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# Synthesis of Antibacterial Agents having both Sulfanilamido- and Nitrofuryl- Groups in the Molecules. I

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The relationship between an index for electronic structure and bacteriostatic activity of sulfonamides was previously sutides.[2] It is expected from the relationship that introducing an electron-attracting group to pyrimidine part of sulfanilamidopyrimidines lowers $\pi$-electron–densities in the sulfanilamido part and consequently increases the bacteriostatic activities. And it was reported[3] that introducing a large conjugated–part having amino group to 5-nitrofuran ring increased the bacteriostatic activities. Sulfanilamidopyrimidines are large conjugated–molecules having amino group, and 5-nitrofuryl group appears to be electron-attracting. The authors, therefore, intended to combine sulfanilamidopyrimidines with 5-nitrofuran in hopes of obtaining more potent bacteriostatic agents.

A dimethylformamide solution of 2-(*p*-aminobenzenesulfonamido)-4-methylpyrimidine (I) was reacted with 5-nitrofurfural (or the derivatives of acetal and diacetate form) and obtained 2-(*p*-aminobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidine (II) in good yield as shown in Chart 1.

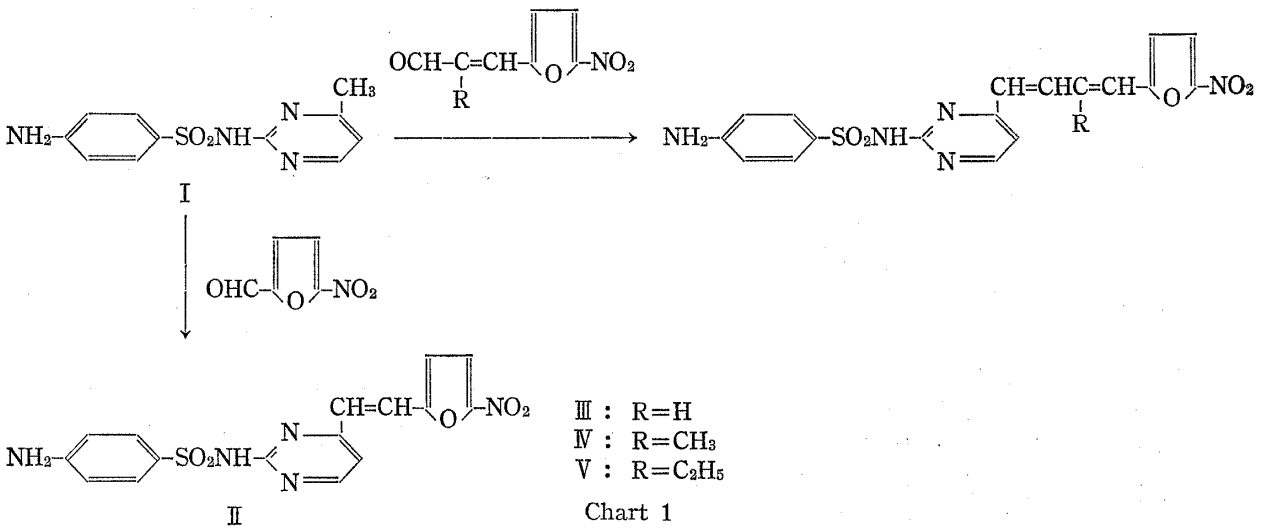


Chart 1

An acidic catalyst such as $H_2SO_4$, $ZnCl_2$, or *p*-toluenesulfonic acid makes the reaction rapid. 2-(*p*-Aminobenzenesulfonamido)-4-[4-(5-nitro-2-furyl)butadienyl]pyrimidine (III) was obtained by the treatment of I with 5-nitro-2-furylacrolein instead of 5-nitrofurfural, and 2-(*p*-aminobenzenesulfonamido)-4[3-alkyl-4-(5-nitro-2-furyl)butadienyl]pyrimidines (alkyl: methyl (IV) and ethyl (V)) were obtained by the similar reaction of I with $\alpha$-alkyl-5-nitro-2-furylacrolein. These products are listed in Table I. The *in vitro* bacteriostatic activity

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2) I. Moriguchi and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **16**, 734 (1968).
3) I. Saikawa and Y. Suzuki, *Yakugaku Zasshi*, **84**, 646 (1964).

