STUDIES ON THE SYNTHESIS OF FURAN COMPOUNDS XXXIV

Synthesis of 5-nitro-2-(hydroxy-carboxystyryl)furan and related compounds*

by

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SYNOPSIS

The Wittig reaction of 5-nitrofurfural with dually substituted benzyltriphenylphosphonium bromides has been investigated. The reaction of 5-nitrofurfural with 3-hydroxy-4-methoxycarbonyltriphenylphosphonium bromide gave a separable mixture of *cis*- and *trans*-isomers of 5-nitro-2-(3-hydroxy-4-methoxycarbonylstyryl)furan in good yield. In the cases of 4-hydroxy-3-methoxycarbonyl- and 2-hydroxy-3-methoxycarbonylstyrylfuran derivatives, the similar reaction gave the corresponding styrylfurans in poor yields (1–4.5%). The use of acetyl protection for the hydroxyl group improved the yield up to 17%. The subsequent hydrolysis of the methoxycarbonylstyrylfuran compound gave 5-nitro-2-(3-hydroxy-4-carboxystyryl)furan, though 2-hydroxy derivative was not obtained by the same method. A number of amide and ester derivatives of 3-hydroxy-4-carboxystyrylfuran were prepared, and the antibacterial activity of the furan compounds was also investigated.

1. INTRODUCTION

A number of nitrofurylethylene derivatives have been synthesized and examined for the antibacterial activity.[1–4] Among them is 5-nitro-2-(4-carboxystyryl)furan which shows an excellent activity against both *Gram*-positive and -negative bacteria.[4] Under the attempt to improve the antibacterial capacity of this type of compound, the substitution of a carboxyl group on the phenyl ring was carried out to *ortho*- or *metha*-position, resulting in the produce of equally good antibacterial compounds.[5,6]

During these synthetic studies, the Wittig reaction has been employed as a key reaction to allow an excellent yield.[4–7] The reaction of 5-nitrofurfural with methoxycarbonylbenzyltriphenylphosphonium salts produced the mixture of *cis*- and *trans*-isomers of 5-nitro-2-methoxycarbonylstyrylfurans. They are separable each other by crystallization and are assigned by NMR.

In the series of the synthetic studies of this type of compounds, it appeared to be of interest to introduce a hydroxyl group on the styrylphenyl moiety. Thus, 5-nitro-2-(hydroxy-carboxystyryl)furan were synthesized. The present paper describes the synthesis of these furan compounds and their amide and ester derivatives. The antibacterial activity of the synthetic compound is also described.

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RESULTS AND DISCUSSION

Synthesis of 5-Nitro-2-(hydroxy-methoxycarbonylstyryl)furans by Wittig Reaction. Figure 1 shows the synthetic route of 5-nitro-2-(hydroxy-carboxystyryl)furans. The precursors, Va–c are the Wittig reaction products from 5-nitrofurfural and hydroxy-methoxycarbonylbenzyltriphenylphosphonium bromides (IVa–c).

