Studies of the Synthesis of Furan Compounds. XXIV.[1] The Synthesis of 5-[2-(5-Nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazole and Its Related Compounds[2]

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5-[2-(5-Nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazoles and -1,3,4-thiadiazoles have been prepared from 3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acrylic acid. All of these compounds exhibited strong antibacterial activities against *Staphylococcus aureus*.

A series of systematic investigations concerning the synthesis of 5-[2-(5-nitro-2-furyl)-1-substituted]vinyl-1,3,4-oxadiazole derivatives has been undertaken in order to obtain information on their chemical properties and on the relations between the chemical structures and the antibacterial activities. With the aim of establishing the influence of the β-substituents of the –C=C– chain upon the antibacterial activities in a continuation of a series of studies concerning the antibacterial properties of nitrofuran derivatives,[3-10] the present work has studied the introduction of a 4-nitrophenyl group into β-carbon, namely, 5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazole (III) and its related compounds.

Results and Discussion

3-(5-Nitro-2-furyl)-2-(4-nitrophenyl)acryloylhydrazine (I) was prepared from the chloride of 3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acrylic acid[11] in the usual method.[3-10] The preparation of I using trichloroethylene or dioxane as a solvent was unsuccessful, but it was achieved by using methylene chloride as the solvent, although 1,2-bis[3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acryloyl]hydrazine was not formed as the by-product.

5-[2-(5-Nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazolone (II) was obtained by the introduction of phosgene into a solution of I in dioxane-water (3:2,

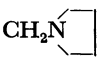
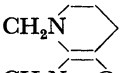
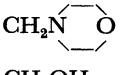
TABLE 1. 1-[3-(5-NITRO-2-FURYL)-2-(4-NITROPHENYL)ACRYLOYL]-THIOSEMICARBAZIDES AND -*S*-METHYLISOTHIOSEMICARBAZIDES

No	R	Mp °C (decomp)	Yield %	Appearance[a]	Formula	Analysis % Found(Calcd) C	H	N
Thiosemicarbazides								
VI	H	177—179	78.1	Y Lf	$C_{14}H_{11}N_5O_6S$	44.37 (44.56)	2.89 (2.92)	18.63 (18.57)
VIa	CH_3	193	80.3	Y Pl	$C_{15}H_{13}N_5O_6S$	45.97 (46.04)	3.17 (3.32)	18.29 (17.90)
VIb	C_2H_5	180	85.1	Pa-Y Nd	$C_{16}H_{15}N_5O_6S$	47.72 (47.41)	3.65 (3.70)	17.65 (17.28)
VIc	C_6H_5	194	75.5	O Pm	$C_{20}H_{15}N_5O_6S$	52.82 (52.98)	3.04 (3.31)	15.27 (15.45)
S-*Methylisothiosemicarbazides*								
V	H	169	77.5	Y Gr	$C_{15}H_{13}N_5O_6S$	45.61 (46.04)	2.95 (3.32)	17.73 (17.90)
Va	CH_3	164	73.5	Y Gr	$C_{16}H_{15}N_5O_6S$	47.19 (47.41)	3.99 (3.70)	17.02 (17.28)
Vb	C_2H_5	173	74.2	Y Gr	$C_{17}H_{17}N_5O_6S$	48.99 (48.69)	4.54 (4.06)	16.32 (16.71)
Vc	C_6H_5	184	71.5	Y Gr	$C_{21}H_{17}N_5O_6S$	54.37 (53.96)	3.56 (3.64)	14.48 (14.99)

a) Abbreviations: Y Lf, yellow leaflets; Y Pl, yellow plates; Pa-Y Nd, pale yellow needles; O Pm, orange prisms; Y Gr, yellow granules.

