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

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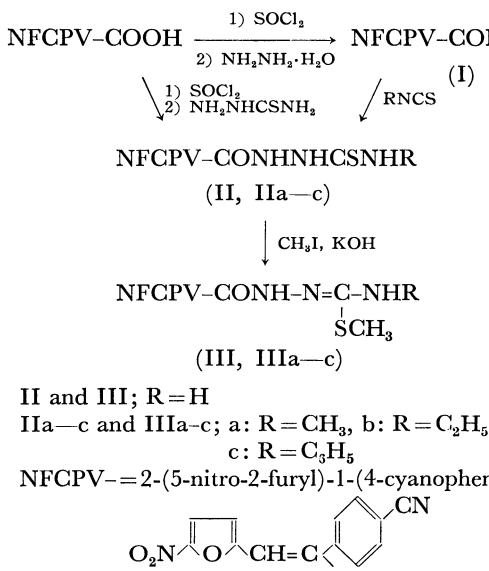
5-Amino-2-[2-(5-nitro-2-furyl)-1-(4-cyanophenyl)vinyl]-1,3,4-oxadiazoles and -1,3,4-thiadiazoles have been synthesized from 3-(5-nitro-2-furyl)-2-(4-cyanophenyl)acrylic acid according to a procedure previously described.[3] All of these compounds exhibit strong antibacterial activity against *Staphylococcus 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 β-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 β-carbon at a –C=C– side chain of the furan ring were bound to hydrogen,[4] methyl,[5] phenyl,[6] 2-furyl,[7] and 4-nitrophenyl[3] 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[8] 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_3, IIb: R=C_2H_5, and IIc: R=C_6H_5) 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_3, b: R=C_2H_5, c: R=C_3H_5

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[9] at 3350 (N–H) and 1772 cm^{-1} (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).

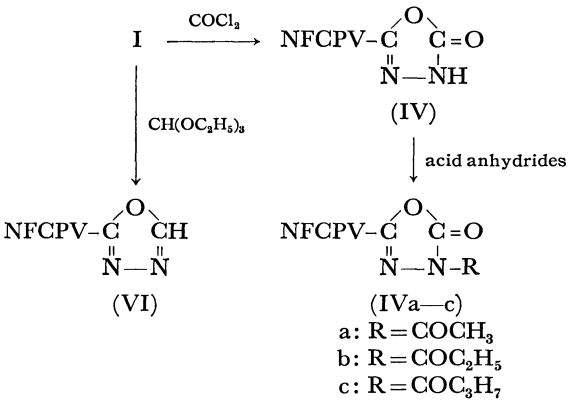
6) Y. Kato and I. Hirao, *ibid.*, **87**, 1336 (1966).

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).

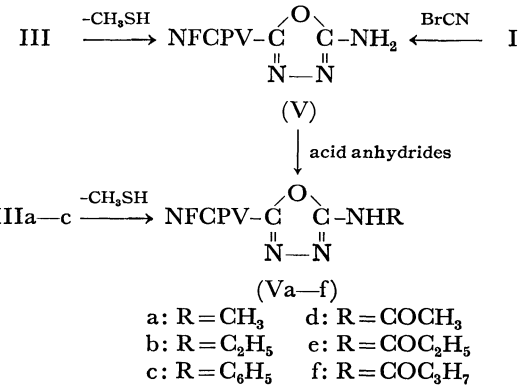
9) The infrared absorption spectra in this experiments were obtained with a Shimadzu IR-27S spectrophotometer with KBr method.

equimolar acid anhydrides in dioxane gave the corresponding monoacyl derivatives (IVa: R=$COCH_3$, IVb: R=COC_2H_5, and IVc: R=COC_3H_7). 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^{-1}, thus eliminating the posibility 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_3, Vb: R=C_2H_5, and Vc: R=C_6H_5). 5-Acylamino derivatives (Vd: R=$COCH_3$, Ve: R=COC_2H_5, Vf: R=COC_3H_7) 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_3, VIIb: R=C_2H_5, and VIIc: R=C_6H_5) 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=$COCH_3$, VIIe: R=COC_2H_5, and VIIf: R=COC_3H_7). All of these compounds are listed in Tables 1 and 2.

