Studies of the Synthesis of Furan Compounds. XXII.[1] Synthesis and Antibacterial Activity of 5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazole and Its Related Compounds[2]

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In continuing our study of the relationship between structures and antibacterial activity, 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazole and related derivatives have been synthesized. Their structures were confirmed by their chemical reactions and by their UV, IR, and NMR spectra. 1,3,4-Thiadiazole and its related derivatives show significant antibacterial activity.

In 1944 Dodd and Stillman[3] reported their finding that furan derivatives with a nitro group in the 5-position possess antibacterial activity; since then, extensive studies of the syntheses of 5-nitrofurans for an antibacterial substance have been undertaken. The substituents at the 2-position of the furan nucleus may be grouped into two types; one is –C=N–N–C=, as proposed by Dodd *et al.*,[4] and the other is –C=C, which has been investigated mainly by Japanese researchers.[5] In comparing the antibacterial activity of these two types, the latter is generally more effective than the former *in vitro*, but less effective *in vivo*. Therefore, the compounds which contain both these two atomic arrangements may be expected to retain a high activity both *in vitro* and *in vivo*. An example is the analog of 5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole, in which the –C=C– system connects the furan nucleus with a heterocycle involving a –C=N–N=C– system; this has been studied in our laboratory.[6] The syntheses of two groups of such compounds, the 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazoles and -1,3,4-oxadiazoles, will be described in this paper.

Results and Discussion

1-[3-(5-Nitro-2-furyl)-2-(2-furyl)acryloyl]thiosemicarbazide(IIa) and hydrazide (III) were, respectively, prepared from thiosemicarbazide and hydrazine hydrate with chloride of acid (Ia)[7] (Chart 1). 5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazole (IV) was obtained from IIa by the method described in a previous report.[8a] In a similar manner, when IIa was treated with phosphoryl chloride at 90—95°C, an isomer (V) of IV was obtained, along with a small amount of its 2-phosphoric amide compound (VI). Compound VI was easily converted to V by heating with water. The *cis-trans* conformations[9] of IV and V were confirmed on the basis of their UV, IR, and NMR spectra (Fig. 1—3) and the chemical reactions of their mother acid and esters.

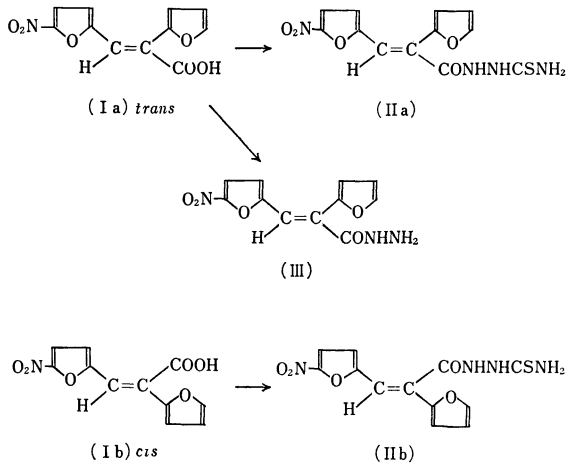


Chart 1

In our previous paper, an unknown isomer (VIIb) of methyl 3-(5-nitro-2-furyl)-2-(2-furyl)acrylate (VIIa) was isolated by the treatment of VIIa with hydrazine hydrate in methanol.[6d] It seems that the hydrazine serves as an isomerization catalyst much like the secondary amines. Thus, the isomerization reactions of the mother acid, Ia, and its esters with ahydrazine catalyst were attempted under several conditions (Table 1). The isomerization was involved in the conversion of the mother acid, Ia, and its benzyl ester (VIIIa) to their isomers (Ib[10] and VIIIb) in rather good yields,

1) Part XXI of this series: Y. Kitamura, M. Yamashita, M. Kashihara, and I. Hirao, *Nippon Kagaku Zasshi*, **90**, 713 (1969).

2) Presented at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1969.

3) M. C. Dodd, W. B. Stillman, M. Roys, and C. Crosby, *J. Pharmacol. Exptl. Therap.*, **82**, 11 (1944).

4) M. C. Dodd, D. L. Cramer, and W. C. Ward, *J. Amer. Pharm. Assoc.*, **39**, 313 (1950).

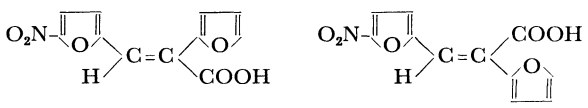
5) See for example, H. Saikachi and H. Ogawa, *J. Amer. Chem. Soc.*, **80**, 3642 (1958).

6) a) I. Hirao and Y. Kato, *Nippon Kagaku Zasshi*, **85**, 693 (1964). b) Y. Kato, Y. Hara, and I. Hirao, *ibid.*, **86**, 957 (1965). c) Y. Kato and I. Hirao, *ibid.*, **87**, 1336 (1966). d) Y. Kato, N. Nakajima, and I. Hirao, *ibid.*, **89**, 955 (1968).

7) H. Saikachi and A. Tanaka, *Yakugaku Zasshi*, **83**, 147 (1963).

8) a) I. Hirao, *Nippon Kagaku Zasshi*, **89**, 713 (1968). b) *ibid.*, **88**, 574 (1967).

9) The *cis* and *trans* conformation were determined on the basis of the structures assigned[7] as follows.



trans acid (Ia) *cis* acid (Ib)

In this case, *trans* isomer (IV) means that 1,3,4-thiadiazole ring is on opposite side of 5-nitrofuran ring toward the ethylene double bond, and *cis* isomer (V) is both of the two rings being on a side.

10) This product did not agree with the compound already reported by Saikachi and Tanaka[7] dealing with the mp, UV, and IR spectrum.

