Chem. Pharm. Bull. 29(6)1624—1628(1981)

Studies on Ketene and Its Derivatives. CV.[1] Photoreaction of Diketene with *sec*-Alcohols

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(Received December 22, 1980)

Irradiation of a solution of acetone and diketene in 2-propanol gave 4-(2-hydroxy-2-methylpropyl)oxetan-2-one (**1**) in 63% yield. 4-(2-Hydroxy-2-methylbutyl)- and 4-(2-hydroxy-2-ethylbutyl)oxetan-2-one (**2** and **3**) were similarly prepared.

Treatment of compound **1** with hydrogen chloride in alcohol gave ethyl (*E*)-5-methyl-2,4-hexadienoate (**4**). Ring transformation of the oxetanones (**1** and **2**) into pyranone derivatives was also investigated.

Keywords——diketene; *sec*-alcohol; photoreaction; radical; 2-oxetanone; 2*H*-pyran-2-one; ring transformation

It is well documented that radicals generated from cyclic acetal,[2] γ-butyrolactone,[3] and ethanol[4] add to olefins under irradiation. While investigating the reactivity of the *exo*-methylene double bond of diketene, we have studied addition reactions of diketene to give a product with the β-lactone ring intact.[5] In this paper, we wish to report similar reactions of diketene with *sec*-alcohols under irradiation.

Irradiation of a solution of diketene and acetone in 2-propanol gave an oil. Purification by silica gel column chromatography gave 4-(2-hydroxy-2-methylpropyl)oxetan-2-one (**1**), bp 80—84° (4 mmHg), in 63% yield. Use of ether as a solvent instead of 2-propanol gave the same product **1** in 17% yield. Similarly, irradiation of a mixture of diketene and 2-propanol in acetone gave the adduct **1** in 56% yield. The structural assignment of the product **1** was made on the basis of elemental analyses and spectral data detailed in the experimental section. Formation of the product **1** can be explained by the addition of a 2-hydroxy-2-propyl radical, produced from acetone or 2-propanol, to the *exo*-methylene of diketene.

Similarly, irradiation of a mixture of diketene and acetone in 2-butanol gave 4-(2-hydroxy-2-methylbutyl)oxetan-2-one (**2**), bp 74—76° (0.02 mmHg), in 20% yield, in addition to a 27% yield of compound **1**. Similar treatment of a mixture of diketene and 2-butanone in 2-butanol afforded a 53% yield of the product **2**.

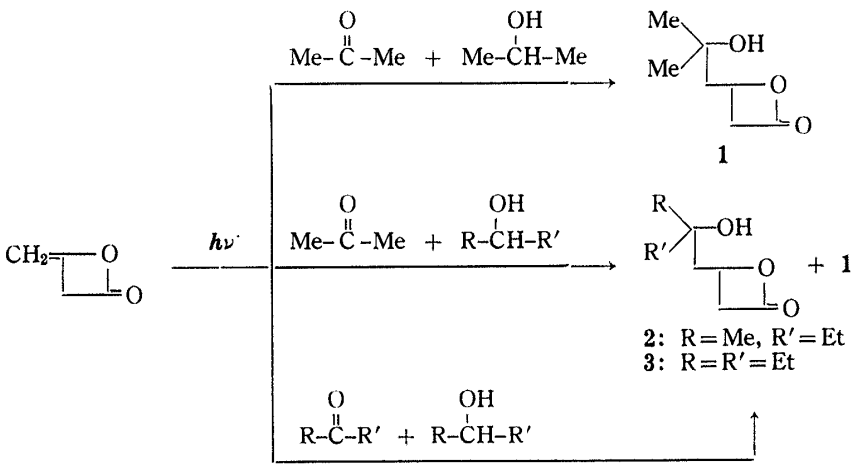

Chart 1

Irradiation of a mixture of diketene and acetone in 3-pentanol gave a 21% yield of 4-(2-ethyl-2-hydroxybutyl)oxetan-2-one (**3**) and a 25% yield of the product **1**. Use of 3-pentanone as a radical initiator instead of acetone resulted in the formation of the adduct **3** in a low yield (8%).

The NMR spectrum of the adduct **2** in benzene-d_6 showed two methyl signals at 0.86 and 0.93 ppm suggesting that the adduct **2** is a 1:1 diastereoisomeric mixture.

