# Synthesis and Thermolysis of Dimeric Glyceraldehyde and Glycolaldehyde Carbonates

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A number of 2,5-bis[[[(aryl- and alkyloxy)carbonyl]oxy]methylene]-3,6-bis[[(aryl- and alkyloxy)-carbonyl]oxy]-1,4-dioxanes (1–4) and 2,5-bis[[(aryl- and alkyloxy)carbonyl]oxy]-1,4-dioxanes (5–7) have been synthesized and thermolyzed in the neat state at 250 °C. Carbonates 5–7 have been shown by NMR analysis to exist in a chair conformation with the substituents in an axial orientation, while carbonates 1–4 have previously been shown to exist in a chair conformation with all the substituents in an equatorial orientation. On thermolysis at 250 °C carbonates 1–4 yielded 40–50% of the alcohol and phenol components while carbonates 5–7 yielded 65%.

Alcohols and phenols often have desirable flavor properties. These compounds are found in a wide variety of food products and have been used as flavoring agents (Fenaroli, 1975). However, their use as flavoring agents can be limited by their low odor threshold and high volatility. As a consequence, a limitation on the amount of the flavoring agent that can be utilized as well as losses on storage result.

To overcome these limitations, the use of a flavor precursor could be employed. The requirements of such a flavor precursor would include being nonvolatile, odorless, and stable in the product on storage. Then, when heat and/or water is applied to the product, the desired flavoring substances would be liberated.

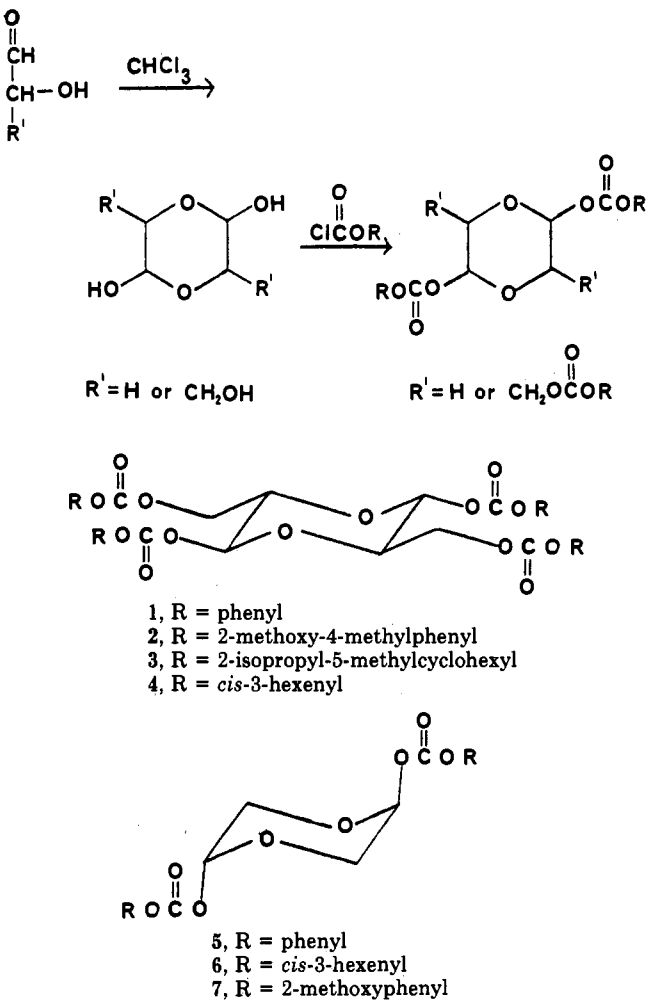
In this study, we were interested in examining the thermal behavior of carbonates derived from dimeric glyceraldehyde and glycolaldehyde. Previous thermal studies have been conducted with simple alkyl carbonates to determine the thermal mechanism utilizing gas-phase thermolysis (Bigley et al., 1976; Bigley and Wren, 1972). Our investigation focuses on the thermolysis of the carbonates at a relatively low temperature (250 °C) and in the neat state, in an attempt to obtain some basic thermolysis data.

## RESULTS AND DISCUSSION

The preparation of the carbonates was conducted by reacting glyceraldehyde or glycolaldehyde in an aprotic organic solvent with the desired chloroformate (Strain et al., 1950), in the presence of a base (Podraza, 1984). The dimeric forms of glyceraldehyde and glycolaldehyde exist, due to the use of an aprotic organic solvent, resulting in the formation of the tetracarbonate and dicarbonate 1,4-dioxane derivatives (1–7) (Scheme I) (Wohl, 1898).

