UDC 615.778[547.722]

94. Teruo Makino: Studies on Alkylated Furan Derivatives. I. Syntheses and Antimicrobial Activity of N-Heterocyclyl-5-nitro-2-furamide. I.

(*Pharmaceutical Institute, Keio University*[*1])

A lot of furan derivatives[1,2] have been submitted in the field of antimicrobial drugs. A greater part of such drugs of furan are considered as 5-nitro-2-furfural derivative form. In contrast to these, it is of interest that several compounds of N-alkyl-5-nitro-2-furamide were found to have stronger antifungal effect against *Trichophyton asteroides*, *Microsporum gypseum* and *Aspergillus niger*.[3]

This finding suggested that 5-nitro-2-furamide might serve as a functional structure for antimicrobial agents, as well as 5-nitro-2-furaldehyde, which has been employed for antimicrobial drugs. According to this anticipation, the present author conceived an idea to make new drugs against microörganisms by introducing heterocyclyl groups into N- position of the furamide.

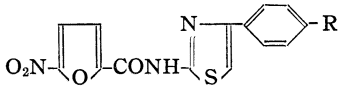
In these studies, it was taken into consideration that some compounds of 2-amino-4-(*p*-alkylphenyl)thiazole were found effective on *Mycobacterium tuberculosis* H_{37} Rv and the Nakayama strain of Japanese B encephalitis virus,[4] and 2-amino-5-ethyl-1,3,4-thiadiazole and 3-amino-6-methoxypyridazine are employed as N-components in sulfathiazole and sulfamethoxypyridazine respectively. Thus, compounds of N-[4-(*p*-alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide, N-(5-alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide and N-(6-alkoxy-3-pyridazinyl)-5-nitro-2-furamide were synthesized to observe their antimicrobial activity.

This paper is concerned with the syntheses and antimicrobial activity of N-[4-(*p*-alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide, N-(5-alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide and N-(6-alkoxy-3-pyridazinyl)-5-nitro-2-furamide.

Syntheses of N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide, N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide and N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide

Any compound of these three series has not been reported to date, in literature.

Table I. N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide



R	m.p. (°C)	Appearance	Formula	Analysis N (%) Calcd.	Found
H	235	Yellow needles	$C_{14}H_9O_4N_3S$	13.33	13.52
CH_3	230~231	〃	$C_{15}H_{11}O_4N_3S$	12.76	12.52
C_2H_5	207	〃	$C_{16}H_{13}O_4N_3S$	12.24	12.19
C_3H_7	203~204	〃	$C_{17}H_{15}O_4N_3S$	11.76	11.54
C_4H_9	142~143	〃	$C_{18}H_{17}O_4N_3S$	11.32	11.37
C_5H_{11}	162~163	〃	$C_{19}H_{19}O_4N_3S$	10.90	10.91
C_6H_{13}	190~191	〃	$C_{20}H_{21}O_4N_3S$	10.52	10.73
C_8H_{17}	166	〃	$C_{22}H_{25}O_4N_3S$	9.83	9.82
$C_{10}H_{21}$	187~188	〃	$C_{24}H_{29}O_4N_3S$	9.23	9.04
$C_{12}H_{25}$	184~185	〃	$C_{26}H_{33}O_4N_3S$	8.69	8.42

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2) K.J. Hayes: U.S. Pat. 2, 610, 181.
3) K. Kawabe, T. Suzuki, M. Iguchi: Yakugaku Zasshi, **80**, 53 (1960).
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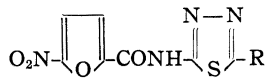
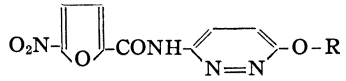
These compounds were synthesized by reacting three kinds of heterocyclic amines, 2-amino-4-(*p*-alkylphenyl)thiazole,[5] 2-amino-5-alkyl-1,3,4-thiadiazole[6] and 3-amino-6-alkoxypyridazine[7] with 5-nitro-2-furoyl chloride in a mixture of acetone and pyridine. The compounds synthesized are shown in Table I, II and III.