TABLE 1. ISOMERIZATION OF 3-(5-NITRO-2-FURYL)-2-(2-FURYL)ACRYLIC ACID AND ITS ESTERS WITH HYDRAZINE HYDRATE

trans Compound (mp°C)	Reaction conditions			Products			
	Hydrazine hydrate/ *trans* Comp. (mol/mol)	Temp. (°C)	Time (hr)	Reaction mixture[a] (%)	Recovered *trans* comp.[b] (%)	*cis* Isomers[b] (%)	(mp °C)
Acid (Ia)	1.0	65	3	80.0	50.0	50.0(Ib)	(183—184)[d]
(177—178)[c]	1.3	65	3	75.4	28.1	71.9	
	1.5	65	3	72.3	0	100[e]	
	2.0	65	3	trace			
	2.0	40	3	75.6	82.6	17.4	
Methyl ester (VIIa)	1.0	10	4	100	100[e]	0	
(98—99)[f]	1.0	20	4	44.4	58.1	0.5(VIIb)	(134—135)[f]
	1.0	24	4	40.6	41.9	4.9	
	1.0	40	1	39.0	52.3	trace	
Benzyl ester(VIIIa)	1.0	40	2.5	37.4	46.0	3.7(VIIIb)	(109—110)
(99—100)	1.0	60	1	48.6	0	53.8	
	1.0	65	1	45.5	0	63.8	
Ethyl ester(IXa)	1.0	25	2.5	38.0	100[e]	0 (IXb)	(152—153)[g]
(68—70)[h]	1.0	50	1.5	23.0	100[e]	0	

a) Yields of crude materials. b) Pure yields, calculated on the basis of crude reaction mixture. c) Lit, mp 177—178°C.[7] d) Lit, mp 176—177°C, reddish plates.[7] e) Purity was satisfactory without purifications. f) Lit, mp 98—99°C and 134—135°C.[6d] g) Prepared from *cis* acid. h) Lit, 68—70°C.[7]

TABLE 2. SPECTROSCOPIC DATA FOR THE GEOMETRICAL ISOMERS OF 3-(5-NITRO-2-FURYL)-2-(2-FURYL)ACRYLIC ACID AND ITS METHYL ESTER

	Acid		Methyl ester	
	Ia	Ib	VIIa	VIIb
mp (°C)	177—178	183—184	98—99	134—135
NMR (δ) in DMSO-d_6				
Vinyl proton	7.42(1H, s)	6.98(1H, s)	7.47(1H, s)	7.06(1H, s)
Nitrofuran ring proton				
-4-H	7.67(1H, d, J=4.0 Hz)	7.71(1H, d, J=4.0 Hz)	7.65(1H, d, J=4.0 Hz)	7.70(1H, d, J=4.0 Hz)
-3-H	6.98(1H, d, J=4.0 Hz)	7.02(1H, d, J=4.0 Hz)	6.97(1H, d, J=4.0 Hz)	7.02(1H, d, J=4.0 Hz)
Furan ring proton				
-3-H	6.97(1H, m)	6.81(1H, m)	6.97(1H, m)	6.75(1H, m)
Other proton				
COOH[a]	*ca.* 7.00	*ca.* 7.81		
$COOCH_3$			3.83(3H, s)	3.99(3H, s)
UV mμ (ε)[b]	307 (9580)	302(12240)	305(10751)	301(10783)
	401(16100)	412(26020)	396(15204)	401(18632)
IR (cm^{-1}) with KBr				
C=O	1693	1705	1712	1730

a) The signal was overlapped with ring protons and disappeared by treating with deuterium oxide.
b) The spectra of Ia and Ib were recorded in methanol, and of VIIa and VIIb were in ethanol previously reported[6d] by the author *et al.*

except for the cases of the methyl (VIIa) and ethyl esters (IXa); the methyl ester, VIIa, was isomerized to its isomer (VIIb) in a lower yield but the ethyl ester (IXa)[7] was not. Furthermore, the author confirmed this reaction to be irreversible (Ib, VIIb, and VIIIb⇏Ia, VIIa, and VIIIa). The isomerization reaction of Ia also took place with sodium hydroxide, but those of the acids (Ia and Ib) and their esters (VIIa, b, VIIIa, b, and IXa) did not occur by means of an acid catalyst such as hydrochloric acid.

The structures of the acids (Ia and Ib) and their methyl esters (VIIa and VIIb) were determined by means of a study of their NMR spectra (Table 2); in the spectra, the chemical shift of the vinyl proton of Ia appeared at a lower magnetic field than that of Ib (Δ_{tc} 0.44 ppm), and also, in the case of the two methyl esters (VIIa and VIIb), the vinyl proton of VIIa revealed a signal lower than that of VIIb (Δ_{tc}

0.41 ppm). The conclusions may be reached from these results that both Ia and VIIa are *trans* and that the other two (Ib and VIIb) are *cis*. A similar conclusion may be reached as to the conformation of the other esters (VIIIa, b, and IXa). The structures of the *cis* esters were further confirmed by the treatment of chloride of the *cis* acid Ib with alcohols to afford the same *cis* esters. Thus, the *cis* isomer (IXb) of the ethyl ester, which could not be obtained by the isomerization of IXa, was prepared (Chart 2). Similarly, the 1,3,4-thiadiazole V was also produced from the *cis* acid Ib *via* its acyl thiosemicarbazide (IIb).

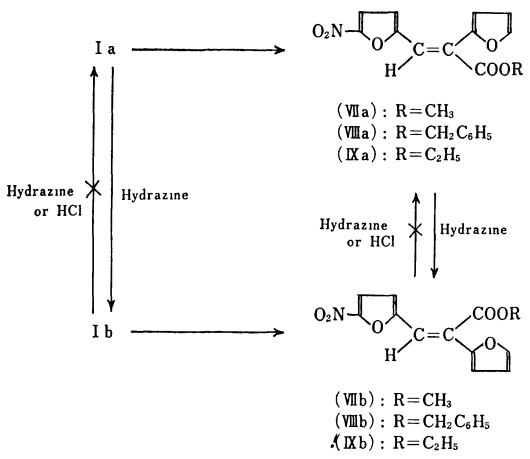


Chart 2

In conclusion, the conformation of V was determined to be *cis* and the compound, IV, which was derived from the *trans* acid, Ia, *via* its acyl thiosemicarbazide, IIa, was determined to be *trans*, since the posibility of the acid-catalytic isomerization of the starting acids (Ib and Ia) during the synthetic routes could be ruled out. The spectral data of these compounds (IV and V) also supported the above conclusion. In the UV spectra, the absorption maximum of V was observed at a slightly shorter wavelength and the extinction coefficient was larger than that of IV (Fig. 1). The IR spectrum of IV contained two medium NH_2 bands, at 3360 and 3300 cm^{-1}, and a medium C=N band at 1645 cm^{-1} due to the thiadiazole ring vibration. However, in the spectrum of V, a medium band (3400 cm^{-1}), a weak band (3300 cm^{-1}), and two medium C=N bands (1640 and 1615 cm^{-1}) were observed (Fig. 2). In comparison with the NMR spectra between IV and V (Fig. 3), the chemical shift of the NH_2 proton of IV was observed at a slightly lower magnetic field than that of V.

