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139. **Haruo Saikachi* and Keizo Suzuki****: Synthesis of Furan Derivatives. XVI. 3-(5-Nitro-2-furyl)acrylamides.

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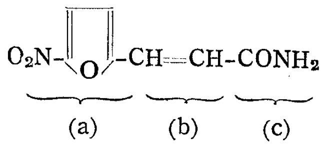
Previous paper[1] dealing with synthesis and antibacterial activity of 3-(5-nitro-2-furyl)-acrylamides has shown that 3-(5-nitro-2-furyl)acrylamide of this system was more effective than 5-nitrofurfural semicarbazone, namely Furacin,[2] against microörganisms *in vitro*.



(I)

For the purpose of discussion, the 3-(5-nitro-2-furyl) acrylamides may be divided into three parts; (a) the 5-nitro-2-furyl group which can be regarded as a group native to physiological system in a sense similar to that chloramphenicol is like *p*-nitrobenzene; (b) the vinyl grouping which is more in the nature of an antibiotics, and (c) the acid amide grouping which is essential to the structure of proteins.

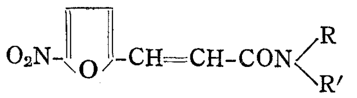
Although the exact mechanism of action is unknown, it may be concluded on the basis of results obtained in this Laboratory[3] that the nitro group is quite essential. In its absence there is very little or no activity, and changes in part (c), described in this paper, result in complete decrease of antibacterial activity. Furtheremore, it is presumed that the vinyl grouping in (b) exhibits supplementary activity to some extent.

Since the solubility of the amide (I) in water is very small, the present attempts to improve the property and activity of the analogs without affecting other two groupings were directed to change of (c) grouping with primary or secondary alkylamines, as listed in Table I. 3-(5-Nitro-2-furyl) acrylic acid was directly prepared by nitration of 3-(2-furyl) acrylic acid with a mixture of conc. nitric acid and acetic anhydride, and the corresponding acid chloride was prepared with thionyl chloride under mild conditions.

Condensation of 3-(5-nitro-2-furyl)acryloyl chloride with various alkylamines was effected in ether, benzene, or chloroform solution (cf. Table I and Experimental section). In the present work, 19 new 3-(5-nitro-2-furyl)acrylamides were prepared and subjected to microbiological screening.

From the screening results shown in table II, it may be concluded that an auxoantibacterial effect of alkylamino group, possessing three to four carbon atoms is more potent than the higher alkylamine groups and the normal alkylamino groups are more effective than the corresponding iso-type compounds.

Consequently, the functional order of alkyl group may be approximately ranked as follows:



$R=H$, $R'=CH_3$, C_2H_5, $n\text{-}C_3H_7$, $iso\text{-}C_3H_7$, $n\text{-}C_4H_9$, $iso\text{-}C_4H_9$, $n\text{-}C_5H_{11}$, $iso\text{-}C_5H_{11}$.

$$CH_3 > C_2H_5 > n\text{-}C_3H_7 > iso\text{-}C_3H_7 > n\text{-}C_4H_9 > iso\text{-}C_4H_9 > n\text{-}C_5H_{11} > iso\text{-}C_5H_{11}$$

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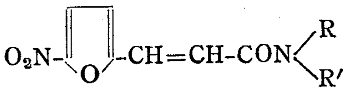
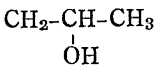
1) H. Saikachi, K. Suzuki: Yakugaku Zasshi, **69**, 286 (1949).

2) M. C. Dodd, W. B. Stillman: J. Pharmacol. Exptl. Therap., **82**, 11 (1944).

3) H. Saikachi, *et al.*: This Bulletin, **3**, 194 (1955); *ibid.*, **3**, 407 (1955).

