# STUDIES ON THE SYNTHESIS OF FURAN COMPOUNDS XXXII.*

## Synthesis of 5-Nitro-2-(3-carboxystyryl)furan and its Derivatives

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Synopsis: The Wittig reaction of 5-nitrofurfural with 3-methoxycarbonylbenzyltriphenylphosphonium salt produces a mixture of cis- and trans-isomers of 5-nitro-2-(3-methoxycarbonylstyryl)furan. The isomers were separated by fractional crystallization of the product. The proportion of the cis-isomer to the trans-isomer is estimated using NMR spectrometry to be from 0.72 to 0.76. The hydrolysis of the methoxycarbonylstyrylfuran produced 5-nitro-2-(3-carboxystyryl)furan. The amides and esters of the carboxystyrylfuran were also prepared. The antibacterial activity of the carboxystyrylfuran and its derivatives was also investigated.

## 1 INTRODUCTION

In previous papers, we have reported the synthesis of 1-(5-nitro-2-furyl)ethylene which was substituted by furyl, thienyl, phenyl and *p*-substituted phenyl at the 2-position of the ethylene moiety[1-3] These derivatives of nitrofuran have shown an excellent antibacterial activity[4]. The antibacterial activity of 5-nitro-2-(4-carboxystyryl)furan and its derivatives have been found to be superior to those of the nitrofurylethylenes. As part of the investigation of the synthesis of furan compounds, it was of interest to synthesize 5-nitro-2-(3-carboxystyryl)furan (I) as an analogue of the 4-carboxystyrylfuran. Furthermore, the effect of the position of the carboxyl group in carboxystyrylfurans on antibacterial activity appears also to be of interest.

In earlier preparations of 4-carboxystyrylfuran, the decarboxylation of 3-(5-nitro-2-furyl)-2-(4-carboxyphenyl)acrylic acid has been employed, and a low yield of styrylfuran was obtained.[1] In general, the Wittig reaction is also favorable for the preparation of 1,2-disubstituted ethylene compounds. The Wittig reaction of 5-nitrofurfural has also been used for the preparation of derivatives of nitrofuran by S. Yoshina et al..[5] Recently, we have reported that a high yield

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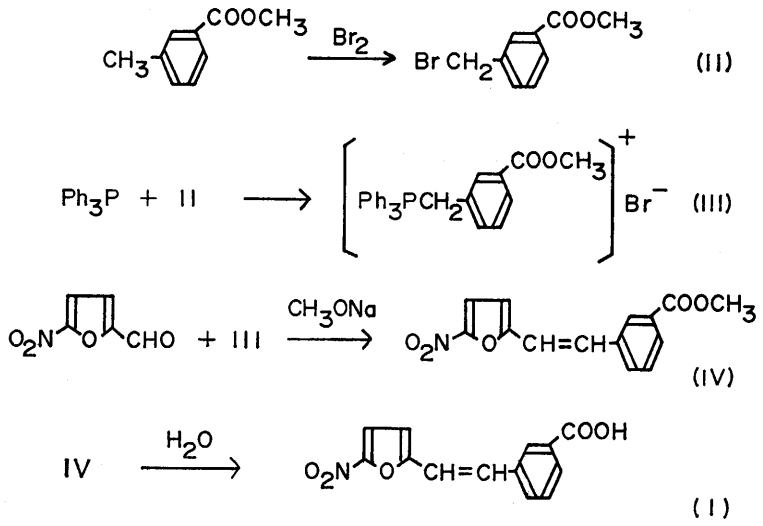
of a mixture of cis- and trans-isomers of 5-nitro-2-(4-methoxycarbonylstyryl)furan was obtained employing the Wittig reaction of 5-nitrofurfural with the corresponding triphenylphosphonium salt.[6] This paper describes the synthesis of 5-nitro-2-(3-carboxystyryl)furan I employing the Wittig reaction of 5-nitrofurfural. Furthermore, the derivatives of I were prepared and the antibacterial activity of these compounds was also investigated.

