Selective Formation of Triose from Formaldehyde Catalyzed by Thiazolium Salt[1]

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Abstract: In the self-condensation of formaldehyde catalyzed by thiazolium salts, dihydroxyacetone (triose), but not glycolaldehyde, was formed selectively and in high yield. This is of much interest as a facile and novel synthesis of triose from this C_1 compound. A mechanism which can account for the selective formation of dihydroxyacetone is described.

Formaldehyde undergoes a condensation reaction in the presence of bases to give a mixture of carbohydrates and their analogues (so-called formose reaction). This reaction has recently caught increasing attention because of its possible importance in the manufacture of edible carbohydrates from a simple material and because of its possible role in the prebiotic synthesis of carbohydrates.[2-5] However, formose reactions catalyzed by inorganic bases (e.g., calcium hydroxide) in aqueous solution generally have a complex nature, as seen from the large number of products (often over 30), some of which are due to the Cannizzaro reaction which proceeds simultaneously. It is, thus, highly desirable to develop a selective formose reaction which yields a specific product in high yield. Although there have been some examples reported so far,[1,4,6,7] the selectively formed products are compounds with branched carbon chains.

It has been considered that the reaction catalyzed by calcium hydroxide starts with the acyloin condensation of two molecules of formaldehyde, thus producing glycolaldehyde. This is followed by successive aldol condensations to give various hydroxy aldehydes and hydroxy ketones with linear or branched structures. The reaction is also accompanied by the interconversion of hydroxy aldehyde and hydroxy ketone forms via ene–diol intermediates and by the cross-Cannizzaro reaction between hydroxy aldehydes or hydroxy ketones and formaldehyde which produces polyols and formic acid.

In our studies on the formose reaction with organic bases, such as a tertiary amine, as catalyst,[1,7,8] it was found that the reaction required the addition of a 1,2-oxy–oxo compound, such as a monosaccharide, and it gave 2-*C*-(hydroxymethyl)glycerol selectively. The fact that the reaction catalyzed by a tertiary amine does not occur at all without an additive indicates that formaldehyde does not undergo the acyloin condensation, to form glycolaldehyde, using a tertiary amine. If glycolaldehyde, a 1,2-oxy–oxo compound, were formed, it should have played the role of an "additive" for the reaction. This finding prompted us to examine the formose reaction with thiazolium salts as acyloin condensation catalyst. In this connection, Castells and co-workers reported the formose ("formoin") reaction in dimethylformamide catalyzed by thiamin or 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride in the presence of triethylamine.[9] However, the selectivity was rather low judging from the complexity of the gas–liquid chromatogram pattern of the products. On the other hand, in our recent study on the reaction in alcohol catalyzed by 3-ethylbenzothiazolium bromide in the presence of a base,[10] we have found that dihydroxyacetone (triose) was obtained with high selectivity. Furthermore, it was quite unexpected and surprising that glycolaldehyde was not detected in the reaction mixture.

The present paper describes in further detail this novel and interesting reaction which yields triose (a C_3 compound) from formaldehyde (C_1). This provides a simple procedure to obtain dihydroxyacetone, which is currently produced from glycerol by microbial dehydrogenation. A mechanism which accounts for the selective formation of dihydroxyacetone is also discussed.

Table I. Reaction of Formaldehyde Catalyzed by Various Thiazolium Salts[a]

catalyst	HCHO consumption, % 5 min	HCHO consumption, % 1 h	selectivity in dihydroxyacetone, % 5 min	selectivity in dihydroxyacetone, % 1 h
3-ethylthiazolium bromide	90	98	50	30
3-methylbenzothiazolium iodide	18	87	95	59
3-ethylbenzothiazolium bromide	40	98	90	70
3-ethylbenzothiazolium iodide	46	96	80	63
3-isopropylbenzothiazolium bromide	42	98	88	53
thiamin hydrochloride[b]	45	*c*	57	*c*

[a] HCHO, 60 mmol; catalyst, 3 mmol; triethylamine, 3 mmol; ethanol, 10 mL; 100 °C. [b] Triethylamine, 6 mmol. [c] Not determined.