Next, ethanolysis of compound **1** was carried out. Thus, treatment of compound **1** in ethanol saturated with dry hydrogen chloride afforded ethyl (*E*)-5-methyl-2,4-hexadienoate (**4**). As detailed in the experimental section, the spectral data are consistent with the structure **4**. In particular, the C_2–H and C_3–H protons appeared at 5.75 ppm and 7.55 ppm as a doublet and a double doublet, respectively, in the NMR spectrum. Since the coupling constant is 15.2 Hz, the configuration of the C_2–C_3 double bond was assigned as *E*-form.

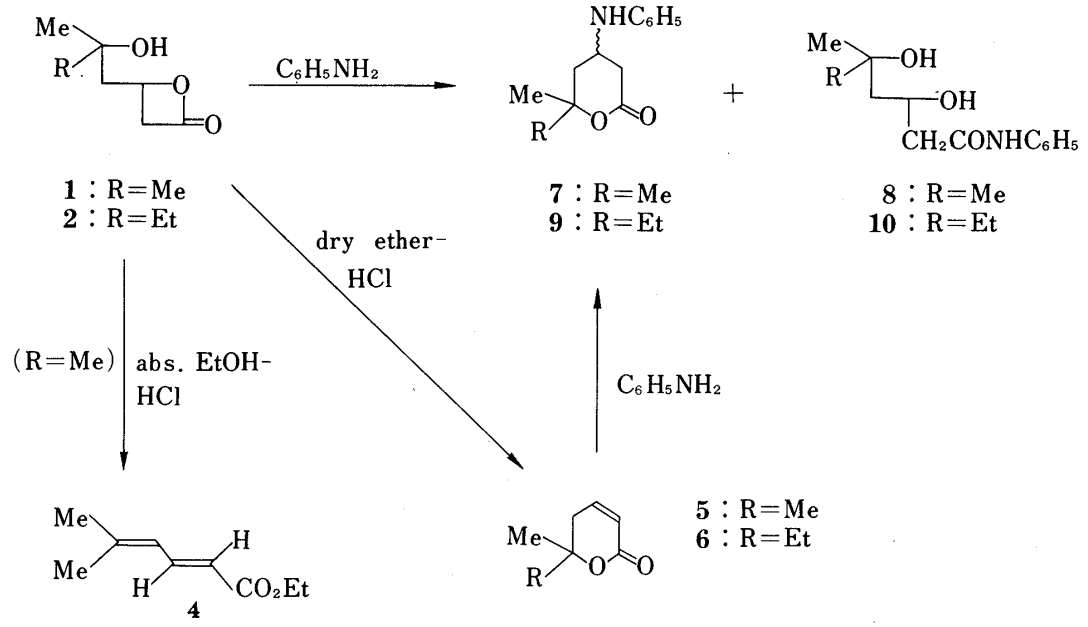

Chart 2

Treatment of compound **1** with hydrogen chloride in dry ether gave 5,6-dihydro-6,6-dimethyl-2*H*-pyran-2-one (**5**) in 65% yield. Similarly, compound **2** was transformed to 5,6-dihydro-6-ethyl-6-methyl-2*H*-pyran-2-one (**6**).

When compound **1** was heated with aniline in ethanol, an oily substance was obtained. Purification by silica gel column chromatography gave tetrahydro-4-anilino-6,6-dimethyl-2*H*-pyran-2-one (**7**) and 3,5-dihydroxy-5-methylhexananilide (**8**) in 27% and 52% yields, respectively. Compound **7** was also obtained by the reaction of compound **5** with aniline in 74% yield. Similarly, compound **2** was allowed to react with aniline to give tetrahydro-4-anilino-6-ethyl-6-methyl-2*H*-pyran-2-one (**9**) and 3,5-dihydroxy-5-methylheptanilide (**10**) in 37% and 33% yields, respectively. Compound **9** was found to be a mixture of *cis* and *trans* isomers, which could not be separated. The stereochemistry of **10** is not clear.

Compound **6** was, on treatment with aniline, also transformed into compound **9** in 60% yield.

Experimental[6]

4-(2-Hydroxy-2-methylpropyl)oxetan-2-one (**1**)——1) A solution of diketene (1.2 g, 14 mmol) and acetone (2.9 g, 50 mmol) in 2-propanol (150 ml) was irradiated with a high pressure UV lamp (400 W) under ice-cooling. After 1 hr, additional diketene (2.4 g) and acetone (2.9 g) were added. Similar addition was repeated every 1 hr. The total amounts of diketene and acetone used were 8.4 g (100 mmol) and 11.6 g

(200 mmol), respectively. Irradiation was continued for an additional 24 hr. The reaction mixture was then concentrated under reduced pressure, during which time the bath temperature was kept below 30°. An oily residue was extracted with ether (30 ml × 3). The ether solution was concentrated, and the residue was vacuum-distilled to give product **1** as an oil, bp 80—84° (4 mmHg), 9.0 g (63%). *Anal.* Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.12; H, 8.74. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 1825 (C=O). NMR ($CDCl_3$) δ: 1.30 (6H, s), 1.70—2.35 (2H, m), 2.45 (1H, br s), 3.22 (1H, dd, J=15.0 Hz, J=5.1 Hz), 3.66 (1H, dd, J=15.0 Hz, J=5.9 Hz), 4.68—5.07 (1H, m).

