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Studies on Ketene and Its Derivatives. XCVII.[1] Photoreactions of Diketene with Maleic Anhydride and Dimethylmaleic Anhydride

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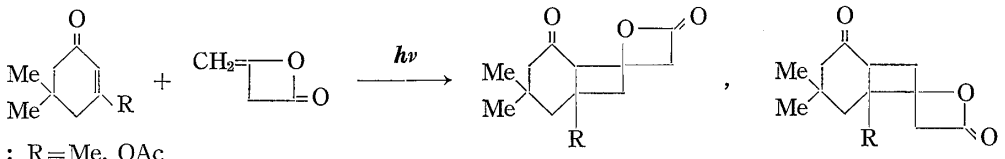
The photoreactions of diketene with maleic anhydride (**4**) and dimethylmaleic anhydride (**6**) gave 2-oxo-1-oxaspiro[3.3]heptane-*cis*-5,6-dicarboxylic anhydride (**5a, b**) and 5,6-dimethyl-2-oxo-1-oxaspiro[3.3]heptane-*cis*-5,6-dicarboxylic anhydride (**7a, b**), respectively.

Treatment of compounds **5** and **7** with hydrogen chloride in ethanol and methanol afforded the corresponding dialkyl 5-alkoxycarbonyl-3-oxoheptanedioate derivatives (**8** and **10**) and (**9** and **11**), respectively.

Keywords——photoreaction; [2+2]cycloaddition; diketene; maleic anhydride; dimethylmaleic anhydride; 2-oxo-1-oxaspiro[3.3]heptane-*cis*-5,6-dicarboxylic anhydrides; 3-oxoheptanedioates

In the preceding paper of this series, we reported the reaction of diketene with olefinic compounds to give spiro-cyclobutane derivatives. For instance, the photolysis of 3,5,5-trimethyl-2-cyclohexenone (**1**, R=Me) and 3-acetoxy-5,5-dimethyl-2-cyclohexenone (**1**, R=OAc) in diketene afforded the spiro-adducts, 8-hydroxy-4,4,6-trimethyl-2-oxo-*cis*-bicyclo[4.2.0]octan-8-ylacetic acid β-lactone (**2**, R=Me) and 6-acetoxy-7-hydroxy-4,4-dimethyl-2-oxo-*cis*-bicyclo-[4.2.0]octan-7-ylacetic acid β-lactone (**3**, R=OAc), in good yields.[3,4] The reaction involves [2+2]cycloaddition between the olefinic double bond of cyclohexene and the exo-methylene double bond of diketene, keeping the β-lactone moiety intact. Since little is known concerning such cycloaddition of diketene, our interest has been focused on the reaction of diketene with maleic anhydride. Robson *et al.*[5] reported that maleic anhydride underwent [2+2]cycloaddition with olefins to give cyclobutane derivatives. On the other hand, the reaction of diketene with maleic anhydride in the presence of azobisisobutyronitrile was reported to give diketene — maleic anhydride copolymer, which can be used as a builder for detergents.[6] We therefore re-investigated the reaction of diketene with maleic anhydride under irradiation, and the results are reported here.



1: R=Me, OAc

2: R=Me

3: R=OAc

Chart 1

1) Part XCVI: T. Kato, T. Chiba, and T. Okada, *Chem. Pharm. Bull.*, **27**, 1186 (1979).
2) Location: *Aobayama, Sendai 980, Japan*; *a*) To whom inquiries should be addressed.
3) T. Kato, M. Sato, and Y. Kitagawa, *J. Chem. Soc., Perkin I*, **1978**, 352.
4) T. Kato, M. Sato, and Y. Kitagawa, *Chem. Pharm. Bull.*, **26**, 632 (1978).
5) R. Robson, P.W. Grubb, and J.A. Barltrop, *J. Chem. Soc.*, **1964**, 2153.
6) K. Hayashi, R. Toepfl, and A. Maeder (Ciba-Geigy A.-G.) Ger. Offen., 2342300 (1974) [*C. A.*, **81**, *p*121399*t* (1974)].