1) Part XXIII of this series: I. Hirao, Y. Kato, T. Hayakawa, and H. Tateishi, This Bulletin, **44**, 780 (1971).
2) Presented at the 23rd Annual Meeting of The Chemical Society of Japan, Tokyo, April, 1970.
3) I. Hirao and Y. Kato, *Nippon Kagaku Zasshi*, **85**, 693 (1964).
4) I. Hirao and Y. Kato, *ibid.*, **86**, 633 (1965).
5) Y. Kato, Y. Hara, and I. Hirao, *ibid.*, **86**, 957 (1965).
6) Y. Kato and I. Hirao, *ibid.*, **87**, 1336 (1966).
7) I. Hirao, *ibid.*, **88**, 574 (1967).
8) Y. Kato, H. Nakajima, and I. Hirao, *ibid.*, **89**, 955 (1968).
9) I. Hirao, *ibid.*, **89**, 713 (1968).
10) Y. Kato, This Bulletin, **44**, 489 (1971).
11) I. Hirao and Y. Kitamura, *Bull. Kyushu Inst. Technol.*, No. **18**, 27 (1968).

TABLE 2. 5-[2-(5-NITRO-2-FURYL)-1-(4-NITROPHENYL)VINYL]-SUBSTITUTED 1,3,4-OXADIAZOLES AND 1,3,4-THIADIAZOLES

No	R	Mp (°C) (decomp)	Yield (%)	Recryst solvent[a)]	Appearance[a)]	Formula	Analysis (%) Found (Calcd) C	H	N
1,3,4-Oxadiazol-2-ones									
II	H	217—218	69.2	EOH	O-Y Lf	$C_{14}H_8N_4O_7$	48.73 (48.84)	2.00 (2.33)	15.85 (16.28)
IIa	$COCH_3$	190—191	89.6	Bz	Y Cb	$C_{16}H_{10}N_4O_8$	49.72 (49.75)	2.25 (2.59)	14.83 (14.51)
IIb	COC_2H_5	194—195	82.4	Bz	Ov-G Nd	$C_{17}H_{12}N_4O_8$	51.90 (51.00)	2.69 (3.00)	14.24 (14.00)
IIc	$COC_3H_7(n)$	131—133	75.8	MOH	Y Gr	$C_{18}H_{14}N_4O_8$	51.97 (52.20)	3.14 (3.38)	13.60 (13.53)
IId	$CH_2N(CH_3)C_6H_5$	180—181	57.1	Bz	O-Y Nd	$C_{22}H_{17}N_5O_7$	57.23 (57.01)	3.53 (3.67)	15.11 (15.12)
IIe	$CH_2N(C_2H_5)C_6H_5$	209—211	62.7	Bz	Re Nd	$C_{23}H_{19}N_5O_7$	57.43 (57.80)	3.63 (3.98)	14.32 (14.68)
IIf		194—195	48.7	MOH-W (1:1)	Re Gr	$C_{19}H_{17}N_5O_7$	53.44 (53.38)	3.83 (3.98)	16.41 (16.40)
IIg		189—191	84.4	MOH	Bw Nd	$C_{20}H_{19}N_5O_7$	54.49 (54.42)	4.16 (4.31)	15.92 (15.88)
IIh		198—200	70.1	EOH	Y Fb	$C_{19}H_{17}N_5O_8$	51.47 (51.45)	3·67 (3.84)	15.44 (15.80)
IIi	CH_2OH	211—213	65.7	EOH	Y Lf	$C_{15}H_{10}N_4O_8$	47.52 (47.87)	2.34 (2.67)	14.89 (14.97)
2-Amino-1,3,4-oxadiazoles									
IV	H	246—247	71.5	EOH	Y Lf	$C_{14}H_9N_5O_6$	48.63 (48.99)	2.55 (2.62)	20.73 (20.41)
IVa	CH_3	227—228	73.8	MOH	O-Y Nd	$C_{15}H_{11}N_5O_6$	50.21 (50.40)	2.82 (3.08)	19.07 (19.21)
IVb	C_2H_5	221—222	50.1	MOH	O-Y Nd	$C_{16}H_{13}N_5O_6$	51.47 (51.75)	3.14 (3.50)	18.68 (18.88)
IVc	C_6H_5	241—242	78.5	MOH	O-Y Pm	$C_{20}H_{13}N_5O_6$	57.18 (57.30)	3.21 (3.10)	16.57 (16.70)
IVd	CH_2OH	231—232	67.2	DMF-W (1:1)	O-Y Pd	$C_{15}H_{11}N_5O_7$	51.51 (51.37)	2.64 (2.77)	17.54 (17.63)
IVe	$COCH_3$	235—237	81.5	MOH	Y Fb	$C_{16}H_{11}N_5O_7$	49.72 (49.87)	2.57 (2.86)	18.09 (18.18)
IVf	COC_2H_5	236—237	86.3	MOH	Y Lf	$C_{17}H_{13}N_5O_7$	51.06 (51.13)	3.52 (3.26)	17.36 (17.54)
IVg	$COC_3H_7(n)$	219—220	82.4	MOH	Y Lf	$C_{18}H_{15}N_5O_7$	52.12 (52.30)	3.51 (3.63)	16.87 (16.93)
2-Amino-1,3,4-thiadiazoles									
VII	H	238—240	42.1	MOH	Re Gr	$C_{14}H_9N_5O_5S$	46.82 (46.80)	2.60 (2.51)	19.09 (19.50)
VIIa	CH_3	214—215	78.5	MOH	Dp-Re Pm	$C_{15}H_{11}N_5O_5S$	48.51 (48.30)	2.71 (2.95)	18.53 (18.79)
VIIb	C_2H_5	226—227	45.1	MOH	O Fb	$C_{16}H_{13}N_5O_5S$	49.34 (49.61)	3.27 (3.36)	18.33 (18.06)
VIIc	C_6H_5	258—260	59.5	MOH	Re Gr	$C_{20}H_{13}N_5O_5S$	54.84 (55.17)	2.64 (2.99)	16.21 (16.09)
VIId	CH_2OH	256—257	48.3	Dx-W (3:2)	Y Gr	$C_{15}H_{11}N_5O_6S$	46.32 (46.27)	2.77 (2.83)	17.86 (17.99)
VIIe	$COCH_3$	294—295	80.6	DMF-W (3:1)	Y Pl	$C_{16}H_{11}N_5O_6S$	47.43 (47.88)	2.72 (2.74)	17.62 (17.46)
VIIf	COC_2H_5	286—287	69.2	DMF-W (4:1)	Y Gr	$C_{17}H_{13}N_5O_6S$	49.20 (49.16)	3.21 (3.13)	16.71 (16.87)
VIIg	$COC_3H_7(n)$	259—260	61.7	Dx	Y Gr	$C_{18}H_{15}N_5O_6S$	50.51 (50.35)	3.45 (3.50)	16.27 (16.32)

