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83. Haruo Saikachi and Keizo Suzuki : Synthesis of Furan Derivatives. XVIII. 2-Cyano-3-(5-nitro-2-furyl)acrylamides and Esters.

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In continuation of the previous work on ω-(5-nitro-2-furyl)-polyenealdehydes[1] and 3-(5-nitro-2-furyl)acrylamides[2] possessing a marked biological interest by a consideration of conjugated double bond suggested the possibility of a more effective compounds in this field. Of the many derivatives prepared earlier, 3-(5-nitro-2-furyl)acrylamide (I) and 5-(5-nitro-2-furyl)pentadienal oxime (II) showed especially high activity against microörganisms.

O_2N-(furan)-CH=CH-CONH$_2$ (I) O_2N-(furan)-CH=CH-CH=CH-CH=NOH (II)

In connection with these compounds, several workers[3] studied biological activity of halogenated derivatives of aromatic acroleins, cinnamic and *p*-nitrocinnamic acids, and recently 2-thienylacrylic acid derivatives were synthetically and biologically studied by Italian workers.[4]

From the considerations of reported activity, it appeared that 3-(5-nitro-2-furyl)acryloyl analogs bearing a cyano group instead of hydrogen atom at the 2-position of the side chain might have better antibacterial activity than the unsubstituted analogs reported previously.[2]

For this object, the important intermediate, 2-cyano-3-(2-furyl)acrylic acid,[5] was prepared by condensation of furfural with ethyl cyanoacetate, and nitration of this compound was effected with a mixed acid (acetic anhydride and fuming nitric acid) without formation of nitroacetine intermediate.

(furan)-CHO $\xrightarrow{NC\cdot CH_2\cdot COOEt}$ (furan)-CH=C(CN)-COOEt ⟶ (furan)-CH=C(CN)-COOH $\xrightarrow[Ac_2O]{HNO_3}$ O_2N-(furan)-CH=C(CN)-COOH $\xrightarrow{PCl_5}$ O_2N-(furan)-CH=C(CN)-COCl

2-Cyano-3-(5-nitro-2-furyl)acryloyl chloride was prepared in quantitative yield by usual manner from 2-cyano-3-(5-nitro-2-furyl)acrylic acid with phosphorus pentachloride.

In order to prepare 24 acrylamides listed in Table I, condensation of 2-cyano-3-(5-nitro-2-furyl)acryloyl chloride with various amines and alcohols in a dry benzene or acetone solution was carried out under several conditions.

In this work, 27 new acrylamides and 7 new esters were prepared, and subjected to

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TABLE I. O_2N-[furan ring]-CH=C(CN)-COR

R	Prepn. Procedure	m.p. (°C)	Yield[a] (%)	Recrystn. solvent	Appearance	N (%) Calcd.	N (%) Found	Max. bacteriostatic concn.[b] (Unit, 10,000) St. aureus	E. coli
-NH	A	260 (d.)	54	EtOH	Brown prisms	20.29	19.98	0.5	0.5
-NH CH_3	A	265 (d.)	50	EtOH	Yellow ndls.	19.00	19.24	0.5	0.5
-$N(CH_3)_2$	A	171~172	58	EtOH	Yellow ndls.	17.87	17.58	0.5	0.5
-NHC_2H_5	B	192~193	58	EtOH	Yellow ndls.	17.87	17.65	0.5	0.5
-NHC_3H_7(n)	B	180~181	45	EtOH	Yellow ndls.	16.86	17.06	0.5	0.5
-$N(C_3H_7)_2$(n)	B	97~ 98	31	EtOH	Yellow ndls.	14.43	14.17	—	—
-NHC_3H_7(iso)	B	178~179	45	EtOH	Yellow ndls.	16.86	16.73	0.5	0.5
-NHC_4H_9(n)	B	173~174	52	EtOH	Yellow prisms	15.96	16.35	0.5	0.5
-NHC_4H_9(iso)	B	175~176	43	EtOH	Pale Yell. pris.	15.96	15.86	0.5	0.5
-NHC_4H_9(sec)	B	160~162	43	EtOH	Pale Yell. pris.	15.96	15.71	0.5	0.5
-NHC_5H_{11}(iso)	B	165~166	41	EtOH	Pale Yell. pris.	15.16	15.24	0.5	0.5
-$N(C_5H_{11})_2$(iso)	B	97~ 98	33	EtOH	Pale Yell. ndls.	12.10	12.04	—	—
-NH-CH_2-CH=CH_2	B	172~173	36	EtOH	Pale Yell. ndls.	17.00	16.73	0.5	0.5
-NH-CH_2-CH(OH)-CH_3	C	185~186	51	EtOH	Light Yell. pris.	15.84	16.03	0.5	0.5
-NHC_2H_4OH	C	177~178	54	EtOH	Light Yell. pris.	16.73	16.94	—	—
-$NHCH_2$-C_6H_5	B	175~177	46	EtOH	Light Yell. pris.	14.14	14.01	0.5	0.5
-NH-[cyclohexyl (H)]	B	193~194	39	EtOH	Light Yell. ndls.	14.53	14.42	—	—
-NH-C_6H_5	D	282 (d.)	59	Dioxan	Yellow prisms	14.83	14.96	—	—
-NH-C_6H_4-CH_3 (p)	D	264 (d.)	53	Dioxan	Yellow prisms	14.14	14.08	0.5	0.5
-NH-C_6H_4-CH_3 (o)	D	182~183	53	Dioxan	Yellow ndls.	14.14	14.25	0.5	0.5
-NH-C_6H_4-OH	D	270 (d.)	53	Dioxan	Red prisms	14.04	14.36	0.5	0.5
-NH-C_6H_4-OCH_3	D	236 (d.)	50	Dioxan	Red prisms	13.42	13.28	0.5	0.5
-NH-C_6H_4-Cl	D	236 (d.)	57	Dioxan	Yellow prisms	13.25	13.41	0.5	0.5
-NH-C_6H_4-Br	D	239 (d.)	50	Dioxan	Yellow prisms	11.61	11.39	0.5	0.5

