of Purdue University is gratefully appreciated.

Registry No. **1b** (acid), 88-45-9; **3b** (acid), 88-21-1; **4b** (Na_2 salt), 94597-19-0; **7b** (acid), 54481-12-8; **8b** (Na_2 salt), 94597-18-9; **2,6-DST** (Na salt), 94597-15-6; **2,6-DST** (Bu_4N salt), 94597-17-8; **4,6-DST** (Na salt), 94597-14-5; **4,6-DST** (Bu_4N^+ salt), 94597-16-7; 2-amino-5-chlorobenzenesulfonic acid, 133-74-4.

Supplementary Material Available: Full electronic absorption and ^1H NMR spectra (470 MHz) for thionine and the 2,6- and 4,6-disulfonated thionines (6 pages). Ordering information is given on any current masthead page.

Selective Cross-Acyloin Condensation Catalyzed by Thiazolium Salt. Formation of 1-Hydroxy 2-Ones from Formaldehyde and Other Aldehydes

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The condensation of formaldehyde with another aldehyde catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine gives selectively 1-hydroxy 2-ones. This selective cross-acyloin condensation indicates an inverse selectivity in the reactions of the conjugate base of thiazolium salt **17** and of the carbanion bound to thiazolium ring **19** toward aldehyde.

Thiamine pyrophosphate (vitamin B_1) is a coenzyme which participates in a number of important biochemical reactions involving formation and breaking of carbon–carbon bonds immediately adjacent to a carbonyl group (acyloins, α-diketones, α-keto acids). Examples include the trans ketol reaction and the decarboxylation of pyruvic acid. The catalytic action of thiamine was found to be due to the thiazolium ring, and catalyses of thiamine or other thiazolium salts in vitro have been studied.[1-17] Among the reactions catalyzed by thiazolium salt, the acyloin condensation, the intermolecular condensation of two molecules of aldehyde to produce an α-hydroxy ketone, is of much interest as a convenient method of carbon–carbon bond formation.

Recently, we found that in the self-condensation of formaldehyde, catalyzed by thiazolium salts, dihydroxyacetone (a triose) was formed selectively and in high yield.[18] It was rather surprising that glycolaldehyde was not detected in the product even in the initial stages of the reaction. The generally accepted mechanism of the acyloin condensation catalyzed by thiazolium salt in the presence of a base ascribes the catalytic role to the conjugate base of the thiazolium ion formed by the deprotonation at the 2-position (Scheme I, **1**).[2] Based on several experimental results, we proposed a mechanism which accounts for the selective formation of dihydroxyacetone (**6**), as described in Scheme I.[19] Of particular interest is that **3** does not cleave off glycolaldehyde (**7**) but, in its isomerized form **4**, exhibits high reactivity toward another molecule of formaldehyde to eventually give a C_3-compound, dihydroxyacetone (**6**).

This suggests that the reactivity of carbanions located at the position immediately adjacent to the thiazolium ring, such as **2** and **4**, are much dependent on their structures. To test this idea the reaction of a mixture of formaldehyde and another aldehyde catalyzed by 3-ethylbenzothiazolium bromide was examined.

In general, cross-acyloin condensation of two different aldehydes gives four different products, two symmetric (Scheme II, **8**, **9**) and two dissymmetric (**10**, **11**). In the reaction involving formaldehyde, the formation of three other products (Scheme III, **6**, **15**, **16**) is also expected by the participation of carbanion such as **4**.

Quite surprisingly, however, we found that the condensation of formaldehyde with another aldehyde catalyzed by 3-ethylbenzothiazolium bromide gave one product, 1-hydroxy 2-one **14**, almost exclusively. It should be noted particularly that dihydroxyacetone was not the main product in the presence of another aldehyde.