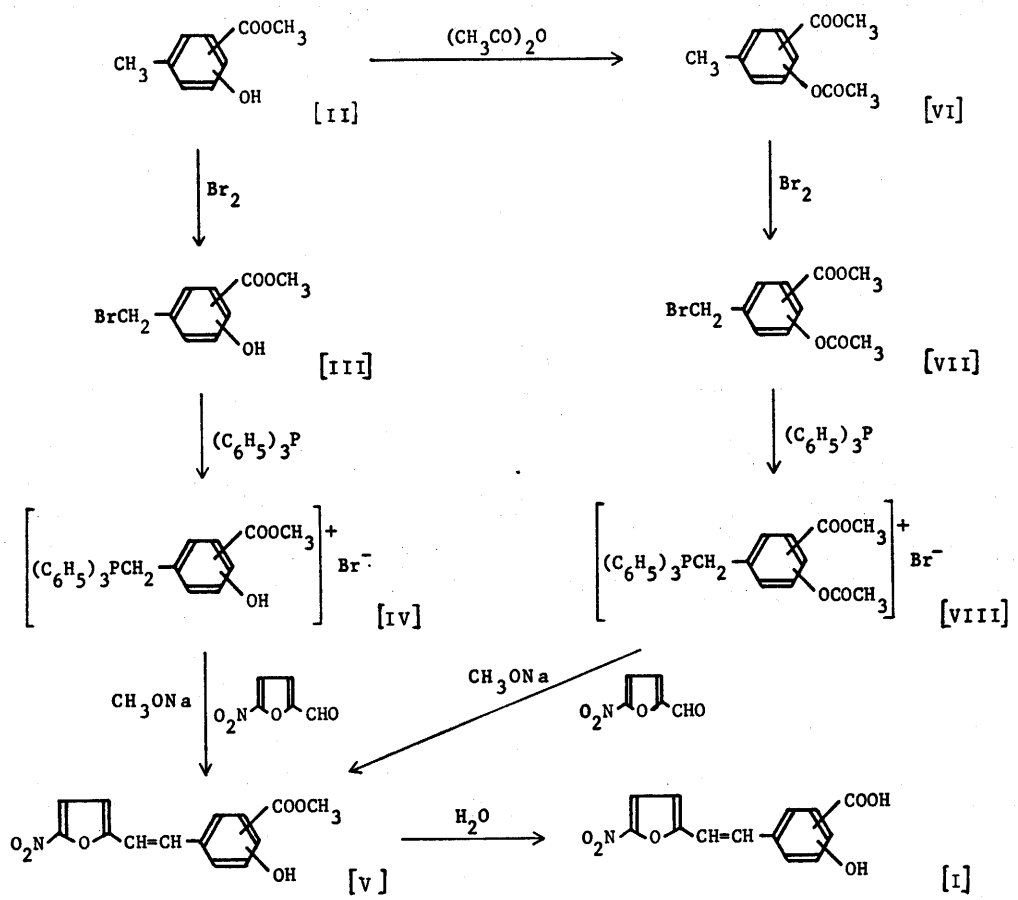

Fig. 1 Synthesis of hydroxy-methoxycarbonylstyrylfurans [V] and hydroxy-carboxystyrylfurans [I].

Methyl 2-hydroxy-4-methylbenzoate (IIa) was prepared from the corresponding benzoic acid and methanol with sulfuric acid. The bromination of IIa was carried out by refluxing the carbon tetrachloride solution in the presence of benzoyl peroxide as described in the literature.[4] The product, methyl 2-hydroxy-4-bromomethylbenzoate (IIIa) was reacted with triphenylphosphine in refluxing benzene to afford 3-hydroxy-4-methoxycarbonyl-benzyltriphenylphosphonium bromide (IVa) in 83% yield.

The Wittig reaction of 5-nitrofurfural with IVa was carried out by the use of twice molar excess of sodium methoxide as base in methanol. The yield of 5-nitro-2-(3-hydroxy-4-methoxycarbonylstyryl)furans (Va) was as good as 88%. The styrylfuran Va showed broad melting point (102–164°C) and IR absorptions at 670 and 960 cm^{-1}, which were assigned to C–H out-of-plane deformation of *cis* and *trans* double bonds, respectively. Thus it appeared that Va was a mixture of *cis*- and *trans*-isomers. The similar results

had been obtained for the Wittig reaction products as described in the previous reports.[4-6]

The isomers, Va–*cis* and Va–*trans* were separated by fractional crystallization of the mixture from dioxane and water. More easily, Va–*trans* could be separated by simple washing with dimethylsulfoxide due to its poor solubility. After separation in this manner, the ratio of Va–*cis* to Va–*trans* was estimated to be 4: 6.

