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Studies on Ketene and Its Derivatives. XCIV.[1] Reaction of Diketene with Diazoacetone and 2-Diazoesters

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The reaction of diketene with diazoacetone (**2**) in the presence of benzophenone under irradiation afforded *trans*-1-acetyl-5-oxo-4-oxaspiro[2,3]hexane (**3**) in 22% yield.

Similarly, the photolysis of diketene and 2-diazoesters such as ethyl 2-diazo-3-oxobutanoate (**4a**) and ethyl 2-diazo-3-oxohexanoate (**4b**), followed by treatment with absolute methanol saturated with dry hydrogen chloride gave diesters; *e.g.*, methyl 3,6-dioxo-5-ethoxycarbonylhexanoate (**8a**) (39%) and methyl 3,6-dioxo-5-ethoxycarbonylnonylate (**8b**) (30%), and/or furan derivatives; *e.g.*, 3-ethoxycarbonyl-5-methoxycarbonylmethyl-2-methylfuran (**9a**) (35%) and 3-ethoxycarbonyl-5-methoxycarbonylmethyl-2-propylfuran (**9b**) (33%).

A similar reaction of diketene with di-*tert*-butyl diazomalonate (**10**) gave rise to dimethyl 2-methoxycarbonyl-4-oxohexane-1,6-dioate (**12**) in 58% yield.

Keywords——photochemical reaction; diketene; diazo compounds; carbene; 5-oxo-4-oxaspiro[2,3]hexanes; β-ketoacids; furans

Previously, we have reported that the reaction of diketene with ethyl diazoacetate in the presence of copper powder or under irradiation affords ethyl *trans*-5-oxo-4-oxaspiro[2,3]-hexane-1-carboxylate (**1**) and its *cis* isomer (**1′**), and that both products serve as reagents for the synthesis of heterocycles.[3,4] As a continuation of our studies on potential uses of diketene, we investigated the reaction of diketene with 2-diazoketone and 2-diazoesters such as diazoacetone (**2**), ethyl 2-diazo-3-oxobutanoate (**4a**), ethyl 2-diazo-3-oxohexanoate (**4b**), and di-*tert*-butyl diazomalonate (**10**).

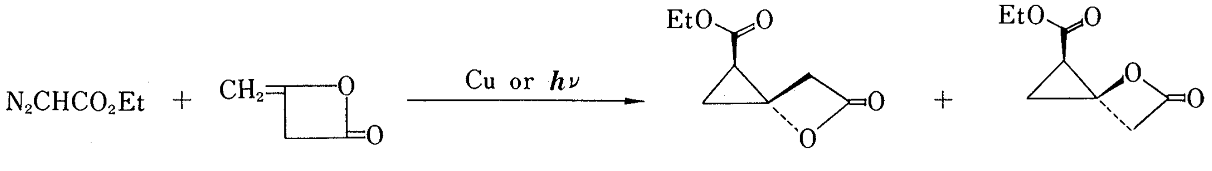

Chart 1

When a solution of diazoacetone (**2**), diketene and benzophenone in dichloromethane was irradiated, an oily product was obtained. Purification by silica gel column chromatography and distillation gave a colorless oil of bp 75—80° (3 mmHg), which, on the basis of elemental analyses and spectral data, was assigned the spiro structure, *trans*-1-acetyl-5-oxo-4-oxaspiro-[2,3]hexane (**3**). Namely, its infrared (IR) spectrum indicated the presence of β-lactone and ketone carbonyls at 1845 and 1700 cm^{-1}, respectively. The assignment of the *trans* configuration (between 1-acetyl and the oxetane ring oxygen) was made by comparison of its nuclear magnetic resonance (NMR) spectrum with those of analogous spiro compounds.[3,4] As shown in Table I, the oxetane methylene protons of *cis*-5-oxo-4-oxaspiro[2,3]hexane appeared as a