Reaction of Diketene with Maleic Anhydride (4)

Irradiation of a solution of diketene and maleic anhydride (**4**) in acetonitrile afforded crystalline products of mp 148—149.5° (**5a**) and mp 166—167° (**5b**); on the basis of their elemental analyses and spectroscopic data, these were assigned 2-oxo-1-oxaspiro[3.3]heptane-*cis*-5,6-dicarboxylic anhydride structures. The configuration of the oxetane oxygen (C_4–O) and the ring junction hydrogen (C_5–H) in the product **5a** is *cis*, while that in **5b** is *trans*.

The infrared (IR) spectra of **5a** and **5b** both showed β-lactone carbonyl [**5a**: 1840 cm^{-1} and **5b**: 1835 cm^{-1}] and acid anhydride [**5a**: 1785 cm^{-1} and **5b**: 1780 cm^{-1}] absorptions. The nuclear magnetic resonance (NMR) spectra showed AB quartet methylene signals [**5a**: 3.69—4.08 ppm and **5b**: 3.38—3.83 ppm] due to C_3-methylene protons and multiplet methine signals [**5a**: 4.15—4.26 ppm and **5b**: 4.07—4.17 ppm] due to the C_5-proton.

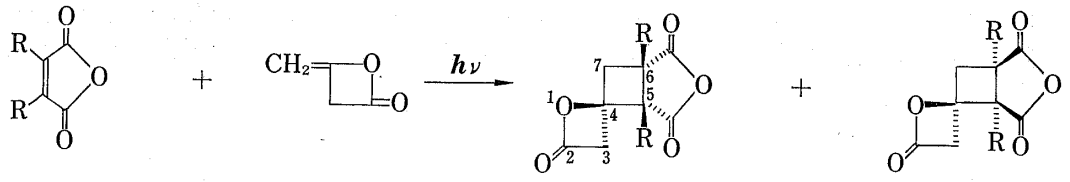
Alcoholysis of compounds **5a** and **5b** resulted in ring fission to give the heptanedioate derivatives (**8** and **9**). That is, compounds **5a** and **5b** were treated with hydrogen chloride in ethanol to give the same product, diethyl 5-ethoxycarbonyl-3-oxoheptanedioate (**8**). The ester (**9**, R′=Me) was also obtained when compounds (**5a** and **5b**) were treated with HCl–methanol. Structure assignment of the esters (**8** and **9**) was made on the basis of elemental analyses and spectroscopic data detailed in the experimental section.

Reaction of Diketene with Dimethylmaleic Anhydride (6)

Irradiation of a solution of diketene and dimethylmaleic anhydride (**6**) in acetonitrile or acetone gave 5,6-dimethyl-2-oxo-1-oxaspiro[3.3]heptane-*cis*-5,6-dicarboxylic anhydride (**7a** and **7b**).

As described in the experimental section, the IR spectra of **7a** and **7b** showed absorptions due to β-lactone carbonyl and anhydride carbonyl at 1835 and 1780 cm^{-1}. Because of the anisotropic effect of the oxetane oxygen, the difference of chemical shifts between the C_5- and C_6-methyl protons of compound **7a** [1.42 ppm and 1.32 ppm: difference, 0.1 ppm] is larger than that in compound **7b** [C_5–CH_3, 1.38 ppm and C_6–CH_3, 1.36 ppm: difference, 0.02 ppm]. Furthermore, the C_3-methylene protons of **7a** appeared at 3.54—3.99 ppm as an AB quartet, while those of **7b** appeared at higher field (3.27—3.95 ppm).

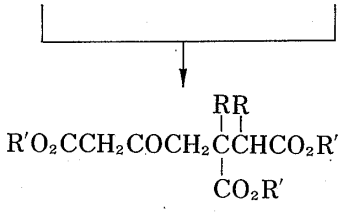
On the basis of these observations, it was inferred that the configuration of the oxetane oxygen (C_4–O) and the ring junction methyl (C_5–CH_3) in compound **7a** is *cis*, and that in **7b** is *trans*.



