

BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 3136—3139 (1971)

## Studies of the Synthesis of Furan Compounds. XXV.<sup>1)</sup> 2-[2-(5-Nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazoles and -1,3,4-thiadiazoles<sup>2)</sup>

Ichiro HIRAO and Yasuhiko KATO

Laboratory of Organic Synthesis, Department of Chemical Engineering,  
Kyushu Institute of Technology, Tobata-ku, Kita-Kyushu

(Received May 10, 1971)

5-Amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazoles and -1,3,4-thiadiazoles have been synthesized from 3-(5-nitro-2-furyl)-2-(4-cyanophenyl)acrylic acid according to a procedure previously described.<sup>3)</sup> All of these compounds exhibit strong antibacterial activity against *Staphylococcus aureus*, but they exhibit a weak activity, or almost no activity, against the other microorganisms tested.

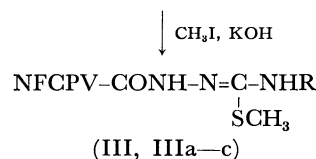
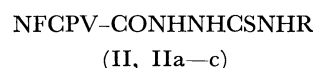
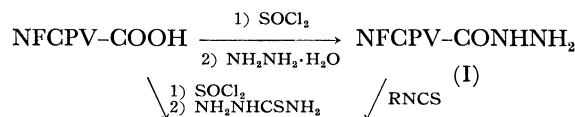
2-[2-(5-Nitro-2-furyl)-1-substituted]vinyl-1,3,4-oxadiazole derivatives have been synthesized in order to investigate the influence of  $\beta$ -substituents at a  $-C=C-$  side chain of the furan ring upon the antibacterial activity. In the course of the investigation, the present authors have previously reported compounds whose  $\beta$ -carbon at a  $-C=C-$  side chain of the furan ring were bound to hydrogen,<sup>4)</sup> methyl,<sup>5)</sup> phenyl,<sup>6)</sup> 2-furyl,<sup>7)</sup> and 4-nitrophenyl<sup>3)</sup> groups. This paper will deal with the introduction of a 4-cyanophenyl group into that position.

### Results and Discussion

3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloylhydrazine (I) was prepared from the chloride of 3-(5-nitro-2-furyl)-2-(4-cyanophenyl)acrylic acid<sup>8)</sup> with hydrazine hydrate by the use of methylene chloride as the solvent and without the formation of 1,2-bis[3-(5-nitro-2-furyl)-2-(4-cyanophenyl)acryloyl]hydrazine as a by-product.

1-[3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloyl]-thiosemicarbazide (II) and its 4-substituted derivatives (IIa: R=CH<sub>3</sub>, IIb: R=C<sub>2</sub>H<sub>5</sub>, and IIc: R=C<sub>6</sub>H<sub>5</sub>) were

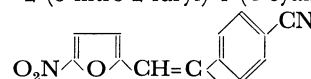
obtained respectively, by the treatment of the corresponding acid chloride with thiosemicarbazide and by the reaction of I with the corresponding isothiocyanates. The treatment of II and IIa—IIc with methyl iodide afforded the corresponding *S*-methylisothiosemicarbazide (III) and its 4-substituted derivatives (IIIa—c).



II and III; R=H

IIa—c and IIIa—c; a: R=CH<sub>3</sub>, b: R=C<sub>2</sub>H<sub>5</sub>,c: R=C<sub>6</sub>H<sub>5</sub>

NFCPV=2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl;



The introduction of phosgene into a solution of I in dioxane-water produced 2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazolone (IV) in a good yield. This compound was confirmed to have the keto-structure from the infrared absorption bands<sup>9)</sup> at 3350 (N—H) and 1772 cm<sup>-1</sup> (C=O). The treatment of IV with a large excess of acid anhydrides or with 2—3

1) Part XXIV of this series: I. Hirao, Y. Kato, and T. Hirota, This Bulletin, (Submitted).

2) Presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970.

3) I. Hirao, Y. Kato, and T. Hirota, This Bulletin, **44**, 1923 (1971).

4) I. Hirao and Y. Kato, *Nippon Kagaku Zasshi*, **85**, 693 (1964); **86**, 633 (1965).

5) Y. Kato, Y. Hara, and I. Hirao, *ibid.*, **86**, 957 (1965).

