powder in AcOH. It gave 0.2 g. of yellow needles, m.p. 179~180° (ligroine), which was found to be identical with 1-bromo-2-methoxyphenazine.

Bromination of 2-Methoxyphenazine 10-Oxide (XII) : 1-Bromo-2-methoxyphenazine 10-Oxide (XIII)—(XII) (0.2 g.) was brominated as described above. It gave a small amount of deep yellow crystals, m.p. 185~188° (ligroine), which showed mixed m.p. depression with 1-bromo-2-methoxyphenazine 5-oxide. *Anal.* Calcd. for $C_{13}H_9O_2N_2Br$: C, 51.16; H, 2.95; N, 9.18. Found : C, 51.48; H, 3.11; N, 8.77. A fair amount of the starting material was recovered.

Reduction of 1-Bromo-2-methoxyphenazine 10-Oxide (XIII)—(XIII) (0.1 g.) was reduced with Zn powder and AcOH. Yellow crystals of m.p. 180° (ligroine) were formed, which were identical with 1-bromo-2-methoxyphenazine by mixed m.p.

Summary

Bromination of phenazine N-oxide, and 1- and 2-methoxyphenazine was carried out and 1-methoxy-4-bromo- and 1-bromo-2-methoxy-phenazines were obtained, but bromo derivative of phenazine N-oxide was not formed. Bromination of 1-methoxyphenazine 5-oxide and 2-methoxyphenazine 5- and 10-oxides was also carried out and each of their bromo derivatives was prepared.

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106. Haruo Saikachi*1 and Keizo Suzuki*2 : Synthesis of Furan Derivatives. XIX. 2-Methyl-3-(5-nitro-2-furyl)acrylamides.

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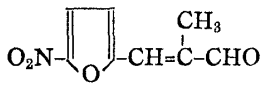
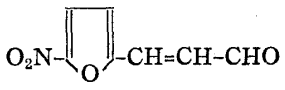
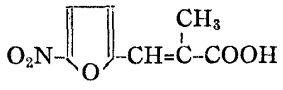
In a previous paper,[1] relationship between antibacterial activity and chemical structure of 3-(5-nitro-2-furyl)acrylamides was described. These experimental results showed that 3-(5-nitro-2-furyl)acrylamide of this series is especially highly active and shows a broad spectrum against microörganisms. It had also been suggested[2] that 2-methyl-3-(5-nitro-2-furyl)acrolein (I) is generally more active than unsubstituted 3-(5-nitro-2-furyl)acrolein (II) as antibacterial compound.



(I)



(II)



(III)

Therefore, it was deduced from above facts that although the functional end group in the side chain is different from either (I) or (II), 2-methyl-3-(5-nitro-2-furyl)acrylic acid (III) would be a new antiauxobacterial compound. It is of interest that the methyl in α-position of (5-nitro-2-furyl)acrylic acid is associated with that of tuberculous metabolic substances, such as C_{27}-phthienoic acid,[3] mycolipenic acid,[4] and 1,2,15-trimethyldocosanoic acid.[5]

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1) H. Saikachi, K. Suzuki : Yakugaku Zasshi, **69**, 36(1949) (C. A., **44**, 5372(1950)).
2) H. Saikachi, *et al.* : This Bulletin, **3**, 407(1956).
3) J. Cason, G. Sumrell : J. Am. Chem. Soc., **72**, 1870(1950).
4) N. Polar, R. Robinson : J. Chem. Soc., **1945**, 1384.
5) S. David, *et al.* : *Ibid.*, **1949**, 1341.

For this reason, attempt was made to synthesize new compounds of strong activity and weak toxicity, and also to elucidate the relationship between chemical structure and antibacterial activity in this area.

The first approach to the synthesis of 2-methyl-3-(5-nitro-2-furyl)acrylic acid was made by nitration of 2-methyl-3-(2-furyl)acrylic acid[6] with a mixture of nitric acid and acetic anhydride. 2-Methyl-3-(5-nitro-2-furyl)acryloyl chloride was prepared from 2-methyl-3-(5-nitro-2-furyl)acrylic acid with thionyl chloride by the usual manner. The over-all reaction route is shown in Chart 1.