IV and V afforded the 2-acylamino (IVa—c and Va—c) and 2-hydroxymethylamino (IVd and Vd) derivatives respectively, when treated with acid anhydrides and 37% formaldehyde respectively in the usual way. 2-Methylamino (Xa), 2-ethylamino (Xb), and 2-anilino-5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-1,3,4-thiadiazole (Xc) were prepared by the treatment of the corresponding 4-substituted 1-[3-(5-nitro-2-furyl)-2-(2-furyl)acryloyl]thiosemicarbazides (IIIa—c)[1] with phosphoryl chloride.

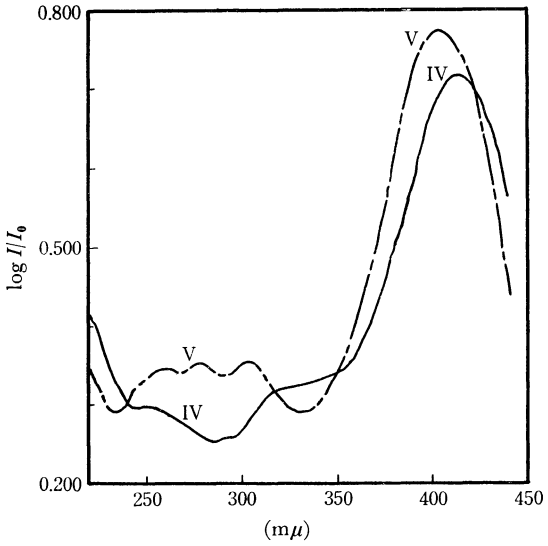


Fig. 1. UV spectra of IV and V (EtOH).

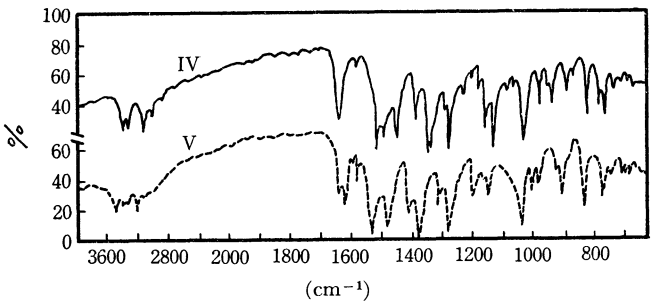


Fig. 2. IR spectra of IV and V (KBr).

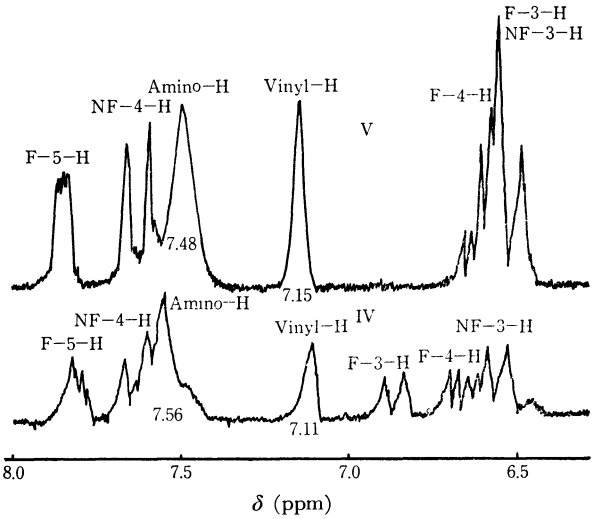


Fig. 3. NMR spectra of IV and V (DMSO-d_6).

F-5-H: C_5-H of furan ring

NF-4-H: C_4-H of 5-nitro-2-furan ring

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-oxadiazole (XI) was prepared according the method of a previous paper.[8b] Two monoacetyl derivatives, XIa and XIIa, were isolated on the treatment of XI with acetic anhydride in refluxing dioxane.