Results and Discussion

Product of Reaction. In the reaction of formaldehyde (as paraformaldehyde) catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine in ethanol at 100 °C, the consumption of formaldehyde was 40% after 5 min. The gas–liquid chromatogram of the trimethylsilylated oxime derivative of the product was surprisingly simple. Upon chromatography of the product on cellulose powder, the main product was isolated and identified as dihydroxyacetone by the direct comparison of its ^1H and ^{13}C NMR spectra with those of the authentic compound. The trimethylsilylated oxime derivative of this isolated product also had IR, ^1H NMR, and ^{13}C NMR spectra and a GLC retention time which agreed with those of the derivative prepared from the authentic compound. From the area of the peak in the gas–liquid chromatogram, the amount of dihydroxyacetone formed was estimated to be 90 wt % of the reacted formaldehyde. Glycolaldehyde was not detected in the product mixture, contrary to our expectations.

Catalysis by Various Thiazolium Salts. Table I shows the consumption of formaldehyde and the selectivity in the formation of dihydroxyacetone in the reaction with various thiazolium salts. The selectivity was evaluated by measuring the ratio of the amount of dihydroxyacetone, as estimated from the GLC peak of the trimethylsilylated oxime derivative, to that of the reacted form-

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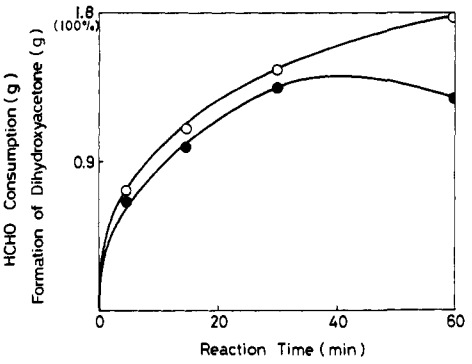
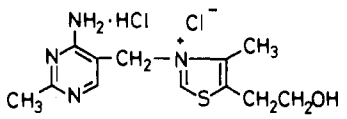


Figure 1. Reaction of formaldehyde catalyzed by 3-ethylbenzothiazolium bromide. The consumption of HCHO and the formation of dihydroxyacetone in grams vs. reaction time: (○) HCHO consumption; (●) formation of dihydroxyacetone. HCHO, 60 mmol; catalyst, 3 mmol; triethylamine, 3 mmol; ethanol, 10 mL; 100 °C.

aldehyde. In the 5-min reaction the selectivity was very high with 3-methylbenzothiazolium iodide, 3-ethylbenzothiazolium bromide, and 3-isopropylbenzothiazolium bromide as catalysts. Although 3-ethylthiazolium bromide exhibited high catalytic activity, the selectivity was lower. As seen in Table I, the catalytic activity and the selectivity were not very sensitive to steric bulk of the N-substituent of the benzothiazolium salt. The effect of the counterion was also small. Thiamin hydrochloride exhibited high



Thiamin Hydrochloride

activity, but the selectivity was not so high. Sodium cyanide, known as an efficient catalyst for the acyloin condensation,[11] was found to be ineffective in the formaldehyde condensation.

Reaction Using the 3-Ethylbenzothiazolium Bromide–Triethylamine System. In the reaction catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine in ethanol at 100 °C, formaldehyde was consumed almost completely in an hour; it was converted to dihydroxyacetone nearly quantitatively up to about 30-min reaction time (Figure 1). A prolonged reaction diminished the amount of dihydroxyacetone. The decrease in dihydroxyacetone is probably caused by an aldol condensation between dihydroxyacetone and formaldehyde or between two molecules of dihydroxyacetone, thus producing compounds with carbon atoms more than three. Several small peaks with longer GLC retention times than that of dihydroxyacetone were in fact observed in the chromatogram of the trimethylsilylated oxime derivatives of the products obtained in the reaction for more than 30 min.