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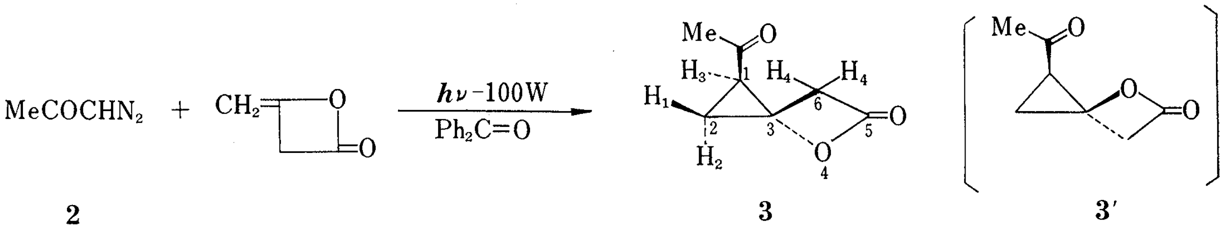
[1] Part XCIII: T. Kato, T. Chiba, S. Tanaka, and T. Sasaki, *Heterocycles*, **11**, 227 (1978).
[2] Location: *Aobayama, Sendai 980, Japan.*
[3] T. Kato and N. Katagiri, *Chem. Pharm. Bull.* (Tokyo), **21**, 729 (1973).
[4] T. Kato, N. Katagiri, and R. Sato, *J. Chem. Soc. Perkin I*, **1979** 525.

singlet signal, while in the NMR spectra of *trans* isomers the oxetane methylene protons gave an AB quartet signal. Since the NMR spectrum of compound (**3**) showed an AB quartet ascribable to methylene protons of the β-lactone ring at 3.30—3.95 ppm, we assigned the *trans*-spiro structure to this product.

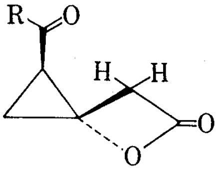
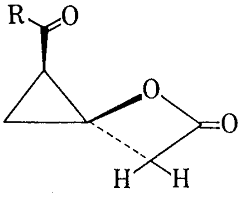
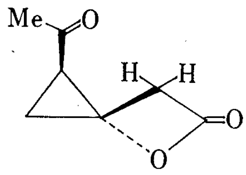
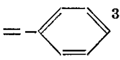
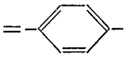
The *cis* isomer (**3′**) was not detected in this reaction.



2 **3** **3′**

Chart 2

Table I. NMR Spectra of 5-Oxo-4-oxaspiro[2,3]hexane Derivatives

	 *trans*	 *cis*	 **3**
R=OEt[3,4),a)]	2.70—3.40 (2H, q, AB type, J=17.00 Hz)	3.22 (2H, s)	3.30—3.95 (2H, q, AB type, J=16.65 Hz)
R=[3), b)]	3.40—3.90 (2H, q, AB type, J=17.00 Hz)	3.77 (2H, s)	
R=-OMe[3), b)]	3.40—3.90 (2H, q, AB type, J=17.00 Hz)	3.76 (2H, s)	

a) Benzene.
b) CDCl$_3$.

Similarly, photolysis of ethyl 2-diazo-3-oxobutanoate (**4a**) and diketene in dichloromethane in the presence of benzophenone afforded 2,5-dioxo-3-ethoxycarbonylhexane (**7**) as a colorless oil. The structure was elucidated on the basis of the elemental analyses and spectral data detailed in the experimental section.

The formation of acetonylacetate (**7**) can be rationalized as follows; the carbene produced from **4a** adds to the exo-methylene of diketene to give the spiro intermediate (**5a**), which is hydrolyzed giving the β-keto acid intermediate (**6**). Decarboxylation of **6** gives the product (**7**).