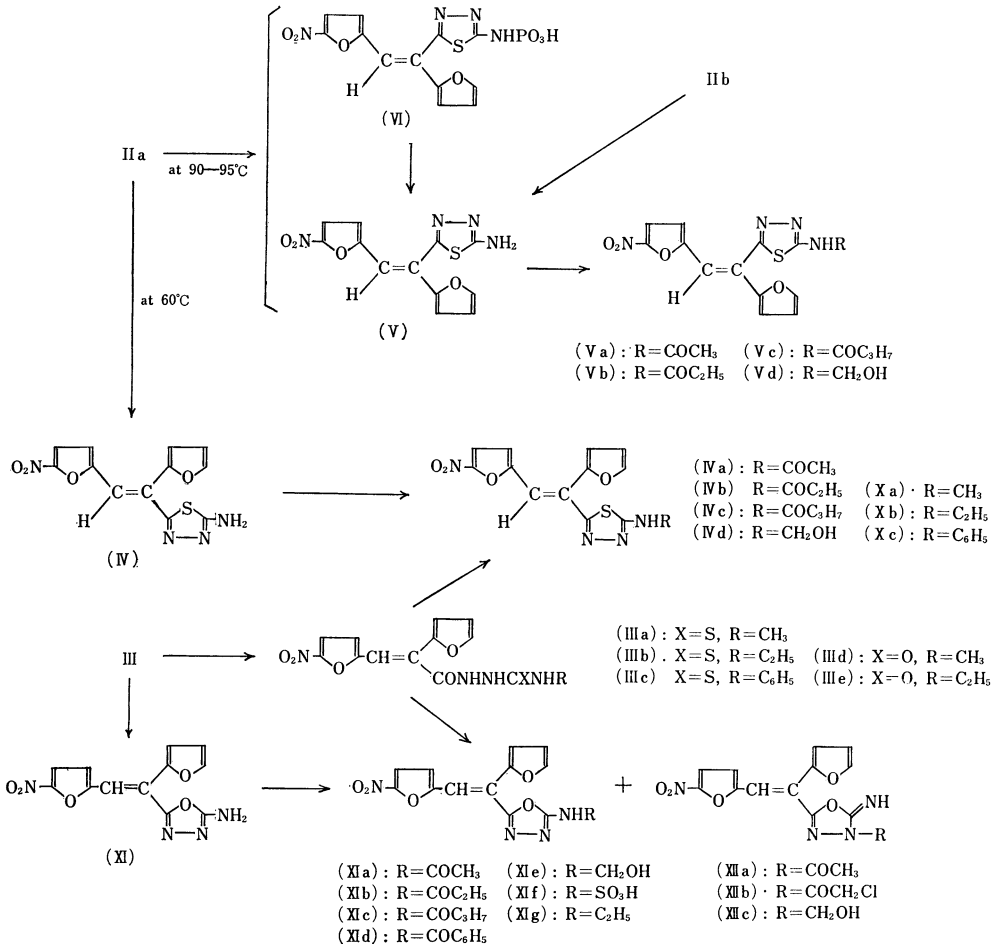


Chart 3

When XI was treated with boiling acetic anhydride without dioxane, XIIa was obtained as the main product. The compound XIa was a normal 2-acetylamino derivative, and the structure of XIIa was confirmed to be that of a ring acetyl compound, 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-3-acetyl-1,3,4-oxadiazol-2-imine, on the basis of the analytical and spectral data. In the IR spectra, both the C=O and C=N stretching frequencies of XIIa were moved, the former to higher frequencies, and the latter to lower, in the order of 20 cm^{-1} compared with those of XIa. A ring-acylated XIIa-type compound, 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-3-chloroacetyl-1,3,4-oxadiazol-2-imine (XIIb), was also produced by the reaction of XI with chloroacetic anhydride in a similar manner. By the reaction of XI with propionic and butyric anhydrides and benzoyl chloride, the corresponding 2-acylamino-type compounds, XIb, XIc, and XId respectively, were obtained. The hydroxymethylation of XI was carried out by treating it with 37% formaldehyde in *N,N*-dimethylformamide; this afforded two products, 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-2-hydroxymethylamino-1,3,4-oxadiazole (XIe) and 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-3-hydroxymethyl-1,3,4-oxadiazol-2-imine (XIIc).

When XI was treated with chlorosulfonic acid in refluxing ethyl acetate, 5-[2-(5-nitro-2-furyl)-1-(2-furyl)-vinyl]-2-hydrosulfoamino-1,3,4-oxadiazole (XIf) was obtained as its monohydrate. The IR spectrum had a strong absorption band at 1740 cm^{-1} due to the ring C=N stretching frequency, which was moved to abnormally higher frequencies by the interaction of a SO_3H group.

An attempt to prepare 2-substituted amino derivatives from the corresponding 4-substituted 1-[3-(5-nitro-2-furyl)-2-(2-furyl)acryloyl]semicarbazide (IIId, e) by the use of phosphoryl chloride was unsuccessful except for 2-ethylamino-5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-1,3,4-oxadiazole (XIg).

Microbiological Assays.[11] The antibacterial activities of the 5-nitrofuran compounds in response to ten microorganisms were examined (Table 3). The minimum amounts necessary for the complete inhibition of growth were determined by the dilution method, using the usual bouillon agar medium. As is shown in Table 3, *cis* and *trans* 5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazole (V and IV) and -1,3,4-oxadiazole (XI) were found to exhibit strong antibacterial activity against most of the microorganisms employed. The antibacterial activity showed little difference between the *cis* and *trans* isomers of 1,3,4-thiadiazole and its 2-acylamino derivatives. 2-Hydroxymethylamino derivatives (Vd and

11) The author is indebted to Dr. R. Ueno and his staff of Ueno Pharmaceutical Company, Ltd., for the assay.