The esterification of 2-hydroxy-5-methylbenzoic acid was followed by bromination and treatment with triphenylphosphine to give the corresponding phosphonium salt (IVb) in the same manner as described above for IVa. The Wittig reaction with 5-nitrofurfural, however, resulted in poor yield of 5-nitro-2-(4-hydroxy-3-methoxycarbonylstyryl)furan (Vb, 4.5%). Vb was obtained as pure Vb–*trans* as found by an IR band at 960 cm^{-1}. The yield of 5-nitro-2-(2-hydroxy-3-methoxycarbonylstyryl)furan (Vc) by the similar Wittig reaction of 5-nitrofurfural and 2-hydroxy-3-methoxycarbonylbenzyltriphenylphosphonium bromide (IVc), which was derived from 2-hydroxy-3-methylbenzoic acid by 3 steps, was poor again (1%).

Since the hydroxyl group was thought to be oxy anion in the present Wittig reaction condition and to reduce the reactivity, the hydroxyl group was protected as acetoxy group. The methylbenzoates (IIa–c) were treated with acetic anhydride to the acetylated compounds VIa–c. Bromination and subsequent treatment with triphenylphosphine gave corresponding phosphonium salts, 3-acetoxy-4-methoxycarbonylbenzyltriphenylphosphonium bromide (VIIIa), 4-acetoxy-3-methoxycarbonylbenzyltriphenylphosphonium bromide (VIIIb), and 2-acetoxy-3-methoxycarbonylbenzyltriphenylphosphonium bromide (VIIIc). Equimolar sodium methoxide was employed for the Wittig reaction of VIIIa–c with 5-nitrofurfural. During the reaction and isolation, the acetyl groups were removed and the hydroxy compounds Va–c were obtained in yields of 93, 17, and 10%. In the cases of the latter two the protection clearly improved the coupling reaction yield, although they are much poorer than the yield of Va, in which hydroxy or acetoxy group is located at the *ortho*- and *para*-positions to the reacting benzyl moiety. One may attribute this to the electron donating capacity of hydroxy oxygen on the benzylphosphonium salt.[8] There seems to be no steric problem for the coupling reaction, for 5-nitro-2-(2-methoxycarbonylstyryl)furan is prepared in good yield.[6]

Synthesis of 5-Nitro-2-(hydroxy-carboxystyryl)furans. The mixture of Va–*cis* and Va–*trans* was hydrolyzed with sulfuric acid in dioxane and water as solvent. 5-Nitro-2-(3-hydroxy-4-carboxystyryl)furan (Ia) was obtained in 83% yield. The product Ia showed a band at 960 cm^{-1} in IR spectrum indicating that Ia has *trans* configuration and Va–*cis* was converted to *trans*-isomer during the hydrolysis reaction.

Vb was similarly hydrolyzed to give 5-nitro-2-(4-hydroxy-3-carboxystyryl)furan (Ib) in 20% yield. However, 5-nitro-2-(2-hydroxy-3-carboxystyryl)furan (Ic) could not be obtained by acid hydrolysis of Vc in various conditions.

Syntheses of 5-Nitro-2-[3-hydroxy-4-(N-substituted carbamoyl)styryl]furans and 5-Nitro-2-(3-hydroxy-4-alkoxycarbonylstyryl)furans. From Ia and thionyl chloride was derived an acid chloride (IX), which was reacted with ethylamine, dimethylamine, and dipropylamine to produce the corresponding amides (Xa–c). The ester derivatives (XIa–f) of Ia was also synthesized from IX with methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, and 2-butanol. The data are summarized in Table 2.

Antibacterial Activity. 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). Most of the compounds synthesized in the present study were effective to *Bacilus subtilis* (0.19 μg/ml), but not to other bacteria tested. Ia was the best antibacterium among them and inhibited the growth of *Streptomyces hem.* (0.19 μg/ml) and *Di. pneumo.* (0.39 μg/ml).

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 Hydroxy-methylbenzoates IIa–c. A solution of 2-hydroxy-4-methylbenzoic acid (152 g) in methanol (260 ml) and concentrated sulfuric acid (50 ml) was refluxed for 8 hr. The reaction mixture was poured into ice water. The product was extracted with carbon tetrachloride. After the removal of the organic solvent, the residual oil was distilled under reduced pressure to afford IIa (142 g, 86%). bp 126–127°C/19 mmHg, lit.[9] 130–132°C/22 mmHg. IR: 1675 cm^{-1} ($\nu_{C=O}$).