a) Abbreviations: EOH, ethanol; Bz, benzene; MOH, methanol; DMF, *N,N*-dimethylformamide; W, water; Dx, dioxane; O, orange; O-Y, orange yellow; Ov-G, olive green; Y, yellow; Re, red; Bw, brown; Dp-Re, deep red; Pa-Y, pale yellow; Lf, leaflets; Cb, cubes; Gr, granules;Nd, needles; Fb, fibers; Pm, prisms; Pd, powder; Pl, plates.

Table 3. Inhibitory activity of ten compounds on microorganisms

Compound	*Diplococcus pneumoniae* Dp-1	*Stereptococcus hemolyticus* Group A 089	*Staphylococcus aureus* 209P	*Bacillus subtilis* pcl 219	*Salmonella enteritidis* 1891	*Salmonella pullorum* Chuyu 114	*Escherichia coli* 0-55	*Klebsiella pneumoniae* ST-101	*Proteus vulgaris* HX 19	*Pseudomonus aeruginosa* 347
II	12.5	12.5	<0.4	3.2	>25	>25	>25	>25	>25	>25
IIa	12.5	12.5	0.8	6.2	>25	>25	>25	>25	>25	>25
IId	25	25	1.6	6.2	>25	>25	>25	>25	>25	>25
IIh	25	12.5	0.8	3.2	>25	>25	>25	>25	>25	>25
IIi	25	12.5	<0.4	6.2	>25	>25	>25	>25	>25	>25
III	6.2	12.5	3.1	25	>25	>25	>25	>25	>25	>25
IV	6.2	6.2	1.5	12.5	>25	>25	>25	>25	>25	>25
IVa	12.5	12.5	1.6	6.2	>25	>25	>25	>25	>25	>25
VII	6.2	6.2	1.5	6.2	>25	>25	>25	>25	>25	>25
VIIa	>25	>25	3.1	12.5	>25	>25	>25	>25	>25	>25
Contrast[a)]	25	0.4	0.8	0.8	0.8	0.8	1.6	0.8	6.2	12.5

a) 3-(5-Nitro-2-furyl)-2-(2-furyl)acrylic amide was used in the test.