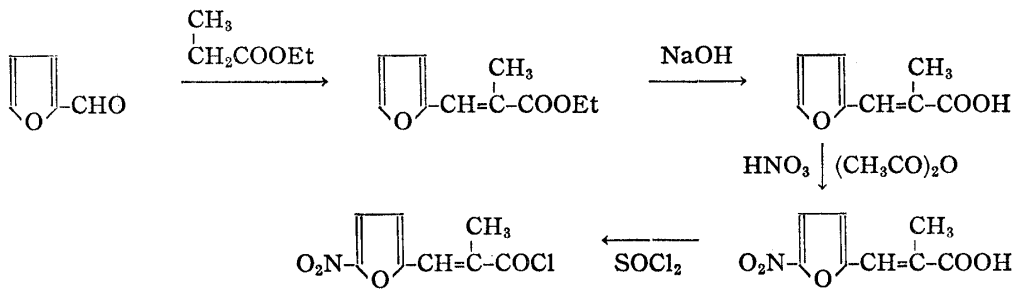


Chart 1.

The acid chloride was treated with one of the amines, amino alcohols, or alcohols in appropriate amount of acetone to obtain the new acid amides and esters listed in Tables I and II. Amines and alcohols used were ammonia, methylamine, ethylamine, propylamine, isopropylamine, butylamine, *sec*-butylamine, isobutylamine, isopentylamine, octylamine, allylamine, ethanolamine, isopropanolamine, hydrazine, ethylenediamine, benzylamine, cyclohexylamine, aniline, *o*-toluidine, *p*-toluidine, 2-naphthylamine, *p*-chloroaniline, *p*-bromoaniline, *m*-hydroxyaniline, *p*-hydroxyaniline, *p*-anisidine, methanol, ethanol, propanol, isopropanol, isobutanol, and *sec*-butanol.

The compounds prepared were submitted to screening against microörganisms. 2-Methyl-3-(5-nitro-2-furyl)acrylic acid and its esters showed almost no activity. Among the condensation products of aliphatic amines, the acryloylamides prepared from lower alkylamines such as methylamine, ethylamine, and ethanolamine, showed higher activity. In general, antibacterial activity of these compounds seemed to be inversely proportional to the number of alkyl carbon atoms with which nitrogen atoms of amides combine. Further, the acrylamides derived from normal alkyl were more active than those from the corresponding isoalkylamines.

In the series of condensate of aromatic amines, both 2-methyl-3-(5-nitro-2-furyl)-acrylic acid *p*-hydroxyanilide and 2-methyl-3-(5-nitro-2-furyl)acrylic acid *m*-hydroxyanilide exerted high activity, as listed in Table I.

From these screening results, it may be concluded that the relationship between chemical structure and antibacterial activity of 2-methyl-3-(5-nitro-2-furyl)acrylamides is very similar to that of (5-nitro-2-furyl)acrylamides. In general, however, it was estimated that the latter, reported previously, is more active except for a specific microörganisms.

The authors express their appreciation to Dr. Aoyama of the Department of Bacteriology, Kōbe Medical College, for microbiological screening.

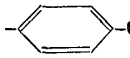
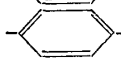
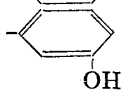
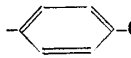
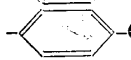
Experimental

2-Methyl-3-(5-nitro-2-furyl)acrylic Acid—To 194 g. (1.9 moles) of Ac_2O, 87.5 g. (1.4 moles) of fuming HNO_3 (sp. gr., 1.514) was added with chilling and stirring to prepare a mixed acid. To this mixed acid, 35 g. (0.23 mole) of 2-methyl-3-(2-furyl)acrylic acid (m.p. 110~114°) was added slowly at −5°

6) T. Kashiwagi: Bull. Chem. Soc. Japan, **2**, 310(1927) (C. A., **22**, 778(1927)).