Table II. N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide



R	m.p. (°C)	Appearance	Formula	Analysis N (%) Calcd.	Found
H	225	Colorless needles	$C_7H_4O_4N_4S$	23.33	23.17
CH_3	294~295	〃	$C_8H_6O_4N_4S$	22.05	21.78
C_2H_5	261	〃	$C_9H_8O_4N_4S$	20.89	21.08
C_3H_7	223~224	〃	$C_{10}H_{10}O_4N_4S$	19.85	19.70
C_5H_{11}	175	〃	$C_{12}H_{14}O_4N_4S$	18.06	18.28
C_7H_{15}	169~170	〃	$C_{14}H_{18}O_4N_4S$	16.56	16.72

Table III. N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide



R	m.p. (°C)	Appearance	Formula	Analysis N (%) Calcd.	Found
CH_3	235~236	Colorless grains	$C_{10}H_8O_5N_4$	21.21	21.14
C_2H_5	218	〃	$C_{11}H_{10}O_5N_4$	20.14	20.00
C_3H_7	201~202	〃	$C_{12}H_{12}O_5N_4$	19.17	19.00
C_4H_9	179	Colorless scales	$C_{13}H_{14}O_5N_4$	18.29	18.36
C_5H_{11}	171~172	〃	$C_{14}H_{16}O_5N_4$	17.49	17.29
C_6H_{13}	164~165	〃	$C_{15}H_{18}O_5N_4$	16.76	16.23
C_8H_{17}	157~158	Light yellow grains	$C_{17}H_{22}O_5N_4$	15.46	15.40
$C_{10}H_{21}$	165~166	〃	$C_{19}H_{26}O_5N_4$	14.35	14.52
$C_{12}H_{25}$	161~162	〃	$C_{21}H_{30}O_5N_4$	13.39	13.41

Screening Tests for Antibacterial and Antifungal Activity of Compounds Synthesized[*2]

As can be seen in Table IV, it may be said that only ethyl derivative was found fairly effective on the bacteria among the compounds of N-[4-(*p*-alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide, any compound of N-(5-alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide uneffective on any of the bacteria, and methyl and ethyl derivatives effective on the bacteria among the compounds of N-(6-alkoxy-3-pyridazinyl)-5-nitro-2-furamide. The above three effective compounds were observed to have effects nearly equal to that of nitrofuran.

*2 Antibacterial activity of the compounds of the three series was surveyed by *in vitro* test, using *Escherichia coli* C14, *Escherichia coli* K12, *Escherichia coli* K12 (CTSSu), *Salmonella enteritidis* No. 11, *Shigella sonnei* I-1196 and *Shigella* 2a66. The experimental procedures were the same as those described in the previous report.[8] The experimental results are shown in Table IV.

Antifungal activity of the compounds was determined by *in vitro* test, using *Candida albicans*, *Candida tropicalis*, *Aspergillus fumigatus*, *Trichophyton asteroides*, *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, *Penicillium citrinum* and *Microsporum canis*. The experimental procedures were the same to those described in the previous report.[2] The results are shown in Table V.

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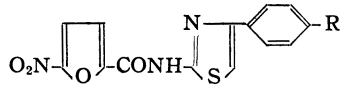
TABLE IV. Antibacterial Activity of N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide, N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide and N-(6-alkoxy-3-pyridazinyl)-5-nitro-2-fnramide

(1) N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide.

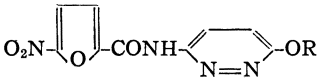


Comp. No.	R	Strain MIC (M) I	II	III	IV	V	VI
1	H	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
2	CH_3	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
3	C_2H_5	10^{-4}	5×10^{-4}	10^{-4}	5×10^{-4}	10^{-4}	10^{-4}
4	C_3H_7	$>5\times10^{-4}$	$>5\times10^{-4}$	10^{-4}	$>5\times10^{-4}$	$>5\times10^{-4}$	5×10^{-4}
5	C_4H_9	$>5\times10^{-4}$	$>5\times10^{-4}$	10^{-4}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
6	C_5H_{11}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
7	C_6H_{13}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
8	C_8H_{17}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
9	$C_{10}H_{21}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
10	$C_{12}C_{25}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$

(2) N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitrofuramide

1	H	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}
2	CH_3	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}
3	C_2H_5	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}
4	C_3H_7	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}
5	C_5H_{11}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}	5×10^{-4}
6	C_7H_{15}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$