4 : R=H
6 : R=Me

5a : R=H
7a : R=Me

5b : R=H
7b : R=Me



8 : R=H , R′=Et
9 : R=H , R′=Me
10 : R=Me, R′=Et
11 : R=Me, R′=Me

Chart 2

Treatment of the mixture of **7a** and **7b** with hydrogen chloride in ethanol and methanol gave the esters **10** and **11**, respectively. Structural assignments were made on the basis of elemetal analyses and spectroscopic data.

Experimental

IR spectra were taken with a Jasco IR-S spectrophotometer. NMR spectra were measured with a Hitachi R-20 instrument and a JEOL JNM-PS-100 instrument using tetramethylsilane as an internal standard. Melting points are uncorrected. The ultraviolet (UV) light source was a Riko UVL-100HA water-cooled high-pressure mercury lamp (Pyrex filter).

Reaction of Diketene with Maleic Anhydride (4)——A solution of maleic anhydride (**4**) (3.92 g, 0.04 mol) and diketene (33.6 g, 0.40 mol) in acetonitrile (200 ml) was irradiated for 8 hr with ice-cooling. Removal of the solvent and excess diketene gave a semicrystalline residue, which was triturated with ethyl acetate. The resulting crystalline substance was washed with acetone, and purified by recrystallization from ethyl acetate to give compound **5b** as needles (0.65 g, 9%) of mp 166—167°. The acetone washing was concentrated and the crystalline residue was recrystallized from ethyl acetate to afford compound **5a** as plates (2.0 g, 28%) of mp 148—149.5°. *Anal.* Calcd for $C_8H_6O_5$ (**5a**): C, 52.75; H, 3.32. Found: C, 52.85; H, 3.35. IR ν_{max}^{KBr} cm^{-1}: 1840 (β-lactone), 1785 (acid anhydride). NMR (DMSO-d_6) δ: 2.73—2.93 (1H, m, C_7–H), 3.04—3.53 (2H, m, C_6– and C_7–H), 3.69—4.08 (2H, ABq, J=16 Hz, 2×C_3–H), 4.15—4.26 (1H, m, C_5–H).

Anal. Calcd for $C_8H_6O_5$ (**5b**): C, 52.75; H, 3.32. Found: C, 52.83; H, 3.44. IR ν_{max}^{KBr} cm^{-1}: 1835 (β-lactone), 1780 (acid anhydride). NMR (DMSO-d_6) δ: 3.07—3.17 (2H, m, 2×C_7–H), 3.38—3.83 (2H, ABq, J=16 Hz, 2×C_3–H), 3.63—3.86 (1H, m, C_6–H), 4.07—4.17 (1H, m, C_5–H).

Diethyl 5-Ethoxycarbonyl-3-oxoheptanedioate (8)——a) A solution of **5a** (55 mg, 0.3 mmol) in abs. ethanol (3 ml) saturated with dry HCl was stirred at room temperature for 3.5 hr. The reaction mixture was concentrated, and the residue was extracted with ether. After washing with 5% $NaHCO_3$ and water, the ether solution was dried over Na_2SO_4. After removal of the ether, the residual oil was distilled under reduced pressure to give 82 mg (90%) of a colorless oil (**8**): bp 116—120° (0.05 mmHg). *Anal.* Calcd for $C_{14}H_{22}O_7$ (**8**): C, 55.62; H, 7.34. Found: C, 55.79; H, 7.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). NMR (CCl_4) δ: 1.16—1.35 (9H, t, J=7 Hz, 3×$OCH_2\underline{CH_3}$), 2.48—2.66 (2H, m, 2×C_6–H), 2.74—2.93 (2H, m, 2×C_4–H), 3.00—3.25 (1H, m, C_5–H), 3.35 (2H, s, 2×C_2–H), 3.96—4.24 (6H, q, J=7 Hz, 3×$O\underline{CH_2}CH_3$).

b) Using the same procedure, treatment of **5b** (55 mg, 0.3 mmol) with hydrogen chloride in abs. ethanol gave **8** (79 mg, 87%).