In the reaction for 1 h at 65, 80, or 100 °C, the reaction proceeded more rapidly at higher temperature, and the selectivity remained as high as 65–70%. Since formaldehyde was supplied as paraformaldehyde (oligo- or poly(oxymethylene)), the process of depolymerization and dissolution of paraformaldehyde in the medium might affect the reaction. However, the reaction using a formaldehyde solution prepared beforehand by heating paraformaldehyde in the solvent gave similar results.

The reaction catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine at 100 °C proceeded also in various solvents except for water as shown in Table II. Formaldehyde was consumed almost completely in 1 h, and the selectivity was very high when dioxane, diglyme, or dimethylformamide was used as the solvent.

Reaction in the Presence of Various Bases. According to the suggested mechanism of the acyloin condensation catalyzed by thiazolium salts,[12] a base is required to abstract a proton at position

Table II. Reaction of Formaldehyde Catalyzed by 3-Ethylbenzothiazolium Bromide in Various Solvents[a]

solvent	HCHO consumption %	selectivity in dihydroxyacetone, %
ethanol	98	70
butanol	97	64
dioxane	98	84
diglyme	97	87
ethyl propionate	95	56
dimethyl sulfoxide	85	72
N,*N*-dimethylformamide	98	89
heptane	97	24
water	14	0

[a] HCHO, 60 mmol; catalyst, 3 mmol; triethylamine, 3 mmol; solvent, 10 mL; 100 °C, 1 h.

Table III. Reaction of Formaldehyde Catalyzed by 3-Ethylbenzothiazolium Bromide in the Presence of Various Bases[a]

base	HCHO consumption, %		selectivity in dihydroxyacetone, %	
	ethanol	dioxane	ethanol	dioxane
triethylamine	98	98	70	84
trioctylamine	85	33	56	96
quinuclidine	94	99	51	92
imidazole	65	91	68	92
pyridine	0	3	*b*	*b*
tetraethylammonium hydroxide	94	37	91	60
sodium ethoxide	93	94	65	61
sodium hydroxide	93	41	50	70

[a] HCHO, 60 mmol; catalyst, 3 mmol; base, 3 mmol; ethanol or dioxane, 10 mL; 100 °C, 1 h. [b] Not determined.

C-2 of the thiazolium ring, forming a carbanion, the active species. As can be seen in Table III, the reaction using 3-ethylbenzothiazolium bromide in ethanol or dioxane at 100 °C for 1 h proceeded with a wide variety of bases such as tertiary amines, a quaternary ammonium hydroxide, an alcoholate, and an inorganic base. On the contrary, when a weak base such as pyridine was used, very little formaldehyde condensation took place.

In the reaction using triethylamine as the base, an equimolar ratio of the base to the thiazolium salt was found to be the optimum with respect to the catalytic activity and the selectivity. An increase in the amount of base enhanced the consumption of formaldehyde but tended to diminish the selectivity in the formation of dihydroxyacetone.

Mechanism. According to the generally accepted mechanism of the acyloin condensation catalyzed by thiazolium salts (see Scheme I),[12] glycolaldehyde (VII) is expected to be cleaved from III to regenerate active species (I) (I → II → III → VII). Therefore, it was rather surprising to us that glycolaldehyde was not detected in the product even in the initial stages of the reaction.

The absence of glycolaldehyde (VII) in the product might indicate that it reacted rapidly with active species such as I, II, or IV, once it was formed. A rapid reaction with I, if it occurred, implies that glycolaldehyde, in a practical sense, is not formed. Glycolaldehyde (VII) could rapidly react with carbanion (II) to give glyceraldehyde (IX) and I, via VIII. Then IX could isomerize to dihydroxyacetone via the ene–diol intermediate (X). There is also the possibility that glycolaldehyde reacts with carbanion (IV) to give XI, which could be converted to IX by the retroacyloin reaction. Compound IX thus formed would afford dihydroxyacetone (VI) as described above.