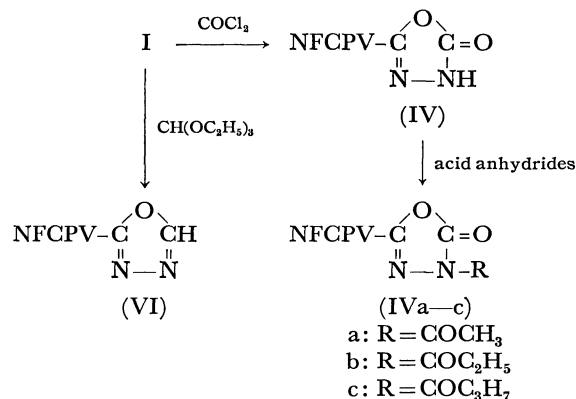
6) Y. Kato and I. Hirao, *ibid.*, **87**, 1336 (1966).

7) I. Hirao, *ibid.*, **88**, 574 (1967); **89**, 713 (1968). Y. Kato, H. Nakajima, and I. Hirao, *ibid.*, **89**, 955 (1968). Y. Kato, This Bulletin, **44**, 489 (1971).

8) I. Hirao and Y. Kitamura, *Bull. Kyushu Inst. Technol.*, No. **18**, 27 (1968).

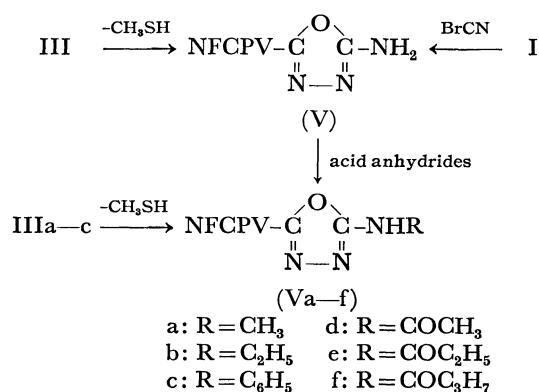
9) The infrared absorption spectra in this experiments were obtained with a Shimadzu IR-27S spectrophotometer with KBr method.

equimolar acid anhydrides in dioxane gave the corresponding monoacyl derivatives (IVa: R=COCH<sub>3</sub>, IVb: R=COC<sub>2</sub>H<sub>5</sub>, and IVc: R=COC<sub>3</sub>H<sub>7</sub>). These compounds seems to be the *N*-acyl compounds, since the IR spectra contained two C=O absorptions, one near 1770 and the other near 1790 cm<sup>-1</sup>, thus eliminating the possibility of *O*-acylation.



When heated in ethanol, III was cyclized to 5-amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazole (V) in a good yield. Compound V was also produced from I and cyanogen bromide. Similar treatment of IIIa—IIIc in refluxing ethanol afforded 5-substituted amino-derivatives (Va: R=CH<sub>3</sub>, Vb: R=C<sub>2</sub>H<sub>5</sub>, and Vc: R=C<sub>6</sub>H<sub>5</sub>). 5-Acylamino derivatives (Vd: R=COCH<sub>3</sub>, Ve: R=COC<sub>2</sub>H<sub>5</sub>, Vf: R=COC<sub>3</sub>H<sub>7</sub>) were similarly prepared by the heating of V with acid anhydrides. 2-[2-(5-Nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazole (VI) was obtained by refluxing I in ethyl orthoformate.

5-Amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)-vinyl]-1,3,4-thiadiazole (VII) was obtained by the dehydration-cyclization of II with surplus phosphoryl



chloride. 5-Alkyl and 5-phenyl-amino-1,3,4-thiadiazoles (VIIa: R=CH<sub>3</sub>, VIIb: R=C<sub>2</sub>H<sub>5</sub>, and VIIc: R=C<sub>6</sub>H<sub>5</sub>) were prepared by the similar treatment of IIa—IIc with phosphoryl chloride, while the treatment of VII with acid anhydrides afforded 5-acylamino derivatives (VIId: R=COCH<sub>3</sub>, VIIe: R=COC<sub>2</sub>H<sub>5</sub>, and VIIf: R=COC<sub>3</sub>H<sub>7</sub>). All of these compounds are listed in Tables 1 and 2.

