STUDIES ON THE SYNTHESIS OF FURAN COMPOUNDS XXXIII*

Synthesis of 5-Nitro-2-(2-carboxystyryl)furan and its Derivatives

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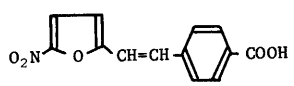
SYNOPSIS

The Wittig reaction of 5-nitrofurfural with 2-methoxycarbonyl- and 2-carboxybenzyltriphenylphosphonium bromides has been investigated to prepare 5-nitro-2-(2-carboxystyryl)furan. The Wittig reaction of 5-nitrofurfural with 2-methoxycarbonylbenzyl triphenylphosphonium bromide gave a mixture of cis- and trans-isomers of 5-nitro-2-(2-methoxycarbonylstyryl)furan in a good yield. The predominant formation of the cis-isomer was observed in the reaction. It was difficult to produce 5-nitro-2-(2-carboxystyryl)furan by the hydrolysis of the methoxycarbonylstyrylfuran. The carboxystyrylfuran was successfully synthesized by the Wittig reaction of 5-nitrofurfural with 2-carboxybenzyltriphenylphosphonium bromide. A number of amides and esters of the carboxystyrylfuran were also prepared. In addition, some derivatives of 5-nitro-2-(4-carboxystyryl)furan were synthesized. The antibacterial activity of the compounds prepared is investigated.

1. INTRODUCTION

In previous papers, we have reported the synthesis of 5-nitro-2-(4-carboxystyryl)-furan (I) by the decarboxylation of the corresponding acrylic acid.[1-3] Carboxystyrylfuran I and its derivatives prepared have shown an excellent antibacterial activity against Gram-positive and -negative bacteria.[4] Recently, it has been found during the investigation of the preparation of I that the Wittig reaction of 5-nitrofurfural with 4-methoxycarbonylbenzyltriphenylphosphonium bromide gave 5-nitro-2-(4-methoxycarbonylstyryl)furan and that the methoxycarbonylstyrylfuran gave I in a good yield by hydrolysis.[5] 5-Nitro-2-(3-carboxystyryl)furan (II) has been prepared in a good yield by a similar way.[6] Carboxystyrylfuran II and its amides and esters have also shown



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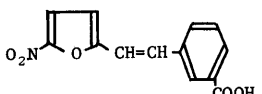

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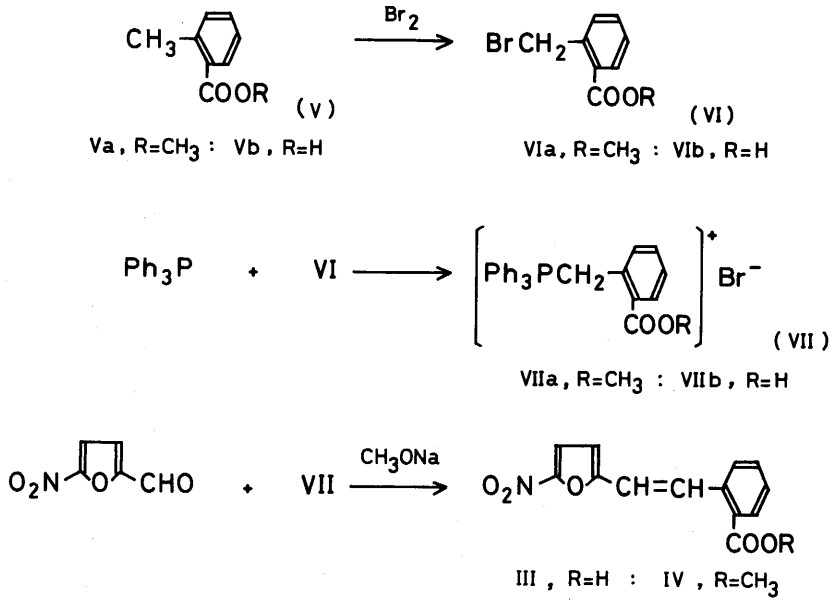
* Part XXXII of this series; I. Hirao, T. Fujimoto, T. Morita, F. Tone and S. Kono, Memoirs of the Kyushu Institute of Technology, Engineering, **5**, 1 (1975).

an excellent antibacterial activity similar to those of carboxystyrylfuran I and its derivatives.[6] As part of the investigation of the synthesis of furan compounds, it is of interest to synthesize 5-nitro-2-(2-carboxystyryl)furan (III) as an analogue of I and II employing the Wittig reaction. The Wittig reaction involved a stabilized phosphorane give generally a mixture of cis- and trans-olefins. For the Wittig reaction of 5-nitrofurfural with 2-methoxycarbonylbenzyltriphenylphosphonium bromide (VIIa), the effect of the methoxycarbonyl group at the 2-position on stereospecificity of the reaction apears to be of interest, but there are no reports on the Wittig reaction of phosphonium salt VIIa with aldehydes. Furthermore, it is of interest to compare the effect of the position of the carboxyl group in these carboxystyrylfurans on antibacterial activity in connection with a role of the carboxyl group in antibacterial action.

