# Efficient synthesis and hydrolysis of cyclic oxalate esters of glycols



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# Efficient Synthesis and Hydrolysis of Cyclic Oxalate Esters of Glycols

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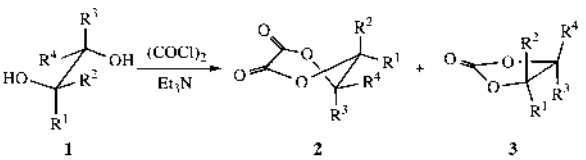
**Based on the mechanism postulated for the formation of the cyclic carbonates 3 in the reactions of glycols 1 with oxalyl chloride in the presence of triethylamine, we present here three efficient syntheses of the cyclic oxalates 2 of various glycols 1 by controlling the formation of 3: replacement of the base by pyridine markedly diminishes yields of 3 in all reactions, realizing dramatic reversals of the product ratios in the reactions with the (*R**,*R**)-compounds 1g—i, q, r and pinacol (1k); although considerable amounts of the oxalate polymers are formed in the reactions with some (*R**,*S**)-glycols, this drawback can be removed by the use of 2,4,6-collidine instead of pyridine; 1,1′-oxalyldiimidazole is useful for the synthesis of two selected cyclic oxalates 2e, f. The cyclic oxalates 2 other than trisubstituted and tetrasubstituted ones were found to be very reactive: kinetic studies on the hydrolysis of 1,4-dioxane-2,3-dione (2a) as well as its mono- and some selected 5,6-disubstituted derivatives 2 have revealed that they undergo hydrolysis 260—1500 times more rapidly than diethyl oxalate (12) in acetate buffer–acetonitrile (pH 5.69) at 25 °C. Although the cyclic oxalate 2l from *cis*-1,2-cyclopentanediol (1l) was 1.5 times more reactive than 2a, it has been shown with other substrates that increasing number of the alkyl substituents decreases the rate of hydrolysis. On the contrary, the phenyl group was found to have somewhat accelerative effect.**

**Key words** glycol cyclocondensation; oxalyl chloride; 1,4-dioxane-2,3-dione hydrolysis; oxalate hydrolysis kinetics; 1,1′-oxalyldiimidazole; stereoelectronic effect

It has been established that for simple carboxylic esters the basic ester skeletal framework CC(O)OC is planar or near planar and that the (*Z*)-form is much more stable than the (*E*)-form.[1] It has been also proposed that diesters of oxalic acid mainly exist as the *s*-trans conformers.[2] Accordingly, a noteworthy feature of cyclic oxalate esters **2** formed from glycols **1** is that two less stable (*E*)-esters are linked to form the unfavorable *s*-cis structure of the 1,2-dicarbonyl system. Probably it accounts for that compounds with a 1,4-dioxane-2,3-dione framework are few notwithstanding that they are predictable to be normal products from reactions between oxalyl chloride and glycols. Examples of this ring system can be seen as a part structure of the cyclic oxalates of unsubstituted[3] and substituted 1,2-benzenediols.[4] Some other compounds with four $sp^2$-hybridized endocyclic carbons have been reported.[5] Fewer examples of compounds with two $sp^3$-hybridized ring carbons have been reported. The prototype of these compounds, 1,4-dioxane-2,3-dione (**2a**), and its 5-methyl derivative **2b** have been well investigated.[6] The cyclic oxalates **2** of *meso*-2,3-butanediol (**1d**),[7] (−)-2,3-butanediol,[7] *meso*- and (±)-hydrobenzoins (**1e**, **h**),[8] *cis*- and *trans*-1,2-cyclohexanediols (**1m**, **p**),[9] and some other cyclic 1,2-diols[10] were reported to be prepared by acylating the corresponding glycols with oxalyl chloride. Tetrachloroethylene oxalate was prepared by chlorination of **2a**.[11] A reaction using (±)-5-vinyl-1,4-dioxane-2,3-dione was reported without characterization and description of a method of preparation of this compound.[12]

We have already disclosed that oxalyl chloride generally reacts with acyclic glycols in tetrahydrofuran (THF) in the presence of triethylamine at 0 °C to form the cyclic oxalates **2** together with the cyclic carbonates **3**: unsubstituted (**1a**), monosubstituted (**1b**, **c**), and *erythro*-1,2-disubstituted ethylene glycols **1d**—**f** produce **2a**—**f** and/or the polymeric oxalates as the major products, while the *threo*-isomers **1g**—**i** afford **3g**—**i** as the major products. Pinacol (**1k**) underwent slow reaction at room temperature to afford the carbonate **3k** together with a small amount of the oxalate **2k**.[13] Although the relationship between the product patterns and the configurations of *cis*-1,2-cycloalkanediols **1l**—**n**, *trans*-1,2-cycloheptanediol (**1q**), and *trans*-1,2-cyclooctanediol (**1r**) was analogous to that obtained for 1,2-disubstituted acyclic ethylene glycols **1d**—**i**, *trans*-1,2-cyclopentanediol (**1o**) and *trans*-1,2-cyclohexanediol (**1p**) were exceptions to give no traces of the cyclic carbonates **3o**, **p**.[14] As most of the cyclic oxalates **2** described above were quite unstable under conditions employed for separation by chromatography or distillation, we failed to isolate **2e**—**i**, **o**, **q**, **r**. Although the cyclic oxalates **2e**, **h** of hydrobenzoins (**1e**, **h**) were once reported to be produced by White,[8] we suppose these were in fact the cyclic carbonates **3e**, **h** (see below). We thus desired to devise a general procedure for the highly selective preparation of the cyclic oxalates **2** for further investigation of chemical properties of this class of compounds. A preliminary account of a part of this work has been published.[15]

According to our proposed mechanism illustrated in Chart 2,[13b] the formation of tetramethylethylene carbonate (**3k**) from pinacol (**1k**) in the presence of oxalyl chloride and tri-




1 2 3

**a**: $R^1 = R^2 = R^3 = R^4 = H$ **b**: $R^1 = R^2 = R^3 = H$; $R^4 = Me$ **c**: $R^1 = R^2 = R^3 = H$; $R^4 = Ph$ **d**: $R^1 = R^3 = H$; $R^2 = R^4 = Me$ **e**: $R^1 = R^3 = H$; $R^2 = R^4 = Ph$ **f**: $R^1 = R^3 = H$; $R^2 = Ph$; $R^4 = Me_2CH$ **g**: $R^2 = R^3 = H$; $R^1 = R^4 = Me$ **h**: $R^2 = R^3 = H$; $R^1 = R^4 = Ph$ **i**: $R^2 = R^3 = H$; $R^1 = Ph$; $R^4 = Me_2CH$ **j**: $R^2 = H$; $R^1 = R^3 = R^4 = Me$ **k**: $R^1 = R^2 = R^3 = R^4 = Me$ **l**: $R^1 = R^3 = H$; $R^2R^4 = (CH_2)_3$ **m**: $R^1 = R^3 = H$; $R^2R^4 = (CH_2)_4$ **n**: $R^1 = R^3 = H$; $R^2R^4 = (CH_2)_6$ **o**: $R^2 = R^3 = H$; $R^1R^4 = (CH_2)_3$ **p**: $R^2 = R^3 = H$; $R^1R^4 = (CH_2)_4$ **q**: $R^2 = R^3 = H$; $R^1R^4 = (CH_2)_5$ **r**: $R^2 = R^3 = H$; $R^1R^4 = (CH_2)_6$

Chart 1

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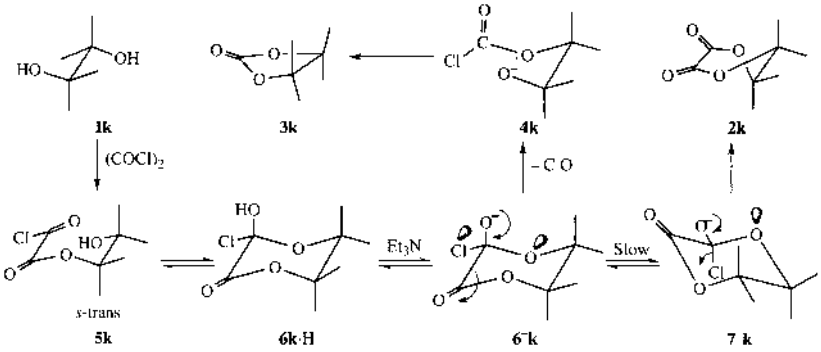