When the photolysis product was treated with absolute methanol saturated with dry hydrogen chloride at —20° for 2 hr, methyl 3,6-dioxo-5-ethoxycarbonylheptanoate (**8a**) was obtained in 35% yield. On the other hand, when the reaction was carried out below —20° for 2 days, 3-ethoxycarbonyl-5-methoxycarbonylmethyl-2-methylfuran (**9a**) was obtained in 35% yield. The furan (**9a**) was also obtained by treatment of the diester (**8a**) with dry hydrogen chloride in absolute methanol with cooling.

Similarly, when ethyl 2-diazo-3-oxohexanoate (**4b**) was allowed to react with diketene in dichloromethane in the presence of benzophenone under irradiation, methyl 3,6-dioxo-5-ethoxycarbonylnonylate (**8b**) and 3-ethoxycarbonyl-5-methoxycarbonylmethyl-2-propylfuran (**9b**) were obtained in 30% and 18% yields, respectively. Treatment of the diester (**8b**) with dry hydrogen chloride in absolute methanol gave a 70% yield of the furan (**9b**).

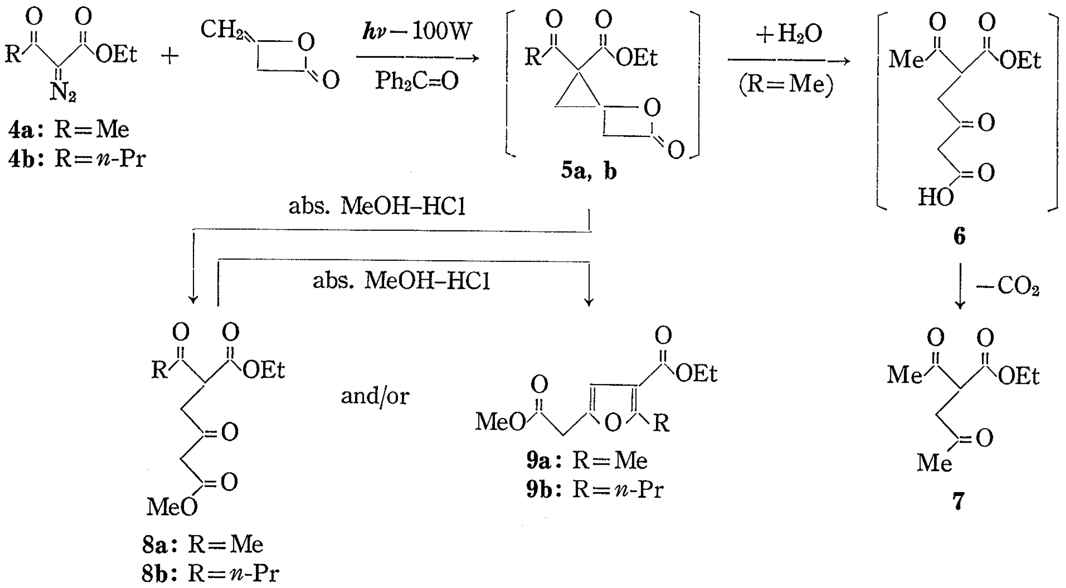


Chart 3

Following the above procedure, di-*tert*-butyl diazomalonate (**10**) was allowed to react with diketene under irradiation. Evaporation of the reaction mixture gave an oily residue. Attempts at purification by silica gel column chromatography and distillation failed. Treatment of the residue with dry hydrogen chloride in absolute methanol gave dimethyl 2-methoxycarbonyl-4-oxohexane-1,6-dioate (**12**) in 58% yield. The formation of the spiro intermediate (**11**) may be the first stage of the reaction, because the IR spectrum of the residue showed β-lactone carbonyl absorption at 1845 cm^{-1}.