This paper describes the syntheses of 5-nitro-2-(2-methoxycarbonylstyryl)furan (IV) and carboxystyrylfuran III employing the Wittig reaction of 5-nitrofurfural with the corresponding benzyltriphenylphosphonium bromides. A number of amides and esters of III were also prepared. In addition, esters of carboxystyrylfuran I, which had not been prepared, were synthesized. Furthermore, the antibacterial activity of these compounds prepared is also investigated.

2. RESULTS AND DISCUSSION

The Wittig Reaction of 5-Nitrofurfural with Phosphonium Salt VIIa.



Scheme 1. Synthesis of carboxystyrylfuran III and methoxycarbonylstyrylfuran IV

Methoxycarbonylstyrylfuran IV was synthesized by the Wittig reaction of 5-nitrofurfural with phosphonium salt VIIa as shown in Scheme 1. Methyl 2-bromomethylbenzoate (VIa) was prepared by the bromination of methyl o-toluate (Va) with bromine in the presence of benzoyl peroxide. Phosphonium bromide VIIa was prepared in a good yield by refluxing VIa and triphenylphosphine in benzene. 5-Nitrofurfural condensed with VIIa in methanol in the presence of sodium methoxide as a base to give methoxycarbonylstyrylfuran IV in a 75% yield. The product, thus obtained, was a mixture of the cis- and trans-isomers of IV as indicated by the broad range of its melting point (93—103℃) and by the presence of absorption in the IR spectrum assigned to C-H out-of-plane deformation of both cis and trans double bonds ($\delta_{C-H,cis}$ and $\delta_{C-H,trans}$) at 730 and 960 cm^{-1}.

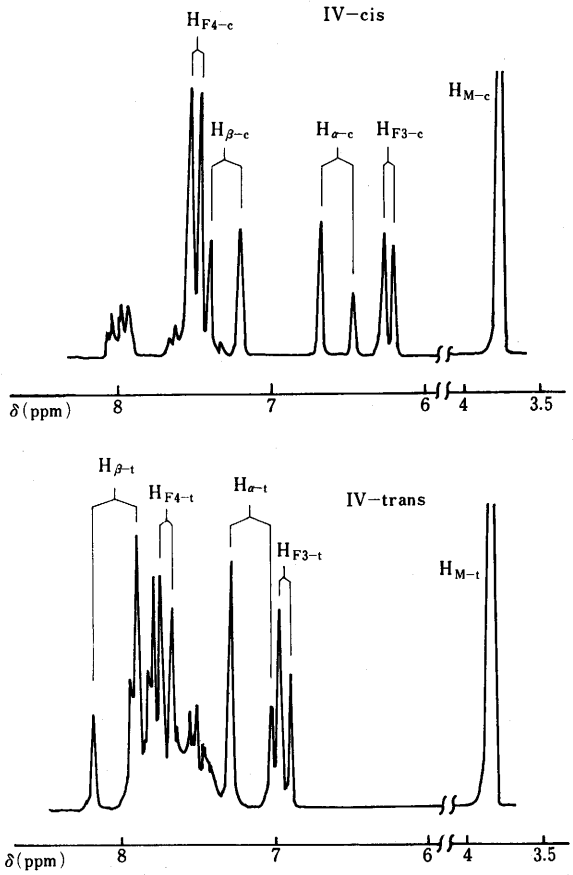


Fig. 1 NMR spectra of IV-cis and IV-trans (in DMSO).

The cis- and trans-isomers were successfully isolated by the fractional crystallization of the mixture from methanol. The cis-isomer (IV-cis) melted at 123—4℃ and was less soluble in methanol, while the trans-isomer (IV-trans) melted at 109—10℃.

The configuration of the isomers was confirmed by the study of the IR and NMR spectra. The absorption in the IR spectra assigned to C–H deformation was observed at 730 cm^{-1} ($\delta_{C-H,cis}$) for IV-cis and at 960 cm^{-1} ($\delta_{C-H,trans}$) for IV-trans. The NMR spectra of the isomers are given in Figure l. Signals of AB type for the ethylenic protons were detected at δ 6.58 ($H_{\alpha-c}$) and 7.25 ($H_{\beta-c}$) with a coupling constant ($J_{\alpha\beta}$) of 12.2 Hz for IV-cis. While the signals for IV-trans were detected at δ 7.20 ($H_{\alpha-t}$) and 8.02 ($H_{\beta-t}$) with $J_{\alpha\beta}$ of 16.5 Hz. The values of $J_{\alpha\beta}$ for IV-cis and IV-trans are in agreement essentially with those of the cis- and trans-isomers of 5-nitro-2-(3-methoxycarbonylstyryl)furan[6] and those of cis- and trans-isomers of substituted stilbenes.[7,8] The signals due to the protons at the 3- and 4-positions of the furan ring were detected as doublets at δ 6.24 (H_{F3-c}) and 7.58 (H_{F4-c})(J=4.0 Hz) for IV-cis and δ 6.98 (H_{F3-t}) and 7.73 (H_{F4-t}) (J=4.0 Hz) for IV-trans. The signals assigned to the protons of the methoxycarbonyl group were observed as singlets at δ 3.78 (H_{M-c}) for IV-cis and δ 3.88 (H_{M-t}) for IV-trans.