Chart 2

Table 1. Temperature Effect on the Reactions of Oxalyl Chloride with Hydrobenzoins (**1e**, **h**) in THF in the Presence of Triethylamine[a)]

| Substrate | Temperature (°C) | Reaction time (min) | Yield (%)[b)] | | |
|---|---|---|---|---|---|
| | | | **2** | **3** | Polymers |
| *meso*-Hydrobenzoin (**1e**) | 0[c)] | 15 | 67 | 33 (29) | 0 |
| | −78[d)] | 195 | 45 | 37 | 18 |
| | −78[d)] | 435 | 29 | 34 | 37 |
| (±)-Hydrobenzoin (**1h**) | 0[c)] | 15 | 36 | 64 (58) | 0 |
| | −78[d)] | 195 | 47 | 53 | 0 |
| | −78[d)] | 435 | 47 | 53 (44) | 0 |

*a*) Hydrobenzoin (1 mmol) was treated with oxalyl chloride (1.1 mmol) in the presence of triethylamine (2.2 mmol) in THF (12 ml). *b*) The yields were estimated by $^1$H-NMR spectroscopy ($CDCl_3$) on the basis of the intensity of the signal of the benzylic protons. Figures in parentheses denote isolated yields. *c*) Taken from ref. 13*b*. *d*) Carried out in a dry ice–acetone bath.

ethylamine is interpreted in terms of stereochemically controlled formation of the tetrahedral intermediate **6k**·H from the initially formed *s*-trans intermediate **5k**, followed successively by deprotonation and stereoelectronically controlled cleavage (two nonbonding electron pairs contributing to bond cleavage of **6**$^-$**k** are shown as shaded lobes) of the C–C bond. The cyclic oxalate **2k** can be formed only after **6**$^-$**k** conformationally changes into **7**$^-$**k**. The almost exclusive formation of **3k** is attributable to the large rotational barrier between the tetrasubstituted tetrahedral intermediates (**6**$^-$**k** and **7**$^-$**k**) compared with the activation energy for the decay of **6**$^-$**k**. However, the barriers to interconversion for the corresponding disubstituted intermediates (**6**$^-$**e**, **h** and **7**$^-$**e**, **h**) from hydrobenzoins (**1e**, **h**) are comparable to the activation energies for their decay.[13b)] Furthermore, the transition-state energy level for the breakdown of the intermediates **6**$^-$**e**, **h** is much higher than that for the breakdown of the other **7**$^-$**e**, **h**.[13b)] Accordingly, we can expect to obtain **2e**, **h** exclusively if we sufficiently retard the fragmentation of the species **6e**, **h** compared to their conformational change into **7e**, **h**.

## Results and Discussion

Table 1 shows that lowering the reaction temperature increased the yield of the cyclic oxalate **2h** from the *threo*-compound **1h** to a slight extent, but resulted in the formation of considerable amounts of the oxalate polymers from the *erythro*-compound **1e** at the cost of the cyclic oxalate **2e**. The formation of the polymers is probably due to slow interconversion among the rotamers (A, B, and C) of the half-ester **5e** at lower temperature: the rotamer C, which is unable to undergo intramolecular cyclization, would react with either another molecule of the rotamer C or the cyclic oxalate **2e**, initiating polymerization as shown in Chart 3. Involvement of **2e** in the polymerization was suggested by the decreasing yield of **2e** with increasing reaction time. It is not surprising that no polymerization occurred in the reaction of **1h**, because the rotamer C′ to undergo polymerization is the most unfavorable one.

The solvent effects on the reactions of **1e**, **h** with oxalyl chloride are summarized in Table 2. It was found that the *threo*-compound **1h** did not provide the oxalate polymers at all in every solvent tested. On the other hand, the *erythro*-compound **1e** produced the polymers when the solvents other than ethers were employed. The polymerization was probably promoted by protonation of **2e** with triethylamine hydrochloride. In the ethereal solvents such as THF, 1,4-dioxane, and diethyl ether, protonation would occur on the solvent molecules rather than **2e**, preventing acid-catalyzed polymerization. It should be noted that the yield of the carbonate **3e** from the *erythro*-compound **1e** exceeded that of the total oxalates in the reaction in a polar solvent acetonitrile. Table 2 finally shows that no better solvent than THF was found for preferential production of **2**. Thus we failed in isolation of pure cyclic oxalates **2e**, **h**, notwithstanding that White reported the preparation of these compounds, without any characterization, by the reactions of **1e**, **h** with oxalyl chloride in the presence of triethylamine in ether.[8)]

The cyclic oxalates **2m**, **p** of *cis*- and *trans*-1,2-cyclohexanediols (**1m**, **p**) have already been prepared by azeotropic distillation of water from a mixture of the diol, oxalic acid, and benzene.[9)] As shown in Chart 4 for the reaction of **1p**, the successful result is conceivable by postulating the tetrahedral intermediate **9**,[14)] which would lead to **2p** through **9**·H$^+$. We indeed obtained **2p** in 79% yield according to this

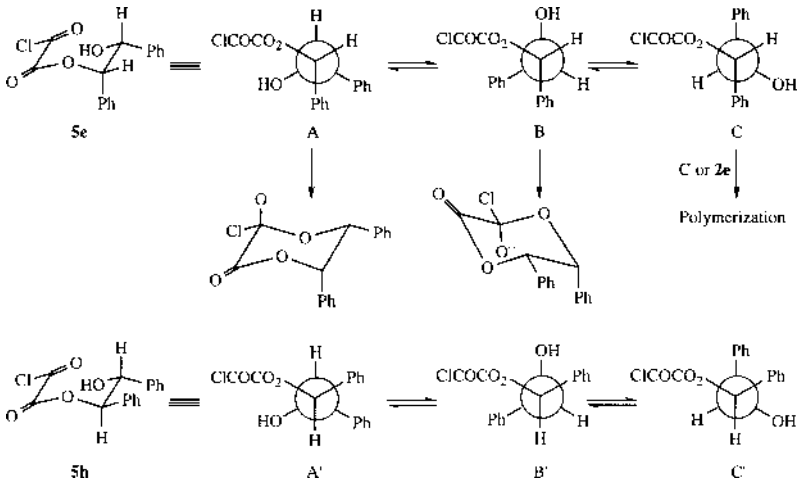



Chart 3

Table 2. Reactions of Oxalyl Chloride with Hydrobenzoins (**1e**, **h**) in the Presence of Triethylamine in Various Solvents[a)]

| Solvent | *meso*-Hydrobenzoin (**1e**) Yield (%)[b)] | | | (±)-Hydrobenzoin (**1h**) Yield (%)[b)] | | |
|---|---|---|---|---|---|---|
| | **2e** | **3e** | Polymers | **2h** | **3h** | Polymers |
| Benzene[c)] | 48 | 33 (30) | 19 | 26 | 74 (60) | 0 |
| Toluene[d)] | 43 | 32 (31) | 23 | 25 | 75 (61) | 0 |
| Chloroform[d)] | 20 | 42 (29) | 38 | 16 | 81 (72) | 0 |
| Dichloromethane[d)] | 26 | 40 (31) | 34 | 17 | 83 (69) | 0 |
| Diethyl ether[d)] | 52 | 48 (41) | 0 | 24 | 68 (62) | 0 |
| THF[d,e)] | 67 | 33 (29) | 0 | 36 | 64 (58) | 0 |
| 1,4-Dioxane[f)] | 55 | 30 (30) | 0 | 31 | 65 (59) | 0 |
| Acetonitrile[d)] | 20 | 54 (45) | 26 | 22 | 78 (58) | 0 |

*a*) Hydrobenzoin (1 mmol) was treated with oxalyl chloride (1.1 mmol) in the presence of triethylamine (2.2 mmol) in the solvent (12 ml) for 20 min. *b*) The yields were estimated by $^1$H-NMR spectroscopy. Figures in parentheses denote isolated yields. *c*) Carried out at 5 °C. *d*) Carried out at 0 °C. *e*) Taken from ref. 13*b*. *f*) Carried out at room temperature.