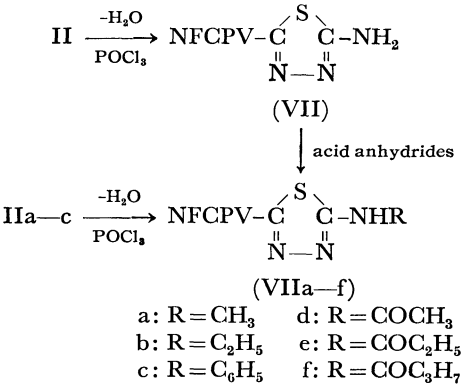


TABLE 1. 1-[3-(5-NITRO-2-FURYL)-2-(4-CYANOPHENYL)ACRYLOYL]-SUBSTITUTED THIOSEMICARBAZIDES AND *S*-METHYLISOTHIOSEMICARBAZIDES

Compound No.	R	Mp, °C (decomp)	Yield %	Recryst solvent[a]	Appearance[b]	Analysis, % Found (Calcd) C	H	N	
Thiosemicarbazides									
II	H	194—195	78	DMF-W	Y Pm	49.92	3.17	19.20	
						(50.42	3.08	19.61	for $C_{15}H_{11}N_5O_4S$)
IIa	CH_3	219—220	80	MOH	Y Gr	51.80	3.35	18.96	
						(51.75	3.50	18.87	for $C_{16}H_{13}N_5O_4S$)
IIb	C_2H_5	187—188	77	MOH	Y Pm	52.91	3.64	18.64	
						(52.99	3.90	18.18	for $C_{17}H_{15}N_5O_4S$)
IIc	C_6H_5	183—184	69	MOH	O Nd	58.19	3.22	15.79	
						(58.20	3.46	16.17	for $C_{21}H_{15}N_5O_4S$)
S-*Methylisothiosemicarbazides*									
III	H	174—175	93		Y Pd	52.11	3.17	18.59	
						(51.75	3.50	18.87	for $C_{16}H_{13}N_5O_4S$)
IIIa	CH_3	183—185	87		Y-O Pd	53.07	3.81	17.95	
						(52.99	3.90	18.18	for $C_{17}H_{15}N_5O_4S$)
IIIb	C_2H_5	175—176	77		Y Pd	54.07	4.53	17.79	
						(54.14	4.26	17.54	for $C_{18}H_{17}N_5O_4S$)
IIIc	C_6H_5	184—186	87		Y Pd	58.98	3.66	15.94	
						(59.06	3.80	15.66	for $C_{22}H_{17}N_5O_4S$)

a) Abbreviations; DMF, *N*,*N*-dimethylformamide; W, water; MOH, methanol
b) Abbreviations; Y, yellow; O, orange: Pm, prisms; Gr, granules; Pd, powder; Nd, needles.