NMR analysis of carbonates 5 and 7 showed a vicinal coupling constant for the anomeric proton of 1.0 Hz for 5 and 1.5 Hz for 7. These values compare favorably with that of 2,5-bis(acetyloxy)-1,4-dioxane (1.45 Hz), which has been shown to exist in a chair conformation with its substituents in a diaxial orientation, whereas 2,5-bis[(trimethylsilyl)oxy]-1,4-dioxane, having a coupling constant of 6.0 Hz, has been shown to bear equatorial substituents (Gardiner, 1966; Hall, 1967; Fuchs et al., 1984). Thus, carbonates 5–7 exist in a chair conformation with the substituents in an axial orientation. As previous reported (Podraza, 1984) carbonates 1–4 exist in a chair conformation with all the substituents in an equatorial orientation. The detailed NMR analysis indicates that the respective carbonates are a single isomer, with the substituents in a trans configuration. However, little can be said about the orientation of the substituents during thermolysis, since rapid ring inversion would occur (Fuchs et al., 1984).

**Scheme I**




1, R = phenyl
2, R = 2-methoxy-4-methylphenyl
3, R = 2-isopropyl-5-methylcyclohexyl
4, R = *cis*-3-hexenyl

5, R = phenyl
6, R = *cis*-3-hexenyl
7, R = 2-methoxyphenyl

The carbonates were subjected to thermolysis in a glass tube tube at 250 °C for 10 min, in the neat state. These thermal conditions resulted in rapid thermal breakdown of the carbonates, providing the opportunity to obtain detailed information about the thermolysis process. The yield of the released alcohol or phenol component in each case was determined by GC quantitation with an authentic sample (Table I). Thermolysis of 2,5-bis[[[(aryl- and alkyloxy)carbonyl]oxy]methylene]-3,6-bis[[(aryl- and alkyloxy)carbonyl]oxy]-1,4-dioxanes 1–4 was found to release 40–50% of the alcohol or phenol component, based on the

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Table I. Thermolysis of Carbonates 1–7

| compd[a] | alcohol or phenol component | yield,[b] % |
|---|---|---|
| 1 | phenol | 50 |
| 2 | 2-methoxy-4-methylphenol | 40 |
| 3 | 2-isopropyl-5-methylcyclohexanol | 45 |
| 4 | *cis*-3-hexenol | 45 |
| 5 | phenol | 65 |
| 6 | *cis*-3-hexenol | 65 |
| 7 | 2-methoxyphenol | 65 |

[a] Conditions: 250 °C/10 min. [b] Determined by GC quantitation with an authentic sample of the alcohol or phenol component. The yield is based on the theoretical release of 2 equiv (carbonates 5–7) or 4 equiv (carbonates 1–4) of the alcohol or phenol component per unit molecule.

theoretical release of 4 equiv of the alcohol or phenol component per unit molecule. In an attempt to obtain more detailed information about the thermal breakdown of the tetracarbonates, a thermolysis GC/MS analysis was conducted with **2**. The sample was thermolyzed at 300 °C in a quartz tube inserted in a furnace, while being swept by helium. The volatile material was condensed on a 30-m DB-5 fused silica capillary column. After the oven temperature was held at 0 °C for 4 min, the column temperature was heated at 5 °C/min to 280 °C. The chromatographic effluent led directly into the ion source of a mass spectrometer and was analyzed. The only volatile component observed was 2-methoxy-4-methylphenol. Additionally, a large amount of charred residue was observed in the ceramic boat. As a consequence of only one volatile component being observed, very little can be said about the thermal mechanism under these thermolytic conditions.

Thermolysis of 2,5-bis[[(aryl- and alkyloxy)carbonyl]-oxy]-1,4-dioxanes **5–7** was conducted in a similar fashion to carbonates **1–4**. Carbonates **5–7** exhibited a 65% release of the alcohol or phenol component, based on the theoretical release of 2 equiv of the alcohol or phenol component per unit molecule. Thermolysis GC/MS analysis was conducted with carbonate **5** using similar conditions to that described for carbonate **2**. The thermolysis at 300 °C resulted in three volatile components. These products were identified from their mass spectral fragmentation patterns to be phenol, 5-[(phenoxycarbonyl)oxy]-1,4-diox-2-ene (**8**), and 5-phenoxy-1,4-diox-2-ene (**9**) (Scheme II).