v/v) at 15—20°C. This compound was found, from the infrared absorptions[12)] at 3360 cm^{-1} (N–H) and 1765 cm^{-1} (C=O), to take the keto structure, at least in the solid state. The treatment of II with a large excess of acid anhydrides or with 2—3 times as many moles of acid anhydrides in dioxane afforded the corresponding monoacyl derivatives, the 3-acetyl (IIa), 3-propionyl (IIb), and 3-butyryl (IIc) derivatives. These acyl derivatives commonly showed two C=O absorptions, near 1780 and 1740 cm^{-1}, but not the absorption at 3360 cm^{-1} characteristic of N–H in the mother compound, II.

As a N–H in an oxadiazolone ring is known to undergo the Mannich reaction to form an *N*-aminomethyl derivative, 3-aminomethyl derivatives (IId—h) were prepared by treating II with 37% formaldehyde and secondary amines (*N*-methylaniline, *N*-ethylaniline, pyrrolidine, pyperidine, and morpholine) in methanol or dioxane in the presence of *N,N*-dimethylformamide. The 3-hydroxymethyl derivative (IIi) was also obtained in a good yield from II and 37% formaldehyde.

When treated with refluxing ethyl orthoformate, I afforded 5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazole (III). 2-Amino-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazole (IV) was prepared by the reaction of I with cyanogen bromide in refluxing methanol or by the cyclization of 1-[3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acryloyl]-*S*-methylisothiosemicarbazide (V) in boiling ethanol, both in satisfactory yields. The similar treatment of 4-alkyl (or aryl)-1-[3-(5-nitro-2-furyl)-2-(4-nitrophenyl) acryloyl]-*S*-methylisothiosemicarbazides (Va—c) gave the 2-R-substituted amino-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)-vinyl]-1,3,4-oxadiazole, IVa, IVb, and IVc, in which R was methyl, ethyl, and phenyl. The treatment of IV with 37% formaldehyde afforded the 2-hydroxymethylamino derivative (IVd), and that with acid anhydrides gave the 2-acetylamino (IVe), 2-propionylamino (IVf), and 2-butyrylamino (IVg) derivatives. V and Va—Vc were each obtained by the reaction of methyl iodide with 1-[3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acryloyl]thiosemicarbazide (VI) or its 4-substituted derivatives (VIa—c), which had been prepared from the acid chloride and thiosemicarbazide or from I and isothiocyanates.

When heated in phosphoryl chloride, VI was cyclized to 2-amino-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)-vinyl]-1,3,4-thiadiazole (VII). 2-Substituted amino derivatives were also obtained by the similar treatment of VIa—VIc in phosphoryl chloride and of VII with 37% formaldehyde or acid anhydrides. Thus, the 2-methylamino (VIIa), 2-ethylamino (VIIb), 2-anilino (VIIc), 2-hydroxymethylamino (VIId), 2-acetylamino (VIIe), 2-propionylamino (VIIf), and 2-butyrylamino (VIIg) derivatives were obtained. All of these compounds are listed in Tables 1 and 2.

Microbiological Assays.[13)] The antibacterial activities of these compounds toward ten microorganisms were examined. The minimum amount of the compounds necessary for the complete inhibition of the growth was determined by the dilution method, using the usual bouillon agar medium (pH 7). Some of the results are shown in Table 3. The compounds of this group exhibited weak antibacterial activity against Gram-positive bacteria, but not against Gram-negative bacteria. In particular, all the compounds tested showed strong activity against *Staphylococcus aureus*. Ultimately, it was found that the introduction of a 4-nitrophenyl group instead of a 2-furyl group[10)] into β-carbon lowered the activity greatly.