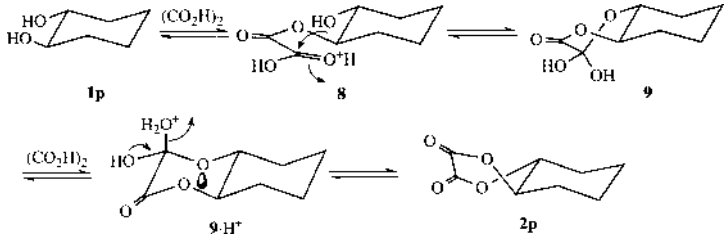



Chart 4

procedure, but **2h** could not be obtained in a similar manner.[16)]

Assuming that the neutral intermediate **6h**·H from **1h** does not undergo fragmentation, but **7h**·H changes into **2h** as illustrated in Chart 5, we might effectively suppress the formation of **3h** by preventing the dissociation of **6h**·H into the anion **6**$^-$**h**. In the absence of a base, however, we already found that **1k** provided **3k** probably through **6k**·$H_2^+$.[13b)] Our next task was accordingly to test an appropriately weaker base than triethylamine. Table 3 summarizes the base effects on the product patterns of the reactions of **1e**, **h**. It was found that the use of pyridine most effectively controlled the formation of **3h**. We thus obtained **2h** in 69% yield for the first time. Although the formation of **3e** was also effectively in-

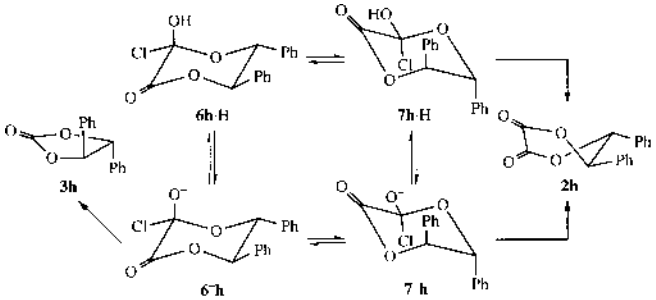



Chart 5

hibited by the use of pyridine, considerable amounts of the oxalate polymers were formed at the cost of the yield of **2e**. The formation of the polymers might be accounted for in view of stronger acidity of pyridine hydrochloride than that of triethylamine hydrochloride. Although it was possible to suppress the formation of the polymers by increasing the volume of the solvent (Table 4, entry 5) or by the use of 2,4,6-collidine instead of pyridine, we failed to remove a small amount of **3e** by means of recrystallization.

The results reported in Table 4 stress the importance of the use of pyridine in place of triethylamine for dramatic reversals of the product ratios in the reactions with other *threo*-compounds **1g**, **i**, *trans*-1,2-cycloalkanediols **1q**, **r** and pinacol (**1k**). Thus compound **2g**, **i**, **q**, **r** were obtained in 50%, 75%, 80%, and 82% yields, respectively, for the first time. Compound **2k**, which had been obtained in only 0.8% yield,[13b)] was produced in 85% yield by the present method. Relatively slow reaction of the tertiary diol **1k** evoked our interest in the reaction products from (±)-2-methyl-2,3-butanediol (**1j**). This compound underwent reaction with oxalyl chloride at 0 °C, giving the cyclic oxalate **2j** and presumably a diastereomeric mixture of bis(2-hydroxy-1,2-dimethylpropyl) oxalates. Although the main product **2j** is not so stable as **2k**, it could be obtained by flash chromatography on silica gel in 16% yield together with the latter (20%). Unfortunately, the reactions of the *erythro*-compounds **1d**, **f** were

Table 3. Reactions of Oxalyl Chloride with Hydrobenzoins (**1e**, **h**) in the Presence of Different Bases in THF[a)]

| Base | *meso*-Hydrobenzoin (**1e**) Yield (%)[b)] | | | (±)-Hydrobenzoin (**1h**) Yield (%)[b)] | | |
|---|---|---|---|---|---|---|
| | **2e** | **3e** | Polymers | **2h** | **3h** | Polymers |
| Triethylamine | 67[c)] | 33 (29)[c)] | 0[c)] | 36 | 64 (58) | 0 |
| Ethyldiisopropylamine | 67 | 31 (26) | 0 | 16 | 84 (70) | 0 |
| Cyclohexyldiethylamine | — | — | — | 26 | 74 (71) | 0 |
| 1,2,2,6,6-Pentamethylpiperidine | 49 | 39 | 0 | 5 | 91 (86) | 0 |
| *N*,*N*-Diethylaniline | —[d)] | —[d)] | —[d)] | 13 | 87 (70) | 0 |
| Pyridine | 27 | 2 (2) | —[e)] | 92 (69) | 7 (5) | 0 |
| 2,6-Lutidine | — | — | — | 87 (38) | 12 (12) | 0 |
| 2,4,6-Collidine | 95 | 5 | 0 | 87 (45) | 13 (8) | 0 |
| 2-Methoxypyridine | — | — | — | 82 (33) | 10 (9) | 0 |
| DBN[f)] | 0 | 0 | 0 | — | — | — |
| Tributylphosphine | 47 | 0 | 6 | — | — | — |
| Butyllithium | —[d)] | —[d)] | —[d)] | —[d)] | —[d)] | —[d)] |
| Sodium hydride | —[d)] | —[d)] | —[d)] | —[d)] | —[d)] | —[d)] |
| Potassium carbonate | 0 | 0 | 0 | — | — | — |

*a*) Hydrobenzoin (0.5 mmol) was treated with oxalyl chloride (0.55 mmol) in the presence of base (2.5 mmol) in THF (12 ml) at 0 °C for 15 min. *b*) The yields were estimated by $^1$H-NMR spectroscopy. Figures in parentheses denote isolated yields. *c*) Taken from ref. 13*b* (2.2 mol eq of triethylamine was used). *d*) A complex mixture of products. *e*) Not determined. *f*) DBN: 1,5-diazabicyclo[4.3.0]non-5-ene.

Table 4. Reactions of Oxalyl Chloride and Glycols **1** in THF in the Presence of Pyridine