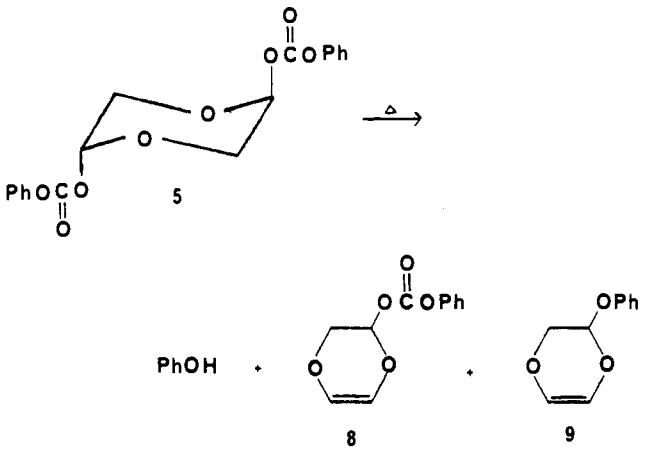
The mechanism of thermal elimination utilizing alkyl carbonates has been shown to occur via a concerted cyclic process, generating an olefin and an unstable carbonic acid that decomposes to an alcohol and carbon dioxide (Bigley et al., 1976). This mechanism accounts for the formation of the unsaturated portion in compounds **8** and **9** produced from the thermolysis of carbonate **5**. The formation of the ether portion in compound **9** may be the result of nucleophilic substitution by the phenoxide, generated from the unstable carbonic acid component, at the C-5 position in carbonate **8**, followed by the displacement of the (phenoxycarbonyl)oxy moiety to yield ether **9** (Jost et al., 1982). Alternatively, a free-radical process may be occurring. In this case, phenoxy radical addition to the double bond of the dioxene followed by hydrogen abstraction would lead to ether **9** (Lunazzi et al., 1983). However, the free-radical pathway is less likely since no other free-radical components were observed.

In summary, the thermolysis at 250 °C of carbonates 1–4 yielded 40–50% of the alcohol or phenol components while carbonates **5–7** yielded 65%.

## EXPERIMENTAL SECTION

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR were recorded on a Perkin-Elmer 283B spectrophotometer. The chemical shifts and coupling constants ($J$) are reported in $\delta$ and Hertz, respectively, on a Bruker WP80 spectrometer, with $Me_4Si$ as the internal standard. Compounds **1–4** were prepared by the method described previously (Podraza, 1984).

Scheme II




**2,5-Bis[(phenoxycarbonyl)oxy]-1,4-dioxane (5).** To a mixture of 2.5 mL of pyridine, 50 mL of chloroform, and 1.0 g (16.7 mmol) of glycolaldehyde, at 0 °C, was added a solution of 2.6 g (16.7 mmol) of phenyl chloroformate in 10 mL of chloroform dropwise. The mixture was stirred for 15 min at 0 °C, then 18–24 h at room temperature. The reaction mixture was washed with water and aqueous saturated sodium bicarbonate and dried over anhydrous $NaSO_4$. Evaporation of the solvent under reduced pressure yielded a residue, to which toluene was added and evaporated under reduced pressure. The semisolid obtained was recrystallized from chloroform/hexane, yielding 1.6 g (53.3%) of **5**: mp 144–146 °C; IR (Nujol mull) 1768 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.63–7.07 (m, 10 H, Ph), 6.00 (d, $J$ = 1.0 Hz, 2 H, CH), 4.40 (dd, $J$ = 14.0, 2.0 Hz, 2 H, CH), 3.88 (d, $J$ = 12.5 Hz, 2 H, CH). Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.86; H, 4.61.

**2,5-Bis[[(3-hexenyloxy)carbonyl]oxy]-1,4-dioxane (6).** The synthesis of **6** was conducted on a 16.7-mmol scale as described for **5**. The liquid product was purified by preparative thin-layer chromatography on silica gel using 10% ethyl acetate/hexane as the eluent to yield 1.7 g (54.8%) of **6**: mp 39–40 °C; IR (film) 1756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.95–5.12 (m, 6 H, CH, CH=CH), 4.42–3.58 (m, 8 H, $CH_2$), 2.46 (quartet, $J$ = 6.6 Hz, 4 H, $CH_2$), 2.08 (quintet, $J$ = 7.0 Hz, 4 H, $CH_2$), 1.0 (t, $J$ = 8.0 Hz, 6 H, $CH_3$). Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.22; H, 7.55.

**2,5-Bis[[(2-methoxyphenoxy)carbonyl]oxy]-1,4-dioxane (7).** The synthesis of **7** was conducted on a 16.7-mmol scale as described for **5**. The solid product was purified by recrystallization from methylene chloride/hexane to yield 1.1 g (31.4%) of **7**: mp 191–193 °C; IR (film) 1765 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.45–6.83 (m, 8 H, Ph), 5.95 (d, $J$ = 1.5 Hz, 2 H, CH), 4.37 (dd, $J$ = 14.0, 2.0 Hz, 2 H, CH), 3.87 (apparent t, $J$ = 6.6 Hz, 8 H, $CH_3$, CH). Anal. Calcd for $C_{20}H_{20}O_{10}$: C, 57.14; H, 4.80. Found: C, 56.97; H, 4.86.