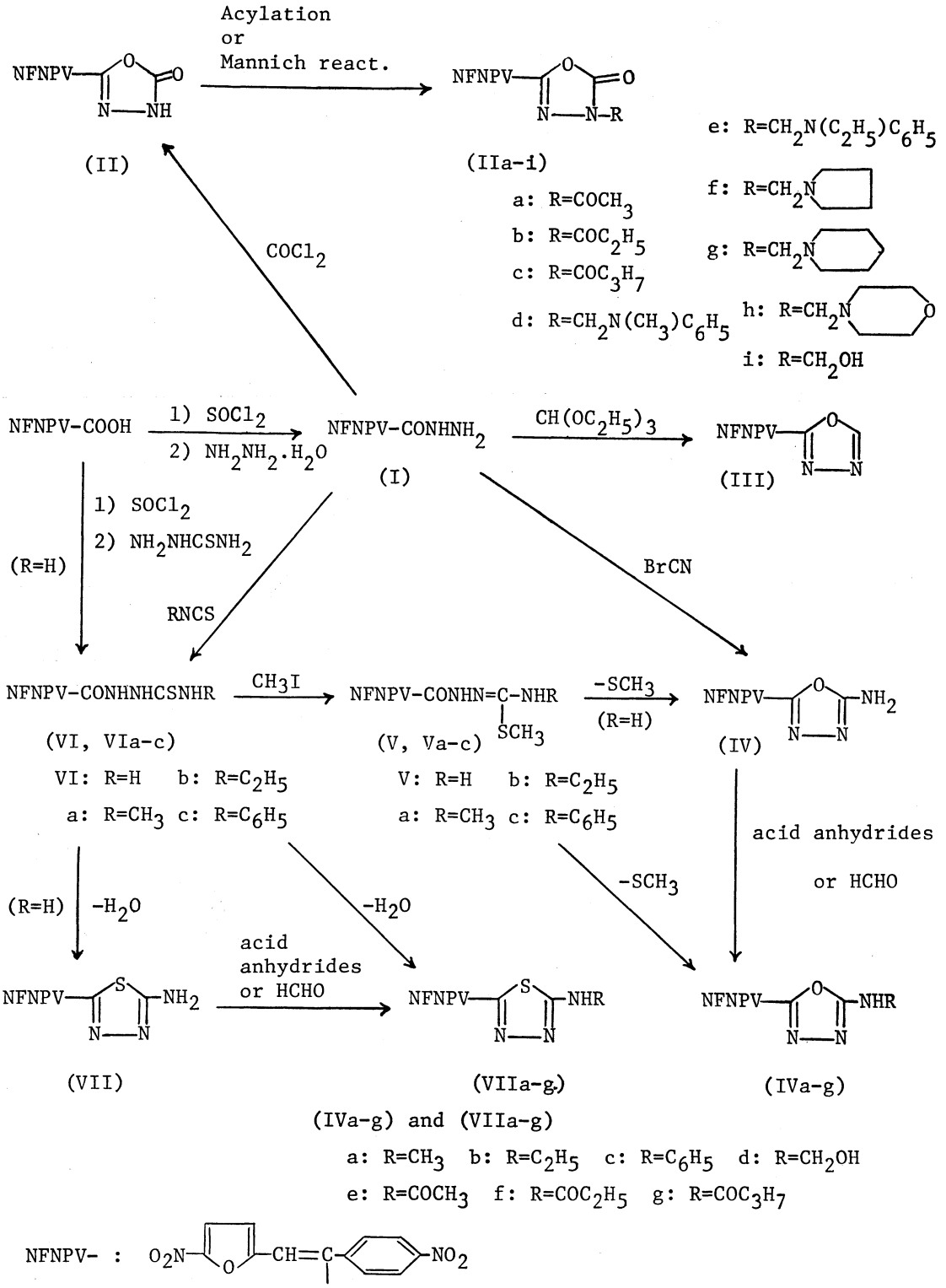
Experimental[14)]

3-(5-Nitro-2-furyl)-2-(4-nitrophenyl)acryloyl chloride. A mixture of 3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acrylic acid[11)] (60.8 g, 0.2 mol), thionyl chloride (36 g, 0.2 mol), *N,N*-dimethylformamide (2 g), and 200 m*l* of monochlorobenzene was stirred at 65—70°C for 1 hr. The resulting solution was cooled with an ice-salt bath; the acid chloride was then separated as yellow crystals, filtered, washed with dry ether, and used in the next experiments without further purification.