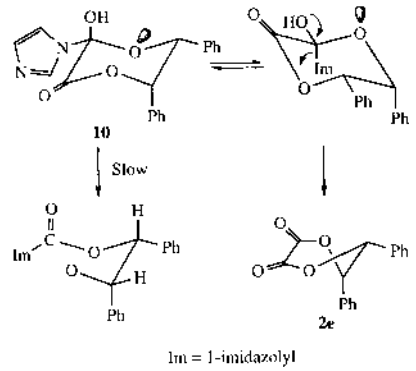
| Entry | Glycol | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Reaction conditions[a)] | | | Yield (%)[b)] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Solvent[c)] (ml) | Temp. (°C) | Time (min) | **2** | **3** | Polymers |
| 1 | **1a** | H | H | H | H | 5 | 0 | 20 | —[d)] (90[e)]) | 0 | —[d)] |
| 2 | **1b**[f)] | H | H | H | Me | 5 | 0 | 25 | 26 (71[e)]) | 0 | 74 |
| 3 | **1c**[f)] | H | H | H | Ph | 110 | 0 | 30 | 81 (48) | 0 | 19 |
| 4 | **1d** | H | Me | H | | 110 | 0 | 40 | 49 (49[e)]) | 0[g)] | 51 |
| 5 | **1e** | H | Ph | H | Ph | 113 | 0 | 60 | 88 (—[h)]) | 4 | 8 |
| 6 | **1f**[f)] | H | Ph | H | $Me_2CH$ | 24 | 0 | 15 | 25 (—[h)]) | 1 | 74 |
| 7 | **1g**[f)] | Me | H | H | Me | 110 | 0 | 40 | 92 (50[e)]) | 0 | 8 |
| 8 | **1h**[f)] | Ph | H | H | Ph | 24 | 0 | 15 | 92 (69) | 7 (5) | 0 |
| 9 | **1i**[f)] | Ph | H | H | $Me_2CH$ | 26 | 0 | 15 | 95 (75) | 4 (2) | 0 |
| 10 | **1j**[f)] | Me | H | Me | Me | 25 | 0 | 60 | —[d)] (16[i,j)]) | 0 | —[d)] |
| 11 | **1k** | Me | Me | Me | Me | 24 | r.t. | 480 | —[d)] (85[i)]) | —[d)] (0.7) | —[d)] |
| 12 | **1l** | $R^1=R^3=H$, $R^2R^4=(CH_2)_3$ | | | | 110 | 0 | 40 | 88 (31[e)]) | 0[g)] | 9 |
| 13 | **1m** | $R^1=R^3=H$, $R^2R^4=(CH_2)_4$ | | | | 110 | 0 | 40 | 79 (58[e)]) | 0 | 14 |
| 14 | **1n** | $R^1=R^3=H$, $R^2R^4=(CH_2)_6$ | | | | 110 | 0 | 40 | 64 (38[e)]) | 3 | 33 |
| 15 | **1o**[f)] | $R^2=R^3=H$, $R^1R^4=(CH_2)_3$ | | | | 110 | 0 | 40 | 10 (—[h)]) | 0 | 90 |
| 16 | **1p**[f)] | $R^2=R^3=H$, $R^1R^4=(CH_2)_4$ | | | | 110 | 0 | 40 | 78 (74[e)]) | 0 | 9 |
| 17 | **1q**[f)] | $R^2=R^3=H$, $R^1R^4=(CH_2)_5$ | | | | 110 | 0 | 40 | 87 (80) | 1 | 12 |
| 18 | **1r**[f)] | $R^2=R^3=H$, $R^1R^4=(CH_2)_6$ | | | | 110 | 0 | 40 | 92 (82[e)]) | 3 (0.9) | 5 |

*a*) Except for entries 4, 7, 12, 15, and 17, the diols **1** were treated with 1.1 mol eq of oxalyl chloride and 5 mol eq of pyridine; compounds **1o**, **q** were treated with 1.3 mol eq of oxalyl chloride and 5 mol eq of pyridine; compounds **1d**, **g**, **l** were treated with 1.5 mol eq of oxalyl chloride and 7.5 mol eq of pyridine. *b*) The yields were estimated by $^1$H-NMR spectroscopy. Figures in parentheses denote isolated yields. *c*) Volume per mmol of **1**. *d*) Not determined. *e*) Obtained by Kugelrohr distillation of a mixture of the products. *f*) Racemic modification. *g*) Determined by means of thin-layer chromatography. *h*) Could not be isolated. *i*) Obtained by flash chromatography on silica gel. *j*) A diastereomeric mixture of bis(2-hydroxy-1,2-dimethylpropyl) oxalates was obtained in 20% yield.

again disturbed by the formation of the polymers. Although **2d** was obtainable by pyrolytic distillation,[13b] isolation of the benzylic compound **2f** was unsuccessful. However, this compound **2f** was obtained in 76% yield by the use of 2,4,6-collidine. On the other hand, neither pyridine (entry 15) nor 2,4,6-collidine[17] had the advantage over triethylamine[14] for the formation of the cyclic oxalate **2o** from *trans*-1,2-cyclopentanediol (**1o**). We have already reported the preparation of the cyclic oxalates **2m**, **p** from *cis*- and *trans*-1,2-cyclohexanediols (**1m**, **p**) by the reaction with oxalyl chloride in the presence of triethylamine.[14] These compounds **2m**, **p** were also obtainable in the presence of pyridine (entries 13 and 16). It should be stated in this connection that syntheses of the cyclic oxalates have already been reported by the reactions of cyclohexanediols such as 1-benzyloxy-5,6,7,8-tetrahydronaphthalene-6,7-diol[10a,b] and methyl 4,6-*O*-benzylidene-$\alpha$-D-glucopyranoside[10c] with oxalyl chloride in the presence of pyridine.

The strategy we finally adopted to obtain hitherto unavailable **2e** was to retard the C–C bond cleavage by canceling the stereoelectronic effect from the chlorine atom in the intermediate (type **6**·H or $\mathbf{6}^-$ in Chart 2), which is formed in the reaction with oxalyl chloride. The reagent we selected was 1,1′-oxalyldiimidazole. Because the nonbonding electron pair on the N(1) atom of the putative intermediate **10** should be employed for aromatization of the imidazole ring, it is of no assistance in breaking the C–C bond as shown in Chart 6. Indeed, no trace of the carbonate **3e** was formed from **1e** in the reaction with 1,1′-oxalyldiimidazole, and the pure cyclic oxalate **2e** was obtained in 64% yield. Compound **2f** was also obtainable in 69% yield according to this procedure.

The cyclic oxalates other than **2j**, **k** were found to be decomposed on silica gel almost instantly. As had been observed with the cyclic oxalates of *meso*-2,3-butanediol (**1d**) and (−)-2,3-butanediol,[7] **2a**—**i**, **l**—**r** were all highly sensitive to hydrolysis even in plain water at room temperature. When a solution of **2h** in water–acetone (1 : 1, v/v) was kept at room temperature for 24 h, (*R**,*R**)-(2-hydroxy-1,2-diphenyl)ethyl hydrogen ethanedioate (**11h**) was obtained in 94% yield. The diastereomer **11e** was not formed, showing that unusual $S_N1$ mechanism did not work in the hydrolysis of **2h**. The half-ester **11h** did not undergo further reaction under these conditions. The rate of the first hydrolysis of **2h**




Im = 1-imidazolyl

Chart 6

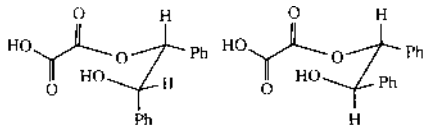



Table 5. Pseudo-First-Order Rate Constants for the First Hydrolysis of the Oxalate Esters in 0.07 M Acetate Buffer (pH 5.69) in Aqueous Acetonitrile at 25 °C

| Entry | Substrate | $k_1$ (min$^{-1}$) | Entry | Substrate | $k_1$ (min$^{-1}$) |
|---|---|---|---|---|---|
| 1 | **12** | $1.5\times10^{-4}$ | 8 | **2c** | $(2.1\pm0.1)\times10^{-1}$ |
| 2 | **2a** | $(1.5\pm0.1)\times10^{-1}$ | 9 | **2h** | $(2.2\pm0.1)\times10^{-1}$ |
| 3 | **2b** | $(1.1\pm0.0)\times10^{-1}$ | 10 | **2i** | $(9.0\pm0.1)\times10^{-2}$ |
| 4 | **2d** | $(7.8\pm0.8)\times10^{-2}$ | 11 | **2l** | $(2.3\pm0.1)\times10^{-1}$ |
| 5 | **2g** | $(8.6\pm0.2)\times10^{-2}$ | 12 | **2m** | $(7.5\pm0.0)\times10^{-2}$ |
| 6 | **2j** | $7.4\times10^{-3}$ | 13 | **2p** | $(6.4\pm0.3)\times10^{-2}$ |
| 7 | **2k** | $1.5\times10^{-4}$ | 14 | **2n** | $(4.7\pm0.0)\times10^{-2}$ |
| | | | 15 | **2r** | $(3.9\pm0.2)\times10^{-2}$ |

was determined in aqueous acetonitrile because the substrate is hardly dissolved in plain water. As it was difficult to follow too rapid hydrolysis of **2h** at pH 6 or above, the pseudo-first-order rate constant was determined for the reaction in 0.07 M acetate buffer in aqueous acetonitrile (pH 5.69) at 25 °C. The result is shown in Table 5 together with those obtained for the reactions of **2a**—**d**, **g**, **i**—**n**, **p**, **r**.