The proportions of IV-cis and IV-trans in the product of the Wittig reaction were estimated using NMR spectrometry. The amount ratio (C/T) of IV-cis to IV-trans was calculated employing the equation

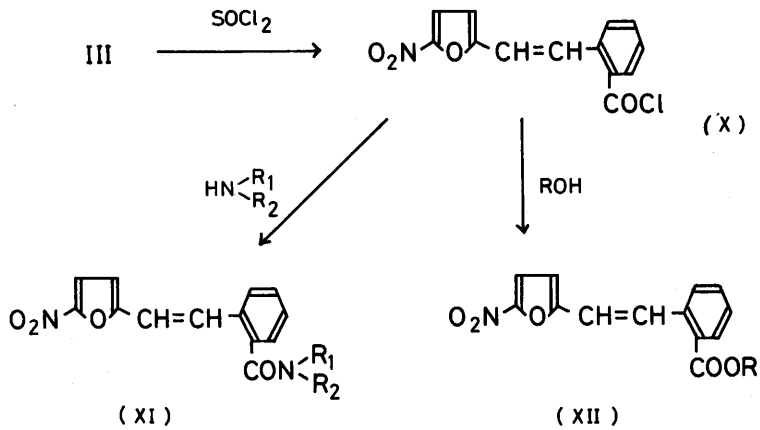
$$\frac{C}{T}=\frac{3I_a}{2I_b-I_a}$$

where I_a represents the sum of the intensities of the H_{F3-c} and $H_{\alpha-c}$ protons, and I_b is the sum of the intensities of the H_{M-c} and H_{M-t} protons. The proportions of IV-cis and IV-trans in the product were evaluated to be 74 : 26 (IV-cis : IV-trans) from the value of C/T (2.80). The proportions were compared with those of the cis- and trans-isomers of 5-nitro-2-(4-methoxycarbonylstyryl)furan (VIII-cis and VIII-trans) in the product which was obtained from 5-nitrofurfural and 4-methoxycarbonylbenzyltriphenylphosphonium bromide (IX)[5] in the same conditions. The proportions of VIII-cis and VIII-trans were estimated similarly using NMR spectrometry. The NMR spectra of VIII-cis and VIII-trans, which were isolated by fractional crystallization from the product, were similar to those of the cis- and trans-isomers of 5-nitro-2-(3-methoxycarbonylstyryl)furan.[6] The proportions which were estimated from the proton intensities in the NMR spectrum of the product were 58 : 42 (VIII-cis : VIII-trans). Nonstereospecificity was observed in the Wittig reaction of 5-nitrofurfural with IX and with 3-methoxycarbonylbenzyltriphenylphosphonium bromide (cis : trans = 43 : 57).[6] However, the predominant formation of cis-isomer was observed in the Wittig reaction of 5-nitrofurfural with VIIa in contrast to the expectation that the formation of the trans-isomer would be favorable because of the steric hindrance of the methoxycarbonyl group in 2-methoxycarbonylbenzylidenetriphenylphosphorane derived from VIIa by sodium methoxide. The observation is of interest with respect to the mechanism of

the Wittig reaction. Although trans-isomers are often formed predominantly in the Wittig reaction, a solvation of intermediate betaines of the reaction in a protic solvent results in an increase in a formation ratio of cis-isomers to trans-isomers.[9,10] Accordingly the solvent effect of methanol used may result in the fact that the formation amounts of the cis- and trans-isomers were essentially the same in the reaction of 5-nitrofurfural with IX and with 3-methoxycarbonylbenzyltriphenylphosphonium bromide. On the other hand, the predominant formation of IV-cis suggests that the solvation of the intermediate betaine of the Wittig reaction of 5-nitrofurfural with VIIa and the steric effect of the methoxycarbonyl group in the intermediate allow to stablize the erthro-isomer of the intermediate which give the cis-isomer by decomposition.

The synthesis of carboxystyrylfuran III was attempted by the hydrolysis of the methoxycarbonylstyrylfuran IV. The hydrolysis of the mixture of IV-cis and IV-trans was carried out under the conditions which have given carboxystyrylfurans I and II from the corresponding methoxycarbonylstyrylfurans. But it was difficult to obtain III by the hydrolysis.

5-Nitro-2-(2-carboxystyryl)furan III. It was difficult to prepare III by the hydrolysis of methoxycarbonylstyrylfuran IV, therefore, the Wittig reaction of 5-nitrofurfural with 2-carboxybenzyltriphenylphosphonium bromide (VIIb) was attempted to prepare III directly (Scheme 1).