TABLE I. 5-Nitrofurylacrylamides



Compd. No.	Prepn. proc.	Yield[a] (%)	R	R′	m.p. (°C)	Crystn. Solvent	Appearance	Formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
(II)	A	60	H	CH_3	195～196 (dec.)	EtOH	Pale yellow needles	$C_8H_8O_4N_2$	48.98	48.64	4.11	4.30	14.28	14.00
(III)	A	60	CH_3	CH_3	194 (dec.)	EtOH-AcOEt (2:3) mixt.	Yellow needles	$C_9H_{10}O_4N_2$	51.42	51.73	4.80	5.13	13.33	13.50
(IV)	B	63	H	C_2H_5	178～180	EtOH-H_2O (1:3) mixt.	Yellow prisms	$C_9H_{10}O_4N_2$	51.42	51.54	4.80	5.02	13.33	13.53
(V)	C	65	C_2H_5	C_2H_5	89～90	EtOH	Yellow crystals	$C_{11}H_{14}O_4N_2$	55.45	55.42	5.92	6.06	11.76	11.90
(VI)	A	60	H	*n*-C_3H_7	170	EtOH	Pale yellow needles	$C_{10}H_{12}O_4N_2$	53.57	53.60	5.39	5.72	12.50	12.21
(VII)	A	56	*n*-C_3H_7	*n*-C_3H_7	78～79	EtOH	Yellow needles	$C_{13}H_{18}O_4N_2$	58.63	58.60	6.81	6.98	10.52	10.20
(VIII)	A	64	H	*iso*-C_3H_7	187～188	EtOH	Yellow plates	$C_{10}H_{12}O_4N_2$	53.57	54.00	5.39	5.64	12.50	12.65
(IX)	B	72	*iso*-C_3H_7	*iso*-C_3H_7	96～98	EtOH	Yellow needles	$C_{13}H_{18}O_4N_2$	58.63	58.60	6.81	6.98	10.52	10.20
(X)	A	67	H	*n*-C_4H_9	116～117	EtOH-H_2O (1:5) mixt.	Yellow needles	$C_{11}H_{14}O_4N_2$	55.45	55.75	5.92	5.74	11.76	11.93
(XI)	C	60	*n*-C_4H_9	*n*-C_4H_9	104～105	EtOH	Fine yellow needles	$C_{15}H_{22}O_4N_2$	60.20	60.48	7.53	7.43	9.52	9.25
(XII)	C	64	H	*iso*-C_4H_9	115～117	EtOH	Fine yellow needles	$C_{11}H_{14}O_4N_2$	55.45	55.72	5.92	5.63	11.76	12.10
(XIII)	A	60	*iso*-C_4H_9	*iso*-C_4H_9	75～76	EtOH	Pale yellow needles	$C_{15}H_{22}O_4N_2$	61.20	61.48	7.53	7.80	9.52	9.82
(XIV)	C	63	H	*sec*-C_4H_9	106～108	EtOH	Pale yellow needles	$C_{11}H_{14}O_4N_2$	55.45	55.83	5.92	6.09	11.76	11.58
(XV)	C	60	H	*n*-C_5H_{11}	108～109	EtOH	Yellow needles	$C_{12}H_{16}O_4N_2$	57.13	57.49	6.39	6.24	11.11	11.40
(XVI)	C	48	H	*iso*-C_5H_{11}	110～111	EtOH	Pale yellow needles	$C_{12}H_{16}O_4N_2$	57.13	57.28	6.39	6.45	11.11	11.48
(XVII)	C	57	*iso*-C_5H_{11}	*iso*-C_5H_{11}	94～95	EtOH	Yellow needles	$C_{17}H_{26}O_4N_2$	63.33	63.74	8.13	8.33	8.69	8.72
(XVIII)	A	60	H	$CH_2 \cdot CH{:}CH_2$	167～168	EtOH	Yellow needles	$C_{10}H_{10}O_4N_2$	54.05	54.26	4.54	4.62	12.61	13.00
(XIX)	D	64	H	 $CH_2\text{-}\underset{\mid \atop OH}{CH}\text{-}CH_3$	156～157	EtOH contg. small amt. dehyd. Et_2O	Yellow needles	$C_{10}H_{12}O_5N_2$	50.00	49.68	5.04	4.89	11.66	11.49
(XX)	A	60	H		116～117	MeOH	Yellow plates	$C_{13}H_{17}O_4N_2$	58.90	59.16	6.41	6.23	10.60	10.41

(a) Calcd. on the basis of 3-(5-nitro-2-furyl) acryloyl chloride used.

TABLE II. Minimum Bacteriostatic Concentration Unit (10,000)

Compd. No.	*Staph. aureus*	*E. coli*	*Salm. typhi.*	*Sh. dysent.*	*Sh. paradysent.* Komagome Bl.
(II)	16	32	16	4	16
(III)	4	4	—	—	—
(IV)	8	8	16	4	8
(V)	2	0.5	—	—	—
(VI)	16	32	8	4	4
(VII)	4	0.5	—	—	—
(VIII)	4	2	—	—	—
(IX)	4	1	—	—	—
(X)	4	1	—	—	—
(XI)	4	1	—	—	—
(XII)	4	1	—	—	—
(XIII)	2	0.5	—	—	—
(XIV)	4	1	—	—	—
(XV)	1	1	—	—	—
(XVI)	2	1	—	—	—
(XVII)	2	1	—	—	—
(XVIII)	16	16	8	4	4
(XIX)	8	8	16	8	16
(XX)	2	1	—	—	—
(Furacin)	14	14	10	8	8

Incubation time, 72 hrs.

It is of interest that N-(2-hydroxypropyl)-3-(5-nitro-2-furyl)acrylamide (XIX) is highly soluble in water and has the strongest activity among these compounds.

The authors are indebted to Miss H. Iwata for the elementary analyses and to Dr. A. Oyama, Microbiological Institute, University of Kyoto, for screening of these compounds.

Experimental

Procedure A: **N-Methyl-3-(5-nitro-2-furyl)acrylamide (II)**—A small excess of dry methylamine was bubbled with cooling through a solution of 2.01 g. (0.1 mole) of 3-(5-nitro-2-furyl)acryloyl chloride in 60 cc. of dehyd. ether until no more crystals deposited. After standing the reaction mixture in an ice-box for 3 hrs., the crystalline product was collected and washed with cold water. Recrystallization of the crude product from EtOH gave 1.17 g. (60%) of pale yellow needles, m.p. 195~196° (decomp.).