The pseudo-first-order rate constant ($1.5\times10^{-1}$ min, $t_{1/2}$ 4.6 min) for the first hydrolysis of the prototype **2a** of a cyclic oxalate (entry 2) was 1000 times larger than that ($1.5\times10^{-4}$ min) of the acyclic analogue **12** (entry 1) under identical conditions. Among **2a**—**d**, **g**—**i**, **l**—**n**, **p**, **r** the cyclopentane derivative **2l** underwent hydrolysis fastest (entry 11), but not more than only six times faster than the most unreactive one **2r** (entry 15). It can be seen from entries 8 and 9 that phenyl substituent(s) rather accelerate the reaction, while alkyl substituents (entries 3—7, 10, 12—15) other than trimethylene (entry 11) retard the reaction. Entries 2—7 show that increasing number of methyl substituents decreases the rate of hydrolysis. Thus the cyclic oxalate **2j** with three methyl groups underwent hydrolysis 20 times more slowly than **2a**. The rate for the hydrolysis of fully substituted one **2k** was as small as that of acyclic oxalate **12**. This exceptionally low reactivity of **2k** may be interpreted in terms of steric hindrance of the methyl groups: as shown in Chart 2, two of the four methyl groups of **2k** are always situated almost perpendicular to the plane consisting of the two carbonyl groups,[18] blocking either side of the carbonyl plane from nucleophilic attack.

In conclusion, various cyclic oxalates **2** have become accessible by the reactions between oxalyl chloride and glycols **1** by controlling the formation of the cyclic carbonates **3** by the use of pyridine instead of triethylamine. 2,4,6-Collidine was shown superior to pyridine in suppressing the formation of polymers for the reactions with *erythro*-1,2-disubstituted ethylene glycols **1e**, **f**, and imidazole was a good choice of bases for the selective formation of the cyclic oxalates **2e**, **f**. Preliminary kinetic studies with some selected cyclic oxalates **2** have revealed that these compounds other than trisubstituted and tetrasubstituted ones undergo hydrolysis 260—1500 times more rapidly than diethyl oxalate (**12**). It also has been suggested that the number and the nature of the substituents largely affect the rate of hydrolysis. More detailed information about the structure–reactivity relationship has to await further studies.

## Experimental

**General Notes** All melting points were determined using a Yamato MP-1 or Büchi model 530 capillary melting point apparatus and values are corrected. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer, a Shimadzu FTIR-8100 or a FTIR-8400 IR spectrophotometer, a JEOL JNM-EX-270 or a JEOL JNM-GSX-500 NMR spectrometer (measured at 25 °C with $Me_4Si$ as an internal standard). For the measurements of pH values, a Toa HM-18ET pH meter equipped with a Toa type GST-5211C glass electrode was employed. Elemental analyses and MS measurements were performed by Dr. M. Takani and her associates at Kanazawa University. The following abbreviations are used: br=broad, d=doublet, dd=doublet-of-doublets, ddd=doublet-of-doublets-of-doublets, dq=doublet-of-quartets, dqq=doublet-of-quartets-of-quartets, m=multiplet, q=quartet, s=singlet, sh=shoulder.

**(±)-2-Methyl-2,3-butanediol (1j)** A 2.3% (w/v) osmium tetroxide solution (1 ml) in 1,1-dimethylethanol was added to a mixture of 2-methyl-2-butene (700 mg, 10 mmol), *N*-methylmorpholine-*N*-oxide monohydrate (1.62 g, 12 mmol), water (5 ml), and acetone (50 ml), and the whole was stirred at room temperature for 3 h. Sodium metabisulfite (2.7 g, 14 mmol) was added to the resulting mixture, and stirring was continued for a further 30 min. The mixture was diluted with water (50 ml), brought to pH 5 with 10% hydrochloric acid, saturated with sodium chloride, and extracted with dichloromethane (3×20 ml) and ethyl acetate (7×20 ml). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to leave a brown oil (662 mg). Flash chromatography [hexane–ethyl acetate (1 : 4, v/v)] of this product provided **1j**[19] (549 mg, 53%) as a colorless oil; IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400 (OH). $^1$H-NMR ($CDCl_3$) $\delta$: 1.16 (3H, d, $J$=6.6 Hz, CHMe), 1.16, 1.21 (3H each, s, $CMe_2$), 1.96 (1H, s, $Me_2COH$), 2.19 (1H, d, $J$=4.0 Hz, CHOH), 3.62 (1H, dq, $J$=4.0, 6.6 Hz, CHMe).

**Reactions of Glycols with Oxalyl Chloride in the Presence of Pyridine** The procedures for the synthesis of new compounds **2g**—**j**, **q**, **r** are described below as typical examples. Other compounds **2a**—**d**, **k**[13b] and **2l**—**n**, **p**[14] obtained under conditions specified in Table 4 were identical (by comparison of the IR and $^1$H-NMR spectra) with their corresponding authentic samples.

**(±)-*trans*-5,6-Dimethyl-1,4-dioxane-2,3-dione (2g)** A solution of **1g** (270 mg, 3 mmol) and pyridine (1.85 ml, 22.9 mmol) in THF (300 ml) was cooled with ice-water and then a solution of oxalyl chloride (0.38 ml, 4.5 mmol) in THF (30 ml) was added dropwise over a period of 30 min. The mixture was stirred at 0 °C for a further 10 min and concentrated *in vacuo* to *ca.* 20 ml. The resulting precipitate was filtered off and washed with THF (20 ml). The filtrate and washings were combined and concentrated *in vacuo.* The residue was submitted to Kugelrohr distillation. The distillate (50 mg) obtained at 120—140 °C and 0.8 mmHg was recrystallized from carbon tetrachloride to give a first crop of **2g** (18 mg), mp 80.5—82 °C (softened below 40 °C). Pure **2g** (151 mg, the total yield was 50%) was obtained as the distillate running at 140—180 °C and 0.8 mmHg, mp 80.5—82 °C (softened below 40 °C). Recrystallization of this sample from carbon tetrachloride gave an analytical sample of **2g** as colorless pillars, mp 82.5—84.5 °C (softened at 30—35 °C). MS *m/z*: 145 ($M^+$+1). UV $\lambda_{max}^{MeCN}$ nm ($\varepsilon$): 272 (54). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1771, 1748 (C=O); $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1780 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.46 (6H, m, two Me's), 4.59 (2H, m, two CH's). $^{13}$C-NMR ($CDCl_3$) $\delta$: 16.4 (Me), 78.8 (CH), 153.3 (C=O). *Anal.* Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.78; H, 5.59.

**(±)-*trans*-5,6-Diphenyl-1,4-dioxane-2,3-dione (2h)** A solution of oxalyl chloride (0.19 ml, 2.2 mmol) in THF (8 ml) was added to an ice-cooled solution of **1h** (429 mg, 2 mmol) and pyridine (0.80 ml, 9.9 mmol) in THF (40 ml) over a period of 5 min. The mixture was stirred at 0 °C for 10 min and concentrated *in vacuo.* The residue was partitioned between ethyl acetate (50 ml) and water (20 ml). The organic layer was washed successively with 5% aqueous citric acid and saturated aqueous sodium bicarbonate (20 ml each), dried over magnesium sulfate, and concentrated to afford a solid residue (526 mg), mp 138—154 °C. The molar ratio of **2h** and **3h** in this product was 93 : 7. Recrystallization of this material from hexane–dichloromethane (2 : 1, v/v) afforded **2h** (370 mg, 69%) as colorless prisms, mp 160.5—163.5 °C. The mother liquor was concentrated and the residue was purified by flash chromatography [hexane–dichloromethane (1 : 10, v/v)] followed by thin-layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] to afford **3h**[13b] (26 mg, 5.4%), mp 107.5—109 °C.

Further recrystallization of crude **2h** from ether–dichloromethane (5 : 1, v/v) afforded an analytical sample of **2h** as colorless prisms, mp 164—165 °C. MS *m/z*: 268 ($M^+$). UV $\lambda_{max}^{MeCN}$ nm ($\varepsilon$): 251 (560), 257 (620), 262 (580), 267 (400). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1782, 1755 (C=O); $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1782 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 5.69 (2H, s, two CH's), 7.07 (4H), 7.21—7.36 (6H) (m each, two Ph's). $^{13}$C-NMR ($CDCl_3$) $\delta$: 84.3 (CH), 127.3, 128.7, 130.0, 131.5 (Ph), 153.0 (C=O). *Anal.* Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.75; H, 4.41.