## 2 RESULTS AND DISCUSSION

*Synthesis of 5-Nitro-2-(3-carboxystyryl)furan I.* The 3-carboxystyrylfuran I was synthesized by hydrolysis of 5-nitro-2-(3-methoxycarbonylstyryl)furan (IV) which was prepared by the Wittig reaction of 5-nitrofurfural with 3-methoxycarbonylbenzyltriphenylphosphonium bromide (III), as shown in Scheme 1.




Scheme 1. Synthesis of carboxystyrylfuran I.

Methyl 3-bromomethylbenzoate (II) was prepared by bromination of methyl *m* toluate. The photochemical bromination of methyl *m*-toluate with bromine has been repored previously.[7] In a paper, methyl *p*-toluate was brominated with bromine in the presence of benzoyl peroxide.[6] In this investigation, the bromination of methyl *m*-toluate with bromine was attempted in the presence of benzoyl peroxide, and bromomethylbenzoate II was obtained in a yield similar to that for photochemical bromination. The bromomethylbenzoate II was refluxed with triphenylphosphine in benzene producing 3-methoxycarbonylbenzyltriphenylphosphonium bromide (III) in a 84 % yield. The phosphonium salt III was recrystallized from dioxane-methanol, and shown to absorb in the IR spectrum at 1720 $cm^{-1}$ ($\nu_{c=o}$) and at 720 and 688 $cm^{-1}$, these bands being assigned to carbon-phosphorus bond.

The phosphonium bromide III was condensed with 5-nitrofurfural in the presence of sodium methoxide to produce the 3-methoxycarbonylstyrylfuran IV in a 85 % yield. The methoxycarbonylstyrylfuran IV, thus produced, was a mixture of the cis- and trans-isomers of IV as indicated by its broad melting point (134–149°C) and by the presence of absorption in the IR spectrum assigned to the C-H out-of-plane deformation of both cis and trans double bonds at 720 and 960 $cm^{-1}$. The cis- and trans-isomers were successfully isolated by fractional crystallization of the mixture from methanol and water. The presence of cis-configuration of the isomer (IV-cis), which melted in the range 91–92°C and was more soluble in methanol, was confirmed by the presence of absorption in the IR spectrum at 720 $cm^{-1}$ ($\delta_{C-H}$, cis), while the trans-isomer (IV-trans), which melted in the range 159–160°C and was less soluble in methanol, absorbed at 960 $cm^{-1}$ ($\delta_{C-H}$, trans) but not at 720 $cm^{-1}$. Furthermore, the configuration of the isomers was supported by NMR spectrometry measurements. The NMR spectra of the isomers are given in Figure 1. Signals of AB type for the ethylenic protons were detected at $\delta$ 6.49 ($H_{\alpha-c}$) and 6.95 ($H_{\beta-c}$) with a coupling constant ($J_{\alpha\beta}$) of 12.8 Hz for IV-cis. While, the signals for IV-trans were detected at $\delta$ 7.01 ($H_{\alpha-t}$) and 7.45 ($H_{\beta-t}$) with a $J_{\alpha\beta}$ of 16.4 Hz. The values

