 4,6-dichloropyrimidine (IV). Displacement of a chlorine atom by such a weak nu-



IV, X = Y = Cl
V, X = Cl, Y = OCH_3
VI, X = Y = I

VII, Y = SCH_3
VIII, Y = OCH_3
IX, Y = I

Fig. 1.

cleophile as iodide ion was effected only through use of an acid catalyst,[16] to yield 4,6-diiodopyrimidine (VI). Evidently, protonation of a ring nitrogen atom facilitates displacement through a low-energy transition state related to an intermediate complex such as XII.

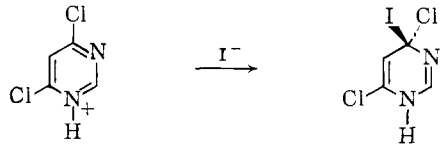
(12) Reported since our work by H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 792 (1961), by methylation of 4,6-pyrimidinedithiol.

(13) Ref. 10, p. 322.

(14) Ref. 10, p. 332.

(15) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 75.

(16) See W. Baker, R. F. Curtis, and M. G. Edwards, *J. Chem. Soc.*, 83 (1951), for a similar reaction.



XI XII

Treatment of IV, V and VI with sodium methylmercaptide in methanol yielded respectively 4,6-bis-(methylthio)pyrimidine (VII),[12] 4-methoxy-6-methylthiopyrimidine (VIII) and 4-iodo-6-methylthiopyrimidine (IX). The latter was ozidized to 4-iodo-6-methylsulfonylpyrimidine (X). Oxidation of 4,6-dimethoxypyrimidine[1] with peracetic acid at 70° gave the corresponding 1-oxide.

The relative antibacterial potencies of the new 4-sulfanilamidopyrimidines, shown in Table I, are based on a value of 1.0 for the standard, sulfadiazine. The data show that, in addition to the 6-methoxy derivative,[1] the 6-ethoxy and 6-trifluoroethoxy derivatives displayed higher antibacterial potencies than sulfadiazine. Furthermore, the 6-ethoxy, 6-isopropoxy and 6-*n*-propoxy derivatives were more persistent than sulfadiazine, based on the relative activities displayed in pre-infection and post-infection treatment. From the pK_a's of the 4-sulfanilamidopyrimidines, it is evident that the inductive power of the trifluoromethyl group overcomes the electron-donating character of the alkoxy group: (6-substituent, pK_a), H, 6.00; C_2H_5O, 6.10; F_3CCH_2O, 5.60; CH_3S, 6.10 (determined in 30% acetone).

Experimental[17]

The general preparative procedure for the 4-sulfanilamidopyrimidines involved reaction of 6-chloro-4-sulfanilamidopyrimidine with 2.7 moles of sodium alkoxide in excess of the corresponding alkanol at reflux temperature, or at temperatures up to 100° by the procedure previously outlined in detail.[1] In the case of the methylthio derivative, an ethanol solution, containing the calculated amount of sodium ethoxide, was saturated with methanethiol before addition of the 4-sulfanilamido-6-chloropyrimidine.

4,6-Dimethoxypyrimidine-1-oxide.—This was prepared from 4,6-dimethoxypyrimidine[1] essentially by the method employed by Hunt, *et al.*,[18] for 4,6-dimethylpyrimidine-1-oxide. The crude product was recrystallized from acetone (100 ml./g.) to yield white crystals (7%) melting at 142–142.5°.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.2; H, 5.2; N, 18.0. Found: C, 46.5; H, 5.3; N, 17.9.

4-Methoxy-6-methylthiopyrimidine (VIII).—A solution of 4.47 g. (0.194 mole)

(17) All melting points have been corrected.

(18) R. R. Hunt, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 525 (1959).

of sodium in 100 ml. of methanol was saturated with methanethiol at 5°. This solution was added, dropwise with stirring during 1 hr. to a solution of crude[19] 4-chloro-6-methoxypyrimidine[1] [containing 23.9 g. (0.165 mole) of V and 4.2 g. (0.028 mole) of 4,6-dichloropyrimidine (IV)]. The mixture (copious precipitate) was refluxed for 30 min. and vacuum evaporated to a semi-solid residue which was stirred with 100 ml. of hexane. Removal of salt and concentration of the filtrate left a pale yellow liquid weighing 25.2 g. Distillation through a 11.4 cm. Vigreux column yielded a 20 g. fraction, b.p. 51–53° (0.01–0.04 mm.) and 3 g. of crude (VII). Distillation of the former through a Todd Precise Fractionation Assembly (5 mm. column) at 0.05 mm. gave 3 fractions: 4.2 g. at 59–60.5°; 8.3 g. at 60.5–62°; 5.3 g. at 62–63.5°, having almost identical infrared absorption curves. Vapor phase chromatography of each on an Apiezon column showed no 4,6-dimethoxypyrimidine[1] or 4,6-bis(methylthio)-pyrimidine (below) contaminants. Total yield of 4-methoxy-6-methylthiopyrimidine was 17–19 g. (about 80%); $n^{20}D$ 1.5718.

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.1; H, 5.2; N, 17.9; S, 20.5. Found: C, 46.4; H, 5.4; N, 17.7; S, 20.1.