Table 3. Inhibitory activity of twenty-one compounds on microorganisms

Minimum inhibitory concentration, μg/ml

Compound		*Di. pneumoniae* Dp-1	*Str. haemolyticus* Group A 089	*St. aureus* 209P	*B. subtilis* PCI-219	*Sal. enteritidis* 1891	*Sal. pullorum* Chuyu 114	*E. coli* O-55	*Kle. pneumoniae* ST-101	*Pr. vulgaris* HX 19	*Ps. aeruginosa* Iijima
2-Amino-1,3,4-thiadiazole	(IV) *t*	<0.15	<0.15	0.8	<0.2	0.8	0.8	3	0.8	3	0.8
	(V) *c*	<0.15	0.3	0.8	<0.2	1.5	1.5	1.5	0.4	1.5	1.5
2-Phosphoric amide-	(VI) *c*	>0.15	>0.15	0.8	<0.2	0.8	3	3	0.8	1.5	1.5
2-Acetylamino-	(IVa) *t*	2.5	1.2	1.5	<0.2	>12.5	>12.5	>12.5	>12.5	>12.5	>12.5
	(Va) *c*	5	0.6	1.5	0.8	6	25	25	12.5	25	>25
2-Propionylamino-	(IVb) *t*	>5	1.2	>6	0.8	>6	>6	>6	>6	>6	>6
	(Vb) *c*	20	2.5	3	0.4	>25	>25	>25	25	>25	>25
2-Butyrylamino-	(IVc) *t*	>5	>5	>6	0.4	>6	>6	>6	>6	>6	>6
	(Vc) *c*	>20	20	>25	0.4	>25	>25	>25	>25	>25	>25
2-Hydroxymethylamino-	(Vd) *c*	0.3	<0.15	0.8	<0.2	0.8	1.5	1.5	0.4	1.5	1.5
2-Methylamino-	(Xa)	3	1.5	0.8	<0.2	1.5	6	12.5	1.6	1.6	25
2-Ethylamino-	(Xb)	12.5	6.25	3.13	1.56	25	>25	25	6.25	12.5	>25
2-Phenylamino	(Xc)	>1.2	>1.2	>1.5	0.4	>1.5	>1.5	>1.5	>1.5	>1.5	>1.5
2-Amino-1,3,4-oxadiazole	(XI)	<0.15	0.6	0.4	<0.2	1.5	0.8	3	3	1.5	<0.2
2-Acetylamino-	(XIa)	0.31	0.62	0.78	1.56	6.25	3.13	6.25	25	3.13	3.13
2-Propionylamino-	(XIb)	1.2	0.6	0.8	0.4	1.5	3	12	15	6	25
2-Butyrylamino-	(XIc)	5	2.5	1.5	0.4	3	6	12	3	6	12
2-Hydroxymethylamino-	(XIe)	1.2	1.2	0.8	0.4	1.5	6	3	1.5	6	3
2-Hydrosulfoamino-	(XIf)	20	20	>25	6	>25	>25	>25	>25	>25	>25
3-Acetyl-1,3,4-oxadiazol-2-imine	(XIIa)	0.6	0.6	0.8	<0.2	0.8	3	12	1.5	3	3
3-Hydroxymethyl-	(XIIc)	2.5	1.2	3	0.4	1.5	6	6	12	12	25
Contrast[a]		10	0.6	1.5	0.4	0.8	1.5	3	0.4	6	3

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

XIe) still retain the high antibacterial activity of the mother compounds (V and XI). 3-Substituted 1,3,4-oxadiazol-2-imine-type compounds (XIIa and XIIc) slightly lowered the activity of XI. The substituted amino derivatives showed decreasing activity in the order: $R=CH_2OH \gg CH_3 \geq COCH_3 \approx C_2H_5 > COC_2H_5 > COC_3H_7$, SO_3H. This decreasing tendency of the activity is parallel with the increase in the carbon number of the substituent, R. These results suggest that the free amino group may be one of the dominant factors in antibacterial activity and that the long carbon chain blocks the reactivity of the amino group by steric hindrance.

Experimental

All the melting and decomposing points are uncorrected. Microanalyses were carried out with a Yanagimoto C. H. N. Corder, MT-2 type. The ultraviolet absorption spectra (UV) were recorded on a Shimadzu photoelectric spectrophotometer, Model QV-50. The infrared absorption spectra (IR) were obtained with a Shimadzu IR-27 S spectrophotometer. The nuclear magnetic resonance spectra (NMR) were determined by means of a Nihon-Denshi NMR spectrometer, JMN C-60HL (60 MHz). All the spectra were measured in dimethylsulfoxide, with tetramethylsilane as the internal standard; the peak positions were expressed in δ-values.

trans-*5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazole (IV).* This product was prepared according to a procedure described before.[8a] Red needles (recrystallized from methanol); mp 169—170°C; decomposition. The yield was 55%. UV : λ_{max}^{EtOH} mμ(ε) 252sh(8652), 317sh (9284), 414(21104).

cis-*5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-thiadiazole (V) and Its 2-Phosphoric Amide Compound (VI). From 1-[3-(5-nitro-2-furyl)-2-(2-furyl)acryloyl]thiosemicarbazide (IIa):* A mixture of 16.1 g (50 mmol) of IIa[8a] and 50 ml of phosphoryl chloride was heated for 2 hr on a steam bath, cooled, and then poured onto ice with agitation. The solidified material was filtered off and washed with hot water. The crude product was purified by recrystallization from methanol to afford 5.75 g (37.8%) of yellow plates (V): mp 178—179°C dec. UV: λ_{max}^{EtOH} mμ(ε) 261(10126), 278(10617), 303(10757), 405(22750).

Found: C, 47.60; H, 2.90; N, 17.90%. Calcd for $C_{12}H_8N_4O_4S$: C, 47.36; H, 2.65; N, 18.41%.

A small amount of an oily substance was separated during the recrystallization of V; it solidified on standing and was crystallized from methanol to give 0.85 g (4.4%) of orange needles (VI), mp 160°C dec. Compound VI was easily converted to V by boiling it with water for several minutes. UV: λ_{max}^{EtOH} mμ(ε) 258(10754), 280(10934), 303(10756), 405(24272). IR: (KBr) cm^{-1} 3300(N–H), 1640(C=N). Qualitative analyses: Cl(−), S(+), and P(+).

Found: C, 37.16; H, 2.64; N, 14.19%. Calcd for $C_{12}H_8N_4O_7SP$: C, 37.50; H, 2.34; N, 14.60%.

From cis-*1-[3-(5-Nitro-2-furyl)-2-(2-furyl)acryloyl]thiosemicarbazide (IIb):* The method used here was virtually identical with that described for IV,[8a] but 9.8 g (30 mmol) of IIb were used instead of IIa; a 23% yield of V was obtained. Mp 178—179°C dec, undepressed upon admixture with a sample prepared by the above method.

Compound IIb was obtained by treating *cis* acid chloride

(mp 111—113°C dec) with thiosemicarbazide in dioxane according to a previously-established procedure;[8a] mp 179—180°C dec; yellow needles (methanol). The yield was 67.3%.

Found: C, 44.97; H, 3.61; N, 17.03%. Calcd for $C_{12}H_{10}N_4O_5S$: C, 44.72; H, 3.12; N, 17.39%.

trans-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-acetylamino-1,3,4-thiadiazole (IVa). Compound IV (0.9 g, 3 mmol) was covered with acetic anhydride (10 m*l*) and warmed on a steam bath for 1 hr. On cooling, the separated product was collected and washed with water, thus affording 1.0 g (99%) of orange-yellow needles; mp 231—234°C dec. Recrystallization from methanol raised the melting point to 239—239.5°C dec. IR: (KBr) cm^{-1} 1703(C=O).