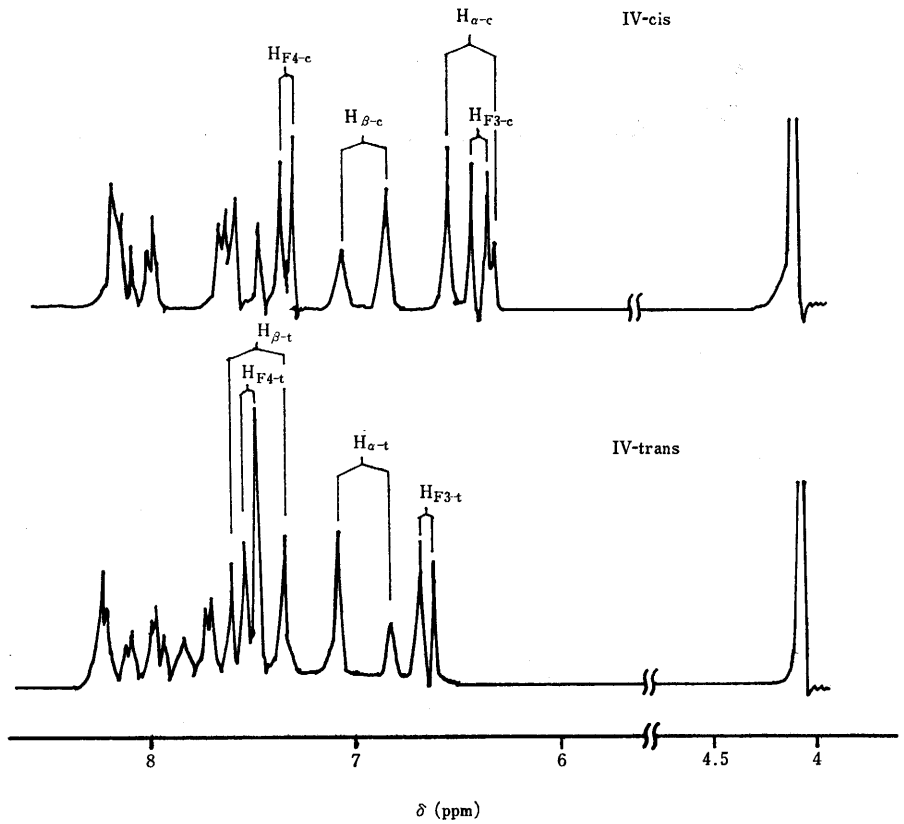



Figure 1. NMR spectra of IV-cis and IV-trans.

of $J_{\alpha\beta}$ for the isomers are in agreement with those of substituted cis- and trans-stil benes.[8,9] The signals due to the protons at the 3- and 4-positions of the furan ring were detected as doublets at $\delta$ 6.42 ($H_{F3-c}$) and 7.36 ($H_{F4-c}$) ($J$=4.0 Hz) for IV-cis and at $\delta$ 6.67 ($H_{F3-t}$) and 7.50 ($H_{F4-t}$) ($J$=4.0 Hz) for IV-trans.

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

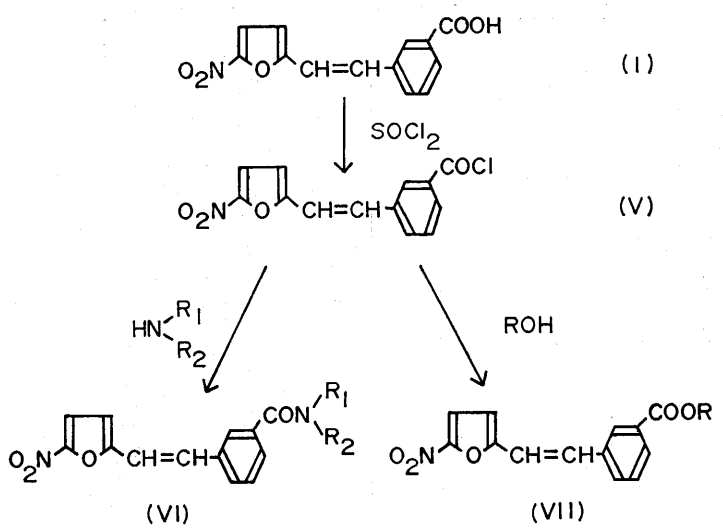
$$\frac{C}{T}=\frac{I_a-I_b}{2I_b-I_a}$$

where $I_a$ is the sum of the intensities of the $H_{F3-c}$, $H_{F3-t}$ and $H_{\alpha-c}$ protons, and $I_b$ represents the sum of the intensities of the $H_{\beta-c}$ and $H_{\alpha-t}$ protons. The proportions of IV-cis and IV-trans in the product obtained were estimated to be 43: 57 (IV-ciss: IV-trans) from the value of C/T (0.72-0.76). The nonstereospecificity in the Wittig reaction of 5-nitofurfural with III was comparable with that of semistabilized ylides in polar solvents.[10,11]

Hydrolysis of a mixture of IV-cis and IV-trans in aqueous dioxane in the presence of sulfuric acid produced 3-carboxystyrylfuran I in a good yield. The carboxystyrylfuran I, thus obtained, was only of trans-form. The trans-configuration was confirmed using IR (958 $cm^{-1}$, $\delta_{C-H}$, trans) and NMR (16.4 Hz of $J_{\alpha\beta}$) spectrometry techniques.