In order to obtain information about reactivity of glycolaldehyde, its reaction with 3-ethylbenzothiazolium bromide in the presence of triethylamine, without formaldehyde, was examined in dioxane at 100 °C for 0.5 h. The gas–liquid chromatogram of the reaction mixture (previously subjected to oximation and trimethylsilylation) revealed that little reaction took place; almost

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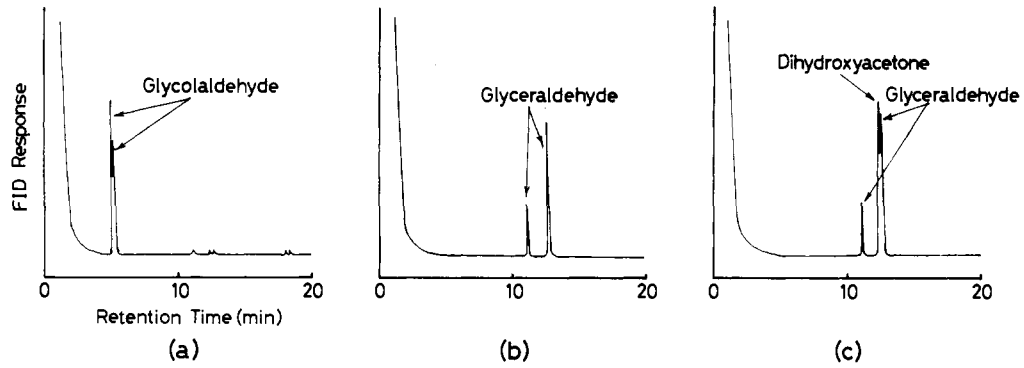
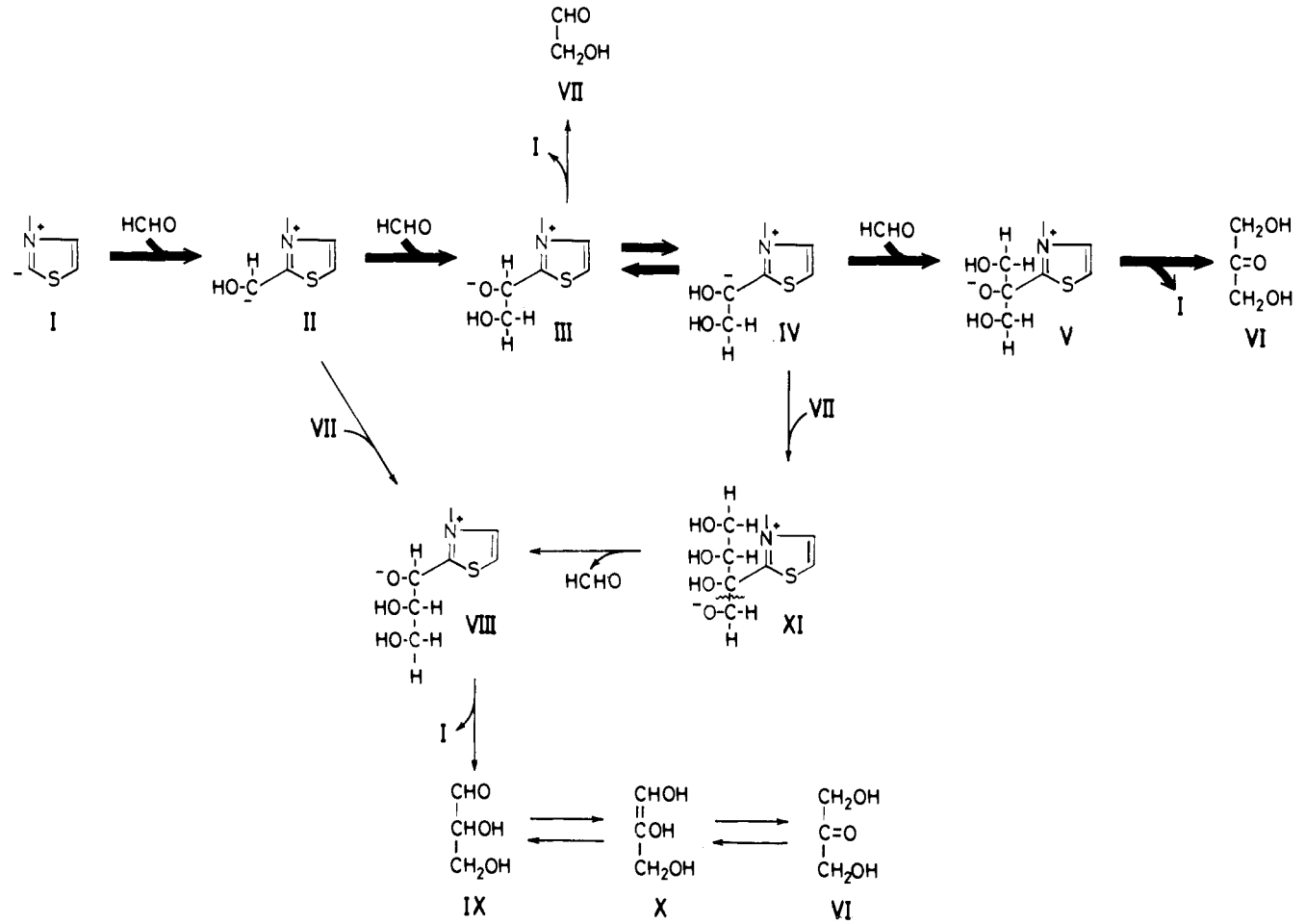