Procedure B: **N,N-Diisopropyl-3-(5-nitro-2-furyl)acrylamide (IX)**—A solution of a small excess of isopropylamine in 2.0 cc. of dehyd. $CHCl_3$ was added dropwise into a solution of 2.01 g. (0.1 mole) of 3-(5-nitro-2-furyl)acryloyl chloride in 60 cc. of dehyd. $CHCl_3$ with cooling. After standing at room temperature for 5 hrs., the crystals that deposited were collected and washed well with cold water. The crude crystals were recrystallized 3 times from EtOH to give 1.75 g. (70%) of yellow needles melting at 96~98°.

Procedure C: **N,N-Dibutyl-3-(5-nitro-2-furyl)acrylamide (XI)**.—A solution of 2.3 g. of dibutylamine in 50 cc. of dehyd. benzene was added with shaking into a solution of 2.01 g. (0.1 mole) of 3-(5-nitro-2-furyl)acryloyl chloride in 50 cc. of benzene. After standing the reaction mixture at room temperature for 3 hrs., the crystalline mass was collected, and washed well with a cold mixture of EtOH and water (1:5). Recrystallization from EtOH yielded 1.65 g. (60%) of fine yellow needles melting at 104~105°.

Procedure D: **N-(2-Hydroxypropyl)-3-(5-nitro-2-furyl)acrylamide (XIX)**—A solution of 1.8 g. of 1-amino-2-hydroxypropane in 30 cc. of dehyd. EtOH was added dropwise into a stirred solution of 2.01 g. (0.1 mole) of 3-(5-nitro-2-furyl)acryloyl chloride in 40 cc. of a mixture of dehyd. ether and EtOH (1:2). After removal of the solvents, the residue gradually solidified when stood in an ice-box. The crude crystals were collected and washed well with a very small amount of dehyd. ether to 1.75 g. (62%) of yellow needles melting at 156~157°.

Summary

Nineteen kinds of 3-(5-nitro-2-furyl)acrylamides were prepared by condensation of 3-(5-nitro-2-furyl)acryloyl chloride and alkylamines. Among these acid amides, N-(2-

hydroxypropyl)-3-(5-nitro-2-furyl)acrylamide (XIX) showed a higher solubility in water and a strong antibacterial activity.

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140. **Tsutomu Furuya**: Studies on the Metabolism of Naturally Occurring Coumarins. IV.[1] Urinary Metabolites of Dimethylesculetin and Scopoletin.

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Dimethylesculetin is obtained from the immature fruits of *Artemisia capillaris* Thunb. The alcoholic extracts of this plant is being used as a remedy for jaundice in this country. In connection with its remedial effect it seemed worthwhile to study the metabolic fate of this compound on which the present study chiefly concerns.

As a reference the metabolism of scopoletin obtained from Belladonna roots and other Solanaceous plants has also been studied.

The author is indebted to Prof. S. Shibata and Assist. Prof. M. Fujita for their kind advices and suggestions in carrying out the present study. Deep gratitude is expressed for the kind gift of dimethylesculetin by Dr. K. Imai, Takamine Research Laboratory, Sankyo Co. Ltd.

Experimental

Material—Dimethylesculetin, m.p. 144°, recrystallized from hydr. EtOH, was used.

Animal, Diet, and Dosage—Same as described in the preceding paper.[1]

Identification of Metabolites—The 48-hr. urine after oral administration of 540 mg. herniarin was acidified with dil. H_2SO_4 and continuously extracted with ether for 6 hrs. The F and C fractions, which were obtained by respective extraction with ether before and after hydrolysis as indicated in the case of herniarin, were examined by paper chromatography.

Esculetin 7-methyl ether, scopoletin (esculetin 6-methyl ether), and unchanged dimethylesculetin were detected in the urinary metabolites as shown in Table I.

TABLE I. Indentification of Metabolites in Urine by Paper Chromatography

Compound	F	C
Dimethylesculetin	trace	—
Esculetin 7-methyl ether	++	++++
Scopoletin	++	+
Esculetin	trace	+

Isolation of Metabolites—The 48-hr. urine after dosage of 540 mg. of dimethylesculetin was acidified with 100 cc. of 18*N* H_2SO_4 and extracted continuously for 6 hrs. after hydrolysis by heating on a boiling water bath. The ethereal solution was shaken twice with 8.8*N* buffer solution, referring to the result of multibuffered paper chromatography.[2] The brownish residue obtained from the ethereal extract was recrystallized repeatedly from water, decolorizing with addition of charcoal. Colorless needles, m.p. 184° (160 mg.), were obtained, which showed no depression on admixture with the authentic sample of esculetin 7-methyl ether.

The alkaline solution was acidified with dil. HCl, extracted with ether using a continuous extractor, and the ethereal extract was evaporated. The pale brownish residue (40 mg.), whose solution gave an intensive fluorescence, was recrystallized from water to give scopoletin, m.p. 205°.

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[1] Part III: This Bulletin, **6**, 520(1958).

[2] This Bulletin, **6**, 513(1958).