12) The infrared absorption spectra in this experiments were obtained with a Shimadzu IR-27S spectrophotometer with KBr method.

13) The authors are indebted to Dr. R. Ueno and his staff of the Ueno Pharmaceutical Company, Ltd., for the assay.

14) All melting and decomposition points are uncorrected. Microanalyses were carried out with a Yanagimoto C. H. N. Corder MT-2 type.



3-(5-Nitro-2-furyl)-2-(4-nitrophenyl)acryloylhydrazine (I). To a stirred, ice-salt, cooled (−5—0°C) mixture of 80% hydrazine hydrate (20.2 g, 0.4 mol), water (60 m*l*) and methylene chloride (140 m*l*), we added, drop by drop, a solution of the acid chloride (32.3 g, 0.1 mol) in 700 m*l* of methylene chloride during a period of 1.5 hr. After the addition had been completed over, the temperature was allowed to rise to room temperature and stirring was continued for an additional 2 hr. The resulting suspension was filtered, and the residue was washed with 50% aqueous methanol and then dried. This afforded 21.6 g (67.9%) of yellow crystals melting, with decomposition, at 165—168°C. Recrystallization from methanol gave ochreous prisms; mp 182—184°C dec. The yield was 20.4 g (64.2%).

Found: C, 49.16; H, 3.09; N, 17.79%. Calcd for $C_{13}H_{10}N_4O_6$: C, 49.06; H, 3.14; N, 17.62%.

1-[3-(5-Nitro-2-furyl)-2-(4-nitrophenyl)acryloyl]thiosemicarbazide (VI). A solution of the acid chloride (32.3 g, 0.1 mol) in dry dioxane (200 m*l*) was added slowly to a stirred suspension of thiosemicarbazide (18.2 g, 0.2 mol) and sodium bicarbonate (45 g, 0.54 mol) in 80 m*l* of dioxane. The suspension was stirred for 2 hr at room temperature and then

heated on a steam bath for 1 hr. After cooling, yellow precipitates were filtered out and poured into aqueous hydrochloric acid. The insoluble product was collected on a filter, washed with water, and then dried. In this way we obtained 29.4 g (78%) of a crude product melting at 143—148°C dec. Crystallization from methanol gave yellow leaflets.

4-Substituted 1-[3-(5-nitro-2-furyl)-2-(4-nitrophenyl)acryloyl]-thiosemicarbazides (VIa—c). A mixture of I (3.18 g, 10 mmol), alkylisothiocyanate (12 mmol), and methanol (140 m*l*) was refluxed for 2 hr. The resulting solution was cooled, and the precipitated product was collected by filtration. Recrystallization from methanol gave a pure product (Table 1).

1-[3-(5-Nitro-2-furyl)-2-(4-nitrophenyl) acryloyl]-S-methylisothiosemicarbazide (V) and Its 4-Substituted Derivatives (Va—c). To a stirred mixture of 5 mmol of VI (or VIa—c), methyl iodide (15 mmol), and ethanol (10—20 m*l*), we added, drop by drop, a solution of potassium hydroxide (5 mmol) in 20 m*l* of ethanol. After the addition, stirring was continued for 12 hr at room temperature. The resulting suspension was filtered, and the residue was washed with a small amount of ethanol and dried. If the product were heated in solvents, decomposition occurred and methyl mercaptane was evolved. Therefore, recrystallization from solvents could not be achieved, but these products were pure enough for elemental analyses.