**5-[(Phenoxycarbonyl)oxy]-1,4-diox-2-ene (8)**: MS (70 eV) $m/e$ (rel intensity) 222 (2), 178 (2), 94 (31), 85 (100), 77 (54).

**5-Phenoxy-1,4-diox-2-ene (9)**: MS (70 eV) $m/e$ (rel intensity) 178 (23), 94 (28), 84 (100), 77 (19).

**Thermolysis of Carbonates 1–7.** A 10–50-mg sample of each of the carbonates was thermolyzed in a glass tube at 250 °C for 10 min. The residue was cooled to room temperature and extracted with methylene chloride. The extract was diluted to 1 mL with methylene chloride in a volumetric flask. Injection of a 10-μL sample into a Varian 3700 gas chromatograph equipped with a 6 ft, 0.125-in. o.d., OV-101 column, was used to examine the extract. An external standard solution of the particular alcohol or phenol component, in conjunction with a Hewlett-Packard 3390A integrater, was used to quantitate the yield of the released component in each case.

**Thermolysis GC/MS Analysis.** A 25–75-μg sample of the carbonate was weighed into a clean ceramic boat and placed into the section of a quartz tube maintained at room temperature. The remainder of the tube passed through a furnace and was connected to the injection port of a gas chromatograph (Bendix Model 2200). After air from the tube was purged with helium, the sample and boat were pushed into the thermolysis zone maintained at 300 °C. The volatile material was condensed on a 30-m DB-5 fused silica capillary column. After the oven temperature was held at 0 °C for 4 min, the column temperature was heated at 5 °C/min to 280 °C. The chromatographic effluent led directly into the ion source of a Finnigan Model 3300 mass spectrometer. The products were identified from their mass spectral fragmentation patterns.

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**Registry No.** 1, 94192-23-1; 2, 94192-24-2; 3, 94219-44-0; 4, 94192-22-0; 5, 103478-49-5; 6, 103478-50-8; 7, 103478-51-9; 8, 103478-52-0; 9, 103478-53-1; $C_6H_5OCOCl$, 1885-14-9; (*Z*)-$ClCO_2(CH_2)_2CH{=}CHCH_2CH_3$, 94192-19-5; 2-$ClCO_2C_6H_4OCH_3$, 2293-75-6; (*Z*)-$HO(CH_2)_2CH{=}CHCH_2CH_3$, 928-96-1; 2-$CH_3OC_6H_4OH$, 90-05-1; glycolaldehyde, 141-46-8; 2-methoxy-4-methylphenol, 93-51-6; 2-isopropyl-5-methylcyclohexanol, 1490-04-6.

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# Identification and Quantitation of 1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid and 1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid in Beer and Wine

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Tetrahydro-β-carboline-3-carboxylic acid (THBC-3-COOH) and 1-methyltetrahydro-β-carboline-3-carboxylic acid (1-MeTHBC-3-COOH) were identified and quantitated in beer and wine. The analytical procedure employed aqueous derivatization with methyl chloroformate to facilitate the isolation, to improve the liquid chromatographic separation, and to eliminate the potential for artifactual formation of these compounds during sample preparation. Identification and quantitation were accomplished through a combination of high-performance liquid chromatography and mass spectrometry. The concentration of THBC-3-COOH in beer and wine ranged between 2.7–10.9 and 0.8–1.7 μg/mL, respectively, and the concentration of 1-MeTHBC-3-COOH ranged between 0.3–4.2 and 1.3–9.1 μg/mL, respectively.

More than a decade ago, it was suggested that some of the effects of ethanol consumption might be mediated by the formation of endogeneous alkaloids formed by the reaction of acetaldehyde with a biogenic amine (Davis and Walsh, 1970; Cohen and Collins, 1970). One example of this process is the reaction of an aldehyde with an (aminoethyl)indole to produce, via a Pictet–Spengler reaction, a 1,2,3,4-tetrahydro-β-carboline (THBC). Such reactions occur readily under physiological conditions (Whaley and Govindachari, 1951), and a generalized reaction is shown in Figure 1.

THBC compounds have been increasingly implicated in alcoholism through their ability to function as neurotransmitters or neutromodulators that alter serotonergic function in the central nervous system (Buckholtz, 1980; Bloom et al., 1982). Acute and chronic administration of THBC compounds to rats has been reported to significantly alter their consumption of ethanol (Geller and Purdy, 1975; Myers and Melchoir, 1977; Tuomisto et al., 1982). Recently several THBC compounds have been identified and quantitated in food and alcoholic beverages

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