Scheme 2. Synthesis of derivatives of carboxystyrylfuran III.

Phosphonium salt VIIb was prepared from triphenylphosphine and 2-bromomethylbenzoic acid (VIb) which was obtained by the bromination of o-toluic acid with bromine in the presence of benzoyl peroxide. 5-Nitrofurfural condensed with VIIb in the presence of two equivalents of sodium methoxide in methanol to give only the trans-isomer (III-trans) of III in a 42% yield. The trans-configuration of the product was indicated by absorption in the IR spectrum at 960 cm^{-1} ($\delta_{C-H,trans}$) and by the

value (16.5 Hz) of a coupling constant of signals of AB type for the ethylenic protons. In contrast to the predominant formation of IV-cis in the condensation with VIIa, the trans-isomer of III was formed exclusively in the reaction with VIIb. It may be one of possible explanations for the predominant formation of III-trans that the cis-isomer of III formed isomerized to the trans-isomer during the reaction or at the treatment of the reaction mixture.

Table 1. Amides of carboxystyrylfuran III.

Compound	R_1[a]	R_2[a]	Mp (℃)	Yield (%)	Cryst. Form	Analysis (%) Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N
XIa	H	H	198–9	86	Yellow needles[b]	60.20	4.16	10.84	60.46	3.90	10.85
XIb	H	CH_3	185–7	85	Yellow fibers[c]	62.12	4.47	10.14	61.76	4.41	10.29
XIc	H	C_2H_5	185–7	80	Yellow powder[d]	62.70	4.99	9.08	62.93	4.58	9.17
XId	H	C_3H_7(n)	179–80	82	Ochreous powder[b]	64.14	5.34	9.00	63.99	5.37	9.33
XIe	H	C_6H_5	183–6	88	Yellow needles[d]	67.90	4.12	8.13	68.25	3.92	8.38
XIf	H	$C_6H_4CH_3$(p)	177–9	72	Yellow needles[b]	68.61	4.59	8.02	68.96	4.63	8.04
XIg	H	C_6H_4OH(p)	190–1	72	Yellow powder[c]	65.32	4.15	7.82	65.14	4.03	8.00
XIh	CH_3	CH_3	150–1	83	Yellow leaflets[c]	63.12	5.10	9.99	62.93	4.93	9.78
XIi	CH_3	C_6H_5	169–70	88	Ochreous needles[e]	68.75	4.63	8.18	68.96	4.63	8.04
XIj	C_2H_5	C_2H_5	124–5	84	Yellow powder[f]	64.95	5.75	8.52	64.96	5.78	8.91
XIk	C_2H_5	C_6H_5	180–3	77	Yellow needles[g]	69.47	4.96	7.55	69.60	5.01	7.73
XIl			176–7	76	Yellow fibers[e]	62.09	4.84	8.66	62.19	4.91	8.53
XIm			159–61	75	Yellow powder[e]	66.25	5.56	8.58	66.55	5.41	8.16

a) R_1 and R_2 in XI are given. b) From methanol-water. c) From acetone-water. d) From ethanol-water. e) From dioxane-water. f) From methaol. g) From ethanol.

Derivatives of Carboxystyrylfuran III. The various amides (XIa-XIm) of III were prepred by condensing the acid chloride (X) of III with aqueous ammonia, methylamine, ethylamine, n-propylamine, aniline, 4-toluidine, 4-aminophenol, dimethylamine, N-methylaniline, diethylamine, N-ethylaniline, morpholine and piperidine respectively (Scheme 2). The amides prepared are summerized in Table 1.

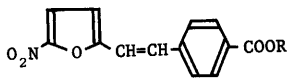
A number of the ester derivatives (XIIa–XIIf) of III were similarly prepared by condensing X with methanol, ethanol, 1-propanol, 2-propanol, 1-butanol and 2-methyl-1-propanol respectively (Scheme 2). The esters obtained are given in Table 2. All of the derivatives prepared were trans form as indicated by absorption in the IR spectra at 950–960 cm^{-1} ($\delta_{C-H,trans}$).

Table 2. Esters of carboxystyrylfuran III.

Compound	R[a]	Mp (℃)	Yield (%)	Cryst. Form	Analysis (%) Found / Calcd. C	H	N
XIIa	CH_3	108–9	93	Yellow prisms[b]	61.85 61.54	4.45 4.06	5.03 5.13
XIIb	C_2H_5	107–10	90	Yellow needles[b]	62.70 62.72	4.57 4.56	5.01 4.88
XIIc	C_3H_7(n)	74–5	85	Yellow powder[c]	63.85 63.78	5.09 5.02	4.72 4.65
XIId	C_3H_7(i)	83–4	83	Yellow powder[d]	63.86 63.78	4.85 5.02	4.90 4.65
XIIe	C_4H_9(n)	78–9	82	Yellow leaflets[c]	64.34 64.75	5.35 5.44	4.59 4.44
XIIf	C_4H_9(i)	72–3	78	Yellow prisms[d]	64.88 64.75	5.23 5.44	4.54 4.44

a) R in XII is given. b) From methanol. c) From ethanol-water.
d) From methanol-water.