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

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

Compound No.	R	Mp, °C (decomp)	Yield %	Recryst solvent[a]	Appearance[b]	Analysis, % Found (Calcd) C	H	N	IR spectrum (KBr) cm^{-1} $\nu_{C\equiv N}$	$\nu_{C=O}$	ν_{C-H}
1,3,4-Oxadiazol-5-ones											
IV	H	175—176	65	EOH	Y Nd	55.67	2.23	17.53	2215	1772	3150, 3050
						(55.56	2.47	17.28 for $C_{15}H_8N_4O_5$)			
IVa	$COCH_3$	228—230	89	Dx-W	Y Gr	55.61	2.98	15.39	2220	1790	3150, 3050,
						(55.74	2.73	15.30 for $C_{17}H_{10}N_4O_6$)		1768	2850—2800
IVb	COC_2H_5	224—225	83	MOH	Y Pd	56.57	3.40	14.99	2220	1790	3150, 3050,
						(56.84	3.16	14.74 for $C_{18}H_{12}N_4O_6$)		1765	2900—2800
IVc	COC_3H_7	163—164	80	MOH	Y Pd	57.74	3.19	14.37	2220	1790	3150, 3050,
						(57.87	3.55	14.21 for $C_{19}H_{14}N_4O_6$)		1765	2900—2800
5-Amino-1,3,4-oxadiazoles											
V	H	248—249	76	MOH	Y Pm	56.02	2.55	21.51	2225		3130
						(55.73	2.85	21.67 for $C_{15}H_9N_5O_4$)			
Va	CH_3	262—263	15	MOH	Y Nd	57.04	2.98	20.44	2220		3140, 3050,
						(56.97	3.26	20.77 for $C_{16}H_{11}N_5O_4$)			2950—2900
Vb	C_2H_5	242—243	37	MOH	O Fb	58.12	3.40	20.05	2220		3140, 3045,
						(58.13	3.70	19.94 for $C_{17}H_{13}N_5O_4$)			2950—2870
Vc	C_6H_5	264—265	34	MOH	Y-O Pm	63.01	3.52	17.45	2215		3150, 3050
						(63.16	3.26	17.54 for $C_{21}H_{13}N_5O_4$)			
Vd	$COCH_3$	245—246	62	MOH	Y Lf	55.89	3.01	19.18	2220	1740	3125, 3045,
						(55.89	2.99	19.31 for $C_{17}H_{11}N_5O_5$)			2950—2890
Ve	COC_2H_5	241—242	54	MOH	Y Fb	56.63	3.30	18.01	2225	1742	3150, 3050,
						(56.99	3.43	18.47 for $C_{18}H_{13}N_5O_5$)			2980—2800
Vf	COC_3H_7	220—221	37	MOH	Y Pm	57.86	3.88	17.71	2225	1740	3150, 3050,
						(58.02	3.82	17.81 for $C_{19}H_{15}N_5O_5$)			2980—2800
5-Amino-1,3,4-thiadiazoles											
VII	H	304—306	21	MOH	Re Nd	52.96	2.83	20.43	2220		3130
						(53.10	2.65	20.65 for $C_{15}H_9N_5O_3S$)			
VIIa	CH_3	239—240	37	MOH	Re Pl	54.41	3.05	19.78	2220		3150
						(54.39	3.12	19.83 for $C_{16}H_{11}N_5O_3S$)			2980—2900
VIIb	C_2H_5	247—248	45	MOH	Re Pd	55.26	3.36	18.80	2220		3130, 3030,
						(55.59	3.54	19.07 for $C_{17}H_{13}N_5O_3S$)			2970—2850
VIIc	C_6H_5	267—269	10	MOH	Re Pd	60.85	2.84	16.51	2220		3145, 3050
						(60.72	3.13	16.87 for $C_{21}H_{13}N_5O_3S$)			
VIId	$COCH_3$	283—284	54	DMF-W	Y Fb	53.09	3.20	18.12	2220	1695	3150, 3030,
						(53.54	2.89	18.37 for $C_{17}H_{11}N_5O_4S$)			2920—2850
VIIe	COC_2H_5	280—282	40	DMF-W	Y-O Gr	54.78	3.49	17.31	2225	1690	3120, 3030,
						(54.78	3.29	17.72 for $C_{18}H_{13}N_5O_4S$)			2920—2830
VIIf	COC_3H_7	269—270	55	Dx	Y Pm	55.41	3.57	16.78	2225	1690	3120, 3030,
						(55.75	3.67	17.12 for $C_{19}H_{15}N_5O_4S$)			2920—2850

a) Abbreviations; EOH, ethanol; Dx, dioxane; W, water; MOH, methanol; DMF, *N,N*-dimethlformamide.
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, μg/ml

Compound	*Diplococcus pneumoniae* Dp-1	*Streptococcus hemolyticus* Group A 089	*Staphylococcus aureus* 209 P	*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	>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
VIId	>12	>12	1.5	6	>12	>12	>12	>12	>12	>12
VIIe	>3	>3	1.5	>3	>3	>3	>3	>3	>3	>3
Contrast[a]	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.[10] 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[3] 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 β-carbon of the –C=C– side chain did not increase the activity.

Experimental[11]

3-(5-Nitro-2-furyl)-2-(4-cyanophenyl)acryloyl Chloride A mixture of 3-(5-nitro-2-furyl)-2-(4-cyanophenyl)acrylic acid[8] (19.9g, 0.07 mol), thionyl chloride (12 g, 0.1 mol), *N,N*-dimethylformamide (1 g), and chlorobenzene (300 m*l*) 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, filtrered, 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 m*l*), and methylene chloride (90 m*l*), we added, drop by drop a solution of the acid chloride (15.2 g, 0.05 mol) in 350 m*l* 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 m*l*) was stirred slowly into a suspension of thiosemicarbazide (3.28 g, 0.036 mol) and sodium bicarbonate (10 g, 0.12 mol) in 70 m*l* 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 m*l*) 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-methylisothiosemicarbazide (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 m*l*) was added, drop by drop, a solution of potassium hydroxide (5 mmol) in 40 m*l* 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 m*l* 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 m*l* of acid anhydride (or 0.4 g of acid anhydride and 5 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 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 m*l*) 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 m*l*) 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 m*l* 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 m*l*) 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 m*l*) and heated on a steam bath for 2—3 hr. Water (30 m*l*) 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.