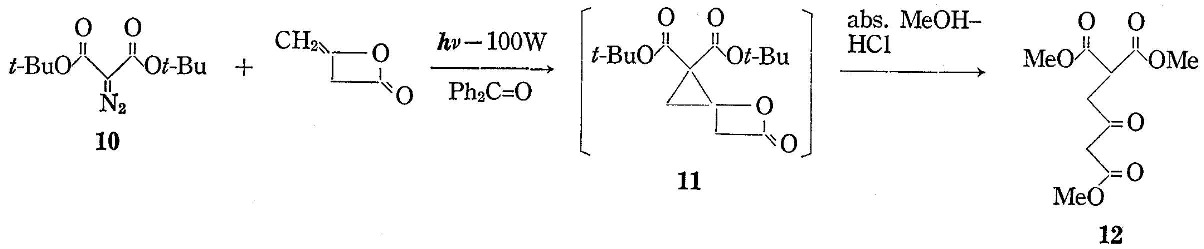


Chart 4

In conclusion, diketene reacted with diazo compounds under irradiation to give spiro oxetane derivatives initially. However, in the case of 2-diazoesters the spiro compounds (**5a**, **5b**, and **11**) formed were not stable enough to be isolated. This might be attributable to the presence of two electron-withdrawing groups on the cyclopropane ring.

The yields of the isolated products were generally low except for compound (**12**). In each reaction many products were detected on thin-layer chromatography (TLC), presumably as a result of photodecomposition of spiro compounds.

Experimental

IR spectra were taken on a JASCO IR-S spectrophotometer. NMR spectra were measured with a Hitachi R-20 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).

***trans*-1-Acetyl-5-oxo-4-oxaspiro[2,3]hexane** (3)——A solution of diazoacetone (2)[5] (2.5 g, 0.031 mol), benzophenone (5.64 g, 0.031 mol), and diketene (20 g, 0.238 mol) in dichloromethane (100 ml) was irradiated with a mercury lamp (100 W) with ice-cooling for 3 hr. The reaction mixture was evaporated down *in vacuo*, and the residue (8 g) was subjected to silica gel (30 g) column chromatography using *n*-hexane and benzene as eluants. Elution with *n*-hexane gave benzophenone, and elution was continued with benzene to give an oily substance, which was distilled to give a colorless oil, bp 75—80° (3 mmHg). Yield, 0.96 g (22%). *Anal.* Calcd. for $C_7H_8O_3\cdot 1/4\ H_2O$ (3): C, 58.13; H, 5.88. Found: C, 58.57; H, 6.28. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1845, 1700. NMR ($CDCl_3$) ppm: 1.45—1.95 (2H, m, H_1, H_2), 2.35 (3H, s), 2.72 (1H, dd, $J=6.90$ Hz, $J=9.75$ Hz, H_3), 3.30—3.95 (2H, q, AB type, $J=16.65$ Hz, $2\times H_4$).

Reaction of Ethyl 2-Diazo-3-oxobutanoate (4a) with Diketene——i) A solution of ethyl 2-diazo-3-oxobutanoate (**4a**)[6] (5 g, 0.032 mol), benzophenone (5.84 g, 0.032 mol), and diketene (20 g, 0.238 mol) in dichloromethane (100 ml) was irradiated with ice-cooling for 2.5 hr. The reaction mixture was evaporated down on a water bath (50°) under reduced pressure. The residue was subjected to silica gel (30 g) column chromatography using *n*-hexane and benzene as eluants. Elution with *n*-hexane gave benzophenone, and elution was continued with benzene to give a colorless oil, which was purified by distillation to give 1.78 g (30%) of the ester (**7**), bp 81—82° (3 mmHg) (lit.[7] bp 126—128° (14 mmHg)). *Anal.* Calcd. for $C_9H_{14}O_4$ (**7**): C, 58.05; H, 7.58. Found: C, 57.92; H, 7.32. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1735, 1705. NMR ($CDCl_3$) ppm: 1.27 (3H, t, $J=7.2$ Hz), 2.17 (3H, s), 2.31 (3H, s), 2.55—3.63 (2H, m, $\underline{\mathrm{AB}}\mathrm{X}$ type), 3.88—4.67 (3H, m, $\mathrm{AB}\underline{\mathrm{X}}$ type, and $\text{-O}\underline{\mathrm{CH}_2}\mathrm{CH}_3$).