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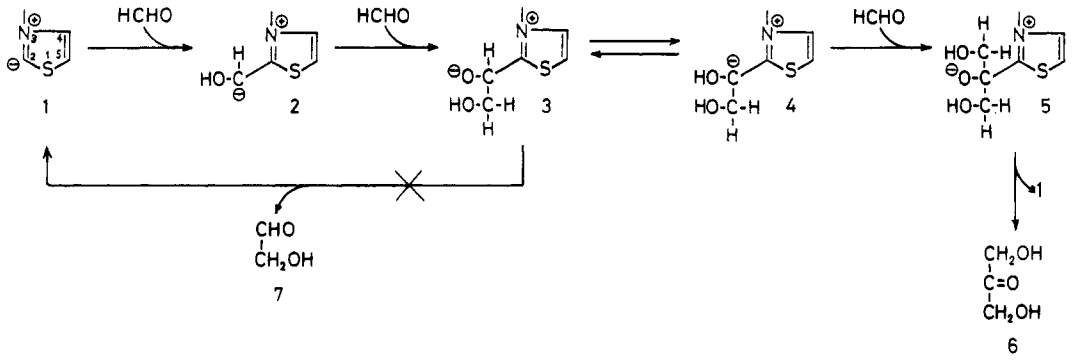
Scheme I



Scheme II

$$^{1}RCHO + {}^{2}RCHO \rightarrow \underset{\mathbf{8}}{{}^{1}RCOCH(OH)^{1}R} + \underset{\mathbf{9}}{{}^{2}RCOCH(OH)^{2}R} + \underset{\mathbf{10}}{{}^{1}RCOCH(OH)^{2}R} + \underset{\mathbf{11}}{{}^{2}RCOCH(OH)^{1}R}$$

Scheme III

$$HCHO + RCHO \rightarrow \underset{\mathbf{7}}{HCOCH_2OH} + \underset{\mathbf{12}}{RCOCH(OH)R} + \underset{\mathbf{13}}{HCOCH(OH)R} + \underset{\mathbf{14}}{RCOCH_2OH} + \underset{\mathbf{6}}{HOCH_2COCH_2OH} + \underset{\mathbf{15}}{RCH(OH)COCH_2OH} + \underset{\mathbf{16}}{RCH(OH)COCH(OH)R}$$

As to the cross-acyloin condensations so far reported, Stetter et al.[7d] found that 5-(2-hydroxyethyl)-3,4-dimethyl-1,3-thiazolium iodide catalyzed the acyloin condensation of dissimilar aldehydes to give mixtures, in most cases, of the two possible dissymmetric acyloins (**10**, **11**). In a few cases, where an excess of aromatic aldehyde (e.g., *o*-chlorobenzaldehyde) or of heterocyclic aldehyde (e.g., furfural) to aliphatic aldehyde (e.g., isobutyraldehyde) was employed, one of the dissymmetric acyloins was obtained predominantly and the symmetric acyloins were the minor products. In the reaction of two different aliphatic aldehydes the yield was poor.

Although 1-hydroxy 2-one can be an important intermediate in organic synthesis with a keto and a hydroxyl group, it has so far been synthesized from limited types of diols such as 1,2-butanediol by partial oxidation with expensive palladium catalyst.[20] Therefore, the present reaction affords a facile method for the synthesis of 1-hydroxy 2-one. The selectivity observed is of much importance for the elucidation of the reactivities of the aldehyde and the thiazolium salt.

