[Chem. Pharm. Bull. 17(11)2364—2365(1969)]

UDC 615.31.011.5 : 615.281.07

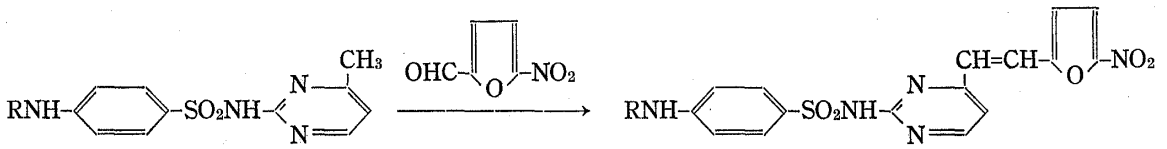
Synthesis of Antibacterial Agents having both Sulfanilamido- and Nitrofuryl- Groups in the Molecules. II.[1]

KENJI KUMAKI, SAKAE WADA,[2] and IKUO MORIGUCHI[2a]

Research Laboratories, Chugai Pharmaceutical Co., Ltd.[2]

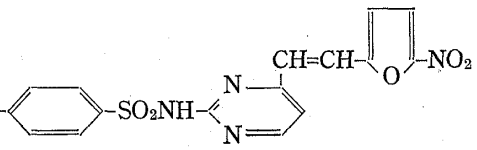
(Received May 6, 1969)

It was reported in the previous paper[1] 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 deseases 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.



I : R=CH_3CO– Ⅳ : R=*o*-HOOC–C_6H_4CO–
Ⅱ : R=C_6H_5CO– Ⅴ : R=*m*-Cl–C_6H_4CO–
Ⅲ : R=HOOC–$(CH_2)_2CO$–

Chart 1

TABLE I. Chemical Properties RNH– 

No.	R	Yield (%)	Appearance (recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
I	CH_3CO–	57	yellow needles (2-methoxyethanol)	272	$C_{18}H_{15}O_6N_5S$	50.34	3.54	16.70	50.12	3.67	16.37
II	C_6H_5CO–	53	yellow needles (acetic acid glacial)	263	$C_{23}H_{17}O_6N_5S$	56.21	3.49	14.25	56.30	3.55	14.22
III	HOOC–$(CH_2)_2CO$–	68	yellow needles (acetic acid glacial)	283	$C_{20}H_{17}O_8N_5S$	49.27	3.51	14.36	49.91	3.53	14.36
IV	*o*-HOOC–C_6H_4CO–	54	yellow needles (acetic acid glacial)	285	$C_{24}H_{17}O_8N_5S$	53.82	3.20	13.08	53.50	3.25	13.41
V	*m*–Cl–C_6H_4CO–	59	yellow needles (pyridine-water (1:1))	278	$C_{23}H_{16}O_6N_5SCl$	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).
2) Location: *3-41-8, Takada, Toshima-ku, Tokyo*; *a*) Present adress: *School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo.*
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 (μg/ml)
	H–	0.08
I	CH_3CO–	0.31
II	C_6H_5CO–	0.63
III	$HOOC-(CH_2)_2CO$–	1.25
IV	*o*-$HOOC-C_6H_4CO$–	1.25
V	*m*-$Cl-C_6H_4CO$–	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 N^4-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 ofice–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]

Acknowledgement The authors are indebted to Miss Y. Takasaki and Miss T. Nishizawa for technical assistance. Thanks are also due to the members of the analytical section for elementary analysis.

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