ii) A solution of **4a** (1.66 g, 10.6 mmol), benzophenone (1.94 g, 10.6 mmol), and diketene (8.9 g, 0.106 mol) in dichloromethane (60 ml) was irradiated with ice-cooling. The reaction mixture was evaporated down *in vacuo* to give an oily residue, keeping the temperature below 20°. The residue was dissolved in absolute methanol (30 ml) and the solution was saturated with dry hydrogen chloride under ice-salt cooling. After 2 hr, the mixture was evaporated down *in vacuo*, keeping the temperature below 20°. The resulting residue (4 g) was subjected to silica gel (30 g) column chromatography. Elution with *n*-hexane gave benzophenone and the product **8a** as a colorless oil, bp 98—100° (0.003 mmHg). Yield, 1 g (39%). *Anal.* Calcd. for $C_{11}H_{16}O_6$ (**8a**): C, 54.09; H, 6.60. Found: C, 54.45; H, 6.70. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1740, 1720. NMR ($CDCl_3$) ppm: 1.29 (3H, t, $J=7.5$ Hz), 2.40 (3H, s), 3.09—3.32 (2H, m, $\underline{\mathrm{AB}}\mathrm{X}$ type), 3.57 (2H, s), 3.69 (3H, s), 3.92—4.51 (3H, m, $\mathrm{AB}\underline{\mathrm{X}}$ type, and $\text{-O}\underline{\mathrm{CH}_2}\mathrm{CH}_3$).

iii) A solution of **4a** (2 g, 0.013 mol), benzophenone (2.3 g, 0.013 mol), and diketene (10.77 g, 0.13 mol) in dichloromethane (60 ml) was irradiated with ice-cooling. Following the method described above, the mixture was evaporated down and the residual oil was treated with dry hydrogen chloride in absolute methanol (30 ml). The solution was allowed to stand in a refrigerator at −20° for 2 days. The mixture was evaporated down *in vacuo* at 20°, and the residue was purified by silica gel column chromatography and distillation to give the furan (**9a**) as a colorless oil, bp 84—85° (1 mmHg). Yield, 1 g (35%). *Anal.* Calcd. for $C_{11}H_{14}O_5$ (**9a**): C, 58.40; H, 6.24. Found: C, 58.33; H, 6.14. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1740, 1700, 1620, 1590. NMR ($CDCl_3$) ppm: 1.29 (3H, t, $J=7.5$ Hz), 2.52 (3H, s), 3.60 (2H, s), 3.68 (3H, s), 4.24 (2H, q, $J=7.5$ Hz), 6.45 (1H, s).

Cyclization of 8a to 9a——The diester (**8a**) (0.12 g) was dissolved in absolute methanol (15 ml), and the solution was saturated with dry hydrogen chloride under ice-cooling. The reaction mixture was kept in a refrigerator (−20°) for 2 days. A procedure similar to that described above afforded the furan (**9a**). Yield, 0.168 g (86%).