Results and Discussion

Reaction of Formaldehyde and Benzaldehyde. The reaction of formaldehyde (as paraformaldehyde) and benzaldehyde catalyzed by 3-ethylbenzothiazolium bromide or 3-ethylthiazolium bromide in the presence of triethylamine was examined in ethanol or dioxane at 60 °C for 1 day. In the gas–liquid chromatogram of the Me_3Si–oxime derivative of the product prepared in ethanol by using 3-ethylbenzothiazolium bromide as catalyst in the presence of triethylamine, where formaldehyde was consumed almost completely in a day at 60 °C, almost no other peaks other than the peak corresponding to 2-hydroxyacetophenone were observed.[21] On the other hand, when the reaction catalyzed by 3-ethylthiazolium bromide was carried out in dioxane, the peaks corresponding to dihydroxyacetone, 2-hydroxyacetophenone, and benzoin were observed in comparable strengths. The peak corresponding to 2-hydroxy-2-phenylethanal was not detected at all at any stage of the reaction. The gas–liquid chromatographic pattern of the Me_3Si–oxime derivative of the product prepared by using 3-benzylthiazolium bromide as catalyst was similar to that prepared by using 3-ethylthiazolium bromide.

Neither sodium cyanide[22-24] nor imidazolium salt[1b] (1,3-dimethylimidazolium iodide prepared from 1-methylimidazole and methyl iodide[25]) in the presence of triethylamine, known as efficient catalysts for benzoin condensation, was found to be effective in the condensation of formaldehyde with benzaldehyde. The reaction with 3-ethylbenzothiazolium bromide in ethanol at 60 °C proceeded in the presence of a wide variety of bases such as tertiary amine, quaternary ammonium hydroxide, sodium alcoholate, sodium acetate, and sodium hydroxide. Especially, the selectivity in the formation of 2-hydroxyacetophenone was very high when a tertiary amine with high basicity, such as triethylamine, was used. The reaction catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine at 60 °C proceeded in various solvents except for water. Alcohols were most effective with respect to the reactivity and the selectivity. In the reaction at 60, 80, or 100 °C for 1 h, higher temperatures

Table I. Synthesis of 1-Hydroxy 2-Ones ($RCOCH_2OH$) from Formaldehyde and the Corresponding Aldehydes (RCHO) with 3-Ethylbenzothiazolium Bromide as Catalyst[a]

aldehyde R	HCHO convern, %	selectivity in $RCOCH_2OH$, %
methyl	76	100
ethyl	74	89
n-propyl	93	73
isopropyl	100	100
cyclohexyl	94	64
phenyl	96	100
2-furyl	88	81

[a] Paraformaldehyde, 5 mmol (as HCHO); aldehyde, 5 mmol; 3-ethylbenzothiazolium bromide, 0.5 mmol; triethylamine, 0.5 mmol; ethanol, 5 mL; 60 °C, 24 h.

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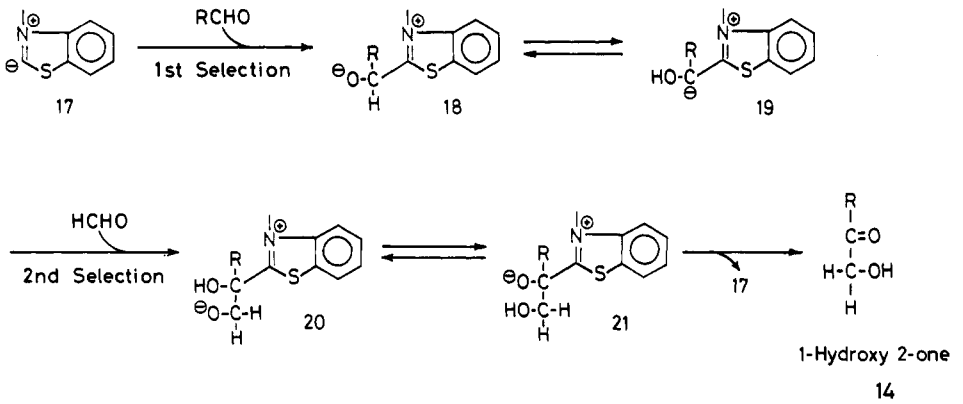
Scheme IV



reduced the selectivity from 94% to 75%, although the reaction proceeded more rapidly. In the reaction catalyzed by 3-ethylbenzothiazolium bromide in ethanol at 65 °C, formaldehyde was consumed almost completely in a day and the selectivity in the formation of 2-hydroxyacetophenone remained high throughout the reaction.