Derivatives of Carboxystyrylfuran I. Some of amide derivatives of I had been synthesized, but the esters (XIVa–XIVh) of I had not been prepared. These esters were prepared to investigate the effect of the functional groups on antibacterial activity. Esters XIVa–XIVh were prepared by condensing the acid chloride (XIII) of I with methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, 1-pentanol and 3-methyl-1-butanol respectively. The esters prepared are given in Table 3.



(XIV)

Microbiological Assays. The antibacterial activities of the compounds prepared in the present investigation were examined for ten microorganisms. The minimum amount of the compound necessary for the complete inhibition of growth was determined. The results are given in Tables 4, 5 and 6. Carboxystyrylfuran III was inactive against the bacteria employed here for the test in contrast to the strong

activities of carboxystyrylfurans I and II.[4,6] The amide derivatives of III were active toward St. aureus and B. subtilis, but inactive against the other. Methyl ester XIIa inhibited effectively the growth of the bacteria employed here, although the other esters of III showed a low activity similar to those of the amides of III. Among the

Table 3. Esters of carboxystyrylfuran I.

Compound	R[a]	Mp (℃)	Yield (%)	Cryst. Form	Analysis (%) Found / Calcd. C	H	N
XIVa	CH_3	189–90	76	Yellow needles[b]	61.62 61.54	4.13 4.06	5.18 5.13
XIVb	C_2H_5	167–8	83	Yellow needles[c]	62.85 62.72	4.72 4.56	5.03 4.88
XIVc	C_3H_7(n)	146–7	86	Yellow fibers[b]	63.89 63.78	5.10 5.02	4.80 4.65
XIVd	C_3H_7(i)	133–4	82	Orange needles[b]	63.85 63.78	4.98 5.02	4.83 4.65
XIVe	C_4H_9(n)	82–3	70	Brown prisms[b]	64.63 64.76	5.66 5.44	4.40 4.44
XIVf	C_4H_9(i)	133–4	75	Orange prisms[b]	64.78 64.76	5.22 5.44	4.63 4.44
XIVg	C_5H_{11}(n)	91–2	76	Yellow leaflets[b]	65.44 65.65	5.85 5.78	4.44 4.26
XIVh	C_5H_{11}(i)	100–1	73	Yellow needles[b]	66.01 65.65	5.82 5.78	4.43 4.26

a) R in XIV is given. b) From methanol. c) From dioxane-water.

Table 5. Inhibitory activity of esters of carboxystyrylfuran III.[a]

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 0-55	Kle. pneumoniae ST-101	Pr. vulgaris HX 19	Ps. aeruginosa 347
XIIa	1.56	< 0.19	0.78	<0.19	3.13	12.5	6.25	3.13	12.5	25
XIIb	>25	0.78	1.56	<0.19	1.56	>25	>25	>25	>25	>25
XIIc	>25	0.78	1.56	<0.19	12.5	>25	>25	>25	>25	>25
XIId	>25	3.13	<0.19	<0.19	>25	>25	>25	>25	>25	>25
XIIe	>25	1.56	3.13	<0.19	>25	>25	>25	>25	>25	>25
XIIf	>25	1.56	6.25	<0.19	>25	>25	>25	>25	>25	>25
Contrast[b]	6.25	0.39	1.56	<0.19	0.78	0.78	1.56	0.78	6.25	25

a) The activitiy is represented by minimum inhibitory concentration (μg/ml).

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

esters of carboxystyrylfuran I, the methyl ester, XIVa, was also active toward the bacteria. As a whole, the derivatives of III were less active toward bacteria in comparison with those of the derivatives of carboxystyrylfurans I and II.

Table 4. Inhibitory activity of carboxystyrylfuran III and its amides.[a)]

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 0-55	Kle. pneumoniae ST-101	Pr. vulgaris HX 19	Ps. aeruginosa 347
III	>25	>25	>25	25	>25	>25	>25	>25	>25	>25
XIa	>25	>25	6.25	0.39	>25	>25	>25	>25	>25	>25
XIb	>25	>25	12.5	<0.19	>25	>25	>25	>25	>25	>25
XIc	>25	>25	6.25	0.39	>25	>25	>25	>25	>25	>25
XId	>25	>25	6.25	0.78	>25	>25	>25	>25	>25	>25
XIe	>25	>25	25	12.5	>25	>25	>25	>25	>25	>25
XIf	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25
XIg	>25	>25	12.5	3.13	>25	>25	>25	>25	>25	>25
XIh	>25	12.5	6.25	0.39	12.5	>25	>25	>25	>25	>25
XIi	>25	>25	6.25	0.78	>25	>25	>25	>25	>25	>25
XIj	>25	>25	12.5	0.78	>25	>25	>25	>25	>25	>25
XIk	>25	>25	>25	0.39	>25	>25	>25	>25	>25	>25
XIl	>25	>25	12.5	<0.19	>25	>25	>25	>25	>25	>25
XIm	>25	>25	6.25	0.78	>25	>25	>25	>25	>25	>25

a) The activity is represented by minimum inhibitory concentration (μg/ml). Contrast is given in Table 5.