a) Calculated on the basis of the acid chloride.
b) Incubated for 98 hr.

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microbiological screening as shown in Tables I and II. As mentioned above, all these compounds did not show desired activity.

Table II. O_2N-(furan)-CH=C(CN)-COOR

R	m.p. (°C)	Yield[a] (%)	Recrystn. solvent	Appearance	N (%) Calcd.	N (%) Found	Max. bacteriostatic concn.[b] (Unit, 10,000) St. aureus	E. coli
$-CH_3$	214 (d.)	50	EtOH	Yell. ndls.	12.61	12.96	—	—
$-C_3H_7$(*n*)	144∼146	45	EtOH	Light Yell. pris.	11.20	11.32	—	—
$-C_3H_7$(*iso*)	176∼177	45	EtOH	Light Yell. pris.	11.20	11.57	0.5	0.5
$-C_4H_9$(*n*)	125∼126	51	EtOH	Light Yell. pris.	10.60	10.24	—	—
$-C_4H_9$(*iso*)	135∼136	48	EtOH	Light Yell. pris.	10.60	10.83	0.5	0.5
$-C_4H_9$(*sec*)	124∼125	51	EtOH	Light Yell. pris.	10.60	10.93	—	—
$-C_5H_{11}$(*iso*)	117∼118	57	EtOH	Light Yell. pris.	10.07	10.24	—	—

a) Calculated on the basis of the acid chloride.
b) Incubated for 98 hr.

Of the resulting 34 derivatives (Tables I and II), 27 were screened for bacteriological activity; unfortunately all these compounds proved to be not active, at least, against both *Staphylococcus aureus* and *Escherichia coli*. It seems likely that this unexpected effect might be due to the smaller solubility of these compounds and the inactive cyano group at the 2-position of the side chain.

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Experimental

2-Cyano-3-(5-nitro-2-furyl)acryloyl Chloride—A mixture of 76 g. (0.34 mole) of 2-cyano-3-(5-nitro-2-furyl)acrylic acid and 104 g. (0.50 mole) of PCl_5 in 100 cc. of dehyd. benzene was refluxed on a water bath until complete solution. After the end of this reaction the benzene and $POCl_3$ produced were distilled off under a reduced pressure to dryness. The yellowish brown residue was recrystallized from dehyd. benzene to give 50∼55 g. of yellowish prisms melting at 128∼130°. *Anal.* Calcd. for $C_8H_3O_4N_2Cl$: C, 42.40; H, 1.34; N, 12.37. Found : C, 42.61; H, 1.28; N, 12.12.

N,N-Dimethyl-2-cyano-3-(5-nitro-2-furyl)acrylamide (Method A)—The following representative procedure was applied for preparation of three same type compounds listed in Table I. Into a solution of 1.0 g. (0.005 mole) of 2-cyano-3-(5-nitro-2-furyl)acryloyl chloride in 50 cc. of dehyd. benzene, a small excess of dry dimethylamine was bubbled under cooling until no more crystals deposited. After standing the reaction mixture at room temperature over night, the crystalline product was collected and washed thoroughly with cold water. Three recrystallizations of the crude product from EtOH gave 0.6 g. of pale yellow needles.