Reaction of Formaldehyde and Various Aldehydes. Based on the above results, the condensation reactions of formaldehyde with a variety of aldehydes were examined by using 3-ethylbenzothiazolium bromide as catalyst in the presence of triethylamine in ethanol at 60 °C for a day. The gas-liquid chromatogram of the Me_3Si–oxime derivative of the products obtained in the reaction of formaldehyde with acetaldehyde revealed that 1-hydroxy-2-propanone was formed selectively. Under the same conditions, the reaction between formaldehyde and furfural gave not only 2-hydroxy-1-(2-furyl)ethanone, the major product, but also minor products such as dihydroxyacetone and furoin.

The selectivity in the formation of 1-hydroxy 2-one was evaluated by the molar ratio of its amount estimated from the GLC peak area of the Me_3Si–oxime derivative to that of the reacted formaldehyde and is summarized in Table I. The selectivity was generally high in the reactions of formaldehyde with a variety of aldehydes. The reaction between formaldehyde and acetaldehyde, isobutyraldehyde, or benzaldehyde was found to give selectively 1-hydroxy-2-propanone, 1-hydroxy-3-methyl-2-butanone, or 2-hydroxyacetophenone, respectively.

Mechanism. In view of the selectivity observed to form 1-hydroxy 2-one from formaldehyde and another aldehyde, there should be considered an "inverse" selectivity in the reactions of the conjugate base of thiazolium ion (**17**, in Scheme IV) and of the carbanion directly bound to the C-2 carbon of thiazolium ring (**19**) toward aldehyde.

The conjugate base (**17**), formed by the abstraction of a proton at the C-2 position of thiazolium ion by a base, attacks selectively the carbonyl carbon of aldehyde other than formaldehyde, but not the latter, to produce **18** (first selection). In contrast, carbanion **19**, formed by the isomerization of **18** and resonance stabilized by virtue of the thiazolium ring, reacts preferentially with formaldehyde but not the other aldehyde to afford **20** (second selection). Finally, 1-hydroxy 2-one is cleaved off from **20**, via **21**, to regenerate **17**. The possible formation of 1-hydroxy 2-one **14** by the base-catalyzed isomerization of 2-hydroxyaldehyde (**13**) initially formed may be excluded by the fact that glyceraldehyde does not isomerize to dihydroxyacetone in the presence of thiazolium salt and triethylamine.[19]

The first selection is probably due to the difference in the stability between anions **19** with different R groups. Anion **19** formed from aldehyde other than formaldehyde is considered more stabilized by virtue of the alkyl or phenyl group on the carbanion than that formed from formaldehyde. On the other hand, in the step corresponding to the second selection, it is of much interest to note that the difference in electrophilicity between two aldehydes plays a decisive role in determining the selectivity; it is well-known that formaldehyde has a higher electrophilicity than aldehyde with alkyl or phenyl group.[26] In the intermediate product of this step, alkoxide anion **20** or **21**, the substituent group of aldehyde may not directly affect the stability. The possible low equilibrium concentration of free formaldehyde in the solvents examined may play some role in the selectivity observed.

Experimental Section

Materials. Ethanol was dried with CaO, refluxed with CaH_2, and then fractionally distilled. Dioxane was purified according to the reported procedure.[27] Triethylamine and pyridine were refluxed with CaH_2 and fractionally distilled. Ethyl bromide was refluxed with P_2O_5 and then fractionally distilled. Thiazole, benzothiazole, trimethylchlorosilane, and hexamethyldisilazane were purified by fractional distillation. Acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, and cyclohexanecarboxaldehyde were dried with $CaSO_4$ and then fractionally distilled in nitrogen. Benzaldehyde was washed with aqueous Na_2CO_3 solution, followed by drying with $CaSO_4$, and then fractionally distilled in nitrogen under reduced pressure. Furfural was distilled twice over Na_2CO_3 and then purified by fractional distillation in nitrogen under reduced pressure. Paraformaldehyde was of commercial grade. 3-Ethylbenzothiazolium bromide and 3-ethylthiazolium bromide were synthesized as described in the previous paper.[19]

