

Synthesis of Antibacterial Agents having both Sulfanilamido- and Nitrofuryl- Groups in the Molecules. II.¹⁾

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It was reported in the previous paper¹⁾ that under consideration of the electronic structure of the molecules several compounds were synthesized for chemotherapeutic uses by combining sulfanilamidopyrimidines with 5-nitrofuran, and that the new products showed high bacteriostatic activities *in vitro*. But the products were poor in the solubilities to water and organic solvents, and accordingly might be poor in the gastro-intestinal absorption. Perhaps for this reason the compounds did not show so high therapeutic effects on the experimental infectious diseases in animals.³⁾ The present work was intended to obtain N^{4'}-substituted derivatives of 2-(4'-aminobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidine for the purpose of improving the gastro-intestinal absorption of the original compounds.

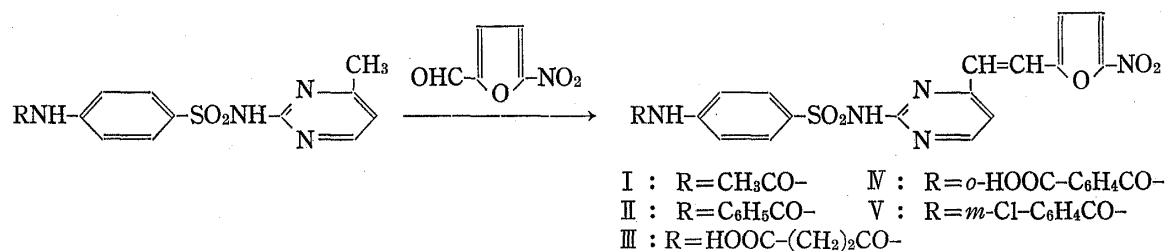


Chart 1

TABLE I. Chemical Properties

No.	R	Yield (%)	Appearance (recryst. solvt.)	mp (°C)	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
I	CH ₃ CO-	57	yellow needles (2-methoxyethanol)	272	C ₁₈ H ₁₅ O ₆ N ₅ S	50.34	3.54	16.70	50.12	3.67	16.37
II	C ₆ H ₅ CO-	53	yellow needles (acetic acid glacial)	263	C ₂₃ H ₁₇ O ₆ N ₅ S	56.21	3.49	14.25	56.30	3.55	14.22
III	HOOC-(CH ₂) ₂ CO-	68	yellow needles (acetic acid glacial)	283	C ₂₀ H ₁₇ O ₈ N ₅ S	49.27	3.51	14.36	49.91	3.53	14.36
IV	o-HOOC-C ₆ H ₄ CO-	54	yellow needles (acetic acid glacial)	285	C ₂₄ H ₁₇ O ₈ N ₅ S	53.82	3.20	13.08	53.50	3.25	13.41
V	m-Cl-C ₆ H ₄ CO-	59	yellow needles (pyridine-water (1:1))	278	C ₂₃ H ₁₆ O ₆ N ₅ SCl	52.52	3.07	13.31	52.81	3.34	13.06

1) S. Wada, K. Kumaki, and I. Moriguchi, *Chem. Pharm. Bull. (Tokyo)*, **17**, 2168 (1969).

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3) Unpublished data from the Biological Section of These Laboratories.

A dimethylformamide solution of 2-(*p*-acetoamidobenzenesulfonamido)-4-methylpyrimidine was reacted with 5-nitro-2-furaldehyde and obtained 2-(*p*-acetoamidobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidine (I) in good yield as shown in Chart 1. The compounds, II—V in Chart 1, were similarly obtained from the corresponding 2-(*p*-acylamidobenzenesulfonamido)-4-methylpyrimidines with 5-nitro-2-furaldehyde. These products are listed in Table I.

The *in vitro* bacteriostatic activities of these compounds against *Staphylococcus aureus* 209 P were shown in Table II.

TABLE II. Bacteriostatic Activity Against *Staphylococcus aureus* 209 P

No.	R	Minimum bacteriostatic concentration ($\mu\text{g/ml}$)
	H-	0.08
I	$\text{CH}_3\text{CO}-$	0.31
II	$\text{C}_6\text{H}_5\text{CO}-$	0.63
III	$\text{HOOC}-(\text{CH}_2)_2\text{CO}-$	1.25
IV	<i>o</i> - $\text{HOOC}-\text{C}_6\text{H}_4\text{CO}-$	1.25
V	<i>m</i> - $\text{Cl}-\text{C}_6\text{H}_4\text{CO}-$	1.25
	Control	5.0

control: 2-(*p*-aminobenzenesulfonamido)-4-methylpyrimidine

As indicated in Table II, the bacteriostatic activities of all compounds, I—V, are higher than 2-sulfanilamido-4-methylpyrimidine. It is interesting to note that these products indicate high bacteriostatic activities though N⁴-substituted derivatives are inactive.⁴⁾ Solubilities and gastro-intestinal absorption of these products will be reported later.

Experimental

2-(*p*-Acetoamidobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidine (I)—A solution of 3.0 g of 2-(*p*-acetoamidobenzenesulfonamido)-4-methylpyrimidine dissolved in 10 ml of dimethylformamide was cooled, and conc. H_2SO_4 (3 ml) was added slowly. Then 1.5 g of 5-nitro-2-furaldehyde was added to this solution and the mixture was kept at 50—60° for 30 min. The solution was poured into 50 ml office-water. The resulting precipitate was filtered and washed with H_2O and then methanol.

2-(*p*-Benzamidobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidine (II)—A solution of 3.7 g of 2-(*p*-benzamidobenzenesulfonamido)-4-methylpyrimidine dissolved in 30 ml of methanol was cooled, and *p*-toluenesulfonic acid (6 g) was dissolved. Then 2.4 g of 5-nitro-2-furaldehyde diacetate was added to this solution and the treatment was followed by the same way as described the above experiment.

2-(*p*-Acylamidobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidines (Acyl:3'-Carboxypropionyl- (III), *o*-Carboxybenzoyl- (IV), and *m*-Chlorobenzoyl- (V))—The compounds, III, IV and V, were obtained by the treatment of 5-nitro-2-furaldehyde diacetate with 2-(*p*-acylamidobenzenesulfonamido)-4-methylpyrimidines. The treatment was followed by the same way as described the above experiment.

Test of *in Vitro* Bacteriostatic Activity—Bacteriostatic activity was tested against *Staphylococcus aureus* 209 P in a modified Kuwabara's medium as previous paper.¹⁾

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4) P. H. Bell and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 2905 (1942); M. Tsuruoka, *Yakugaku Zasshi*, **71**, 336 (1951).