N-Propyl-2-cyano-3-(5-nitro-2-furyl)acrylamide (Method B)—The following general procedure was applied for preparation of 12 acrylamides listed in Table I. To a stirred solution of 1.0 g. (0.005 mole) of 2-cyano-3-(5-nitro-2-furyl)acryloyl chloride in 300 cc. of dehyd. benzene, 0.6 g. of propylamine was gradually added under cooling. The reaction mixture was allowed to stand at room temperature (20°) for 3 hr., the crystalline mass that deposited was collected, and washed well with a cold mixture of EtOH and water (3:2). Two recrystallizations from a mixture of EtOH and water (3:1) gave 0.4 g. of yellow needles.

N-(2-Hydroxyethyl)-2-cyano-3-(5-nitro-2-furyl)acrylamide (Method C)—This procedure was applied for 3 compounds listed in Table I. To a stirred solution of 1.0 g. of 2-cyano-3-(5-nitro-2-furyl)-acryloyl chloride in 200 cc. of dehyd. acetone a mixture of 10 cc. of an acetone solution containing 0.61 g. (0.01 mole) of ethanolamine was added dropwise under cooling. The reaction mixture was allowed to stand at room temperature for 3 hr. The mixture was distilled, and diluted with a large amount of water The yellowish brown precipitate was collected and washed well with a small amount of cold water. Two recrystallizations from EtOH gave 0.6 g. of light yellow plates.

2-Cyano-3-(5-nitro-2-furyl)-*p*-acrylotoluidide (Method D)—This procedure was applied for 7 compounds listed in Table I.

To a stirred solution of 1.0 g. of 2-cyano-3-(5-nitro-2-furyl)acryloyl chloride in 30 cc. of dehyd. benzene, 1.10 g. (0.01 mole) of *p*-toluidine and a few drops of pyridine were added gradually. After

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standing at room temperature over night, the crystalline mass produced was collected and washed thoroughly with benzene and then a small amount of water. Recrystallization of the crude crystalline mass gave 0.7 g. of pale yellow prisms.

Preparation of Methyl 2-Cyano-3-(5-nitro-2-furyl)acrylate—The following general procedure was used for preparation of the 7 esters listed in Table II. A solution of 1.0 g. (0.005 mole) of 2-cyano-3-(5-nitro-2-furyl)acryloyl chloride in 30 cc. of MeOH containing a few drops of pyridine was heated on a water bath for 1 hr. and then allowed to cool. The reaction mixture was diluted with about 50 cc. of water, the crude crystalline mass that separated was collected, and washed well with water. The crude crystals were recrystallized from EtOH.

Summary

Thirty-one new 2-cyano-3-(5-nitro-2-furyl)acrylamides and esters were synthesized by condensation of 2-cyano-3-(5-nitro-2-furyl)acryloyl chloride and various amines and alcohols. Unexpectedly, these derivatives did not show the desired antibacterial activity *in vitro*. It seemed that this might be due to a small solubility of these derivatives in water.

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84. Jun Okuda and Kunio Yagi : Metabolism of Flavin Nucleotides. IV. Properties of the Enzyme for Dephosphorylation of Flavin Mononucleotide in the Small Intestine.

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In previous papers of this series,[1,2] the decomposition of flavin nucleotides in the digestive canal was reported. Dephosphorylation of flavin mononucleotide (FMN) was demonstrated chiefly in the cavity of the small intestine. The homogenate of the mucosa of the small intestine was found to dephosphorylate FMN very rapidly. Then, the histochemical study[3] showed that the enzyme for dephosphorylation of FMN was localized mainly in the epithelial and endothelial cells of the mucosa. Furthermore, the distribution of this enzyme in the subcellular fraction of the mucosa was examined and its highest activity was found in the cytoplasm fraction of jejunum and duodenum.[4]

To find the physiological action of this enzyme present in the mucosa attempt was made to extract and purify this enzyme and to examine its enzymatic properties, results of which are reported in this paper.

Materials

FMN—Chemically synthesized and supplied as its monosodium salt.

Buffer solutions—A mixture of 1 cc. each of 0.1*M* citrate, 0.1*M* veronal, and 0.1*M* borate was adjusted to pH 2∼13 by addition of 0.5*N* HCl or 0.5*N* NaOH, and made up to 10 cc. with distilled water.

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