The methyl esters of 2-hydroxy-5-methylbenzoic acid and 2-hydroxy-3-methylbenzoic acid were prepared in the same manner: IIb, yield 80%; bp 115–118°C/13 mmHg, lit.[10] 245–247°C; IR: 1670 cm^{-1} ($\nu_{C=O}$). IIc, yield 83%; bp 112–113°C/15 mmHg, lit.[11] 145–146°C/54 mmHg, IR: 1675 cm^{-1} ($\nu_{C=O}$).

Methyl Hydroxy-bromomethylbenzoates IIIa–c. To a refluxing solution of IIa (66.5 g) and benzoyl peroxide (0.5 g) in carbon tetrachloride (150 ml) was added dropwise bromine (64 g) in the same solvent (30 ml). The mixture was refluxed until bromine was completely consumed, then washed with water. The residual oil was remained after the evaporation of the solvent. Distillation gave IIIa (60 g, 61%), bp 100–104°C/0.10 mmHg, IR: 1680 cm^{-1} ($\nu_{C=O}$), 548 cm^{-1} (C–Br). Found: C, 43.96; H, 3.49%. Calcd for $C_9H_9O_3Br$: C, 44.11; H, 3.70%.

Methyl Acetoxy-methylbenzoates VIa–c. The compound IIa (66.5 g) was treated with acetic anhydride (150 ml) and conc. sulfuric acid (2 ml) at 110°C for 2 hr. The product was extracted into ethyl ether from the ice water diluate. Ether was removed, the residual oil being distilled to give VIa (69 g, 83%), bp 92–93°C/0.12 mmHg, lit.[12] 105–107°C/0.10 mmHg, IR: 1772 cm^{-1}, 1728 cm^{-1} ($\nu_{C=O}$).

Acetylation of IIb and IIc was carried out in the similar manner to give VIb, yield 89%, bp 101°C/0.36 mmHg, lit.[12] 124°C/2 mmHg, IR: 1770 cm^{-1}, 1728 cm^{-1} ($\nu_{C=O}$) and VIc, yield 84%, bp 97–98°C/0.22 mmHg, lit.[12] 100–102°C/0.25 mmHg, IR: 1765 cm^{-1}, 1725 cm^{-1} ($\nu_{C=O}$).

Methyl Acetoxy-bromomethylbenzoates VIIa–c. The compounds VIa–c were brominated in the same manner as described for the preparation of IIIa.

VIIa: yield 59%, bp 128–130°C/0.10 mmHg, IR: 1772 cm^{-1}, 1728 cm^{-1} ($\nu_{C=O}$), 610 cm^{-1} (C–Br). Found: C, 46.10; H, 3.82%. Calcd. for $C_{11}H_{11}O_4Br$: C, 46.02; H, 3.86%.

VIIb: yield 70%, bp 111–118°C/0.30 mmHg, NMR $\delta(CCl_4)$, 2.22 (3H, s, CH_3CO–), 3.83 (3H, s, CH_3OCO–), 4.34 (2H, s, $-CH_2Br$), 6.97 (1H, J = 2.25 Hz, $H_{(3)}$), 7.44 (1H, m, $H_{(4)}$), 7.93 (1H, J = 2.25 Hz, $H_{(6)}$).

VIIc: yield 64%, mp 96–98°C, lit.[12] 101°C, IR: 1780 cm^{-1}, 1725 cm^{-1} ($\nu_{C=O}$), 620 cm^{-1} (C–Br).

Phosphonium Salts IVa–c and VIIa–c. To a refluxing solution of IIIa (51.5 g) in benzene (300 ml) was added a solution of triphenylphosphine (56.1 g) in benzene (200 ml), the mixture being refluxed for 1.5 hr. After cooling, the precipitated material was collected, washed with benzene, and dried. White needles (IVa) were obtained in a yield of 87.1 g (83%). mp 207–212°C, IR: 1670 cm^{-1} ($\nu_{C=O}$), 680 cm^{-1} (P–C).