Condensation Reaction. In a 10-mL flask were placed paraformaldehyde (0.15 g, 5 mmol), thiazolium salt (0.5 mmol), aldehyde (5 mmol), solvent (5 mL), and then triethylamine (0.07 mL, 0.5 mmol), and dry nitrogen was bubbled into the mixture. Then the flask was tightly closed with a glass stopper. The reaction was started by immersing the flask in an oil bath adjusted to the required temperature with stirring magnetically. After the prescribed time the reaction was quenched by immersing the flask in solid CO_2–ethanol. The amount of formaldehyde was determined colorimetrically with chromotropic acid.[28] An aliquot (0.5 mL) of the reaction mixture was allowed to react with hydroxylamine hydrochloride (0.1 g) in pyridine (8 mL) at 70 °C for 1 h, followed by trimethylsilylation by adding 2 mL of a mixture of hexamethyldisilazane and trimethylchlorosilane (2:1 in volume).[21] The solution containing the trimethylsilylated (Me_3Si)

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oxime derivative of the product was subjected to gas–liquid chromatography (GLC) under the following conditions: glass capillary column of 30 m × 0.28 mm id; adsorber, silicone SF-96; column temperature, 100–200 °C, rising at a rate of 3 °C min^{-1}. The amount of the main product was estimated by the use of GLC by comparing the peak area of the Me_3Si–oxime derivative of the main product with that of the authentic compound, using hexamethylbenzene as internal standard. The selectivity in the formation of the main product was evaluated by the molar ratio of its amount to that of the reacted formaldehyde.

Isolation of the Main Product. General Procedure. A mixture of paraformaldehyde (1.5 g, 50 mmol) and another aldehyde (50 mmol) was heated with 3-ethylbenzothiazolium bromide (1.22 g, 5 mmol) as catalyst in the presence of triethylamine (0.7 mL, 5 mmol) in ethanol or dioxane (50 mL), with stirring magnetically at 60 or 100 °C for 1–4 days.

The main product was isolated, in most cases, by fractional distillation under reduced pressure.

2-Hydroxyacetophenone. Benzaldehyde (5 g) was allowed to react with paraformaldehyde in ethanol at 60 °C for a day. The reaction mixture was evaporated, and then a mixture of ether (160 mL) and petroleum ether (40 mL) was added. After the resulting precipitate was removed by filtration, petroleum ether (120 mL) was added to the filtrate and then the mixture was kept standing overnight in a refrigerator. The white precipitate was filtered and washed with a small amount of cold ether, followed by drying in vacuo to give crude crystals. Repeated recrystallization from ether–petroleum ether gave white crystals (1.0 g, 17%): mp 87–89 °C (ether–petroleum ether) (lit.[29] mp 86–87 °C (water)); ^1H NMR ($CDCl_3$) δ 3.53 (1 H, OH), 4.89 (2 H, CH_2), 7.53 (2 H, *m*-position of benzene ring), 7.64 (1 H, *p*-position), 7.94 (2 H, *o*-position); ^{13}C NMR ($CDCl_3$) δ 65.4 (t, J = 143 Hz, CH_2OH), 127.7 (d, J = 162 Hz, C-2 and C-6 position of benzene ring), 128.9 (d, J = 162 Hz, C-3 and C-5), 133.4 (s, C-1), 134.2 (d, J = 165 Hz, C-4), 198.4 (s, C=O); IR (KBr) cm^{-1} 3500–3200 (broad, OH), 1680 (C=O), 1450, 1405, 1230, 1100, 755, 745, 690.