**(±)-*trans*-5-Isopropyl-6-phenyl-1,4-dioxane-2,3-dione (2i)** Compound **1i** (83 mg, 0.46 mmol) was treated with oxalyl chloride in a manner similar to that described for the preparation of **2h**, and the reaction mixture was concentrated *in vacuo.* The residue was partitioned between ethyl acetate (20 ml) and water (10 ml). The organic layer was washed successively with 5% aqueous citric acid and saturated aqueous sodium bicarbonate (10 ml each), dried over magnesium sulfate, and concentrated to afford a solid residue (106 mg), mp 96—103 °C. The molar ratio of **2i** and **3i** in this product was 96 : 4. Recrystallization of this material from hexane–ether (1 : 1, v/v) afforded **2i** (81 mg, 75%) as colorless prisms, mp 113.5—116 °C. The mother liquor of recrystallization was concentrated and the residue was purified by thin-layer chromatography on silica gel [hexane–ethyl acetate (4 : 1, v/v)] to afford **3i**[13b] (2 mg, 2.1%) as a colorless viscous oil.

Further recrystallization of **2i** afforded an analytical sample of **2i** as colorless prisms, mp 118—119.5 °C. MS *m/z*: 234 ($M^+$). UV $\lambda_{max}^{MeCN}$ nm ($\varepsilon$): 250

(280), 257 (320), 262 (300), 267 (210). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1790, 1761 (C=O); $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1784 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.02, 1.06 (3H each, d, $J$=6.8 Hz, $Me_2$), 1.66 (1H, dqq, $J$=6.8, 6.8, 2.4 Hz, C<u>H</u>$Me_2$), 4.67 (1H, dd, $J$=2.4, 8.8 Hz, C<u>H</u>CHMe$_2$), 5.57 (1H, d, $J$=8.8 Hz, PhC<u>H</u>), 7.36—7.42 (2H), 7.44—7.51 (3H, m each, Ph). $^{13}$C-NMR ($CDCl_3$) $\delta$: 14.8, 19.4 ($Me_2$), 28.4 (<u>C</u>$Me_2$), 82.1 (<u>C</u>CMe$_2$), 85.8 (Ph<u>C</u>), 127.3, 129.4, 130.5, 132.2 (Ph), 153.2, 153.5 (C=O). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.67; H, 5.99.

**5,5,6-Trimethyl-1,4-dioxane-2,3-dione (2j)** A solution of oxalyl chloride (0.27 ml, 3.2 mmol) in THF (12 ml) was added to an ice-cooled solution of **1j** (297 mg, 2.85 mmol) and pyridine (1.15 ml, 14.2 mmol) in THF (60 ml) over a period of 10 min. The mixture was stirred at 0 °C for 50 min and concentrated *in vacuo.* The residue was partitioned between ethyl acetate (30 ml) and water (10 ml). The organic layer was washed successively with water, 5% aqueous citric acid, water, and saturated aqueous sodium bicarbonate (10 ml each), dried over magnesium sulfate, and concentrated to afford a colorless oil (272 mg). This was a mixture of **2j** and bis(2-hydroxy-1,2-dimethylpropyl) oxalates (the molar ratio was 3 : 1). Flash chromatography [hexane–ethyl acetate (1 : 1, v/v)] of this product gave **2j** (74 mg, 16%) as a colorless oil, MS *m/z*: 159 ($M^+$+1). IR $\nu_{max}^{neat}$ cm$^{-1}$: 1779 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.45 (3H, d, $J$=6.6 Hz, CH<u>Me</u>), 1.49 (6H, s, $CMe_2$), 4.70 (1H, q, $J$=6.6 Hz, C<u>H</u>Me). $^{13}$C-NMR ($CDCl_3$) $\delta$: 15.7, 20.5, 24.8 (Me), 80.1 (<u>C</u>HMe), 84.0 (<u>C</u>Me$_2$), 153.1, 153.5 (C=O).

Further elution of the column afforded a 1 : 1 mixture of *meso*- and (±)-bis(2-hydroxy-1,2-dimethylpropyl) oxalates (76 mg, 20%) as a colorless oil, MS *m/z*: 245 ($M^+$−OH). IR $\nu_{max}^{neat}$ cm$^{-1}$: 3409 (OH), 1765, 1732 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.25 (24H, s, four $CMe_2$'s), 1.33 (12H, d, $J$=6.3 Hz, four CH<u>Me</u>'s), 1.85, 2.48 (2H each, br, four OH's), 4.91, 4.92 (2H each, q, $J$=6.3 Hz, four C<u>H</u>Me's). $^{13}$C-NMR ($CDCl_3$) $\delta$: 14.6, 14.7, 24.2, 24.4, 26.2 (Me), 71.79, 71.83 (<u>C</u>HMe), 80.4 (<u>C</u>Me$_2$), 157.4, 157.5 (C=O).

**(±)-*trans*-Hexahydro-5*H*-cyclohepta-1,4-dioxin-2,3-dione (2q)** A solution of **1q**[20] (260 mg, 2 mmol) and pyridine (0.8 ml, 10 mmol) in THF (200 ml) was cooled with ice-water and then a solution of oxalyl chloride (0.22 ml, 2.6 mmol) in THF (20 ml) was added dropwise over a period of 30 min under nitrogen. The mixture was stirred at 0 °C for a further 10 min, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo*, and the solid residue was recrystallized from carbon tetrachloride to give **2q** (301 mg, 80%). Further recrystallization from carbon tetrachloride and drying over phosphorus pentoxide at 2 mmHg and room temperature for 17 h afforded an analytical sample of **2q** as colorless needles, mp 80—84.5 °C. MS *m/z*: 185 ($M^+$+1). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1767, 1749 (C=O); $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1778 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.42—1.93 (8H), 2.09—2.17 [2H, m each, $(CH_2)_5$], 4.53 (2H, m, two CH's). $^{13}$C-NMR ($CDCl_3$) $\delta$: 21.8, 26.3, 28.8 ($CH_2$), 83.4 (CH), 153.6 (C=O). *Anal.* Calcd for $C_9H_{12}O_4 \cdot 1/4H_2O$: C, 57.29; H, 6.68. Found: C, 57.26; H, 6.69.

**(±)-*trans*-Octahydrocycloocta-1,4-dioxin-2,3-dione (2r)** A solution of **1r** (288 mg, 2 mmol) and pyridine (0.81 ml, 10 mmol) in THF (200 ml) was cooled with ice-water and then a solution of oxalyl chloride (0.19 ml, 2.2 mmol) in THF (20 ml) was added dropwise over a period of 30 min. The mixture was stirred at 0 °C for a further 10 min and concentrated *in vacuo* to *ca.* 20 ml. The resulting precipitate was filtered off and washed with THF (30 ml). The filtrate and washings were combined and concentrated *in vacuo.* The residue was submitted to Kugelrohr distillation. Compound **2r** (325 mg, 82%) was collected at 200—250 °C and 0.8 mmHg, mp 111—117 °C. Recrystallization of this product from carbon tetrachloride gave an analytical sample of **2r** as colorless pillars, mp 119—120 °C. MS *m/z*: 199 ($M^+$+1). UV $\lambda_{max}^{CH_3CN}$ nm ($\varepsilon$): 273 (56). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1779, 1771, 1759, 1750 (C=O); $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1779 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 1.61 (4H), 1.75 (4H), 1.99 (2H), 2.11 (2H) [m each, $(CH_2)_6$], 4.71 (2H, m, two CH's). $^{13}$C-NMR ($CDCl_3$) $\delta$: 22.8, 25.6, 28.3 ($CH_2$), 82.3 (CH), 153.9 (C=O). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.53; H, 7.06.