By the similar procedure was obtained IVb, IVc, and VIIIa–c with characteristics as follows.

IVb: yield 97%, mp 174–177°C, IR: 1670 cm^{-1} ($\nu_{C=O}$), 682 cm^{-1} (P–C).

IVc: yield 87%, mp 154–155°C, IR: 1670 cm^{-1} ($\nu_{C=O}$), 682 cm^{-1} (P–C).

VIIIa: yield 78%, mp 123–125°C, IR: 1760 cm^{-1}, 1718 cm^{-1} ($\nu_{C=O}$), 680 cm^{-1} (P–C).
VIIIb: yield 92%, mp 61–68°C, IR: 1765 cm^{-1}, 1725 cm^{-1} ($\nu_{C=O}$), 685 cm^{-1} (P–C).
VIIIc: yield 64%, mp 192–193°C, IR: 1770 cm^{-1}, 1730 cm^{-1} ($\nu_{C=O}$), 685 cm^{-1} (P–C).
These phosphonium salts were used in the next step without further purification.

5-Nitro-2-(hydroxy-methoxycarbonyl-styryl)furans Va–c. To a solution of IVa (50.7 g, 0.10 mol) and 5-nitrofurfural (14.1 g, 0.10 mol) in dry methanol (150 ml) was added sodium methoxide (10.8 g, 0.2 mol) in methanol (40 ml) dropwise at 5°C. The reaction mixture was stirred for an hr at room temperature, and neutralized by the addition of conc. hydrochloric acid (10 ml) below 10°C. The precipitated material was collected, washed with water, and dried. The yield of the yellow powder (Va) was 25.3 g (88%) with mp 102–164°C. IR: 690 cm^{-1} ($\delta_{CH=CH}$, *cis*), 970 cm^{-1} ($\delta_{CH=CH}$, *trans*).

The product Va was separated by the fractional crystallization from dioxane-water to the *cis*-isomer (Va-*cis*, mp 101–102°C) and the *trans*-isomer (Va-*trans*, mp 192–193°C). Otherwise, the mixture Va (5.70 g) was suspended on dimethylsulfoxide (9 times in weight) and stirred for 30 min at room temperature. The insoluble Va-*trans* (2.75 g) was collected by filtration. By adding the filtrate into water, Va-*cis* (1.65 g) was precipitated. Thus simpler separation was achieved using the drastic difference in solubility.

The Wittig reaction of 5-nitrofurfural with IVb and IVc were carried out in the similar manner to afford Vb and Vc in yields of 4.5% and 1%, respectively. The melting points and other data were summarized in Table 1.

Table 1. Analytical Data for Hydroxy-methoxycarbonylstyrylfurans (V) and Hydroxy-carboxystyrylfurans (I)

Compound	mp (°C)	Appearance[a]	Analysis (%)						IR (cm^{-1})		
			Found			Calcd.					
			C	H	N	C	H	N	$\nu_{C=O}$	ν_{sNO_2}	$\delta_{CH=CH}$
Va-*cis*	101–102	yellow fibers	58.24	3.61	4.84	58.13	3.83	4.83	1675	1340	670
Va-*trans*	192–193	yellow needles	57.92	3.91	4.92	58.13	3.83	4.84	1660	1350	960
Vb	189–190	yellow leaflets	58.12	3.96	4.79	58.13	3.83	4.84	1665	1350	960
Vc	163–164	brown needles	58.12	3.72	4.74	58.13	3.83	4.84	1670	1350	958
Ia	276 (dec)	orange powder	56.93	3.42	5.36	56.73	3.30	5.09	1640	1350	960
Ib	236 (dec)	orange powder	56.63	3.34	4.74	56.73	3.30	5.09	1670	1350	950

[a] from dioxane-water

The reaction of 5-nitrofurfural with VIIIa–c were carried out with equimolar amount of sodium methoxide, and gave corresponding styryl compounds Va, Vb, and Vc in the yields of 94.5%, 17% and 11%, respectively.