Figure 2. Gas–liquid chromatograms of trimethylsilylated oxime derivatives of the products obtained by the reactions starting from (a) glycolaldehyde, (b) glyceraldehyde, and (c) glyceraldehyde and formaldehyde. HCHO, 0.45 g (15 mmol) when used; glycolaldehyde, 0.45 g (0.75 mmol); glyceraldehyde, 0.45 g (5 mmol); 3-ethylbenzothiazolium bromide, 3 mmol; triethylamine, 3 mmol; dioxane, 10 mL; 100 °C, 0.5 h.

Scheme I



no decrease was observed in the peak corresponding to glycolaldehyde and the peak corresponding to dihydroxyacetone did not appear (Figure 2a). Under the same conditions, no reaction took place between 3-ethylbenzothiazolium bromide and glyceraldehyde (Figure 2b). These facts indicate that dihydroxyacetone was formed neither from glycolaldehyde alone nor by the isomerization of glyceraldehyde. Therefore, the mechanism for the formation of dihydroxyacetone via glyceraldehyde may be excluded.

The reaction of a mixture of formaldehyde and glyceraldehyde catalyzed by 3-ethylbenzothiazolium bromide yielded dihydroxyacetone in an amount corresponding to formaldehyde, but glyceraldehyde remained unchanged (Figure 2c). In the reaction of a mixture of glycolaldehyde and formaldehyde with 3-ethylbenzothiazolium bromide as catalyst, it is of much interest to note that dihydroxyacetone was formed in an amount corresponding to the sum of glycolaldehyde and formaldehyde. This fact indicates that I reacted preferentially with glycolaldehyde, not with formaldehyde, to form IV, which then reacted with formaldehyde to afford dihydroxyacetone. If I had reacted preferentially with formaldehyde to give II, the reaction of the latter with glycolaldehyde should have resulted in the formation of glyceraldehyde.