(3) N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide



1	CH_3	5×10^{-5}	5×10^{-4}	10^{-4}	$>5\times10^{-4}$	5×10^{-5}	5×10^{-5}
2	C_2H_5	10^{-4}	5×10^{-4}	10^{-4}	$>5\times10^{-4}$	5×10^{-5}	10^{-4}
3	C_4H_9	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	5×10^{-4}	$>5\times10^{-4}$
4	C_6H_{13}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
5	C_8H_{17}	10^{-4}	$>5\times10^{-4}$	10^{-4}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
6	$C_{10}H_{21}$	$>5\times10^{-4}$	$>5\times10^{-4}$	10^{-4}	$>5\times10^{-4}$	$>5\times10^{-4}$	$>5\times10^{-4}$
7	$C_{12}H_{25}$	$>5\times10^{-4}$	$>2\times10^{-4}$	$>5\times10^{-4}$	$>5\times10_{0}^{-4}$	$>5\times10^{-4}$	$>5\times10^{-}{}_{4}$

incubated for 98 hr.

I *Escherichia coli* C14
II *Escherichia coli* K12
III *Escherichia coli* K12 (CTSSu)
IV *Salmonella enteritidis* No. 11
V *Shigella sonnei* I-1196
VI *Shigella* 2a66

As shown in Table V, it may be said that all compounds of the three series were more or less effective on both *Trichophyton asteroides* and *Aspergillus fumigatus*, but uneffective against the other fungi.

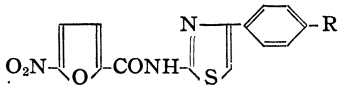
This fact coincides with the finding of Kawabe *et al.* with N-alkyl-2-furamide, N-alkyl-5-nitro-2-furamide and 5-alkyl-2-furamide. Particularly, it is of interest that the lower alkyl members were observed more effective than the higher among compounds of the three series. This tendency was somewhat different from that found by Kawabe *et al.*

These findings suggest that the introduction of N-substituent groups into 2-furamide should give rise to antifungal activity and the results of this experiments might offer a opportunity to find more effective agents than the known compounds of N-substituted 2-furamide.

The works on this problem are in progress. The results of these works will be published in near future.

Table V. Antifungal Activity of N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide, N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide and N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide against Various Fungi.

(1) N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide

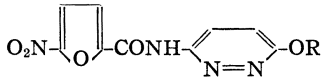


No.	R\Strain	MIC (γ/cc.) I	II	III	IV	V	VI	VII	VIII
1	H	>200	>200	1	>200	<0.1	100	>200	>200
2	CH_3	>200	>200	1	>200	<0.1	>200	>200	>200
3	C_2H_5	>200	>200	1	>200	<0.1	>200	>200	100
4	C_3H_7	>200	>200	10	>200	<0.1	>200	>200	100
5	C_4H_9	>200	>200	100	>200	<0.1	>200	>200	>200
6	C_5H_{11}	>200	>200	100	>200	<0.1	>200	>200	>200
7	C_6H_{13}	>200	>200	100	>200	<0.1	>200	>200	>200
8	C_8H_{17}	>200	>200	200	>200	<0.1	>200	>200	>200
9	$C_{10}H_{21}$	>200	>200	>200	>200	<0.1	>200	>200	>200
10	$C_{12}H_{25}$	>200	>200	>200	>200	1.0	>200	>200	>200

(2) N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide

1	H	>200	>200	>200	>200	<0.1	>200	>200	>200
2	CH_3	>200	>200	>200	>200	<0.1	>200	>200	>200
3	C_2H_5	>200	>200	>200	>200	<0.1	>200	>200	>200
4	C_3H_7	>200	>200	>200	>200	<0.1	>200	>200	>200
5	C_5H_{11}	>200	>200	>200	>200	<0.1	>200	>200	>200
6	C_7H_{15}	>200	>200	>200	>200	<0.1	>200	>200	>200

(3) N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide



1	CH_3	>200	>200	100	>200	<0.1	>200	>200	>200
2	C_2H_5	>200	>200	200	>200	<0.1	>200	>200	>200
3	C_3H_7	>200	>200	200	>200	<0.1	>200	>200	>200
4	C_4H_9	>200	>200	>200	>200	<1.0	>200	>200	>200
5	C_5H_{11}	>200	>200	>200	>200	<0.1	>200	>200	>200
6	C_6H_{13}	>200	>200	>200	>200	<0.1	>200	>200	100
7	C_8H_{17}	>200	>200	>200	>200	<0.1	>200	200	100
8	$C_{10}H_{21}$	>200	>200	>200	>200	<0.1	>200	>200	100
9	$C_{12}H_{25}$	>200	>200	>200	>200	<1.0	>200	200	100
Centian violet		10	100	1	>200	1	100	>200	100