5-Nitro-2-(hydroxy-carboxystyryl)furan Ia and Ib. The *cis*- and *trans*-mixture, Va was dissolved in dioxane (200 ml) and 50% sulfuric acid (140 ml), the solution being refluxed for 15 hr. After cooling, the reaction mixture was diluted into ice water (500 g). The precipitated material was collected, washed with water, and dried. The recrystallization from dioxane-water gave orange-colored powder (Ia, 15.1 g, 83%), mp 276°C (dec).

The hydrolysis of Vb gave Ib in 20% yield. The analytical date are given in Table 1. The acid hydrolysis of Vc failed in various conditions to give Ic.

5-Nitro-2-[3-hydroxy-4-(N-substituted carbamoyl)styryl]furan Xa–c. To a solution of Ia (14.7 g) in dioxane (50 ml) was added thionyl chloride (100 ml), the mixture being refluxed for 2 hr. The removal of thionyl chloride and dioxane by distillation remained

the corresponding acid chloride (IX). A solution of IX (2.0 g) in dioxane was dropped into a cold solution of ethylamine (70% aqueous, 1.4 g) in dioxane. After stirring at room temperature for 2 hr, water was added to precipitate the product. Recrystallization from the mixture of acetone-water gave 5-nitro-2-[3-hydroxy-4-(N-ethylcarbamoyl)styryl] furan (Xa, 0.89 g, 47%). mp 208–209°C.

Xb and Xc were also prepared using dimethylamine and dipropylamine as reactions to the acid chloride IX. The date are summarized in Table 2.

5-Nitro-2-(hydroxy-alkoxycarbonylstyryl)furans. XIa–f. The acid chloride IX (1.00 g) was dissolved in methanol, and the solution was refluxed for 1 hr. The product, 5-nitro-2-(3-hydroxy-4-methoxycarbonylstyryl)furan (XIa = Va) was precipitated after cooling and recrystallized from dioxane and water (0.77 g, 78%). mp 190–191°C.

Similarly, IX was reacted with ethanol, 1-propanol, 2-propanol, 1-butanol, and 2-butanol to give XIb–f, respectively. The data are given in Table 2.

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Table 2. Analytical Data for Derivatives of Hydroxy-carboxystyrylfuran (Ia)

Compound	R[a]	mp (°C)	Yield (%)	Appearance	Analysis (%) Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N	IR (cm^{-1}) $\nu_{C=O}$	ν_{asNO_2}	$\delta_{CH=CH}$
Xa	$CONHC_2H_5$	208–209	47	yellow needles[d]	60.08	4.55	8.74	59.60	4.67	9.27	1640	1350	958
Xb	$CON(CH_3)_2$	214–215	53	yellow needles[b]	59.06	4.59	8.56	59.60	4.67	9.27	1620	1345	958
Xc	$CON(C_3H_7)_2$ (*n*)	168–169	85	yellow needles[b]	63.14	6.40	7.35	63.67	6.19	7.82	1570	1350	960
XIa	$COOCH_3$	190–191	78	yellow needles[b]	58.38	3.62	4.86	58.13	3.81	4.84	1660	1352	958
XIb	$COOC_2H_5$	148–151	83	yellow leafllets[c]	59.77	4.40	4.29	59.40	4.32	4.62	1663	1352	970
XIc	$COOC_3H_7$ (*n*)	132–133	60	yellow leaflets[c]	60.87	4.55	4.17	60.56	4.77	4.41	1668	1350	960
XId	$COOC_3H_7$ (*iso*)	149–150	66	yellow fibers[c]	60.21	4.64	4.42	60.56	4.77	4.41	1663	1358	960
XIe	$COOC_4H_9$	135–136	55	pale green leaflets[c]	61.23	5.33	4.40	61.23	5.17	4.23	1660	1350	950
XIf	$COOC_4H_9$ (*iso*)	140–143	50	brown yellow leaflets[c]	61.60	5.03	3.79	61.23	5.17	4.23	1665	1354	955

[a] R represents carbamoyl group in X and alkoxycarbonyl group in XI. [b] from dioxane-water. [c] from methanol-water. [d] from acetone-water.

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