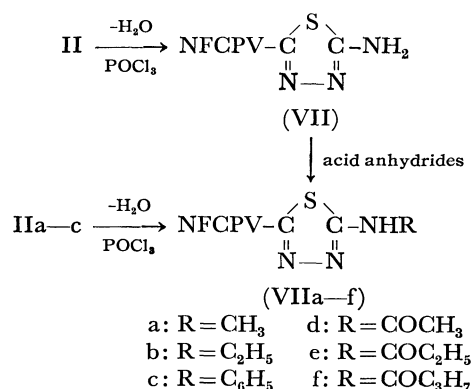


TABLE 1. 1-[3-(5-NITRO-2-FURYL)-2-(4-CYANOPHENYL)ACRYLOYL]-SUBSTITUTED THIOSEMICARBAZIDES AND *S*-METHYLISOTHIOSEMICARBAZIDES

| Compound                             |                               | Mp, °C<br>(decomp) | Yield<br>% | Recryst<br>solvent <sup>a)</sup> | Appearance <sup>b)</sup> | Analysis, %<br>Found (Calcd) |              |                |                                                                     |
|--------------------------------------|-------------------------------|--------------------|------------|----------------------------------|--------------------------|------------------------------|--------------|----------------|---------------------------------------------------------------------|
| No.                                  | R                             |                    |            |                                  |                          | C                            | H            | N              |                                                                     |
| <i>Thiosemicarbazides</i>            |                               |                    |            |                                  |                          |                              |              |                |                                                                     |
| II                                   | H                             | 194—195            | 78         | DMF-W                            | Y Pm                     | 49.92<br>(50.42)             | 3.17<br>3.08 | 19.20<br>19.61 | for C <sub>15</sub> H <sub>11</sub> N <sub>5</sub> O <sub>4</sub> S |
| IIa                                  | CH <sub>3</sub>               | 219—220            | 80         | MOH                              | Y Gr                     | 51.80<br>(51.75)             | 3.35<br>3.50 | 18.96<br>18.87 | for C <sub>16</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub> S |
| IIb                                  | C <sub>2</sub> H <sub>5</sub> | 187—188            | 77         | MOH                              | Y Pm                     | 52.91<br>(52.99)             | 3.64<br>3.90 | 18.64<br>18.18 | for C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O <sub>4</sub> S |
| IIc                                  | C <sub>6</sub> H <sub>5</sub> | 183—184            | 69         | MOH                              | O Nd                     | 58.19<br>(58.20)             | 3.22<br>3.46 | 15.79<br>16.17 | for C <sub>21</sub> H <sub>15</sub> N <sub>5</sub> O <sub>4</sub> S |
| <i>S-Methylisothiosemicarbazides</i> |                               |                    |            |                                  |                          |                              |              |                |                                                                     |
| III                                  | H                             | 174—175            | 93         |                                  | Y Pd                     | 52.11<br>(51.75)             | 3.17<br>3.50 | 18.59<br>18.87 | for C <sub>16</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub> S |
| IIIa                                 | CH <sub>3</sub>               | 183—185            | 87         |                                  | Y-O Pd                   | 53.07<br>(52.99)             | 3.81<br>3.90 | 17.95<br>18.18 | for C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O <sub>4</sub> S |
| IIIb                                 | C <sub>2</sub> H <sub>5</sub> | 175—176            | 77         |                                  | Y Pd                     | 54.07<br>(54.14)             | 4.53<br>4.26 | 17.79<br>17.54 | for C <sub>18</sub> H <sub>17</sub> N <sub>5</sub> O <sub>4</sub> S |
| IIIc                                 | C <sub>6</sub> H <sub>5</sub> | 184—186            | 87         |                                  | Y Pd                     | 58.98<br>(59.06)             | 3.66<br>3.80 | 15.94<br>15.66 | for C <sub>22</sub> H <sub>17</sub> N <sub>5</sub> O <sub>4</sub> S |

a) Abbreviations; DMF, *N,N*-dimethylformamide; W, water; MOH, methanol

b) Abbreviations; Y, yellow; O, orange: Pm, prisms; Gr, granules; Pd, powder; Nd, needles.