TABLE I. O_2N-(furan)-$CH=C(CH_3)$-$CONH$-R

R	Prepn. procedure (crystn. solvent)	m.p. (°C)	Yield[a] (%)	Appearance	Nitrogen (%) Calcd.	Nitrogen (%) Found	Min. bacteriostatic concn.[b] (Unit, 10,000) *St. aureus*	*E. coli*	*S. typhi*	*Sh. dysent.*	*Sh. Paradysent*
H	A (MeOH)	165	30	Yellow plates	14.28	14.23	16	16	32	16	32
CH_3	A (MeOH)	138~139	32	Yellow needles	13.33	13.13	8	4	16	8	16
C_2H_5	A (MeOH)	117~119	40	Light yellow needles	12.50	12.13	4	4	4	4	8
C_3H_7	B (MeOH)	111~113	35	Light yellow needles	11.77	11.86	2	2	—	—	—
iso-C_3H_7	B (MeOH)	146~147	42	Yellow needles	11.77	11.53	2	5	—	—	—
C_4H_9	B (MeOH)	90~92	40	Light yellow needles	11.11	10.92	4	1	—	—	—
iso-C_4H_9	B (MeOH)	111~112	42	Light yellow needles	11.11	10.06	2	5	—	—	—
sec-C_4H_9	B (MeOH)	116~118	50	Light yellow needles	11.11	10.98	1	5	—	—	—
iso-C_5H_{11}	B (MeOH)	100~101	52	Light yellow needles	10.53	10.61	1	5	—	—	—
C_8H_{17}	B (MeOH)	95~96	48	Light yellow needles	9.10	9.34	5	5	—	—	—
CH_2-CH=CH_2	B (MeOH)	115~116	55	Yellow needles	11.87	11.90	2	2	—	—	—
C_2H_4OH	C (MeOH)	144~146	45	Yellow needles	11.67	11.88	8	4	8	4	8
CH_2-$CH(OH)$-CH_3	C (MeOH)	149~150	40	Yellow needles	11.02	11.05	4	2	2	2	2
$NH\cdot CO$-$C(CH_3)$=CH-(furan)-NO_2	D (dioxane)	242 (d.)	40	Yellow needles	14.36	14.12	2	5	—	—	—
$CH_2\cdot CH_2\cdot NH$-CO-$C(CH_3)$=CH-(furan)-NO_2	D (dioxane)	226 (d.)	50	Yellow prisms	13.40	13.16	1	5	—	—	—
-(benzene)-H	D (dioxane)	142~144	40	Bright yellow plates	10.06	10.21	1	5	—	—	—
CH_2-(benzene)	B (MeOH)	111~113	48		9.79	9.42	5	5	—	—	—
-(benzene)	B (MeOH)	174~175	75	Bright yellow needles	10.29	10.53	1	5	—	—	—
-(benzene)-CH_3	B (MeOH)	189~191	70	Bright yellow needles	9.79	9.83	5	5	—	—	—
-(benzene)-CH_3	B (MeOH)	149~151	74	Bright yellow needles	9.79	9.69	—	—	—	—	—
(naphthalene)	B (MeOH)	159~161	70	Bright yellow needles	8.65	8.57	2	1	—	—	—

	B (MeOH)	196～197	73	Bright yellow needles	9.12	9.00	5	5	—	—	—
	B (MeOH)	207～208 (d.)	60	Bright yellow needles	7.84	7.99	5	5	—	—	—
	B (MeOH)	250 (d.)	45	Orange yellow needles	9.73	9.79	8	2	2	2	2
	B (MeOH)	260 (d.)	40	Orange needles	9.73	9.79	16	4	4	4	4
	B (MeOH)	190～191 (d.)	70	Reddish (yellow) needles	9.27	9.24	1	5	—	—	—

a) Calculated from acryloyl chloride and on the basis of the recrystallized products.
b) Incubated for 98 hr.

TABLE II.

R	Procedure (crystn. solvent)	m.p. (°C)	Yield[a] (%)	Appearance	Nitrogen (%)		Min. bacteriostatic concn. (Unit, 10,000)	
					Calcd.	Found	*St. aureus*[b]	*E. coli*[b]
CH_3	E (MeOH)	125～127	50	Yellow needles	6.64	6.36	2	2
C_2H_5	E (MeOH)	80～82	60	Light yellow needles	6.22	6.04	5	5
C_3H_7	E (MeOH)	56～57	50	Light yellow needles	5.86	5.72	1	5
iso-C_3H_7	E (MeOH)	75～76	60	Light yellow needles	5.86	5.67	5	5
iso-C_4H_9	E (MeOH)	45～46	50	Light yellow needles	5.53	5.28	2	5
sec-C_4H_9	E (MeOH)	40～42	55	Light yellow needles	5.53	5.21	1	5

Insoluble in 5,000 volumes of broth.
a) Calculated from acryloyl chloride and on the basis of the recrystallized products.
b) Incubated for 98 hr.

and the reaction mixture was allowed to stand for additional 1 hr. at the same temperature. The yellowish crystalline precipitate was collected, washed well with cold water, and dried at room temperature shielded from light. The crude product was recrystallized twice from MeOH to 27 g. of pale yellow needles, m.p. 211~212°(decomp.). *Anal.* Calcd. for $C_8H_7O_4N$: C, 48.72; H, 3.58; N, 7.10. Found : C, 48.48; H, 3.41; N, 7.35.