Table 6. Inhibitory activity of esters of carboxystyrylfuran I.[a)]

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 0-55	Kle. pneumoniae ST-101	Pr. vulgaris HX 19	Ps. aeruginosa 347
XIVa	3.13	0.39	1.56	<0.19	0.39	3.13	1.56	1.56	1.56	3.13
XIVb	>25	0.78	6.25	<0.19	12.5	>25	>25	>25	>25	>25
XIVc	>25	3.13	12.5	<0.19	>25	>25	>25	>25	>25	>25
XIVd	>25	6.25	25	<0.19	25	>25	>25	>25	>25	>25
XIVe	>25	<0.19	1.56	<0.19	12.5	25	>25	12.5	>25	>25
XIVf	>25	0.39	1.56	<0.19	25	>25	>25	25	>25	>25
XIVg	>25	>25.	>25	<0.19	>25	>25	>25	>25	>25	>25
XIVh	>25	6.25	6.25	0.39	>25	>25	>25	>25	>25	>25

a) The activity is represented by minimnm inhibitory concentration (μg/ml). Contrast is given in Table 5.

3. EXPERIMENTAL

All of the melting points are uncorrected. The IR and NMR spectra were obtained on JASCO Model IR A-2 and Japan Electron Optics JNM-C-60HL spectrometers respectively. The NMR spectra were measured with tetramethylsilane as an internal reference.

Methyl 2-Bromomethylbenzoate VIa. A solution of bromine (160 g) in carbon tetrachloride (100 ml) was added dropwise to a solution of methyl o-toluate (Va, 150 g) and benzoyl peroxide (1.0 g) in carbon tetrachloride (200 ml) under reflux. The mixture was refluxed until the bromine was completely consumed. The carbon tetrachloride was removed from the reaction mixture by evaporation. Thus VIa was obtained as a residual oil (210 g) and was used in the subsequent experiments without purification by distillation since the bromide readily decomposed by heating.[11]

2-Methoxycarbonylbenzyltriphenylphosphonium Bromide VIIa. A solution of triphenylphosphine (131 g) in benzene (200 ml) was added to a refluxing solution of methyl 2-bromomethylbenzoate (115 g) in benzene (200 ml). The mixture was further refluxed for 1 hr. After cooling, the precipitated product was collected, washed with benzene and dried. Recrystallization from dioxane-methanol gave 172 g of VIIa as colorless granules, mp 238-9°C. Found: C, 65.85; H, 4.50%. Calcd for $C_{27}H_{24}O_2PBr$: C, 66.00; H, 4.92%. IR (KBr): 1690 cm^{-1} ($\nu_{C=O}$), 725 and 695 cm^{-1} (P—C).

5-Nitro-2-(2-methoxycarbonylstyryl) furan (IV-cis and IV-trans). A solution of sodium methoxide (5.4 g) in methanol (40 ml) was added dropwise to a solution of VIIa (49.1 g) and 5-nitrofurfural (14.1 g) in methanol (100 ml) at a temperature below 30°C. After the addition, the mixture was stirred for 1 hr at room temperature. On cooling, the precipitated product was filtered, washed with water and dried to give yellow powder (21.6 g, 79.5%), which melted in the range from 93 to 103°C. IR (KBr): 730 cm^{-1} ($\delta_{C-H,cis}$) and 960 cm^{-1} ($\delta_{C-H,trans}$). The fractional crystallization of the product from methanol gave IV-cis as yellow needles which was less soluble in methanol, mp 123—4°C, and IV-trans as yellow leaflets, mp 109—10°C.

IV-cis. Found: C, 61.54; H, 4.05; N, 5.25%. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13%. IR(KBr): 1710 cm^{-1} ($\nu_{C=O}$), 1355 cm^{-1} ($\nu_{s\ NO_2}$) and 730 cm^{-1} ($\delta_{C-H,cis}$). NMR (DMSO): δ 6.58 (d, $J_{\alpha\beta}$=12.2 Hz, ethylenic proton $H_{\alpha-c}$, 1H); 7.25 (d, $J_{\alpha\beta}$= 12.2 Hz, ethylenic proton $H_{\beta-c}$, 1H); 6.24 (d, J=4.0 Hz, furan ring proton H_{F3-c}, 1H); 7.58 (d, J=4.0 Hz, furan ring proton H_{F4-c}, 1H); 3.78 (s, -$COOCH_3$, 3H).