Dimethyl 5-Methoxycarbonyl-3-oxoheptanedioate (9)——A mixture of **5a** and **5b** (110 mg, 0.6 mmol) was added to methanol (6 ml) saturated with dry hydrogen chloride. The reaction mixture was stirred at room temperature for 4 hr. After removal of methanol, the residue was treated as described above to give 140 mg (90%) of a colorless oil (**9**): bp 109—110° (0.02 mmHg). *Anal.* Calcd. for $C_{11}H_{16}O_7$ (**9**): C, 50.77; H, 6.20. Found: C, 50.49; H, 6.24. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=O). NMR (CCl_4) δ: 2.50—2.70 (2H, m, 2×C_6–H), 2.75—3.05 (2H, m, 2×C_4–H), 3.05—3.35 (1H, m, C_5–H), 3.38 (2H, s, 2×C_2–H), 3.63 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.70 (3H, s, OCH_3).

Reaction of Diketene with Dimethylmaleic Anhydride (6)——A solution of dimethylmaleic anhydride (**6**) (2.52 g, 0.02 mol) and diketene (16.8 g, 0.20 mol) in acetone (200 ml) was irradiated for 5 hr with ice-cooling. The solution was concentrated *in vacuo*, and the resulting residue was crystallized from ether (20 ml) to give 3.5 g (83%) of a crystalline solid [mixture of **7a** and **7b**]. Recrystallization from ethyl acetate gave compound **7a** as prisms of mp 167—168° (dec.). *Anal.* Calcd for $C_{10}H_{10}O_5$ (**7a**): C, 57.14; H, 4.80. Found: C, 56.90; H, 4.90. IR ν_{max}^{KBr} cm^{-1}: 1835 (β-lactone), 1780 (acid anhydride). NMR (DMSO-d_6) δ: 1.32 (3H, s, C_6–CH_3), 1.42 (3H, s, C_5–CH_3), 2.94 (2H, s, 2×C_7–H), 3.54—3.99 (2H, ABq, J=17 Hz, 2×C_3–H). The mother liquor was concentrated, and the residue was purified by recrystallization from benzene to give colorless prisms (**7b**) of mp 146—148°. *Anal.* Calcd for $C_{10}H_{10}O_5$ (**7b**): C, 57.14; H, 4.80. Found: C, 57.22; H, 4.89. IR ν_{max}^{KBr} cm^{-1}: 1835 (β-lactone), 1780 (acid anhydride). NMR (DMSO-d_6) δ: 1.36 (3H, s, C_6–CH_3), 1.38 (3H, s, C_5–CH_3), 2.66—3.28 (2H, ABq, J=15 Hz, 2×C_7–H), 3.27—3.95 (2H, ABq, J=17 Hz, 2×C_3–H).

Diethyl 5-Ethoxycarbonyl-5,6-dimethyl-3-oxoheptanedioate (10)——A suspension of the mixture of **7a** and **7b** (2.1 g, 0.01 mol) in abs. ethanol (30 ml) saturated with hydrogen chloride was stirred at room temperature for 5 hr. The solvent was evaporated off under reduced pressure, and the residue was extracted with ether. The organic layer was washed with 5% $NaHCO_3$ and water. After drying over Na_2SO_4, the ether layer was evaporated down, and the residual oil was distilled to give 2.38 g (72%) of a colorless oil (**10**): bp 110—114° (0.02 mmHg). *Anal.* Calcd for $C_{16}H_{26}O_7$ (**10**): C, 58.17; H, 7.93. Found: C, 57.91; H, 7.78. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O), IR ν_{max}^{neat} cm^{-1}: 1725 (C=O), 1740 (C=O). NMR ($CDCl_3$) δ: 1.11—1.38 (9H, m, 3×$OCH_2\underline{CH_3}$), 1.12 (3H, d, J=7 Hz, C_6–CH_3), 1.27 (3H, s, C_5–CH_3), 2.67—3.30 (2H, ABq, J=18 Hz, 2×C_4–H), 2.76 (1H, q, J=7 Hz, C_6–H), 3.42 (2H, s, 2×C_2–H), 3.95—4.35 (6H, m, 3×$O\underline{CH_2}CH_3$).