Found: C, 48.65; H, 3.04; N, 16.20%. Calcd for $C_{14}H_{10}N_4O_5S$: C, 48.56; H, 2.91; N, 16.18%.

cis-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-acetylamino-1,3,4-thiadiazole (Va). A similar treatment of 0.9 g (3 mmol) of V instead of IV (0.9 g) afforded 0.93 g (94%) of Va; mp 241°C dec. Crystallization from methanol gave yellow needles; mp 243°C dec. IR: (KBr) cm^{-1} 1709(C=O).

Found: C, 48.48; H, 2.77; N, 15.92%. Calcd: same value as the IVa above.

trans-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-propionylamino-1,3,4-thiadiazole (IVb). This was prepared in the same way as was IVa, but using propionic anhydride (8 m*l*). In this way, 1.05 g (quantitative) of IVb were obtained; mp 244—245°C dec. Crystallization from 2-methoxyethanol gave orange needles; mp 248—249°C dec. IR: (KBr) cm^{-1} *ca.* 2920—2800(CH_3, CH_2), 1702(C=O).

Found: C, 50.13; H, 3.72; N, 15.57%. Calcd for $C_{15}H_{12}N_4O_5S$: C, 50.00; H, 3.53; N, 15.55%.

cis-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-propionylamino-1,3,4-thiadiazole (Vb). This was prepared by the method used for IVa, using 0.3 g (1 mmol) of V and 3 m*l* of propionic anhydride. Work-up as above afforded 0.29 g (84.2%) of Vb as orange needles; mp 230°C dec (from 2-methoxyethanol). IR: (KBr) cm^{-1} *ca.* 2900—2780(CH_3, CH_2), 1700(C=O).

Found: C, 49.87; H, 3.19; N, 15.14%. Calcd: same value as the IVb above.

trans-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-butyrylamino-1,3,4-thiadiazole (IVc). Yellow needles; mp 217.5—218°C dec (2-methoxyethanol). The yield was 91%. IR: (KBr) cm^{-1} *ca.* 2800(CH_3, CH_2), 1696(C=O).

Found: C, 51.56; H, 3.44; N, 14.66%. Calcd for $C_{16}H_{14}N_4O_5S$: C, 51.33; H, 3.77; N, 14.79%.

cis-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-butyrylamino-1,3,4-thiadiazole (Vc). Orange needles; mp 186°C dec (2-methoxyethanol). Yield: 72.5%. IR: (KBr) cm^{-1} *ca.* 2900(CH_3, CH_2), 1700(C=O).

Found: C, 51.24; H, 3.66; N, 15.35%. Calcd: same value as the IVc above.

trans-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-hydroxymethylamino-1,3,4-thiadiazole (IVd). A mixture of IV (0.3 g, 1 mmol) and 37% formaldehyde (3 m*l*) was warmed at 60°C for 1 hr. After cooling, 6 m*l* of water were added. The solidified product was collected and washed with water, ether, and ethanol successively. The product was obtained as an orange powder, mp 121°C dec., weighing 0.27 g (80.5 %). Recrystallization was unsuccessful because of the instability.

Found: C, 46.31; H, 2.57; N, 16.91%. Calcd for $C_{13}H_{10}N_4O_5S$: C, 46.70; H, 2.99; N, 16.80%.

cis-5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-hydroxymethylamino-1,3,4-thiadiazole (Vd). A similar treatment of V instead of IV afforded 0.23 g (72.1%) of an orange powder, Vd; mp 168°C dec.

Found: C, 46.49; H, 3.03; N, 16.77%. Calcd: same value as the IVd above.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-methylamino-1,3,4-thiadiazole (Xa). 4-Methyl-1-[3-(5-nitro-2-furyl)-2-(2-furyl)acryloyl]thiosemicarbazide (IIIa)[1] (1.8 g, 5.4 mmol) and phosphoryl chloride (10 m*l*) were heated together under reflux for 2 hr. After cooling, the mixture was poured onto crushed ice, and the precipitate was filtered, washed with water, and extracted with hot ether (*ca.* 4 *l*). On the concentration of the extracts, a red-colored residue was obtained; mp 120—155°C; 0.7 g. Recrystallization from benzene gave red prisms; mp 179—180°C dec. The yield was 0.31 g (18%).

Found: C, 49.41; H, 3.17; N, 17.92%. Calcd for $C_{13}H_{10}N_4O_4S$: C, 49.06; H, 3.14; N, 17.61%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-ethylamino-1,3,4-thiadiazole (Xb). This was prepared in a way similar to that used for Xa above, using IIIb ($R=C_2H_5$)[1] (2 g, 5.7 mmol) and phosphoryl chloride (5 m*l*). Red prisms; mp 171°C (benzene). Yield, 26%.

Found: C, 51.06; H, 3.57; N, 16.33%. Calcd for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.61; N, 16.87%.

5-[2-(Nitro-2-furyl)-1-(2-furyl)vinyl]-2-anilino-1,3,4-thiadiazole (Xc). A mixture of 1.5 g (20 mmol) of acetyl chloride and IIIc ($R=C_6H_5$) (2 g, 5 mmol) was heated at 45—55°C for 20 min, and then it was poured into water. Cooling gave a crude product; mp 168—178°C dec. Crystallization from benzene provided 0.45 g (23.7%) of red crystals; mp 209.5—211°C dec.

Found: C, 55.74; H, 3.17; N, 14.45%. Calcd for $C_{18}H_{12}N_4O_4S$: C, 55.68; H, 3.16; N, 14.74%.

Compound IIIc was obtained as follows: the hydrazide III[6d] (5.2 g, 20 mmol) and phenyl isothiocyanate (3.24 g, 24 mmol) were heated under reflux in 100 m*l* of methanol for 1.5 hr. Cooling provided 6.34 g (79.7%) of the product, IIIc; mp 163—164°C dec. Recrystallization from ethanol gave orange-yellow prisms; mp 166—167°C dec.