**Reaction of (±)-*erythro*-3-Methyl-1-phenylbutane-1,2-diol (1f) with Oxalyl Chloride in the Presence of 2,4,6-Collidine** A solution of oxalyl chloride (0.056 ml, 0.66 mmol) in THF (2.5 ml) was added to an ice-cooled solution of **1f** (108 mg, 0.599 mmol) and 2,4,6-collidine (0.40 ml, 3 mmol) in THF (12 ml) over a period of 5 min. The mixture was stirred at 0 °C for 10 min and concentrated *in vacuo.* The residue was partitioned between ethyl acetate (30 ml) and water (10 ml). The organic layer was washed successively with 5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, and water (10 ml each), dried over magnesium sulfate, and concentrated to afford a colorless solid (135 mg), mp 89.5—95 °C. The molar ratio of **2f** and **3f** in this product was 94 : 6. Recrystallization of this material from carbon tetrachloride afforded (±)-*cis*-5-isopropyl-6-phenyl-1,4-dioxane-2,3-dione (**2f**) (107 mg, 76%) as colorless prisms, mp 93—94.5 °C. The mother liquor of recrystallization was concentrated and the residue was purified by thin-layer chromatography on silica gel [hexane–ethyl acetate (2 : 1, v/v)] to afford **3f**[13b] (7 mg, 6%), mp 60—61.5 °C.

Further recrystallization of crude **2f** from carbon tetrachloride afforded an analytical sample of **2f** as colorless prisms, mp 95.5—96.5 °C. MS *m/z*: 234 ($M^+$). UV $\lambda_{max}^{CH_3CN}$ nm ($\varepsilon$): 250 (sh) (510), 257 (470), 262 (430), 268 (sh) (310). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1790, 1761 (C=O); $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1784, 1765 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 0.98, 1.07 (3H each, d, $J$=6.8 Hz, $Me_2$), 1.88 (1H, m, C<u>H</u>$Me_2$), 4.67 (1H, dd, $J$=2.9, 7.8 Hz, C<u>H</u>CHMe$_2$), 5.80 (1H, d, $J$=2.9 Hz, PhC<u>H</u>), 7.32—7.37 (2H), 7.43—7.48 (3H) (m each, Ph). $^{13}$C-NMR ($CDCl_3$) $\delta$: 18.3, 19.2 ($Me_2$), 28.6 (<u>C</u>$Me_2$), 80.9 (<u>C</u>CMe$_2$), 85.2 (Ph<u>C</u>), 127.1, 129.3, 129.9, 131.8 (Ph), 153.0, 153.4 (C=O). *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.43; H, 5.98.

**Reaction of *meso*-Hydrobenzoin (1e) with Oxalyl Chloride in the Presence of Imidazole** Oxalyl chloride (0.17 ml, 1.99 mmol) was added dropwise to an ice-cooled solution of imidazole (545 mg, 8.01 mmol) in THF (20 ml), and the mixture was stirred at 0 °C for 10 min under nitrogen. To the resulting yellow suspension was added a solution of **1e** (429 mg, 2 mmol) in THF (20 ml) over a period of 10 min. The mixture was then stirred at room temperature under nitrogen for 24 h. The resulting precipitate was filtered off and washed with THF (10 ml). The filtrate and washings were combined and concentrated *in vacuo.* The residue was partitioned between ethyl acetate (70 ml) and water (30 ml). The organic layer was washed successively with 5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, and water (30 ml each), dried over magnesium sulfate, and concentrated *in vacuo*, leaving *cis*-5,6-diphenyl-1,4-dioxane-2,3-dione (**2e**) (342 mg, 64%) as a colorless solid, mp 125—128 °C. Recrystallization of this product from hexane–ethyl acetate (1 : 1, v/v) afforded an analytical sample of **2e** as colorless prisms, mp 128—129.5 °C. MS *m/z*: 268 ($M^+$). UV $\lambda_{max}^{CH_3CN}$ nm ($\varepsilon$): 257 (930), 262 (800), 267 (sh) (570). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1777, 1771, 1765 (C=O); $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1788, 1769 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 6.01 (2H, s, two CH's), 6.88—6.94 (4H), 7.25—7.32 (4H), 7.33—7.38 (2H) (m each, two Ph's). $^{13}$C-NMR ($CDCl_3$) $\delta$: 82.0 (CH), 126.8, 128.6, 129.6, 130.7 (Ph), 153.1 (C=O). *Anal.* Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.67; H, 4.46.

**(*R**,*S**)-2-Hydroxy-1,2-diphenylethyl Hydrogen Ethanedioate (11e)** Water (15 ml) was added to a solution of a mixture of **2e** and **3e** (the molar ratio was 2 : 1, 514 mg) in acetone (15 ml), and the resulting solution was allowed to stand at room temperature for 24 h. The solution was concentrated to half the initial volume *in vacuo*, and saturated aqueous sodium bicarbonate (30 ml) was added to the resulting suspension. The solution thus obtained was washed successively with chloroform (30 ml) and ethyl acetate (2×30 ml), brought to pH 1 by addition of 10% hydrochloric acid, and extracted with ether (2×20 ml). The ethereal extracts were dried over magnesium sulfate and concentrated *in vacuo*, leaving **11e** (233 mg) as a colorless solid, mp 117—120 °C (dec.). Recrystallization of this product from hexane–ethyl acetate (1 : 1, v/v) afforded an analytical sample of **11e** as colorless prisms, mp 129.5—130.5 °C (dec.). MS *m/z*: 286 ($M^+$). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3328 (OH), 1761, 1698 ($COCO_2H$). $^1$H-NMR [$(CD_3)_2SO$] $\delta$: 3.4, 5.8 (1H each, br, OH and $CO_2H$), 4.95 (1H, d, $J$=5.9 Hz, C<u>H</u>OH), 5.86 (1H, d, $J$=5.9 Hz, C<u>H</u>OCOCO$_2$H), 7.19—7.32 (10H, m, two Ph's). $^{13}$C-NMR [$(CD_3)_2SO$] $\delta$: 74.0 (<u>C</u>HOH), 80.4 (<u>C</u>HCHOH), 127.1, 127.4, 127.6, 127.8, 128.0, 136.4, 140.9 (Ph), 158.2, 159.1 ($COCO_2H$). *Anal.* Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.95; H, 4.87.

**(*R**,*R**)-2-Hydroxy-1,2-diphenylethyl Hydrogen Ethanedioate (11h)** Water (7 ml) was added to a solution of **2h** (188 mg, 0.701 mmol) in acetone (7 ml), and the resulting solution was allowed to stand at room temperature for 24 h. The solution was concentrated to half the initial volume *in vacuo*, and saturated aqueous sodium bicarbonate (20 ml) was added to the resulting suspension. The solution thus obtained was washed with dichloromethane (2×10 ml), brought to pH 1 by addition of 10% hydrochloric acid, and extracted with ethyl acetate (3×30 ml). The ethyl acetate layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*, leaving **11h** (188 mg, 94%), mp 126—127.5 °C (dec.). Recrystallization of this product from hexane–ether (1 : 1, v/v) afforded an analytical sample of **11h** as colorless prisms, mp 139.5—140.5 °C (dec.). Chemical ionization (CI)-MS *m/z*: 269 ($M^+$−OH). UV $\lambda_{max}^{MeCN}$ nm ($\varepsilon$): 247 (sh) (330), 252 (380), 258 (440), 263 (360). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3338 (OH), 1759, 1715 ($COCO_2H$). $^1$H-NMR [$(CD_3)_2SO$] $\delta$: 3.4, 5.8 (1H each, br, OH and $CO_2H$), 4.94 (1H, d, $J$=6.8 Hz, C<u>H</u>OH), 5.87 (1H, d, $J$=6.8 Hz, C<u>H</u>OCOCO$_2$H), 7.12—7.26 (10H, m, two Ph's). $^{13}$C-NMR [$(CD_3)_2SO$] $\delta$: 74.6 (<u>C</u>HOH), 81.4 (<u>C</u>HCHOH), 127.2, 127.4, 127.5, 127.7, 127.9, 128.1, 136.4, 140.7 (Ph), 158.5, 159.3 ($COCO_2H$). *Anal.* Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.04; H, 4.88.