Reaction of Ethyl 2-Diazo-3-oxohexanoate (4b) with Diketene——i) Employing the procedure described for obtaining the furan (**9a**) from the diazoester (**4a**), ethyl 2-diazo-3-oxohexanoate[8] (**4b**) (2 g, 0.011 mol) was allowed to react with diketene (9.13 g, 0.11 mol) in dichloromethane (60 ml) in the presence of benzophenone (1.98 g, 0.011 mol). The reaction mixture was evaporated down *in vacuo* at room temperature (below 20°), then the residue was dissolved in absolute methanol (15 ml) and the solution was saturated with dry hydrogen chloride. The mixture was kept in a refrigerator (−20°) for 3 days, and evaporated down *in vacuo* at 20°. The residue (4 g) was subjected to silica gel column chromatography. Elution with *n*-hexane gave benzophenone and the furan (**9b**) as a colorless oil, bp 85—87° (0.005 mmHg). Yield, 0.5 g (18%). *Anal.* Calcd. for $C_{13}H_{18}O_5$ (**9b**): C, 61.40; H, 7.14. Found: C, 61.55; H, 7.09. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1750, 1720, 1620, 1590. NMR ($CDCl_3$) ppm: 0.93 (3H, m), 1.30 (3H, t, $J=7.3$ Hz), 1.75—2.05 (2H, m), 2.97 (2H, t, $J=6.7$ Hz), 3.66 (2H, s), 3.74 (3H, s), 4.31 (2H, q, $J=7.3$ Hz), 6.57 (1H, s).

Elution was continued with *n*-hexane to give the diester (**8b**), bp 97—100° (0.002 mmHg). Yield, 0.9 g (30%). *Anal.* Calcd. for $C_{13}H_{20}O_6$ (**8b**): C, 57.34; H, 7.40. Found: C, 57.80; H, 7.22. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1740, 1715. NMR ($CDCl_3$) ppm: 0.75—1.14 (3H, m), 1.28 (3H, t, $J=7.5$ Hz), 1.32—1.90 (2H, m), 2.58—2.85 (2H, m), 3.10—3.31 (2H, m, $\underline{\mathrm{AB}}\mathrm{X}$ type), 3.57 (2H, s), 3.79 (3H, s), 3.90—4.55 (3H, m, $\mathrm{AB}\underline{\mathrm{X}}$ type, and $\text{-O}\underline{\mathrm{CH}_2}\mathrm{CH}_3$).

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[5] F. Arnde and J. Amende, *Ber.*, **61**, 1122 (1928).

[6] M. Regitz and A. Liedhegener, *Chem. Ber.*, **99**, 3128 (1966).

[7] C.D. Hurd and K. Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948).

[8] H.J. Bestmann and J. Kolm, *Chem. Ber.*, **96**, 1948 (1963).

ii) In a fashion similar to that described above, reaction of **4b** (2.5 g) with diketene (11.4 g) in dichloromethane (60 ml) in the presence of benzophenone (2.48 g) gave an oily product, which was treated with dry hydrogen chloride in absolute methanol. The mixture was kept in a refrigerator (−20°) for 6 days to give the furan (**9b**) in 33% (1.14 g) yield.

Cyclization of 8b to 9b——Following the procedure given for obtaining **9a** from **8a**, the diester (**8b**) (0.258 g) was dissolved in absolute methanol (15 ml), and the solution was saturated with dry hydrogen chloride under ice-cooling. The mixture was kept in a refrigerator (−20°) for 3 days. Removal of the solvent by evaporation gave an oily residue, which was purified by silica gel column chromatography and distillation to give the furan (**9b**) in 70% (0.165 g) yield.

Reaction of Di-*tert*-butyl Diazomalonate (10) and Diketene——Using the method described above, photolysis of di-*tert*-butyl diazomalonate[9] (**10**) (2 g, 8 mmol), benzophenone (1.5 g, 8 mmol), and diketene (6.94 g, 80 mmol) in dichloromethane (60 ml), followed by methanolysis, gave the triester (**12**), bp 90—100° (0.003 mmHg). Yield, 1.17 g (58%). *Anal.* Calcd. for $C_{10}H_{14}O_7$ (**12**): C, 48.78; H, 5.73. Found: C, 49.26; H, 5.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745. NMR ($CDCl_3$) ppm; 3.21 (2H, d, J=7.0 Hz), 3.57 (2H, s), 3.77 (9H, s), 3.95 (1H, t, J=7.0 Hz).

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9) B.W. Peace, F. Carman, and D.S. Wulfman, *Synthesis*, **1971**, **658**.