1-Hydroxy-2-propanone. The reaction mixture prepared by allowing acetaldehyde (2.2 g) to react with paraformaldehyde in dioxane at 60 °C for 4 days was concentrated by evaporation to give dark red liquid. Upon fractional distillation of the residue a colorless fraction (0.5 mL) boiling at 50 °C (20 mmHg) was obtained (lit.[30] bp 44–45 °C (15 mmHg)). ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H, CH_3), 3.71 (s, 1 H, OH), 4.27 (s, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 25.3 (q, J = 128 Hz, CH_3), 67.1 (t, J = 142 Hz, CH_2), 207.8 (s, C=O); IR (thin film) cm^{-1} 3550–3100 (broad, OH), 2980, 2900, 1720 (C=O), 1570, 1410, 1350, 1185, 1080.

1-Hydroxy-2-butanone. The reaction mixture obtained by allowing propionaldehyde (2.9 g) to react with paraformaldehyde in ethanol at 60 °C for 2 days was concentrated by evaporation to give dark red liquid. Upon fractional distillation of the residue a colorless fraction (0.5–1.0 mL) boiling at 30.5 °C (3 mmHg) was obtained (lit.[31] bp 56–57 °C (22 mmHg)). ^1H NMR ($CDCl_3$) δ 1.16 (t, 3 H, CH_3), 2.45 (q, 2 H, CH_2Me), 3.55 (s, OH), 4.25 (s, 2 H, CH_2OH), $J_{3,4}$ = 7.3 Hz; ^{13}C NMR (CD_3OD) δ 6.7 (q, J = 132 Hz, CH_3), 31.1 (t, J = 124 Hz, CH_2), 67.4 (t, J = 141 Hz, CH_2OH), 211.9 (s, C=O); IR (thin film) cm^{-1} 3650–3100 (broad, OH), 2970, 2930, 2880, 1720 (C=O), 1455, 1405, 1375, 1090, 1020, 970.

1-Hydroxy-2-pentanone. Butyraldehyde (3.6 g) was allowed to react with paraformaldehyde in dioxane at 100 °C for 2 days. The solvent was removed by evaporation, and then a colorless fraction (0.5 mL) boiling at 70 °C (20 mmHg) was obtained upon fractional distillation of the residue. ^{13}C NMR ($CDCl_3$) δ 13.8 (q, J = 128 Hz, C-5), 17.3 (t, J = 126 Hz, C-4), 40.2 (t, J = 124 Hz, C-3), 68.2 (t, J = 142 Hz, C-1), 210.8 (s, C-2); IR (thin film) cm^{-1} 3600–3100 (broad, OH), 2960, 2930, 2870, 1720 (C=O), 1460, 1405, 1380, 1100, 1020.

1-Hydroxy-3-methyl-2-butanone. Isobutyraldehyde (3.6 g) was allowed to react with paraformaldehyde in dioxane at 100 °C for 2 days. The mixture was concentrated by evaporation to give a brown liquid. Upon fractional distillation of the concentrate a colorless liquid (0.3 mL) boiling at 65 °C (20 mmHg) was obtained (lit.[32] bp 189.60 °C (760 mmHg)). ^1H NMR (CD_3OD) δ 1.16 (d, 6 H, $(CH_3)_2$), 1.20 (q, 1 H, $CHMe_2$), 4.32 (s, 2 H, CH_2), $J_{3,4}$ = 6.7 Hz; ^{13}C NMR ($CDCl_3$) δ 18.0 (q, J = 128 Hz, $(CH_3)_2$), 37.2 (d, J = 127 Hz, CH), 66.2 (t, J = 143 Hz, CH_2OH), 213.7 (s, C=O); IR (thin film) cm^{-1} 3650–3150 (broad, OH), 2980, 2940, 2880, 1720 (C=O), 1470, 1390, 1230, 1100, 1020.