2) In the manner described above, a solution of diketene (1.2 g, 14 mmol) and 2-propanol (3 g, 50 mmol) in acetone (150 ml) was irradiated for 1 hr. At 1 hr intervals, a mixture of diketene (2.8 g, 28.5 mmol) and 2-propanol (3 g, 50 mmol) was added; this addition was repeated 3 times. Irradiation was continued for an additional 24 hr. Work-up as described above afforded 8.0 g (56%) of the product **1**, whose IR spectrum was identical with that of the sample obtained above.

3) A solution of diketene (6.72 g, 80 mmol) and acetone in ether (200 ml) was irradiated with a high pressure UV lamp (400 W) for 11 hr. The reaction mixture was concentrated under reduced pressure on a water bath, during which time the bath temperature was kept below 20°. The resulting residue (*ca.* 7 g) was subjected to silica gel (70 g) column chromatography. After elution with 2 l of a mixture of hexane and chloroform (5: 1), elution was continued with chloroform to give an oily substance, which was purified again by silica gel (20 g) column chromatography using mixtures of hexane and chloroform (10: 1, 5: 1, and then 3: 1). The last elution (3: 1 mixture) gave 1.9 g (17%) of the product **1**, whose IR spectrum was identical with that obtained in the above run.

4-(2-Hydroxy-2-methylbutyl)oxetan-2-one (2)——1) By a procedure similar to that given for compound **1**, a mixture of diketene (1.2 g, 14 mmol) and acetone (2.9 g, 50 mmol) in 2-butanol (150 ml) was irradiated for 1 hr. At 1 hr intervals, a mixture of diketene (2.4 g) and acetone (2.9 g) was added; this was repeated 3 times. After being irradiated for an additional 24 hr, the mixture was concentrated *in vacuo* at room temperature to give an oil (10 g), which was subjected to silica gel (150 g) column chromatography. After elution with hexane (1 l) and then with 5: 1 and 3: 1 hexane–chloroform mixtures (each 1 l), elution with chloroform (1 l) afforded an oil (fraction 1), and elution was continued with the same solvent to give another oil (fraction 2). Fraction 1, on further purification by silica gel (30 g) column chromatography using a mixture of hexane–chloroform as the eluent, gave the product **2**, bp 74—76° (0.02 mmHg), 2.8 g (20%). *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.89; H, 8.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640 (OH), 1830 (C=O). NMR ($CDCl_3$) δ: 0.75—2.30 (10H, m), 2.41 (1H, br s), 3.22 (1H, dd, J=16.5 Hz, J=5.1 Hz), 3.64 (1H, dd, J=16.5 Hz, J=5.9 Hz), 4.69—5.07 (1H, m). Fraction 2 gave 3.9 g (27%) of compound **1**.

2) In the manner described for compound **2**, a solution of diketone (1.2 g) and 2-butanone (3.6 g, 50 mmol) in 2-butanol (150 ml) was irradiated for 1 hr. A mixture of diketene (2.4 g) and 2-butanone (3.6 g) was added 3 times at 1 hr intervals under irradiation. After being irradiated for an additional 24 hr, the reaction mixture was concentrated. The resulting residue (*ca.* 10 g) was purified by silica gel (100 g) column chromatography using hexane and chloroform as eluents. The chloroform elution gave 8.3 g (53%) of compound **2**.

4-(2-Ethyl-2-hydroxybutyl)oxetan-2-one (3)——1) By the procedure given for compound **1**, a solution of diketone (0.36 g, 4 mmol) and acetone (1.64 g, 28 mmol) in 3-pentanol (50 ml) was irradiated for 1 hr. At 1 hr intervals, a mixture of diketene (1 g, 12 mmol) and acetone (1 g, 17 mmol) was added; this was done 3 times. The mixture was irradiated for an additional 12 hr, and then concentrated. The residue (*ca.* 5 g) was purified by silica gel (100 g) column chromatography using hexane and chloroform as eluents. Elution with a mixture of hexane–chloroform afforded an oily substance, and subsequent elution with chloroform gave compound **1**, 1.4 g (25%). The oily substance was again subjected to silica gel (10 g) column chromatography using the same solvents, to give the product **3** as an oil, bp 79—82° (0.03 mmHg), 1.4 g (21%). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.38; H, 9.21. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 1830 (C=O). NMR ($CDCl_3$) δ: 0.73—1.00 (6H, m), 1.35—2.32 (6H, m), 2.19 (1H, br s), 3.24 (1H, dd, J= 16.5 Hz, J=5.1 Hz), 3.64 (1H, dd, J=16.5 Hz, J=5.9 Hz), 4.68—5.07 (1H, m).