I *Candida albicans*
II *Candida tropicalis*
III *Aspergillus fumigatus*
IV *Trichophyton asteroides* incubated for 7 days
V *Saccharomyces cerevisiae*
VI *Cryptococcus neoformans*
VII *Penicillium citrinum*
VIII *Microsporum canis*

Experimental

I) General Procedure for the Synthesis N-[4-(*p*-Alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide—— 0.0044 mole of 2-amino-4-(*p*-alkylphenyl)thiazole[5] was dissolved in a mixture of 10 cc. of Me_2CO and 3 cc. of pyridine and placed in an ice-water to cool. To this solution, 0.004 mole of 5-nitro-2-furoyl chloride in 5 cc. of Me_2CO was slowly added. Then the mixture was refluxed on a water-bath for 15~30 min. After distillation of the solvent under reduced pressure, 10% HCl solution was added onto the residue. Crude solid was crystallized from EtOH. Recrystallization gave yellow needle crystals.

II) General Procedure for the Synthesis N-(5-Alkyl-1,3,4-thiadiazol-2-yl)-5-nitro-2-furamide—— 0.0044 mole of 2-amino-5-alkyl-1,3,4-thiadiazole[6] was dissolved in a mixture of 20 cc. of Me_2CO and 4 cc. of pyridine and placed in an ice-water to cool. To this solution, 0.004 mole of 5-nitro-2-furoyl chloride in 5 cc. of Me_2CO was slowly added. Then the mixure was refluxed on a water-bath for

30～60 min. After distillation of the solvent under reduced pressure, 10% HCl solution was added onto the residue. Crude solid was crystallized from EtOH. Recrystallization gave colorless needles.

III) General Procedure for the Synthesis N-(6-Alkoxy-3-pyridazinyl)-5-nitro-2-furamide——0.0044 mole of 3-amino-6-alkoxypyridazine[7] was dissolved in a mixture of 10 cc. of Me_2CO and 10 cc. of pyridine and placed in an ice-water to cool. To this solution, 0.004 mole of 5-nitro-2-furoyl chloride in 5 cc. of Me_2CO was slowly added. Then the mixture was refluxed on a water-bath for 30 min. After distillation of the solvent under reduced pressure, 10% HCl solution was added onto the residue. Crude solid was crystallized from EtOH. Recrystallization gave colorless grains.

The author expresses his deepest thanks to Prof. Takeo Ueda for kind guidance throughout the course of this work.

Summary

Compounds of N-[4-(*p*-alkylphenyl)-2-thiazolyl]-5-nitro-2-furamide (I), N-(5-alkyl-1,3,4-thiadiazolyl)-5-nitro-2-furamide (II), and N-(6-alkoxy-3-pyridazinyl)-5-nitro-2-furamide (III) were synthesized to observe their antibacterial and antifungal activity. On the bacteria, ethyl derivative among the compounds of (I) series and, methyl and ethyl derivatives of (III) series were observed to have effects nearly equal to that of nitrofuran.

Antifungal activity of the compounds of three series were more or less effective on both *Trichophyton asteroides* and *Aspergillus fumigatus*, but uneffective on the other fungi.

(Received April 25, 1961)

UDC 615.778[547.852.2]

95. Tatsuya Horie(Ishida), Kiyokatsu Kinjo, and Takeo Ueda : Studies on Pyridazine Derivatives. I.*1 Synthesis and Antimicrobial Activity of 6-Substituted 3-Aminopyridazine and its Sulfonamido Derivatives.

(*Pharmaceutical Institute, Keio University**2)

As pyridazine is related structurally to pyrimidine, it is of interest to utilize pyridazine ring as an antagonistic group against naturally occuring substances containing pyrimidine ring, in connection of finding new antimicrobial agents.

In fact, attempts were made by many workers[1~5] to introduce pyridazine ring into the structures of sulfa drugs, since Anderson[6] had reported the synthesis and antibacterial activity of 3-sulfanilylamidopyridazine. Above all, it should be noted that 3-sulfanilylamido-6-methoxypyridazine was confirmed to be valuable by Nichole[7,8] as

*1 Papers were read at the Annual Meeting of Pharm. Soc. of Japan, No. 78 (1958) and 80 (1960).

*2 Shinano-machi, Shinjuku-ku, Tokyo (堀江達也, 金城清勝, 上田武雄).

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