**(±)-*trans*-2-Hydroxycyclohexyl Hydrogen Ethanedioate (11p)** Water (24 ml) was added to a solution of **2p** (285 mg, 1.67 mmol) in acetonitrile (6 ml), and the resulting solution was allowed to stand at room temperature for 15 h. The solution was brought to pH 2 by addition of 10% hydrochloric acid, saturated with sodium chloride, and extracted with ether (8×15 ml). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*, leaving crude **11p** (270 mg), mp 130—137 °C. Recrystallization of this product from hexane–ethyl acetate (5 : 1, v/v) afforded **11p** (210 mg, 67%), mp 137.5—139 °C. Further recrystallization from hexane–ethyl acetate (2 : 1, v/v) afforded an analytical sample of **11p** as colorless prisms, mp 140.5—141.5 °C. CI-MS *m/z*: 189 ($M^+ + 1$). UV $\lambda_{max}^{MeCN}$ nm ($\varepsilon$): 258 (sh) (44). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3455 (OH), 1761, 1732 ($COCO_2H$). $^1$H-NMR [$(CD_3)_2SO$] $\delta$: 1.16—1.41 (4H), 1.61 (2H), 1.86 (2H) [m each, $(CH_2)_4$], 3.44 (1H, m, C<u>H</u>OH), 4.60 (1H, ddd, $J$=4.4, 8.8, 10.3 Hz, C<u>H</u>OCOCO$_2$H). $^{13}$C-NMR [$(CD_3)_2SO$] $\delta$: 23.1, 23.3, 29.2, 33.1 ($CH_2$), 70.1 (CHOH), 79.2 (<u>C</u>HOCOCO$_2$H), 158.7, 159.5 ($COCO_2H$). *Anal.* Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 50.93; H, 6.61.

**Kinetic Procedure** The solvent for the hydrolysis of **2** was prepared by diluting 0.1 M acetate buffer (pH 5.00 at 25 °C, 14 ml) with acetonitrile to make the whole volume 20 ml, showing pH 5.69 at 25 °C. The reactions of **2** were followed for 1.48—1.56×$10^{-3}$ M solutions by means of UV spectrophotometric analysis through at least 85% completion of the reaction with at least nine measurements and were found to obey pseudo-first-order kinetics. Each reaction of **2a**—**d**, **g**—**i**, **l**—**n**, **p**, **r** was carried out in duplicate, and the averaged rate constants are collected in Table 5. The pH values of the reaction mixtures after the reactions decreased by not more than 0.03. The hydrolysis of **2h** is described below as a typical example.

Compound **2h** (4.07 mg) was dissolved as quickly as possible in the solvent described above in an ultrasonic bath maintained at 25 °C to make the whole volume 10 ml. The solution (1.52×$10^{-3}$ M) was transferred to a cuvette, which was placed in a cell compartment maintained at 25 °C, without delay. Absorbances ($A_t$) of the mixture at selected times were determined at 262 nm. The absorbance ($A_\infty$) on completion of the reaction was reached in *ca.* 40 min (12 half-lives). A plot of $\ln(A_t - A_\infty)$ against time gave a straight line ($r$=0.999 for 16 determinations) and $k_1$=2.1×$10^{-1}$ $min^{-1}$ was estimated by linear regression analysis.[21] Compound **11h** (4 mg) was obtained from the reaction mixture.

Compounds **2a**, **b**, **d**, **g**, **j**, **k**, **l**—**n**, **p**, **r** having no phenyl group have absorption maxima at 272—273 nm in acetonitrile. Hydrolyses of these compounds were monitored by measuring the decrease in absorbance at 275 nm. The UV spectrum of every reaction mixture at completion was coincident with that of **11p**.

The slow reaction of diethyl oxalate (**12**) was monitored with a solution (1.9×$10^{-3}$ M) by measuring the increase in absorbance at 250 nm. It was shown by thin-layer chromatography that the product was ethyl hydrogen ethanedioate and that oxalic acid was absent in the reaction mixture.[22]

## References and Notes


1) Jones G. I. L., Owen N. L., *J. Mol. Struct.*, **18**, 1—32 (1973).
2) *a*) Stäglich P., Thimm K., Voß J., *Justus Liebigs Ann. Chem.*, **1974**, 671—689; *b*) Katon J. E., Lin S.-L., *J. Mol. Struct.*, **48**, 335—342 (1978); *c*) Jones G. P., Cornell B. A., Horn E., Tiekink E. R. T., *J. Crystallogr. Spectrosc. Res.*, **19**, 715—723 (1989).
3) Schmidt S. P., Schuster G. B., *J. Org. Chem.*, **43**, 1823—1824 (1978).
4) *a*) Wimmer T., Ger. Offen. 2,263,814 [*Chem. Abstr.*, **79**, 79182*y* (1973)]; *b*) Marhold A., Klauke E., Ger. Offen. DE 3,329,126 [*Chem. Abstr.*, **103**, 22602*v* (1985)]; *c*) Nakayama S., Ikeda F., Eur. Pat. Appl. EP 261,977 [*Chem. Abstr.*, **109**, 54784*w* (1988)].
5) *a*) Verter H. S., Potter H., Dominic R., *Chem. Commun.*, **1968**, 973—974; *b*) Forgione P. S., U. S. 3,431,278 [*Chem. Abstr.*, **70**, 96396*c* (1969)]; *c*) Steglich W., Schmidt H., Hollitzer O., *Synthesis*, **1978**, 622—624.
6) *a*) Carothers W. H., Arvin J. A., Dorough G. L., *J. Am. Chem. Soc.*, **52**, 3292—3300 (1930) and earlier references cited therein; *b*) Davies A. G., Hua-De P., Hawari J. A.-A., *J. Organomet. Chem.*, **256**, 251—260 (1983).
7) Ripley L. G., Watson R. W., *Can. J. Chem.*, **29**, 970—973 (1951).
8) White R. C., *Tetrahedron Lett.*, **21**, 1021—1022 (1980).
9) Lloyd W. D., Navarette B. J., Shaw M. F., *Org. Prep. Proced. Int.*, **7**, 207—210 (1975).
10) *a*) Hauck F. P., U. S. 3,943,149 [*Chem. Abstr.*, **85**, 62847*v* (1976)]; *b*) *Idem*, U. S. 4,082,773 [*Chem. Abstr.*, **89**, 108823*x* (1978)]; *c*) Roseman S., Link K. P., *Carbohydr. Res.*, **69**, 301—304 (1979).
11) Ellingboe E. K., Melby L. R., U. S. 2,816,287 [*Chem. Abstr.*, **52**, P12899*g* (1958)].
12) Jäger V., Schohe R., Paulus E. F., *Tetrahedron Lett.*, **24**, 5501—5504 (1983).
13) *a*) Itaya T., Iida T., Eguchi H., *Chem. Pharm. Bull.*, **41**, 408—410 (1993); *b*) Iida T., Itaya T., *Tetrahedron*, **49**, 10511—10530 (1993).
14) Itaya T., Iida T., Natsutani I., Ohba M., *Chem. Pharm. Bull.*, **50**, 83—86 (2002).
15) Itaya T., Iida T., *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1671—1672.
16) This method was also unsuccessful in the preparation of **2l** from *cis*-1,2-cyclopentanediol (**1l**).
17) When 2,4,6-collidine was employed, the estimated yields of **2o** and the oxalate polymers were 29% and 71%, respectively.
18) This structure was supported by X-ray crystallographic analysis: Iida T., Ph. D. Dissertation, Kanazawa University, January 1994.
19) Buist G. J., Bunton C. A., Miles J. H., *J. Chem. Soc.*, **1957**, 4567—4574.
20) Hayashi M., Terashima S., Koga K., *Tetrahedron*, **37**, 2797—2803 (1981).
21) For example, see Bunnett J. F., "Investigation of Rates and Mechanisms of Reactions," 3rd ed., Part I, ed. by Lewis E. S., John Wiley and Sons, New York, 1974, pp. 145—153.
22) For neutral hydrolysis of diethyl oxalate (**12**) in aqueous organic solvents, see Geheb D., Kasanskaja N. F., Beresin I. W., *Ber. Bunsenges. Phys. Chem.*, **76**, 160—169 (1972).