Dimethyl 5-Methoxycarbonyl-5,6-dimethyl-3-oxoheptanedioate (11)——Using the method described for **10**, a suspension of the mixture (**7a** and **7b**, 2.1 g, 0.01 mol) in methanol (20 ml) saturated with dry hydrogen

chloride was stirred for 5 hr at room temperature. Treatment as described above afforded 2.1 g (73%) of a colorless oil (**11**): bp 132—134° (0.5 mmHg). *Anal.* Calcd for $C_{13}H_{20}O_7$ (**11**): C, 54.16; H, 6.99. Found: C, 54.22; H, 6.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=O), IR ν_{max}^{neat} cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, C_6–CH_3), 1.29 (3H, s, C_5–CH_3), 2.72 (1H, q, J=7 Hz, C_6–H), 2.58—3.36 (2H, ABq, J=18 Hz, $2\times C_4$–H), 3.45 (2H, s, $2\times C_2$–H), 3.65 (6H, s, $2\times OCH_3$), 3.72 (3H, s, OCH_3).

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Organic Sulfites containing a 1,2-Oxazine Ring[1)]

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The reaction of 5-hydroxy-2-phenyltetrahydro-2*H*-1,2-oxazin-3-one derivatives (**2**) with thionyl chloride in the presence of pyridine afforded a mixture of stereoisomers of bis(3-oxo-2-phenyltetrahydro-2*H*-1,2-oxazine-5-yl) sulfite derivatives (**3**) in total yields of 75—83%. On high-performance liquid chromatography, two meso-diastereoisomers (3-I and 3-II) and a racemic compound (3-III) were isolated.

Keywords——organic sulfites; bis(2-aryl-3-oxotetrahydro-2*H*-1,2-oxazine-5-yl) sulfite; 1,2-oxazine derivatives; thionyl chloride; esterification; stereoisomer; HPLC; separation

In the previous paper,[1)] we reported syntheses of 2-phenyltetrahydro-2*H*-1,2-oxazine-3,5-dione derivatives (**1**) from γ-bromoacetoacetyl bromide and N-phenylhydroxylamines. As a continuation of our studies on these heterocycles, we have investigated the reduction of the C_5-carbonyl group of **1** to give 2-phenyltetrahydro-2*H*-1,2-oxazin-3-one. In this connection, we have already reported the transformation of 1,2-diphenylhexahydropyridazine-3,5-dione (**4**) to give 1,2-diphenyl-1,2,3,6-tetrahydropyridazin-3-one (**6**) *via* 5-hydroxy-1,2-diphenylhexahydropyridazin-3-one (**5**).[3)] Namely, reduction of the dione (**4**) with sodium borohydride gave the 5-hydroxy derivative (**5**), which, on treatment with phosphorus oxychloride was transformed into the pyridazinone (**6**). Using this procedure, 2-phenyltetrahydro-2*H*-1,2-oxazine-3,5-dione (**1a**, R=H) was reduced with sodium borohydride to give 5-hydroxy-2-phenyltetrahydro-2*H*-1,2-oxazin-3-one (**2a**). Reaction of **2a** with phosphorus oxychloride or phosphorus trichloride in pyridine resulted in recovery of the starting material. However, treatment of **2a** with thionyl chloride in the presence of pyridine did not give the dehydrated compound but a mixture of organic sulfites containing a 1,2-oxazine ring, on which we now report.

Compound **2a** was allowed to react with a half equivalent of thionyl chloride in the presence of one equivalent of pyridine in carbon tetrachloride under reflux to afford a colorless crystalline product (**3a**). The product did not have a sharp melting point and thin-layer

1) This paper forms Part II of "Reaction of γ-Bromoacetoacetyl Bromide with N-Phenylhydroxylamine Derivatives." Part I: K. Tabei, E. Kawashima, and T. Kato, *Chem. Pharm. Bull.*, **27**, 1842 (1979).
2) Location: *a) Horinouchi, 1432–1, Hachioji city, Tokyo, 192-03, Japan*; *b) Aobayama, Sendai, 980, Japan.*
3) T. Kato, M. Sato, and K. Tabei, *J. Org. Chem.*, **39**, 3205 (1974).