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

| Compound                          |                                 | Mp, °C<br>(decomp) | Yield<br>% | Recryst<br>solvent <sup>a)</sup> | Appear-<br>ance <sup>b)</sup> | Analysis, %<br>Found (Calcd) |              |                                                                                     | IR spectrum<br>(KBr) cm <sup>-1</sup> |              |                          |
|-----------------------------------|---------------------------------|--------------------|------------|----------------------------------|-------------------------------|------------------------------|--------------|-------------------------------------------------------------------------------------|---------------------------------------|--------------|--------------------------|
| No.                               | R                               |                    |            |                                  |                               | C                            | H            | N                                                                                   | $\nu_{C\equiv N}$                     | $\nu_{C=O}$  | $\nu_{C-H}$              |
|                                   |                                 |                    |            |                                  |                               |                              |              |                                                                                     |                                       |              |                          |
| <i>1,3,4-Oxadiazol-5-ones</i>     |                                 |                    |            |                                  |                               |                              |              |                                                                                     |                                       |              |                          |
| IV                                | H                               | 175—176            | 65         | EOH                              | Y Nd                          | 55.67<br>(55.56)             | 2.23<br>2.47 | 17.53<br>17.28 for C <sub>15</sub> H <sub>8</sub> N <sub>4</sub> O <sub>5</sub> )   | 2215                                  | 1772         | 3150, 3050               |
| IVa                               | COCH <sub>3</sub>               | 228—230            | 89         | Dx-W                             | Y Gr                          | 55.61<br>(55.74)             | 2.98<br>2.73 | 15.39<br>15.30 for C <sub>17</sub> H <sub>10</sub> N <sub>4</sub> O <sub>6</sub> )  | 2220                                  | 1790<br>1768 | 3150, 3050,<br>2850—2800 |
| IVb                               | COC <sub>2</sub> H <sub>5</sub> | 224—225            | 83         | MOH                              | Y Pd                          | 56.57<br>(56.84)             | 3.40<br>3.16 | 14.99<br>14.74 for C <sub>18</sub> H <sub>12</sub> N <sub>4</sub> O <sub>6</sub> )  | 2220                                  | 1790<br>1765 | 3150, 3050,<br>2900—2800 |
| IVc                               | COC <sub>3</sub> H <sub>7</sub> | 163—164            | 80         | MOH                              | Y Pd                          | 57.74<br>(57.87)             | 3.19<br>3.55 | 14.37<br>14.21 for C <sub>19</sub> H <sub>14</sub> N <sub>4</sub> O <sub>6</sub> )  | 2220                                  | 1790<br>1765 | 3150, 3050,<br>2900—2800 |
| <i>5-Amino-1,3,4-oxadiazoles</i>  |                                 |                    |            |                                  |                               |                              |              |                                                                                     |                                       |              |                          |
| V                                 | H                               | 248—249            | 76         | MOH                              | Y Pm                          | 56.02<br>(55.73)             | 2.55<br>2.85 | 21.51<br>21.67 for C <sub>15</sub> H <sub>9</sub> N <sub>5</sub> O <sub>4</sub> )   | 2225                                  |              | 3130                     |
| Va                                | CH <sub>3</sub>                 | 262—263            | 15         | MOH                              | Y Nd                          | 57.04<br>(56.97)             | 2.98<br>3.26 | 20.44<br>20.77 for C <sub>16</sub> H <sub>11</sub> N <sub>5</sub> O <sub>4</sub> )  | 2220                                  |              | 3140, 3050,<br>2950—2900 |