2) In the manner described for compound **3**, a solution of diketene (0.36 g, 4.3 mmol) and 3-pentanone (2.38 g, 27.7 mmol) in 3-pentanol (50 ml) was irradiated (100 W high pressure UV lamp) under ice-cooling. At 1 hr intervals, a mixture of diketene (1 g, 12 mmol) and 3-pentanone (1.5 g, 17.4 mmol) was added (3 times in all), and irradiation was continued for an additional 12 hr. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue was purified by silica gel (100 g) column chromatography. Elution with hexane–ethyl acetate (5: 1) gave the product **3**, 0.6 g (8%).

Ethyl (*E*)-5-Methyl-2,4-hexadienoate (4)——A solution of compound **1** (0.9 g) in absolute ethanol (5 ml) was saturated with dry hydrogen chloride under ice-cooling. After being refluxed for 24 hr, the mixture was concentrated. The residue was dissolved in ether and the solution was washed with water. The ether solution was dried over magnesium sulfate and concentrated, and the resulting residue was purified by silica gel (50 g) column chromatography. Elution with hexane–ethyl acetate (30: 1) gave an oil, which was distilled to give the product **4**, bp 52—53° (0.5 mmHg) [lit.,[7] bp 81° (1 mmHg)], 0.4 g (42%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (C=O), 1635 (C=C), 1615 (C=C). NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.3 Hz, CH_3), 1.85 (6H, s, $2\times CH_3$), 4.21 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 5.75 (1H, d, J=15.2 Hz, C_2–H), 5.97 (1H, d, J=12.0 Hz), 7.55 (1H, dd,

$J=15.2$ Hz, $J=12.0$ Hz, C_3–H).

5,6-Dihydro-6,6-dimethyl-2*H*-pyran-2-one (5)——A solution of compound **1** (1.4 g) in dry ether (10 ml) was saturated with dry hydrogen chloride under ice-cooling. After being allowed to stand at room temperature for 2 days, the reaction mixture was concentrated. The residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with water, dried over sodium sulfate, and concentrated. The resulting residue was subjected to silica gel (50 g) column chromatography. Elution with hexane–ethyl acetate (15:1) gave the product **5** as an oil, bp 60° (0.4 mmHg) [lit.,[8] bp 78—80° (1 mmHg)], 0.8 g (65%). *Anal.* Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.41; H, 7.77. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O), 1620 (C=C). NMR ($CDCl_3$) δ: 1.45 (6H, s), 2.44 (2H, dd, $J=4.0$ Hz, $J=2.0$ Hz), 6.05 (1H, dt, $J=10.0$ Hz, $J=2.0$ Hz), 6.82 (1H, dt, $J=10.0$ Hz, $J=4.0$ Hz).

5,6-Dihydro-6-ethyl-6-methyl-2*H*-pyran-2-one (6)——By the procedure given for compound **5**, compound **2** (1.5 g) was treated with dry ether (20 ml) saturated with hydrogen chloride to give the product **6** as an oil, bp 68° (0.5 mmHg), 1.0 g (75%). *Anal.* Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.65. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O), 1625 (C=C). NMR ($CDCl_3$) δ: 0.97 (3H, t, $J=7.2$ Hz), 1.40 (3H, s), 1.60—2.00 (2H, m), 2.33—2.50 (2H, m), 5.98 (1H, dt, $J=10.0$ Hz, $J=2.0$ Hz), 6.75 (1H, dt, $J=10.0$ Hz, $J=4.0$ Hz).

Reaction of Compound 1 with Aniline——A solution of compound **1** (1 g, 7 mmol) and aniline (0.65 g, 7 mmol) in absolute ethanol (5 ml) was refluxed for 8 hr. The mixture was concentrated *in vacuo*, and the residue was subjected to silica gel (30 g) column chromatography. Elution with hexane–ethyl acetate (10:1) afforded compound **7** as colorless needles (from benzene–hexane), mp 100°, 0.4 g (27%). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.29; H, 7.75; N, 6.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1715 (C=O). NMR ($CDCl_3$) δ: 1.23—2.47 (3H, m), 1.47 (6H, s), 2.80—3.32 (2H, m), 3.70—4.23 (1H, m), 6.52—7.32 (5H, m).