***Synthesis of Amides and Este. of Carboxystyrylfuran I.*** The amides (VIa-VIf) and esters (VIIa-VIIg) of I were synthesized by condensing the acid chloride (V) of I with various amines and alcohols (Scheme 2). The acid chloride V was obtained by refluxing I with thionyl chloride. The prepared amides and esters are summerized in Table 1. All of the derivatives were of trans-form, as indicated by the IR spectra (958-960 $cm^{-1}$).

***Microbiological Assays.*** The antibacterial activities of the compounds prepared in the investigation were examined for ten microorganisms. The results are shown in Table 2. Carboxystyrylfuran I and its amides, especially carbamoylstyrylfuran VIa and N-methyl-carbamoylstyrylfuran VIb, showed strong antibacterial activity against most of the microorganisms employed here. For the esters, methoxycaronyl- (VIIa) and 2-hydroxyethoxycarbonylstyrylfuran (VIIg) showed high activities similar to that of I. The other esters also showed strong activity against Gram-positive bacteria, but not against Gram-negative bacteria. The activities of the amides in decreasing order are: $-CONH_2 > -CONHCH_3 > -CONHC_2H_5 \simeq -CONHCH_2CH_2OH > -CONHC_3H_7(n) > -CON(CH_3)_2$. For the esters, the activity decreased with an increase in chain length of the alcohol moiety. In comparison with the activity of 4-carboxystyrylfuran and its derivatives,[4] the introdutcion of a carboxyl group into the 3-position of the styrylfuran raised slightly its antibacterial activity.




VIa ; $R_1=R_2=H$
VIb ; $R_1=H$, $R_2=CH_3$
VIc ; $R_1=H$, $R_2=C_2H_5$
VId ; $R_1=H$, $R_2=C_3H_7(n)$
VIe ; $R_1=H$, $R_2=CH_2CH_2OH$
VIf ; $R_1=R_2=CH_3$

VIIa ; $R=CH_3$
VIIb ; $R=C_2H_5$
VIIc ; $R=C_3H_7(n)$
VIId ; $R=C_3H_7(i)$
VIIe ; $R=C_4H_9(n)$
VIIf ; $R=C_4H_9(i)$
VIIg ; $R=CH_2CH_2OH$

Scheme 2. Synthesis of derivatives of carboxystyrylfuran I.

## 3 EXPERIMENTAL

All of the melting points are uncorrected. The IR and NMR spectra were obtained with JASCO Model IRA-2 and Japan Electron Optics JNM-C-60HL spectrometers, respectively. The NMR spectra were obtained in trifluoroacetic acid using tetramethylsilane as an internal reference.

*Methyl 3-Bromomethylbenzoate II.* A solution of bromine (160 g, 1.00 mol) in carbon tetrachloride (100 ml) was added drop by drop to a solution of methyl *m*-toluate (150 g, 1.00 mol) and benzoyl peroxide (1.0 g) in carbon tetrachloride (200 ml) under reflux. The mixture was refluxed until the bromine was absorbed completely. The carbon tetrachloride was removed from the reaction mixture by evaporation and the residual oil was distilled in vacuo. II (196 g) wes obtained as a colorless oil in a yield of 86 %; bp 87-8°C/0.15 mmHg (lit. 100-9°C/0.2 mm Hg)[7]. Found: C, 47.40; H, 3.36 %. Calculated for $C_9H_9O_2Br$: C, 47.19; H, 3.29 %.

*3-Methoxycarbonylbenzyltriphenylphosphonium Bromide III.* A solution of II (62.5 g, 0.273 mol) and triphenylphosphine (71.5 g, 0.273 mol) in benzene (250 ml) was refluxed for 1 hr. After cooling, the precipitate was isolated, washed with benzene and dried. Recrystallization from dioxane-methanol (9 : 1) produced 111.9 g (84 %) of III in the form of colorless granules; mp 231-2°C. Found: C, 65.94; H, 4.98 %.