All these findings indicate that in the condensation of formaldehyde catalyzed by thiazolium salt dihydroxyacetone is directly formed from formaldehyde, rather than with the intervention of free glycolaldehyde. With two hydrogen atoms on the carbonyl carbon in formaldehyde, III may isomerize to carbanion (IV) which exhibits unexpectedly high reactivity toward another molecule of formaldehyde to eventually give the C_3 compound, dihydroxyacetone (VI). But III is not cleaved to give the C_2 compound (VII). Thus, reactive intermediate (IV) is suggested to be useful as an activated C_2 unit to be combined with various electrophiles.

Experimental Section

Materials. Paraformaldehyde, glycolaldehyde, glyceraldehyde, dihydroxyacetone, and thiamin hydrochloride were of commercial grade. Thiazole and benzothiazole were purified by fractional distillation. Triethylamine and pyridine were purified by refluxing over calcium hydride, followed by distillation and storage under nitrogen. Imidazole was purified by recrystallization from benzene, and quinuclidine by sublimation in vacuo.

Synthesis of Catalysts. Thiazolium salts were prepared by reacting thiazole or benzothiazole with the corresponding alkyl halides. For example, 3-ethylbenzothiazolium bromide was synthesized as follows: benzothiazole (24.9 g, 184 mmol) was heated with a small excess of ethyl bromide (21.8 g, 200 mmol) at 70–80 °C under nitrogen, and the solidified product was collected and purified by recrystallization from ethanol–ether to give white needles (21.1 g, 47%).

3-Ethylthiazolium bromide: mp 156–157 °C (ethanol–ether) (lit.[13] mp 160–161 °C); ^{1}H NMR (CD_3OD) δ 1.60 (t, 3 H, CH_3), 4.56 (q, 2 H, CH_2), 8.08 (m, 1 H, C-5 proton of thiazolium ring), 8.32 (m, 1 H, C-4 proton), 9.90 (m, C-2 proton, exchanged partially with deuterium of solvent). Anal. (C_5H_8BrNS) C, H, N.

3-Methylbenzothiazolium iodide: mp 218–220 °C (ethanol) (lit.[13] mp 208–210 °C); ^{1}H NMR (CD_3OD) δ 4.54 (s, 3 H, CH_3), 7.88–8.60 (m, 4 H, benzene ring). Anal. (C_8H_8INS) C, H, N.

3-Ethylbenzothiazolium bromide: mp 212–213 °C (ethanol–ether); ^{1}H NMR (CD_3OD) δ 1.69 (t, 3 H, CH_3), 4.78 (q, 2 H, CH_2), 7.48–8.24 (m, 4 H, benzene ring), 10.22 (s, C-2 proton, exchanged partially). Anal. ($C_9H_{10}BrNS$) C, H, N.

3-Ethylbenzothiazolium iodide: mp 145–147 °C (ethanol); ^{1}H NMR (CD_3OD) δ 1.70 (t, 3 H, CH_3), 4.85 (q, 2 H, CH_2), 7.52–8.32 (m, 4 H, benzene ring), 10.44 (s, C-2 proton, partially exchanged). Anal. ($C_9H_{10}INS$) C, H, N.

3-Isopropylbenzothiazolium bromide: mp 154–156 °C (ethanol–ether); ^{1}H NMR (CD_3OD) δ 1.78 (d, 6 H, $(CH_3)_2$), 5.49 (m, 1 H, $CHMe_2$), 7.64–8.48 (m, 4 H, benzene ring), 10.63 (s, C-2 proton, partially exchanged). Anal. ($C_{10}H_{12}BrNS$) C, H, N.