4,6-Bis(methylthio)pyrimidine (VII).—A solution of 5.65 g. (0.246 mole) of sodium in 140 ml. of anhydrous methanol was saturated with methanethiol at 0° and added during 45 min. to a stirred solution of 18.0 g. of (IV) in 100 ml. of methanol at 35–40°. The mixture was stirred at 28° for 16 hr., refluxed for 1 hr., then cooled, and the sodium chloride was filtered. Concentration under vacuum left white crystals, which were partially dissolved in 130 ml. of hexane. The pale yellow filtrate was cooled in ice-salt to give 11.6 g. of white crystals, m.p. 52–53°; the mother liquor yielded 6.8 g., m.p. 52–53°; total yield 88%. After sublimation at 60° (0.02 mm.) the melting point was 53–54°.

Anal. Calcd. for $C_6H_8N_2S_2$: C, 41.8; H, 4.7; N, 16.3; S, 37.2. Found: C, 41.7; H, 4.7; N, 16.3; S, 37.0.

4,6-Diiodopyrimidine (VI).—A mixture of 14.9 g. (0.100 mole) of 4,6-dichloropyrimidine, 30.6 g. (0.204 mole) of sodium iodide and 1.30 ml. (0.0100 mole) of 57% hydriodic acid in 300 ml. of acetone, was refluxed for 5 hr. Addition to the filtrate of 4 volumes of water and then 1 *N* sodium hydroxide to pH 7.5 yielded white granules, weighing 14.9 g. and melting at 105.5–106.5°. Recrystallization from 200 ml. of hexane gave 8.6 g. of white crystals, m.p. 107.5–108.5°, unchanged by vacuum sublimation (85°, 0.025 mm.). The filtrate, on concentration to 75 ml., yielded an additional 4.25 g. of white crystals melting at 107–108° (total yield 39%). An infrared spectrum of this product was devoid of absorption in the 1600–1750 $cm.^{-1}$ region indicating no hydrolysis to a pyrimidone had occurred.

Anal. Calcd. for $C_4H_2I_2N_2 \cdot 0.2\ H_2O$: C, 14.3; H, 0.7; N, 8.4; I, 75.7; H_2O, 1.07. Found: C, 14.5; H, 0.8; N, 8.4; I, 75.3; H_2O, 1.02 (Karl Fischer Method).

4-Iodo-6-methylthiopyrimidine (IX).—A solution of 0.23 g. (0.01 mole) of sodium in 13 ml. of methanol was saturated with methanethiol at 5° and added dropwise, with stirring, to 3.32 g. (0.01 mole) of 4,6-diiodopyrimidine in 40 ml. of methanol at 40°. After stirring for 18 hr. at 30°, the methanol was removed under vacuum to leave a tan, oily solid. This was refluxed with 100 ml. of hexane, the salt was filtered and the hexane was vacuum evaporated. The solid residue sublimed at 65° (0.05 mm.) to yield 1.82 g. (70%) of a pale yellow solid, m.p. 41.5–49.0°. Recrystallization from 21 ml. of hexane gave 0.95 g. of white

(19) Separable by vapor phase chromatography on a column containing GE-SF96 silicone.

crystals, m.p. 46.5–49°. A second recrystallization from hexane raised the melting point to 50–51.5°, λ_{max}^{MeOH} 243, 262, 280 (ϵ 9200, 8950, 8800). An infrared spectrum of the product was devoid of absorption in the 1600–1750 cm.$^{-1}$ region indicating absence of any pyrimidone.

Anal. Calcd. for $C_5H_5IN_2S$: C, 23.8; H, 2.0; I, 50.4; N, 11.1; S, 12.7. Found: C, 23.2; H, 2.1; I, 50.9; N, 10.4; S, 12.4.

4-Iodo-6-methylsulfonylpyrimidine (X).—Chlorine was passed through a solution of 0.25 g. (1.0 mmole) of 4-iodo-6-methylthiopyrimidine in 10 ml. of 70% methanol surrounded by an ice-bath for 1 hr., a copious yellow precipitate appearing after 10 min. Recrystallization from 1:1 ethanol–hexane with charcoal treatment gave 93 mg. (33%) of fine, white needles, m.p. 124.5–127.5°, unstable at room temperature. An infrared spectrum of this material displayed the characteristic S–O stretching modes at 1165 cm.$^{-1}$ and 1320 cm.$^{-1}$

Anal. Calcd. for $C_5H_5IN_2O_2S$: I, 44.7; S, 11.3. Found: I, 38.9; S, 12.6.

2,6-Dimethoxy-4-sulfanilamidopyrimidine (III).[7,8]—A mixture of 0.218 g. (0.001 mole) 4-methylsulfonyl-2,6-dimethoxypyrimidine,[9] 0.388 g. (0.002 mole) sodium sulfanilamide and 2.0 ml. of dimethyl sulfoxide was agitated in an oil-bath at 60° for 2 hr. The reaction mixture, dissolved in 22 ml. of water, was adjusted with 1 *N* HCl to pH 8 (no precipitate) and then to pH 5. The white precipitate (m.p. 198–199°, 70% yield) did not depress the melting point of authentic 2,6-dimethoxy-4-sulfanilamidopyrimidine, mixture m.p. 198–199°. Paper chromatography (9:1:8 butanol–ammonia–water)[1] indicated about 40% conversion after 3 min. and a quantitative conversion after 1 and 2 hr., with no discernible byproducts. The product had the same R_f (0.35) as authentic material. The reaction proceeded rapidly even at room temperature. Dimethylformamide was also a satisfactory solvent for this reaction.

When 4-chloro-2,6-dimethoxypyrimidine reacted under identical conditions, a conversion of less than 5% was obtained after 2 hr. A byproduct, N^1-methylsulfanilamide (R_f 0.76), was formed in a yield of 5–10% along with a fluorescent, non-diazotizable by-product of R_f 0.13.

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