Table 1. Derivatives of carboxystyrylfuran I.

| Compound | Mp (°C) | Yield (%) | Cryst. Form | Analysis (%) (Calcd) | | | IR ($cm^{-1}$)[f] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | | | |
| VIa | 234- 5 | 83 | Brown leaflets[a] | 60.31 (60.46) | 3.93 (3.87) | 10.58 (10.85) | 1650 | 1345 | 960 |
| VIb | 161- 2 | 81 | Orange powder[a] | 61.50 (61.76) | 4.65 (4.41) | 9.86 (10.29) | 1630 | 1350 | 958 |
| VIc | 196- 7 | 84 | Orange needles[b] | 62.69 (62.93) | 4.70 (4.93) | 9.50 (9.78) | 1630 | 1350 | 960 |
| VId | 153- 5 | 72 | Yellow fibers[b] | 64.07 (63.99) | 5.52 (5.37) | 9.09 (9.33) | 1630 | 1355 | 958 |
| VIe | 194- 5 | 73 | Orange needles[b] | 59.80 (59.60) | 4.84 (4.67) | 9.22 (9.27) | 1630 | 1352 | 958 |
| VIf | 114- 5 | 81 | Orange prisms[b] | 62.62 (62.93) | 4.91 (4.89) | 9.44 (9.79) | 1620 | 1345 | 960 |
| VIIa | 159-60 | 81 | Yellow leaflets[b] | 61.60 (61.54) | 3.95 (4.06) | 5.27 (5.13) | 1713 | 1355 | 960 |
| VIIb | 126- 7 | 79 | Yellow needles[c] | 62.72 (62.71) | 4.47 (4.53) | 4.86 (4.87) | 1713 | 1353 | 960 |
| VIIc | 102- 3 | 76 | Yellow leaflets[d] | 63.68 (63.78) | 5.02 (4.98) | 4.40 (4.65) | 1713 | 1355 | 960 |
| VIId | 131- 2 | 72 | Yellow needles[b] | 63.52 (63.78) | 4.95 (4.98) | 4.37 (4.65) | 1713 | 1348 | 960 |
| VIIe | 68- 9 | 65 | Orange needles[b] | 64.66 (64.76) | 5.37 (5.44) | 4.21 (4.44) | 1713 | 1360 | 960 |
| VIIf | 86- 7 | 60 | Yellow powder[b] | 64.78 (64.76) | 5.29 (5.44) | 4.56 (4.44) | 1715 | 1348 | 958 |
| VIIg | 131- 2 | 73 | Yellow leaflets[e] | 59.96 (59.41) | 4.35 (4.32) | 4.90 (4.62) | 1713 | 1350 | 960 |

a) From dioxane. b) From methanol. c) From ethanol. d) From propanol-water. e) From dioxane-water. f) $\nu_{C=O}$, $\nu_{s\,NO_2}$ and $\delta_{C-H}$ trans, respectively.

Calculated for $C_{27}H_{24}O_2PBr$: C, 66.00; H, 4.92%. IR (KBr): 1720 $cm^{-1}$ ($\nu_{C=O}$); 720, 688 $cm^{-1}$ (C-P).

*5-Nitro-2-(3-methoxycarbonylstyryl)furan IV.* A solution of sodium methoxide (5.4 g, 0.10 mol) in methanol (40 ml) was added drop by drop to a solution of III (49.1 g, 0.10 mol) and 5-nitrofurfural (14.1 g, 0.10 mol) in methanol (130 ml) at a temperature below 30°C. After addition, the reaction mixture was stirred for 1 hr at room temperature. After cooling on an ice-water bath, the precipitated mixture of cis- and trans-isomers of IV was filtered, washed with water and dried. The yield of the product was 23.5 g (85.3 %). The product melted between 134 and 149°C. The proportion (C/T) of cis- and trans-isomers in the product was between 0.72 and 0.76 as measured using NMR spectrometry. Fractional crystallization of the product from methanol containing water gave IV-cis (11.0 %), IV-trans (37.4%) and a mixture of the isomers.