Condensation Reaction. In a 30-mL flask were placed paraformaldehyde (1.8 g, 60 mmol as formaldehyde), thiazolium salt (3 mmol), solvent (10 mL), and then base (3 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 stirred magnetically in an oil bath adjusted to the required temperature. After the prescribed time the reaction was quenched by immersing it in solid CO_2–ethanol. Formaldehyde was determined colorimetrically after the reaction with chromotropic acid on a JASCO UVIDEC-1 spectrophotometer.[14]

Analysis of Products. An aliquot (1 mL) of the reaction mixture was poured into distilled water (20 mL). The aqueous solution was evaporated to dryness, in order to remove unreacted formaldehyde, giving a syrupy product. The syrup was reacted with hydroxylamine hydrochloride (0.4 g) in pyridine (25 mL) at 70 °C for 1 h, and then hexamethyldisilazane (4 mL) and trimethylchlorosilane (2 mL) were added to the reaction mixture.[15] The resulting solution containing the trimethylsilylated oxime derivative of the product was subjected to gas–liquid chromatography on an Ohkura Model-103 chromatograph equipped with a flame-ionization detector. The following conditions were employed: glass capillary column of 30 m × 0.28 mm i.d.; adsorber, silicone SF-96; column temperature, 100–200 °C, rising at a rate of 3 °C min^{-1}. The amount of dihydroxyacetone, the main product, was estimated by comparing the peak area of the trimethylsilylated oxime derivative corresponding to dihydroxyacetone with that of the authentic compound.

Isolation and Identification of Main Product. The reaction mixture obtained by reacting paraformaldehyde (7.2 g) with 3-ethylbenzothiazolium bromide in the presence of triethylamine in ethanol was poured into a mixture of distilled water and ether. After vigorous shaking, the water layer was separated and concentrated by evaporation. The resulting syrup was dissolved in butanol saturated with water (10 mL), and the solution was placed on the top of a column of 45 cm × 3.6 cm o.d. packed with Cellulose Microkristallin (Merck). It was developed with butanol saturated with water at a constant flow rate (1.5 mL min^{-1}). The eluted solution was fractionated into 10-mL portions, and the content of the main product in each fraction was monitored by high-performance liquid chromatography using a JASCO TWINCLE chromatograph equipped with an RI detector under the following conditions: stainless steel columns, Shodex Ionpak S-801 and KS-801 (connected in series); flow rate of distilled water, 1 mL min^{-1}; column temperature, 60 °C. The fractions containing the main product were collected, and the solvent was removed by evaporation to give a white solid (1.2 g). The isolated product was dissolved in deuterium oxide, and the ^{1}H and ^{13}C NMR spectra were taken on a JEOL JNM-PS-100 and a JEOL JNM-PET-100 spectrometer, respectively, using sodium 3-(trimethylsilyl)propanesulfonate as an internal standard. An NMR spectral determination was also made for the trimethylsilylated oxime derivative of the isolated product in $CDCl_3$. The IR spectrum of the derivative was taken on a HITACHI 260-30 infrared spectrophotometer by the thin-film method.

Registry No. Benzothiazole, 95-16-9; ethyl bromide, 74-96-4; 3-ethylthiazolium bromide, 63423-96-1; 3-methylbenzothiazolium iodide, 2786-31-4; 3-ethylbenzothiazolium bromide, 32446-47-2; 3-ethylbenzothiazolium iodide, 3119-94-6; 3-isopropylbenzothiazolium bromide, 90867-00-8; paraformaldehyde, 30525-89-4; dihydroxyacetone, 96-26-4; thiamin hydrochloride, 67-03-8; ethanol, 64-17-5; butanol, 71-36-3; dioxane, 123-91-1; diglyme, 111-96-6; ethyl propionate, 105-37-3; dimethyl sulfoxide, 67-68-5; *N,N*-dimethylformamide, 68-12-2; heptane, 142-82-5; water, 7732-18-5; triethylamine, 121-44-8; trioctylamine, 1116-76-3; quinuclidine, 100-76-5; imidazole, 288-32-4; pyridine, 110-86-1; tetraethylammonium hydroxide, 77-98-5; sodium ethoxide, 141-52-6; sodium hydroxide, 1310-73-2; formaldehyde, 50-00-0.

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