2-Hydroxy-1-cyclohexylethanone. Cyclohexanecarboxaldehyde (5.6 g) was allowed to react with paraformaldehyde in dioxane at 100 °C for 2 days. The solvent was removed from the reaction mixture by evaporation to give dark reddish brown liquid, and then upon fractional distillation of the liquid a brown fraction (5 mL) boiling at about 100 °C (10–20 mmHg) was obtained, which was found to contain the product and unreacted cyclohexanecarboxaldehyde by gas–liquid chromatography. This fraction was placed on the top of a column of 30 cm × 1 cm od packed with silica gel and was developed with 100 mL of hexane and then 100 mL of methanol. The eluted solution was fractionated, and the content of the product in each fraction was monitored by gas–liquid chromatography. The fractions containing the product, which were eluted with methanol, were collected and the solvent was removed by evaporation to give colorless liquid (0.5 mL). ^1H NMR ($CDCl_3$) δ 1.29 (m, 4 H, 3- and 5-positions of cyclohexane ring), 1.41 (m, 2 H, 4-position), 1.82 (m, 4 H, 2 and 6-positions), 2.39 (m, 1 H, 1-position), 4.30 (s, 2 H, CH_2); ^{13}C NMR (CD_3OD) δ 25.5 (t, J = 126 Hz, C-3 and 5 of cyclohexane ring), 25.8 (t, J = 126 Hz, C-4), 28.3 (t, J = 130 Hz, C-2 and 6), 46.6 (d, J = 116 Hz, C-1), 66.3 (t, J = 140 Hz, CH_2OH), 213.6 (s, C=O); IR (thin film) cm^{-1} 3600–3100 (broad, OH), 2920, 2850, 1710 (C=O), 1450, 1110, 1075, 1055, 990.

2-Hydroxy-1-(2-furyl)ethanone. Furfural (4.8 g) was allowed to react with paraformaldehyde in ethanol at 60 °C for a day. The solvent and unreacted furfural were removed from the reaction mixture by evaporation at room temperature. The oily dark brown residue gave a pale yellow solid by sublimation at 80 °C (3 mmHg). The solid was purified by two further sublimations and then by two recrystallizations from ether to give white needles (0.4 g, 6%): mp 84–86 °C (ether); ^1H NMR ($CDCl_3$) δ 3.43 (broad s, 1 H, OH), 4.75 (s, 2 H, CH_2), 6.61 (dd, 1 H, 4-position of furan ring), 7.31 (d, 1 H, 3-position), 7.64 (d, 1 H, 5-position), $J_{3,4}$ = 3.66 Hz, $J_{4,5}$ = 1.83 Hz, $J_{3,5}$ = 0.00 Hz; ^{13}C NMR ($CDCl_3$) δ 65.2 (t, J = 144 Hz, CH_2), 112.6 (d, J = 179 Hz, C-4 of furan ring), 147.2 (d, J = 203 Hz, C-5), 150.3 (s, C-2), 187.9 (s, C=O); IR (KBr) cm^{-1} 3500–3200 (broad, OH), 3120, 3110, 1680 (C=O), 1560, 1470, 1420, 1270, 1165, 1110, 1025, 980, 910, 875.

Measurements. The gas–liquid chromatogram was taken on an Ohkura Model-103 chromatograph equipped with a flame-ionization detector. UV and IR spectra were measured on a JASCO UVIDEC-1 spectrophotometer and a HITACHI 260-30 infrared spectrophotometer, respectively. The ^1H NMR spectrum was taken on a JEOL 400-MHz high-resolution nuclear magnetic resonance spectrometer Model JNM-GX-400 in $CDCl_3$ containing 1 wt-% tetramethylsilane at room temperature. The ^{13}C NMR spectrum was observed in CD_3OD or $CDCl_3$ at room temperature using a JEOL 25-MHz high-resolution nuclear magnetic resonance spectrometer Model JNM-PEF-100. Multiplicities and C-H coupling constants were based on a proton gated-decoupled spectrum.

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