IV-trans. Found: C, 61.60; H, 4.18; N, 5.22%. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13%. IR (KBr): 1710 cm^{-1} ($\nu_{C=O}$), 1360 cm^{-1} ($\nu_{s\ NO_2}$) and 960 cm^{-1} ($\delta_{C-H,trans}$). NMR (DMSO): δ 7.20 (d, $J_{\alpha\beta}$=16.5 Hz, ethylenic proton $H_{\alpha-t}$, 1H); 8.02 (d, $J_{\alpha\beta}$=16.5 Hz, ethylenic proton $H_{\beta-t}$, 1H); 6.98 (d, J=4.0 Hz, furan ring proton H_{F3-t}, 1H); 7.73 (d, J=4.0 Hz, furan ring proton H_{F4-t}, 1H); 3.88 (s, -$COOCH_3$, 3H).

For the calculation of the ratio C/T, the NMR spectra of the products were measured in dimethyl sulfoxide and C/T of 2.80 was obtained.

5-Nitro-2-(4-methoxycarbonylstyryl)furan (VIII-cis and VIII-trans). The mixture of VIII-cis and VIII-trans (mp 102–186°C) was obtained in a 99% yield using 5-nitrofurfural (14.1 g) and IX (49.1 g)[5] under the same conditions to that for the preparation of IV. VIII-cis and VIII-trans were isolated by the fractional crystallization of the mixture from dioxane-water.

VIII-cis. Yellow needles, mp 113–4°C. Found: C, 61.69; H, 4.24; N, 5.40%. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.09%. IR(KBr): 1720 cm^{-1} ($\nu_{C=O}$), 1365 cm^{-1} ($\nu_{s\ NO_2}$) and 735 cm^{-1} ($\delta_{C-H,cis}$). NMR(CF_3COOH): δ 6.53(d, $J_{\alpha\beta}$=12.8 Hz, ethylenic proton $H_{\alpha-c}$, 1H); 6.96(d, $J_{\alpha\beta}$=12.8 Hz, ethylenic proton $H_{\beta-c}$, 1H); 6.40(d, J=4.0 Hz, furan ring proton H_{F3-c}, 1H); 7.34(d, J=4.0 Hz, furan ring H_{F4-c}, 1H); 4.07(s, -$COOCH_3$, 3H).

VIII-trans. Yellow leaflets, mp 189–90°C. Found: C, 61.40; H, 4.20; N, 5.09%. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.09%. IR (KBr): 1708 cm^{-1} ($\nu_{C=O}$), 1355 cm^{-1} ($\nu_{s\ NO_2}$), 960 cm^{-1} ($\delta_{C-H,trans}$). NMR (CF_3COOH): δ 6.96 (d, $J_{\alpha\beta}$=16.5 Hz, ethylenic proton $H_{\alpha-t}$, 1H); 7.37(d, $J_{\alpha\beta}$=16.5 Hz, ethylenic proton $H_{\beta-t}$, 1H); 6.65 (d, J=4.0 Hz, furan ring proton H_{F3-t}, 1H); 7.49 (d, J=4.0 Hz, furan ring proton H_{F4-t}, 1H); 4.05 (s, -$COOCH_3$, 3H).

For the calculation of the amount ratio C/T of the isomers of VIII in the product, the NMR spectra were measured in trifluoroacetic acid, and the ratio was calculated employing the equation $C/T=(I_c-I_d)/(2I_d-I_c)$ where I_c is the sum of the intensities of the H_{F3-c}, H_{F3-t} and $H_{\alpha-c}$ protons, and I_d represents the sum of the intensities of the $H_{\beta-c}$ and $H_{\beta-t}$ protons.

2-Bromomethylbenzoic Acid (VIb). The acid was prepared by the bromination of o-toluic acid Vb (68.0 g) with bromine (80.0 g) in carbon tetrachloride (400 ml) by a similar method to that for VIa. The recrystallization of the product from methanol-water gave VIb (98 g, 92%) as colorless leaflets; mp 141–2°C (lit. 146°C).[12] Found: C, 44.92; H, 3.23%. Calcd for $C_8H_7O_2Br$: C, 44.65; H, 3.26%.

2-Carboxybenzyltriphenylphosphonium Bromide (VIIb). The phosphonium salt VIIb was prepared by a similar method to that for VIIa using VIb (98 g) and triphenylphosphine (121 g). The recrystallization of the product from methanol-water gave VIIb (183 g, 83%) as colorless granules; mp 267–71°C. Found: C, 65.41; H, 4.61%. Calcd for $C_{26}H_{22}O_2PBr$: C, 65.42; H, 4.65%. IR (KBr): 1687 cm^{-1} ($\nu_{C=O}$), 718 and 690 cm^{-1} (P–C).