Found: C, 54.10; H, 3.69; N, 14.38%. Calcd for $C_{18}H_{14}N_4O_5S$: C, 54.27; H, 3.52; N, 14.07%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-amino-1,3,4-oxadiazole (XI). This was obtained according to a procedure previously described.[8b] Deep red needles; mp 224—225°C dec (dioxane). Yield, 90%. The product, XI, was shown to be the same by a study of its IR spectrum and by its failure to depress the melting point when mixed with an authentic sample. UV: λ_{max}^{EtOH} mμ(ε) 246(12733), 407(25933). IR: (KBr) cm^{-1} 3420 and 3280(NH_2), 1655(C=N).

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-acetylamino-1,3,4-oxadiazole (XIa) and 5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]3-acetyl-1,3,4-oxadiazol-2-imine (XIIa). A solution of 4.32 g (15 mmol) of XI and 2.04 g (20 mmol) of acetic anhydride in 200 m*l* of dioxane was heated under reflux for 5 hr. The solvents and the excess acid anhydride were then removed under reduced pressure. The residual crude product was purified by recrystallization from methanol to give a mixture (XIa and XIIa) as light orange-small needles, mp 218—219°C dec, weighing 4.9 g (almost quantitative). IR: (KBr) cm^{-1} 3240(N–H), 1735—1730(C=O), 1660 sh and 1640 (C=N).

Found: C, 51.37; H, 3.10; N, 17.00%. Calcd for $C_{14}H_{10}N_4O_6$(XIa and XIIa): C, 50.91; H, 3.03; N, 16.98%.

This mixture was extracted with 100 m*l* of hot benzene. On the cooling of the benzene extracts, the precipitates were filtered and then they were combined with the solid residue. Two recrystallizations from toluene afforded the pure material of XIa as light brown prisms, mp 189—190°C dec., weighing 0.3 g (6%). The benzene filtrate was taken to dryness under

reduced pressure. The residue and 200 ml of toluene were boiled, filtered, and then recrystallized from 2-methoxyethanol and then from dioxane to give XIIa as orange needles; mp 233—234°C dec. The yield was 0.54 g (11%). IR: (KBr) cm^{-1} XIa; 3240(N–H), 1720(C=O), 1660(C=N). XIIa; 3240(N–H), 1740(C=O), 1640(C=N).

Found: XIa; C, 51.14; H, 3.19; N, 17.11%. XIIa: C, 51.06; H, 2.94; N, 16.99%. Calcd for $C_{14}H_{10}N_4O_6$: C, 50.91; H, 3.03; N, 16.89%.

The 3-acetyl derivative, XIIa, was obtained by the following procedure. Compound XI (4.32 g, 15 mmol) was covered with acetic anhydride (6—10 ml) and heated under a reflux for 10 min. Cooling provided 2.92 g (59.1%) of the product; mp 221—223°C dec. Subsequent crystallization from dioxane gave orange needles; mp 233—234°C dec. The melting point of this product was not depressed by admixture with the sample of XIIa described above. From the mother filtrate small amounts of XIa and XIIa were obtained.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-3-chloroacetyl-1,3,4-oxadiazol-2-imine (XIIb). The procedure outlined above for XIa was followed using chloroacetic anhydride (3.4 g, 20 mmol). The product was obtained as fine yellow crystals; mp 213—214°C dec (dioxane). Yield: 4.74 g (86.8%). IR: (KBr) cm^{-1} 3240(N–H), 1749(C=O), 1640(C=N).

Found: C, 44.51; H, 2.38; N. 15.57%. Calcd for $C_{14}H_9N_4O_6Cl$: C, 44.26; H, 2.55; N, 15.89%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-propionylamino-1,3,4-oxadiazole (XIb). A mixture of 1.44 g (5 mmol) of XI and 30 ml of propionic anhydride was heated at 95—100°C for 2 hr. The excess acid anhydride was removed *in vacuo*, and the residue was washed with water to afford a yellow powder, mp 215—217°C dec, weighing 1.74 g (quantitative). Subsequent recrystallization from methanol gave yellow needles; 216—217°C dec. IR: (KBr) cm^{-1} 2900(CH_2), 1725(C=O), 1630(C=N).

Found: C, 52.33; H, 3.53; N, 16.45%. Calcd for $C_{15}H_{12}N_4O_6$: C, 52.33; H, 3.49; N, 16.28%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-butyrylamino-1,3,4-oxadiazole (XIc). The procedure described above for XIb was employed using butyric anhydride (0.87 g, 5.5 mmol) in 50 ml of dioxane. A work-up as above afforded 1.1 g (58.5%) of ochreous needles; mp 177—178°C dec (dichloroethane). IR: (KBr) cm^{-1} 2900(CH_2), 1725(C=O), 1630(C=N).

Found: C, 53.60; H, 4.09; N, 15.45%. Calcd for $C_{16}H_{14}N_4O_6$: C, 53.63; H, 3.93; N, 15.64%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-benzoylamino-1,3,4-oxadiazole (XId). The procedure outlined above for XIb was followed using benzoyl chloride (1.06 g, 7.5 mmol) in 50 ml of dioxane. Ochre-colored needles; mp 218—219°C dec (methanol). Yield: 1.1 g (69.4%).

Found: C, 57.86; H, 3.18; N, 14.16%. Calcd for $C_{19}H_{12}N_4O_6$: C, 58.16; H, 3.06; N, 14.29%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl]-2-hydroxymethylamino-1,3,4-oxadiazole (XIe) and 5-[2-(5-Nitro-2-furyl)-1-(2-furyl)-vinyl]-3-hydroxymethyl-1,3,4-oxadiazol-2-imine (XIIc). A mixture of XI (1.44 g, 5 mmol), 37% formaldehyde (0.75 g, 9.3 mmol), and 50 ml of *N,N*-dimethylformamide was heated at 60°C for 2 hr. The resulting solution was taken to dryness *in vacuo*, and the residue was washed with ether and methanol. Subsequent reprecipitation from methyl acetate-ether gave 0.21 g of a dark yellow powder XIIc; mp 148—152°C dec. Repeated similar treatment raised the melting point to 163—165°C dec. Yield: 0.12 g (7.6%). On the concentration of the mother methyl acetate - ether filtrate, the product was separated as a dark brown powder, mp 128—130°C, weighing 0.39 g (24.6%). Reprecipitation from methyl acetate - ether brought the melting point to 134—135°C; orange powder; XIe.