5-[2-(5-Nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazol-2-one (II). To a stirred solution of I (7.9 g, 25 mmol) in 360 m*l* of dioxane-water (3:2, v/v), phosgene was introduced under cooling at 15—17°C. After 3 hr, the product was collected and washed with water to give 7 g (81.4%) of crude II, mp 161—163°C dec. Recrystallization from ethanol gave II, melting at 217—218°C dec and weighing 5.95 g (69.2%).

3-Acyl-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazol-2-ones (IIa—c). A mixture of II (0.7 g, 2.30 mmol) and 13 m*l* of acid anhydride or 0.7 g of acid anhydride in 13 m*l* of dioxane was heated on a steam bath for 1—2 hr. The resulting solution was taken to dryness *in vacuo*, and the residue was washed with water, dried, and recrystallized. The yield and mps of products are given in Table 2.

3-Aminomethyl-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazol-2-ones (IId—h). To a stirred solution of II (1.72 g, 5 mmol) in 40 m*l* of dioxane or 100 m*l* of methanol containing *N,N*-dimethylformamide (0.5 g), 37% formaldehyde (0.5 g, 6 mmol), and secondary amine (6 mmol) were added. The solution was stirred for 30 min at room temperature and warmed at 50—65°C for 1 hr. After cooling, the precipitate was filtered. When no precipitate appeared, water was added to the soltuion and the precipitated product was filtered. The yields and mps of the products are given in Table 2.

Hydroxymethylation of II, IV, and VII. A suspension of II, IV, or VII (each 3 mmol) in 37% formaldehyde (10 m*l*) was heated on a steam bath for 2—3 hr. After cooling, water (50—100 m*l*) was added, and the precipitated product was collected by filtration, washed with water, and dried. The product was purified by recrystallization.

5-[2-(5-Nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazole (III). A suspension of I (3.18 g, 10 mmol) in ethyl orthoformate (40 m*l*) was heated under reflux for 12 hr. The resulting solution was concentrated *in vacuo*, and the product was filtered and washed with cold ethanol. Recrystallization from ethanol gave III as yellow prisms; mp 218°C dec. The yield was 2.25 g (69%).

Found: C, 51.27; H, 2.12; N, 17.17%. Calcd for $C_{14}H_8N_4O_6$: C, 51.22; H, 2.44; N, 17.08%.

2-Amino-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-oxadiazole (IV). *Procedure A*: A mixture of I (2 g, 6.3 mmol), cyanogen bromide (1.05 g, 9.4 mmol), and 60 m*l* of methanol was heated under reflux for 1 hr. Cooling provided 2 g, (92.8%) of a yellow powder: mp 236—238°C dec. Crystallization was carried out from ethanol.

Procedure B: A suspension of V (1.6 g, 4.1 mmol) in ethanol (50 m*l*) was refluxed until the evolution of methyl mercaptane had ceased (*ca.* 3—4 hr). The resulting solution was taken to dryness *in vacuo*, and the residue was crystallized from ethanol to give 1 g (71.5%) of IV as yellow leaflets; mp 246—247°C dec, undepressed on admixture with a sample by *Procedure A* as above for IV.

2-Substituted amino-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)-vinyl]-1,3,4-oxadiazoles (IVa—c). These substances were prepared in the same way as IV above (*Procedure B*) using 5 mmol of 4-substituted *S*-methylisothiosemicarbazide derivatives (Va—Vc).

2-Amino-5-[2-(5-nitro-2-furyl)-1-(4-nitrophenyl)vinyl]-1,3,4-thiadiazole (VII) and 2-Substituted Amino Derivatives (VIIa—c). A mixture of 5 mmol of V (or Va—c) and phosphoryl chloride (10 m*l*) was heated under reflux for 2—3 hr. The solution was poured onto crushed ice, and the solidified product was filtered, washed with water, and dried. Two or three recrystallizations gave a pure product.

2-Acylamino Derivatives of IV and VII. Compound IV (or VII) (1.4 mmol) was covered with acid anhydride (5 m*l*) and heated on a steam bath for 2—3 hr. Water (30—40 m*l*) was added to the resulting solution to decompose the surplus acid anhydride. The product was filtered, washed with water, and dried. In this way the corresponding acyl products were obtained; recrystallizations were achieved from solvents or solvent pairs, as is shown in Table 2.