Subsequent elution with hexane–ethyl acetate (4:1) afforded compound **8** as colorless needles (from benzene–hexane), mp 98—99°, 0.85 g (52%). *Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.85; H, 7.97; N, 5.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3330 (OH, NH), 1670 (C=O). NMR (DMSO-d_6) δ: 1.16 (3H, s), 1.18 (3H, s), 1.56 (2H, d, $J=6.4$ Hz), 2.43 (2H, d, $J=6.4$ Hz), 3.38 (1H, s), 4.05—4.47 (1H, m), 4.61 (1H, s), 7.01—7.75 (5H, m).

Reaction of Compound 5 with Aniline——A mixture of compound **5** (75 mg, 0.6 mmol) and aniline (57 mg, 0.6 mmol) was heated at 120° for 25 hr. The mixture was purified by silica gel (20 g) column chromatography. Elution with hexane–ethyl acetate (10:1) gave compound **7**, 0.1 g (74%).

Reaction of Compound 2 with Aniline——A solution of compound **2** (1.3 g, 8 mmol) and aniline (0.77 g, 8 mmol) in absolute ethanol (10 ml) was refluxed for 12 hr. After removal of the solvent from the reaction mixture under reduced pressure, the resulting residue was subjected to silica gel (50 g) column chromatography. Elution with hexane–ethyl acetate (4:1) gave compound **9** as colorless needles (from benzene–hexane), mp 81—82°, 0.7 g (37%). *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.30; H, 8.12; N, 5.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 1715 (C=O). NMR (DMSO-d_6) δ: 0.90, 0.93 (3H, each t, $J=7.1$ Hz), 1.32, 1.40 (3H, each s), 1.52—1.86 (2H, m), 1.97—2.54 (3H, m), 2.76—3.02 (1H, m), 3.24 (1H, br s), 3.72—4.12 (1H, m), 6.48—7.16 (5H, m).

Elution was continued with the same solvent to give compound **10** as colorless needles (from benzene–hexane), mp 109°, 0.7 g (33%). *Anal.* Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.99; H, 8.40; N, 5.32. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3330 (OH, NH), 1675 (C=O). NMR ($CDCl_3$) δ: 0.90 (3H, t, $J=7.0$ Hz), 1.17—1.72 (4H, m), 1.26 (3H, s), 1.50 (2H, d, $J=6.0$ Hz), 3.65 (2H, br s), 4.20—4.75 (1H, m), 7.02—7.80 (5H, m), 8.67 (1H, br s).

Reaction of Compound 6 with Aniline——A mixture of compound **6** (0.1 g, 0.7 mmol) and aniline (0.07 g, 0.7 mmol) was heated at 120° for 24 hr. Similar purification by silica gel column chromatography gave compound **9**, 0.1 g (60%).

Acknowledgement The present work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged. Thanks are due to Mrs. C. Koyanagi for elemental analyses, and to Miss K. Mushiake for NMR measurements.

References and Notes

1) Part CIV: T. Kato, T. Chiba, M. Sasaki, and M. Kamo, *Yakugaku Zasshi*, **101**, 40 (1981).
2) I. Rosenthal and D. Elad, *J. Org. Chem.*, 33, 805 (1968).
3) D. Elad, G. Friedman, and R.D. Youssefyeh, *J. Chem. Soc.* (*C*), **1968**, 870.
4) B. Fraser-Reid, D.R. Hicks, D.L. Walker, D.E. Iley, M.B. Yunker, S. Yik-Kai Tam, and R.C. Anderson, *Tetrahedron Lett.*, **1975**, 297.
5) *e.g.*, T. Kato, *Acc. Chem. Res.*, 7, 267 (1974).
6) IR spectra were taken with a JASCO model IR-S spectrophotometer. NMR spectra were taken on Hitachi R-20, JEOL JNM-PMX 60, and JEOL PS-100 instruments. Chemical shifts are reported on

the δ scale, parts per million downfield from tetramethylsilane as an internal standard. All melting points and boiling points are uncorrected. The ultraviolet (UV) light sources were RIKO UVL-100HA and UVL-400HA lamps.

7) S. Kikumasa, M. Shioji, and H. Masao, *J. Org. Chem.*, **32**, 177 (1967).
8) G. Agnes and G.P. Chinsoli, *Chim. Ind.* (Milan), **1968**, 50 (2), 194 (Ital.); [*C.A.*, **69**, 35352*t* (1968)].