Found: XIe; C, 49.50; H, 3.00; N, 17.93%. XIIc; C, 49.36; H, 2.89; N, 17.72%. Calcd for $C_{13}H_{10}N_4O_6$: C, 49.06; H, 3.17; N, 17.61%.

5-[2-(5-Nitro-2-furyl)-1-(2-furylvinyl]-2-hydrosulfoamino-1,3,4-oxadiazole (XIf). To a stirred, ice-cooled suspension of XI (1.44 g, 5 mmol) in 50 ml of ethyl acetate, we added, drop by drop, a solution of chlorosulfonic acid (10 ml) in 50 ml of ethyl acetate. After the addition, the suspension was heated under reflux for 5 hr and cooled, and the product was collected by filtration; the product was then washed with cold ethyl acetate and crystallized from methanol to give 0.42 g (22.4%) of XIf as yellow needles; mp 190°C (darkened) (depressed to 160—163°C on admixture with the sulfate of XI of mp 174—175°C dec). IR: (KBr) cm^{-1} 1740(C=N), 1205 and 1042(SO_2), 640(S–O).

Found: C, 37.29; H, 2.68; N, 14.01%. Calcd for $C_{12}H_8N_4O_8S \cdot H_2O$: C, 37.31; H, 2.59; N, 14.51%.

5-[2-(5-Nitro-2-furyl)-1-(2-furyl)vinyl-2-ethylmlamo-1,3,4-oxadiazole (XIg).[1] A suspension of 4-ethyl-1-[3-(5-nitro-2-furyl)-2-(2-furyl)acryloyl]semicarbazide (IIIe) (0.67 g, 2 mmol) in phosphoryl chloride (30 ml) was heated gently at 70°C for 4 hr. The resulting solution was taken to dryness *in vacuo*, and the residue was dissolved in 200 ml of ethanol. On cooling, orange needles precipitated; mp 194—195°C dec; weight, 0.53 g (84.1%).

Found: C, 53.11; H, 3.95; N, 17.70%. Calcd for $C_{14}H_{12}N_4O_5$: C, 53.16; H, 3.95; N, 17.72%.

Compounds IIIe and IIId were prepared as follows: the hydrazide III (2.63 g, 10 mmol) and ethyl (or methyl) isocyanate (10 mmol) were heated together at 60—65°C in 50 ml of ethanol (100 ml of methanol) for 2 hr. Cooling provided a crude product, and then recrystallization was carried out. IIIe; yellow needles (ethanol); mp 157—158°C dec. Yield: 2.4 g.

Found: C, 50.44; H, 4.08; N, 16.57%. Calcd for $C_{14}H_{14}N_4O_6$: C, 50.29; H, 4.19; N, 16.76%. IIId (R=CH_3); yellow needles (methanol); mp 161.5—162°C dec. Yield: 2.1g.

Found: C, 48.68; H, 3.59; N, 17.32%. Calcd for $C_{13}H_{12}N_4O_6$: C, 48.75; H, 3.75; N, 17.50%.

Isomerization of 3-(5-Nitro-2-furyl)-2-(2-furyl)acrylic Acid and Its Esters with Hydrazine Hydrate. A mixture of 10 mmol of *trans* acid (or esters) and 80% hydrazine hydrate in 100 ml of methanol was stirred under the reaction conditions indicated in Table 1. The resulting mixture was neutralized with concentrated hydrochloric acid and then taken to dryness *in vacuo*. The residue was washed with cold water to afford a crude reaction mixture. Fractional crystallization from methanol gave pure isomers; the yields are shown in Table 1.

cis *Acid (Ib)*: yellow needles (50% aqueous methanol); mp 183—184°C dec. Found: C, 52.98; H, 3.26; N, 5.44%. Calcd for $C_{11}H_7NO_6$: C, 53.01; H, 2.83; N, 5.62%.

cis *Benzyl Ester (VIIIb)*: yellow-ochre plates (aq. methanol), mp 109—110°C. Found: C, 64.05; H, 3.84; N, 4.02%. Calcd for $C_{18}H_{13}NO_6$: C, 63.72; H, 3.86; N, 4.13%.

The *cis* acid and its esters were not converted to *trans* isomers under the same reaction conditions.

Another isomerization reaction of each *trans* (or *cis*) acid and its esters was carried out in the presence of hydrochloric acid (1/20 fold mol) in refluxing methanol. No isomerization of these *trans* and *cis* isomers was observed.

Preparation of Esters of 3-(5-Nitro-2-furyl)-2-(2-furyl)acrylic Acid. From Chloride: The esters were prepared in a way similar to that described by Saikachi and Tanaka[7] for

the preparation of the *trans* ethyl ester (IXa). Crystallization from aqueous methanol gave pure esters. Yield: 40—75%.

From Sodium Salt: To a warmed (45°C), stirred suspension of acid (10 mmol), alkyl halide (13 mmol) in 100 m*l* of ethanol, we added, drop by drop, a solution of sodium (10 mg atom) in ethanol (50 m*l*). Then the mixture was heated under reflux for 2 hr. On the concentration of the solution, the product separated along with an inorganic salt was washed with water and subsequently dried. Work-up as above afforded pure esters. Yield: 70—90%.

trans Benzyl ester (VIIIa); orange prisms (aq. methanol); mp 99—100°C. Found: C, 63.78; H, 4.01; N, 4.16%. Calcd for $C_{18}H_{13}NO_6$: C, 63.72; H, 3.86; N, 4.13%. *cis* Ethyl ester (IXb); orange-yellow plates (aq. methanol); mp 152—153°C. Found: C, 56.40; H, 4.01; N, 5.08%. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 3.97; N, 5.05%.

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