2-Methyl-3-(5-nitro-2-furyl)acryloyl Chloride—A mixture of 20 g. (0.10 mole) of crude 2-methyl-3-(5-nitro-2-furyl)acrylic acid and 100 g. (0.9 mole) of $SOCl_2$ was refluxed cautiously on a water bath until the crystals dissolved completely. Excess of $SOCl_2$ was distilled off and the residue was distilled under a diminished pressure. The dark yellow, solid residue was recrystallized from benzene to 18.5 g. of pale yellow needles, m.p. 120~122°. *Anal.* Calcd. for $C_8H_6O_4N$: C, 44.57; H, 2.81; N, 6.49. Found C, 44.39; N, 6.72; H. 3.06.

N,2-Dimethyl-3-(5-nitro-2-furyl)acrylamide (Method A)—The following procedure was used for preparation of three acrylamides listed in Table I. Through a solution of 1.0 g. (0.005 mole) of 2-methyl-3-(5-nitro-2-furyl)acryloyl chloride in 30 cc. of dehyd. acetone, a dry methylamine gas was bubbled until the reaction was completed. After standing the reaction mixture at room temperature for 2 hr., the solvent was distilled off under a reduced pressure. The residue obtained was diluted with 30 cc. of water until crystalline mass deposited, and this was collected to give 0.3 g. of pale yellow needles.

N-Butyl-2-methyl-3-(5-nitro-2-furyl)acrylamide (Method B)—This procedure was used for preparation of 18 compounds listed in Table I. To a stirred solution of 1.0 g. (0.005 mole) of 2-methyl-3-(5-nitro-2-furyl)acryloyl chloride in 30 cc. of dehyd. acetone 0.7 g. (0.01 mole) of butylamine was added dropwise under cooling. After standing the mixture at room temperature for 3 hr., the reaction mixture was diluted with 40 cc. of water until a solid mass deposited no longer. The solid mass was collected and washed with water. Two recrystallization from MeOH gave 0.5 g. of light yellowish plates, m.p. 90~92°.

N-(2-Hydroxyethyl)-2-methyl-3-(5-nitro-2-furyl)acrylamide (Method C)—This procedure was used for preparation of 2 compounds listed in Table I. To a stirred solution of 1.0 g. (0.005 mole) of 2-methyl-3-(5-nitro-2-furyl)acryloyl chloride in 30 cc. of dehyd. acetone, a solution of 0.6 g. (0.01 mole) of ethanolamine in 5 cc. of acetone was added at below 5°. The reaction mixture was diluted with 30 cc. of water, the separated crystalline mass was collected, and washed well with cold water. Three recrystallizations from MeOH gave 0.6 g. of pale yellowish needles, m.p. 144~146°.

1,2-Bis[2-methyl-3-(5-nitro-2-furyl)acryloyl]hydrazine (Method D)—This procedure was used for preparation of three acrylamides listed in Table I. To a stirred solution of 1.0 g. (0.005 mole) of 2-methyl-3-(5-nitro-2-furyl)acryloyl chloride in 60 cc. of dehyd. benzene, a solution of 1.5 g. (0.34 mole) of $H_2NNH_2 \cdot H_2O$ in 50 cc. of EtOH was added under cooling with ice water until precipitation no longer occurred. After standing the mixture at room temperature for 2 hr., the crystalline precipitate was collected and washed well with cold water. The mass was recrystallized from dioxane to 0.6 g. of yellowish needles, m.p. 240°(decomp.).

Preparation of Acrylic Acid Esters (Method E)—This proceudre was used for preparation of acrylic esters listed in Table II. A solution of 1.0 g. (0.005 mole) of 3-methylacryloyl chloride in 20 cc. of EtOH was refluxed on a water bath until the crystals dissolved completely. When cool, the reaction mixture was diluted with 50 cc. of cold water and a crystalline mass deposited. Two recrystallizations from MeOH gave pure crystals.

Summary

Twenty-six new 2-methyl-3-(5-nitro-2-furyl)acrylamides and six esters were prepared by condensation of 2-methyl-3-(5-nitro-2-furyl)acryloyl chloride and various amines or alcohols. Antibacterial activity of these derivatives is discussed.

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