IV-cis. Yellow granules, mp 91-2°C. Found: C, 61.84; H, 3.99; N, 5.16 %. Calculated for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13 %. NMR ($\delta$): 6.49 (d, $J_{\alpha\beta} = 12.8$

Table 2. Inhibitory activity of carboxystyrylfuran I and its derivatives on microorganisms.[a)]

| Compound | Di. pneumoniae Dp-1 | Str. haemolyticus Group A 089 | St. aureus 209 P | 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 347 |
|---|---|---|---|---|---|---|---|---|---|---|
| IV | 3.13 | 0.19 | 1.56 | 0.19 | 1.56 | 1.56 | 12.5 | 3.13 | > 25 | > 25 |
| VIa | <0.19 | <0.19 | 0.39 | <0.19 | <0.19 | 1.56 | 0.39 | 0.39 | 1.56 | 6.25 |
| VIb | 0.39 | <0.19 | 0.78 | <0.19 | 0.39 | 6.25 | 1.56 | 0.78 | 6.25 | 6.25 |
| VIc | 0.78 | <0.19 | 0.78 | <0.19 | 1.56 | 6.25 | 3.13 | 3.13 | 12.5 | 12.5 |
| VId | 0.39 | <0.19 | 0.78 | <0.19 | 0.78 | 6.25 | 3.13 | 1.56 | 12.5 | 25 |
| VIe | <0.19 | <0.19 | 0.78 | <0.19 | 0.78 | 3.13 | 3.13 | 1.56 | 6.25 | 25 |
| VIf | > 25 | 3.13 | 3.13 | <0.19 | 6.25 | > 25 | 25 | 6.25 | > 25 | > 25 |
| VIIa | <0.19 | <0.19 | <0.19 | <0.19 | <0.19 | 1.56 | 0.78 | 0.78 | 1.56 | 1.56 |
| VIIb | > 25 | 0.19 | 0.78 | <0.19 | 1.56 | > 25 | > 25 | 12.5 | > 25 | > 25 |
| VIIc | > 25 | 0.39 | 1.56 | <0.19 | > 25 | > 25 | > 25 | 25 | > 25 | > 25 |
| VIId | > 25 | 0.78 | 0.78 | <0.19 | > 25 | > 25 | > 25 | > 25 | > 25 | > 25 |
| VIIe | > 25 | 1.56 | 1.56 | 0.39 | > 25 | > 25 | > 25 | > 25 | > 25 | > 25 |
| VIIf | > 25 | 1.56 | 6.25 | <0.19 | > 25 | > 25 | > 25 | > 25 | > 25 | > 25 |
| VIIg | 0.39 | <0.19 | 0.78 | <0.19 | 1.56 | 6.25 | 3.13 | 1.56 | 6.25 | 6.25 |
| Contrast[b)] | 6.25 | 0.39 | 1.56 | <0.19 | 0.78 | 0.78 | 1.56 | 0.78 | 6.25 | 25 |

a) The activity is represented as the minimum inhibitory concentration ($\mu$g/ml).
b) 3-(5-Nitro-2-furyl)-2-(2-furyl)acrylic amide was employed in the test.

Hz, $H_{\alpha-c}$, 1H); 6.95 (d, $J_{\alpha\beta}$=12.8 Hz, $H_{\beta-c}$, 1H); 6.42 (d, $J$=4.0 Hz, $H_{F3-c}$, 1H); 7.36 (d, $J$=4.0 Hz, $H_{F4-c}$, 1H); 4.05 (s, 3H, $-COOCH_3$). IR ($cm^{-1}$): 1713 ($\nu_{C=O}$); 1357 ($\nu_{s\,NO_2}$); 720 ($\delta_{C-H}$, cis).

IV-trans. Yellow leaflets, mp 159-60°C. Found: C, 61.75; H, 4.04; N, 5.42 %. Calculated for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13 %. NMR ($\delta$): 7.01 (d, $J_{\alpha\beta}$=16.4 Hz, $H_{\alpha-t}$, 1H); 7.45 (d, $J_{\alpha\beta}$=16.4 Hz, $H_{\beta-t}$, 1H); 6.67 (d, $J$=4.0 Hz, $H_{F3-t}$, 1H); 7.50 (d, $J$=4.0 Hz, $H_{F4-t}$, 1H); 4.08 (s, $-COOCH_3$, 3H). IR ($cm^{-1}$): 1713 ($\nu_{C=O}$); 1355 ($\nu_{s\,NO_2}$); 960 ($\delta_{C-H}$, trans).