| Vb                                | C <sub>2</sub> H <sub>5</sub>   | 242—243            | 37         | MOH                              | O Fb                          | 58.12<br>(58.13)             | 3.40<br>3.70 | 20.05<br>19.94 for C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub> )  | 2220                                  |              | 3140, 3045,<br>2950—2870 |
| Vc                                | C <sub>6</sub> H <sub>5</sub>   | 264—265            | 34         | MOH                              | Y-O Pm                        | 63.01<br>(63.16)             | 3.52<br>3.26 | 17.45<br>17.54 for C <sub>21</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub> )  | 2215                                  |              | 3150, 3050               |
| Vd                                | COCH <sub>3</sub>               | 245—246            | 62         | MOH                              | Y Lf                          | 55.89<br>(55.89)             | 3.01<br>2.99 | 19.18<br>19.31 for C <sub>17</sub> H <sub>11</sub> N <sub>5</sub> O <sub>5</sub> )  | 2220                                  | 1740         | 3125, 3045,<br>2950—2890 |
| Ve                                | COC <sub>2</sub> H <sub>5</sub> | 241—242            | 54         | MOH                              | Y Fb                          | 56.63<br>(56.99)             | 3.30<br>3.43 | 18.01<br>18.47 for C <sub>18</sub> H <sub>13</sub> N <sub>5</sub> O <sub>5</sub> )  | 2225                                  | 1742         | 3150, 3050,<br>2980—2800 |
| Vf                                | COC <sub>3</sub> H <sub>7</sub> | 220—221            | 37         | MOH                              | Y Pm                          | 57.86<br>(58.02)             | 3.88<br>3.82 | 17.71<br>17.81 for C <sub>19</sub> H <sub>15</sub> N <sub>5</sub> O <sub>5</sub> )  | 2225                                  | 1740         | 3150, 3050,<br>2980—2800 |
| <i>5-Amino-1,3,4-thiadiazoles</i> |                                 |                    |            |                                  |                               |                              |              |                                                                                     |                                       |              |                          |
| VII                               | H                               | 304—306            | 21         | MOH                              | Re Nd                         | 52.96<br>(53.10)             | 2.83<br>2.65 | 20.43<br>20.65 for C <sub>15</sub> H <sub>9</sub> N <sub>5</sub> O <sub>3</sub> S)  | 2220                                  |              | 3130                     |
| VIIa                              | CH <sub>3</sub>                 | 239—240            | 37         | MOH                              | Re Pl                         | 54.41<br>(54.39)             | 3.05<br>3.12 | 19.78<br>19.83 for C <sub>16</sub> H <sub>11</sub> N <sub>5</sub> O <sub>3</sub> S) | 2220                                  |              | 3150<br>2980—2900        |
| VIIb                              | C <sub>2</sub> H <sub>5</sub>   | 247—248            | 45         | MOH                              | Re Pd                         | 55.26<br>(55.59)             | 3.36<br>3.54 | 18.80<br>19.07 for C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> S) | 2220                                  |              | 3130, 3030,<br>2970—2850 |
| VIIc                              | C <sub>6</sub> H <sub>5</sub>   | 267—269            | 10         | MOH                              | Re Pd                         | 60.85<br>(60.72)             | 2.84<br>3.13 | 16.51<br>16.87 for C <sub>21</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub> S) | 2220                                  |              | 3145, 3050               |
| VIIId                             | COCH <sub>3</sub>               | 283—284            | 54         | DMF-W                            | Y Fb                          | 53.09<br>(53.54)             | 3.20<br>2.89 | 18.12<br>18.37 for C <sub>17</sub> H <sub>11</sub> N <sub>5</sub> O <sub>4</sub> S) | 2220                                  | 1695         | 3150, 3030,<br>2920—2850 |
| VIIe                              | COC <sub>2</sub> H <sub>5</sub> | 280—282            | 40         | DMF-W                            | Y-O Gr                        | 54.78<br>(54.78)             | 3.49<br>3.29 | 17.31<br>17.72 for C <sub>18</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub> S) | 2225                                  | 1690         | 3120, 3030,<br>2920—2830 |
| VIIIf                             | COC <sub>3</sub> H <sub>7</sub> | 269—270            | 55         | Dx                               | Y Pm                          | 55.41<br>(55.75)             | 3.57<br>3.67 | 16.78<br>17.12 for C <sub>19</sub> H <sub>15</sub> N <sub>5</sub> O <sub>4</sub> S) | 2225                                  | 1690         | 3120, 3030,<br>2920—2850 |