Table I. Chemical Properties $NH_2$-⟨⟩-$SO_2NH$-⟨pyrimidine, R⟩

| No. | R | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| II | -CH=CH-⟨furan⟩-$NO_2$ | 65 | 259 | $C_{16}H_{13}O_5N_5S$ | 49.62 | 3.38 | 18.08 | 49.57 | 3.41 | 17.78 |
| III | -CH=CHCH=CH-⟨furan⟩-$NO_2$ | 62 | 289 | $C_{18}H_{15}O_5N_5S$ | 52.27 | 3.66 | 16.95 | 52.18 | 3.84 | 16.59 |
| IV | -CH=CHC($CH_3$)=CH-⟨furan⟩-$NO_2$ | 54 | 301 | $C_{19}H_{17}O_5N_5S$ | 53.39 | 4.01 | 16.39 | 53.04 | 4.12 | 16.46 |
| V | -CH=CHC($C_2H_5$)=CH-⟨furan⟩-$NO_2$ | 58 | 263 | $C_{20}H_{19}O_5N_5S$ | 54.39 | 4.34 | 15.87 | 54.40 | 4.67 | 15.53 |

apearance: yellow needles

of these compounds against *Staphylococcus aureus* 209 P is shown in Table II. As indicated in Table II, the bacteriostatic activity of all the products II—V is higher than I. The results suggest that the compounds having both sulfanilamido- and nitrofuryl- groups in the molecule may be useful for chemotherapy with human and animal.

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

| No. | R | Minimum bacteriostatic concentration ($\mu$g/ml) |
|---|---|---|
| I | $-CH_3$ | 5.00 |
| II | -CH=CH-⟨furan⟩-$NO_2$ | 0.08 |
| III | -CH=CHCH=CH-⟨furan⟩-$NO_2$ | 1.25 |
| IV | -CH=CHC($CH_3$)=CH-⟨furan⟩-$NO_2$ | 0.08 |
| V | -CH=CHC($C_2H_5$)=CH-⟨furan⟩-$NO_2$ | 0.16 |

## Experimental

**2-(*p*-Aminobenzenesulfonamido)-4-[2-(5-nitro-2-furyl)vinyl]pyrimidine (II)**——A solution of 2.6 g of 2-(*p*-aminobenzenesulfonamido)-4-methylpyrimidine (I) dissolved in 10 ml of dimethylformamide was cooled, and conc. $H_2SO_4$ (3 ml) was added slowly. Then 1.5 g of 5-nitrofurfural was added to this solution and the mixture was kept at 50° for 30 min. The solution was poured into 50 ml of ice–water. The resulting precipitate was filtered and washed with $H_2O$ and then methanol. Recrystallization from 2-methoxyethanol gave 2.5 g (65%) of II as yellow needles, mp 259°. *Anal.* Calcd. for $C_{16}H_{13}O_5N_5S$: C, 49.62; H, 3.38; N, 18.08. Found: C, 49.57; H, 3.41; N, 17.78. recrystallization from dioxane instead of 2-methoxyethanol gave II including one dioxane molecule as yellow needles. *Anal.* Calcd. for $C_{16}H_{13}O_5N_5S \cdot C_4H_8O_2$: C, 50.47; H, 4.45; N, 14.73. Found: C, 50.49; H, 4.34; N, 14.85.

**2-(*p*-Aminobenzenesulfonamido)-4-[4-(5-nitro-2-furyl)butadienyl]pyrimidine (III)**——III was obtained by the treatment of I with 5-nitro-2-furylacrolein[4] instead of 5-nitrofurfural. The treatment was followed

4) H. Saikachi and H. Ogawa, *J. Am. Chem. Soc.*, **80**, 3642 (1958).

by the same way as described the above experiment. And the others, IV and V, in Table I were prepared by the same method.

**Test of *in Vitro* Bacteriostatic Activity**——Bacteriostatic activity was tested against *Staphylococcus aureus* 209 P in a modified Kuwabara's medium[5] without choline, base components of nucleic acids, folic acid, biotin, riboflavin, calcium pantothenate, pyridoxine, $Mg^{2+}$ and $Ca^{2+}$. [6] The minium bacteriostatic concentration was estimated from the turbidity of the test solution incubated for 24 hr and 37°.

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6) These omissions were recommended by Dr. H. Ōya of the Laboratories.

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# Complications in Using Rabbits for the Study of Oral Drug Absorption

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In the past, rabbits have often been used by us[2,3] and others[4–13] as a tool in the evaluation of oral absorption characteristics of drugs because of their low cost and ease of handling. However, whether the results obtained from rabbit study will truly reflect the absorption characteristics of drugs from the human gastrointestinal tract have not been reported. It is the purpose of this communication to explore the complications and shortcomings of using rabbits for oral absorption studies.

## Experimental

New Zealand white rabbits weighing from 2.0 to 2.5 kg were given 30 ml of a 25% barium sulfate aqueous suspension through a stomach tube. Anteroposterior radiographs of the abdomen of fasted and unfasted rabbits taken in the upright position were obtained at different times. The stomachs of normal and fasted rabbits were also opened and examined.

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11) M. Mizutani and S. Naito, *Chem. Pharm. Bull.* (Tokyo), **15**, 1422 (1967).
12) S. Naito, *Jap. J. Pharm. Chem.*, **35**, 25 (1963).
13) S. Naito, *Jap. J. Pharm. Chem.*, **35**, 14 (1963).