5-Nitro-2-(2-carboxystyryl)furan (III). A solution of sodium methoxide (21.6 g) in methanol (100 ml) was added dropwise to a solution of 5-nitrofurfural (28.2 g) and VIIb (95.5 g) in methanol (250 ml) at a temperature below 10°C. After the addition, the mixture was stirred for 1 hr at room temperature and acidified with concentrated hydrochloric acid. The precipitate was collected and combined with a precipitate obtained from the filtrate by concentration under reduced pressure. Recrystallization from methanol-water gave III (21.8 g, 42%) as yellow leaflets; mp 175–6°C. Found: C,

60.30 ; H, 3.52 ; N, 5.20%. Calcd for $C_{13}H_9NO_5$: C, 60.24 ; H, 3.50 ; N, 5.40%. IR (KBr) : 1670 cm^{-1} ($\nu_{C=O}$), 1350 cm^{-1} ($\nu_{s\ NO_2}$) and 960 cm^{-1} ($\delta_{C-H,trans}$). NMR (DMSO): δ 7.20 (d, $J_{\alpha\beta}$=16.5 Hz, ethylenic proton H_α, 1H; 8.02 (d, $J_{\alpha\beta}$=16.5 Hz, ethylenic proton H_β, 1H); 6.98(d, J=4.0 Hz, furan ring proton H_{F3}, 1H); 7.73 (d, J=4.0 Hz, furan ring proton H_{F4}, 1H).

Amide Derivatives of Carboxystyrylfuran III (XIa-XIm). A mixture of III (1.0 g), thionyl chloride (10 ml) and dioxane (10 ml) was refluxed gently for 1 hr. The dioxane and the unreacted thionyl chloride were evaporated under reduced pressure to give crude acid chloride X of III ; mp 121-4°C, IR : 1757 cm^{-1} ($\nu_{C=O}$). The acid chloride was used in the subsequent experiments without further purification.

Aqueous ammonia (33%, 10 ml) was added to a solution of X (1.0 g) in dioxane (20 ml), and the mixture was allowed to stand for 1 hr at room temperature. After the addition of water, the precipitate was filtered, washed with water and dried. Recrystallization from methanol-water gave 5-nitro-2-(2-carbamoylstyryl)furan (XIa) (0.86 g, 86%) as yellow needles ; mp 198-9°C. The other amides (XIb-XIm) were prepared by the same method as that for XIa using methylamine, ethylamine, n-propylamine, aniline, 4-toluidine, 4-aminophenol, dimethylamine, N-methylaniline, diethylamine, N-ethylaniline, morpholine and piperidine respectively, instead of ammonia. The results are summerized in Table 1.

Ester Derivatives of Carboxystyrylfuran III (XIIa-XIIf). Acid chloride X (1.0 g) was added to methanol (50 ml) and the mixture was refluxed for 1 hr, and allowed to stand for a day. The precipitate was filtered and recrystallized from methanol to give methyl ester (XIIa) of III as yellow prisms ; mp 108-9°C. The IR and NMR spectra of XIIa were the same to those of IV-trans. The other esters XIIb-XIIf were prepared by the same method as that for XIIa using ethanol, 1-propanol, 2-propanol, 1-butanol and 2-methyl-1-propanol respectively, instead of methanol. The results are summerized in Table 2.

Ester Derivatives of Carboxystyrylfuran I (XIVa-XIVh). Esters XIVa-XIVh were prepared using methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, 1-pentanol and 3-methyl-1-butanol respectively as follows : A mixture of the alcohol and the acid chloride XIII of I, which was prepared from I and thionyl chloride, was heated for 1 hr on a water bath and left standing at room temperature for a day. The precipitated product was collected and recrystllized. The results are given in Table 3.

Microbiological Assays. The minimum amount of the compound necessary for the complete inhibition of growth was determined by the dilution method using usual bouillon agar medium (pH 6.8-7.0). The results are summerized in Tables 4 and 5 for the derivatives of III and Table 6 for the derivatives of I.

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References

1) I. Hirao and Y. Kitamura, Nippon Kagaku Zasshi, **85**, 506 (1964).
2) I. Hirao and Y. Kitamura, Nippon Kagaku Zasshi, **86**, 870 (1965).
3) I. Hirao and Y. Kitamura, Bull. Kyushu Inst. Technol., **18**, 27 (1968).
4) T. Matsuda and I. Hirao, Nippon Kagaku Zasshi, **86**, 1195 (1965).
5) T. Fujimoto, H. Matsumoto, T. Morita, and I. Hirao, This Memoirs, **4**, 21 (1974).
6) I. Hirao, T. Fujimoto, T. Morita, F. Tone, and S. Kono, This Memoirs, **5**, 1 (1975).
7) H. Güsten and M. Salzwedel, Tetrahedron, **23**, 173 (1967).
8) H. Güsten and M. Salzwedel, Tetrahedron, **23**, 187 (1967).
9) H. O. House, V. K. Jones, and G. A. Frank, J. Org. Chem., **29**, 3327 (1964).
10) L. D. Bergelson, L. I. Barsukov, and M. M. Shemyakin, Tetrahedron, **23**, 2709 (1967).
11) A. Singh, L. J. Andrews, and R. M. Keefer, J. Amer. Chem. Soc., **84**, 1179 (1962).
12) J. B. Shoesmith, A. C. Hetherington, and R. H. Slator, J. Chem. Soc., 1312 (1924).