a) Abbreviations; EOH, ethanol; Dx, dioxane; W, water; MOH, methanol; DMF, *N,N*-dimethylformamide.

b) Y, yellow; O, orange; Re, red; Nd, needles; Gr, granules; Pd, powder; Pm, prisms; Fb, fibers; Lf, leaflets; Pl, plates.

TABLE 3. INHIBITORY ACTIVITY OF EIGHT COMPOUNDS ON MICROORGANISMS  
Minimum inhibitory concentration,  $\mu\text{g/ml}$ 

| Compound               | <i>Diplococcus pneumoniae</i><br>Dp-1 | <i>Streptococcus hemolyticus</i><br>Group A 089 | <i>Staphylococcus aureus</i><br>209 P | <i>Bacillus subtilis</i><br>pcl 219 | <i>Salmonella enteritidis</i><br>1891 | <i>Salmonella pullorum</i><br>Chuyu 114 | <i>Escherichia coli</i><br>0—55 | <i>Klebsiella pneumoniae</i><br>ST-101 | <i>Proteus vulgaris</i><br>HX 19 | <i>Pseudomonas aeruginosa</i><br>347 |
|------------------------|---------------------------------------|-------------------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|-----------------------------------------|---------------------------------|----------------------------------------|----------------------------------|--------------------------------------|
| II                     | >25                                   | >25                                             | >25                                   | >25                                 | >25                                   | >25                                     | >25                             | >25                                    | >25                              | >25                                  |
| V                      | 25                                    | 12                                              | 3.1                                   | 12                                  | >25                                   | >25                                     | >25                             | >25                                    | >25                              | >25                                  |
| Vd                     | 12                                    | 6.2                                             | 6.2                                   | 25                                  | >25                                   | >25                                     | >25                             | >25                                    | >25                              | >25                                  |
| Ve                     | 12                                    | 12                                              | 3.1                                   | 12                                  | >25                                   | >25                                     | >25                             | >25                                    | >25                              | >25                                  |
| Vf                     | 6                                     | 6                                               | 1.5                                   | 6                                   | >25                                   | >25                                     | >25                             | >25                                    | >25                              | >25                                  |
| VII                    | 12.5                                  | 6.2                                             | 1.6                                   | 3.1                                 | >25                                   | >25                                     | >25                             | >25                                    | >25                              | >25                                  |
| VIIId                  | >12                                   | >12                                             | 1.5                                   | 6                                   | >12                                   | >12                                     | >12                             | >12                                    | >12                              | >12                                  |
| VIIe                   | >3                                    | >3                                              | 1.5                                   | >3                                  | >3                                    | >3                                      | >3                              | >3                                     | >3                               | >3                                   |
| Contrast <sup>a)</sup> | 12                                    | 0.4                                             | 1.5                                   | 1.5                                 | 0.8                                   | 1.5                                     | 1.5                             | 3                                      | 6                                | 25                                   |

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

**Microbiological Assays.**<sup>10)</sup> The antibacterial activities of the compounds toward ten microorganisms were examined. The minimum amount of each compound necessary for the complete inhibition of growth was determined by dilution method, using the usual bouillon agar medium (pH 6.8–7.0); some of the results are shown in Table 3. The antibacterial activity of this type of compound showed a behavior similar to that of the compounds possessing a 4-nitrophenyl group<sup>9)</sup> previously reported on. All of the compounds tested exhibited a strong activity against *Staphylococcus aureus*, but showed only a weak antibacterial activity at best against the other microorganisms employed. In conclusion, the introduction of a 4-cyanophenyl group into the  $\beta$ -carbon of the  $-C=C-$  side chain did not increase the activity.

### Experimental<sup>11)</sup>

**3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloyl Chloride** A mixture of 3-(5-nitro-2-furyl)-2-(4-cyanophenyl)acrylic acid<sup>8)</sup> (19.9g, 0.07 mol), thionyl chloride (12 g, 0.1 mol), *N,N*-dimethylformamide (1 g), and chlorobenzene (300 ml) was stirred at 65–70°C for 1 hr. The resulting solution was cooled with an ice-salt bath, and the acid chloride was separated as yellow crystals, filtered, washed with dry ether, and used in the following experiments without further purification.

**3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloylhydrazine (I).** To a stirred, cooled (–5–0°C) mixture of 80% hydrazine hydrate (10.1 g, 0.2 mol), water (10 ml), and methylene chloride (90 ml), we added, drop by drop a solution of the acid chloride (15.2 g, 0.05 mol) in 350 ml of methylene chloride in 30 min. After the addition, the temperature was allowed to rise to room temperature, after which stirring was continued for an additional hr. The resulting suspension was filtered, and the residue was washed with aqueous methanol and then dried to afford 11.4 g (76.5%) of a yellow product melting with decomposition at 217–218°C. Recrystallization from methanol gave yellow leaflets; mp 219°C dec. The yield was 9.7 g (65.1%).

Found: C, 56.21; H, 3.21; N, 18.77%. Calcd for  $C_{14}H_{10}N_4O_4$ : C, 56.38; H, 3.36; N, 18.79%.

**1-[3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloyl]thiosemicarbazide (II).** A solution of the acid chloride (9.1 g, 0.03 mol) in dry dioxane (700 ml) was stirred slowly into a suspension of thiosemicarbazide (3.28 g, 0.036 mol) and sodium bicarbonate (10 g, 0.12 mol) in 70 ml of dioxane. The suspension was stirred for 1 hr at room temperature and then heated at 80°C for 3 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 was obtained 8.4 g (77.6%) of a crude product melting with decomposition at 196–197°C. Crystallization from *N,N*-dimethylformamide-water (5:3, vol/vol) gave yellow prisms (Table 1).