*5-Nitro-2-(3-carboxystyryl)furan I.* A mixture of IV-cis and IV-trans (7.0 g, 0.026 mol) was added to a solution of 50 wt % sulfuric acid (20 ml) and dioxane (30 ml) and the reaction mixture was heated under reflux for 8 hr. After cooling, the precipitated product was filtered, washed with water and dried. Recrystallization from dioxane-water resulted in 5.71 g (89 %) of I in the form of a yellow powder; mp 284-5°C. Found: C, 60.29; H, 3.54; N, 5.11 %. Calculated for $C_{13}H_9NO_5$: C, 60,23; H, 3.50; N, 5.40 %. IR ($cm^{-1}$): 1693 ($\nu_{C=O}$); 1350 ($\nu_{s\,NO_2}$); 958 ($\delta_{C-H}$, trans). NMR ($\delta$, in DMSO): 7.25 (d, $J_{\alpha\beta}$=16.4 Hz, vinyl $H_\alpha$, 1H); 7.43 (d, $J_{\alpha\beta}$=16.4 Hz, vinyl $H_\beta$, 1H).

*5-Nitro-2-(3-chloroformylstyryly)furan V.* A mixture of I (5.0 g, 0.020 mol), thion-

yl chloride (7.2 g, 0.059 mol), a few drops of *N*, *N*-dimethylformamide and dioxane (50 ml) was heated under reflux for 1 hr. After cooling, the reaction mixture was poured into ice-water with agitation. The solidified product was collected, washed with water and dried in vacuo. Thus, 5.15 g (95 %) of the crude acid chloride V was obtained. The chloride, melted between 144 and 146°C, was used in subsequent experiments without further purification. IR ($cm^{-1}$): 1762 ($\nu_{C=O}$); 1355 ($\nu_{s\,NO_2}$); 960 ($\delta_{C-H}$, trans).

*Amide Derivatives (VIa-VIf) of Carboxystyrylfuran I.* Aqueous ammonia (33 %, 20 ml) was added to a cooled solution of V (2.0 g, 0.0072 mol) in dioxane (20 ml) and the mixture was stirred for 1 hr at room temperature. The resulting mixture was diluted with water. The precipitated product was filtered, washed with water and dried. Recrystallization from dioxane gave 1.54 g (83 %) of 5-nitro-2-(3-carbamoylstyryl)furan (VIa) in the form of brown leaflets; mp 234-5°C. NMR ($\delta$): 7.01 (d, $J_{\alpha\beta}$=16.4 Hz, vinyl $H_\alpha$, 1H); 7.45 (*d*, $J_{\alpha\beta}$=16.4Hz, vinyl $H_\beta$, 1H); 6.67 (d, $J$=4.0 Hz, furan ring $H_{F3}$, 1H); 7.50 (d, $J$=4.0 Hz, furan ring $H_{F4}$, 1H).

The other amides (VIb-VIf) were prepared in a way similar to that for VIa using methylamine, ethylamine, *n*-propylamine, ethanolamine and dimethylamine, respectively (see Table 1).

*Ester Derivatives (VIIa-VIIg) of Carboxystyrylfuran I.* A mixture of V (1.0 g, 0.0036 mol) and methanol (50 ml) was heated for 1 hr under reflux. After standing for a day at room temperature, the precipitated product was filtered and recrystallized from methanol to produce 0.79 g (81 %) of 5-nitro-2-(3-methoxycarbonylstyryl)furan VIIa in the form of yellow leaflets; mp 159-60°C. The IR and NMR spectra of VIIa, thus obtained, were the same as those of IV-trans.

The other esters (VIIb-VIIg) were prepraed in a way similar to that for VIIa using ethanol, *n*-propanol, iso-propanol, *n*-butanol, iso-butanol and ethylene glycol, respectively (see Table 1).

*Microbiological Assays.* The minimum amount of the compound necessary for the complete inhibition of growth was determined by the dilution method using the usual bouillon agar medium (pH 6.8-7.0) (see Table 2).

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