**4-Substituted 1-[3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloyl]thiosemicarbazides (IIa-c).** A mixture of I (2 g, 6.7 mmol), alkyl (or phenyl) isothiocyanate (10 mmol), and methanol (100 ml) was refluxed for 2–3 hr. The resulting solution was cooled or concentrated, and the precipitated product was collected by filtration. Recrystallization from methanol gave a pure product, as is shown in Table 1.

**1-[3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloyl]-S-methylisothio-**

**semicarbazide (III) and Its 4-Substituted Derivatives (IIIa-c).** To a stirred mixture of 5 mmol of II (or IIa-c), methyl iodide (15 mmol), and ethanol (30–45 ml) was added, drop by drop, a solution of potassium hydroxide (5 mmol) in 40 ml of ethanol. After the addition, stirring was continued for 10–12 hr at room temperature. The resulting suspension was filtered, and the residue was washed with a small amount of cold ethanol and dried. When the products were heated in solvents, decomposition occurred with the evolution of methyl mercaptan, but these products were pure enough, as is shown by the results of elemental analyses (Table 1).

**2-[2-(5-Nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazol-5-one (IV).** To a stirred solution of I (5.96 g, 20 mmol) in 400 ml of dioxane-water (3:2, vol/vol), phosgene was introduced under cooling at 15–17°C. After 2 hr, the precipitated product was collected and washed with water to give 6.4 g (quantitative) of crude IV; mp 182–184°C. Recrystallization was then carried out (Table 2).

**4-Acyl-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazol-5-ones (IVa-c).** A mixture of IV (0.32 g, 1 mmol) and 5 ml of acid anhydride (or 0.4 g of acid anhydride and 5 ml 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 yields and mps of the products are given in Table 2.

**2-[2-(5-Nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazole (VI).** A suspension of I (2.98 g, 10 mmol) in ethyl orthoformate (70 ml) was heated at 100–105°C for 8–10 hr. The resulting solution was concentrated *in vacuo*, and the product was filtered and washed with cold ethanol. Recrystallization from methanol gave VI as ochreous prisms; mp 225–226°C dec. The yield was 2.68 g (87.2%).

Found: C, 58.23; H, 2.42; N, 17.80%. Calcd for  $C_{15}H_8N_4O_4$ : C, 58.44; H, 2.60; N, 18.18%.

**5-Amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazole (V).** **Procedure A:** A suspension of III (3.71 g, 10 mmol) in ethanol (80 ml) was refluxed until the evolution of methyl mercaptan had ceased (*ca.* 4.5 hr). The resulting solution was taken to dryness *in vacuo*, and the residue was crystallized from methanol to give 2.76 g (85.4%) of V as yellow prisms.

**Procedure B:** A mixture of I (1.49 g, 5 mmol), cyanogen bromide (0.85 g, 8 mmol), and 100 ml of methanol was heated under reflux for 2 hr. Cooling then provided 1.46 g (90%) of yellow crystals, mp 167–169°C dec. Recrystallization from methanol raised the melting point to 246–247°C dec; this melting point was undepressed on admixture with a sample prepared by **Procedure A** as above for V.

**5-Substituted Amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazoles (Va-c).** These were prepared in the same way as V above (**Procedure A**) using 5 mmol of 4-substituted *S*-methylisothiosemicarbazide derivatives (IIIa-c).

**5-Amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-thiadiazole (VII) and 5-Substituted Amino Derivatives (VIIa-c).** A mixture of 5 mmoles of II (or IIa-c) and phosphoryl chloride (10 ml) was heated under reflux for 2–3 hr. The solution was then poured onto crushed ice, and the solidified product was filtered, washed with water, and dried. Two or three recrystallizations gave a pure product (Table 2).

**5-Acylamino Derivatives of V and VII.** Compound V (or VII) (2 mmol) was covered with the acid anhydride (7 ml) and heated on a steam bath for 2–3 hr. Water (30 ml) was then added to the resulting solution to decompose the excess acid anhydride. The product was collected, 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.

11) All the melting and decomposition points are uncorrected. The elemental analyses were performed on a Yanagimoto CHN Corder MT-2 type.