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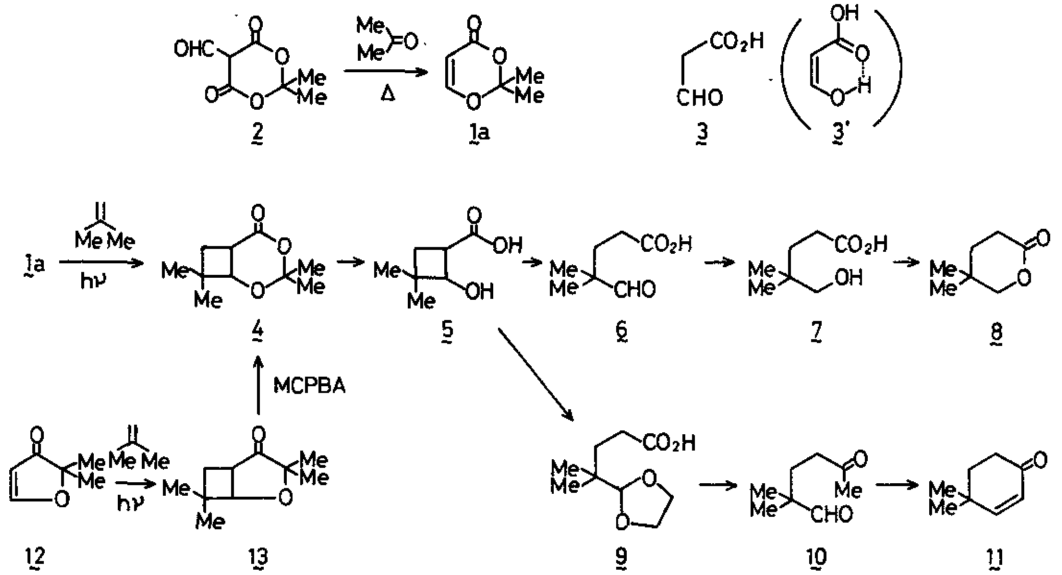
SYNTHESIS OF 1,3-DIOXIN-4-ONES UNSUBSTITUTED AT THE 5- AND 6-POSITIONS AND THEIR PHOTOADDITION TO ALKENES[1]

Masayuki Sato,* Hiromichi Ogasawara, Keiko Sekiguchi, and Chikara Kaneko*
Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

Abstract —— A general synthetic method of 5,6-unsubstituted 1,3-dioxin-4-ones and their photoaddition to alkenes are described. The photoadducts thus obtained were found to give, merely by refluxing in water, alkanes having carboxaldehyde and acetic acid appendages at the vicinal position.

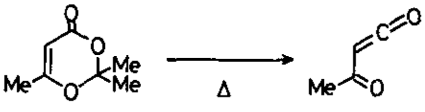
Two of the present authors (M. S. and H. O.) recently reported[2] the synthesis of 2,2-dimethyl-1,3-dioxin-4-one (1a) by heating of formyl Meldrum's acid (2)[3] in toluene in the presence of acetone. The importance of 1,3-dioxin-4-one unsubstituted at the 5- and 6-positions (*e.g.*, 1a) in synthetic organic chemistry was originally pointed out by Baldwin,[4] who regarded it as photochemical equivalent of formyl acetic acid (3)[5] having a specific enol configuration (*i.e.*, 3') by an actual covalent bond. Without 1a at hand, Baldwin *et al.* utilized 2,2-dimethyl-3-(2*H*)-furanone (12) as a viable alternative to 1a. As shown in the chart, the adduct (13) obtained by photoaddition of this furanone to alkenes (isobutene is used as an example) afforded oxalactone (4) by Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid. The lactone (4) should be the same[6] with the product which would arise by direct photoaddition of 1a to the same alkene. Typical reactions of 4 actually realized by Baldwin's group can be classified into three types: i) simultaneous introduction of carboxaldehyde and acetic acid appendages at the vicinal position of an alkene (4⟶6),[7] ii) formation of δ-lactones (8),[7] and iii) cyclohexenone annelation.[4,8] Since an optimization of the yield and an establishment of conditions for a large scale preparation of 1a were not done in our earlier work[2] and compound 1 is potentially important as described above, we have continued our work in order to attain the optimum yield of 1a and to synthesize the related

5,6-unsubstituted dioxinones (1) as well as to examine the photochemical behaviour of 1a. In this report, we describe these results.



We have already noted that 2,2,6-trimethyl-1,3-dioxin-4-one (14) upon heating affords acetylketene (15) by thermally allowed electrocyclic cleavage and the latter can be utilized in the synthesis of a variety of heterocyclic ring systems.[9] By analogy to the conversion of 14 to 15 and the pyrolytic fragmentation of Meldrum's acid (16) to ketene, acetone, and carbon dioxide,[10] the previous conversion of formyl Meldrum's acid (2) to 2,2-dimethyl-1,3-dioxin-4-one (1a) is considered to proceed through similar electrocyclic ring cleavage giving formylketene (17) with concomitant losses of acetone and carbon dioxide. The formylketene thus formed would cyclize with acetone in a 4+2 manner to give 1a. After examining the reaction conditions for the conversion of 2 to 1a, we have succeeded in optimizing the conditions and obtained 1a in 67% yield (the yield of 1a was 31% in our previous procedure[2]). The main alteration from the previous procedure is the use of a large excess of toluene and a portionwise addition of 2 into refluxing toluene containing acetone. The detail of this modified procedure is given in the experimental.

Due to the importance of 5,6-unsubstituted 1,3-dioxin-4-one derivatives, three analogs (1b, 1c, and 1d) were also synthesized according to the above modified procedure all in satisfactory yields.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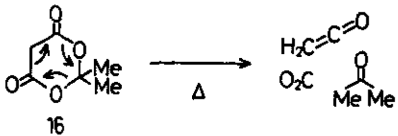
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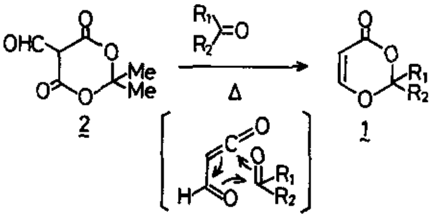
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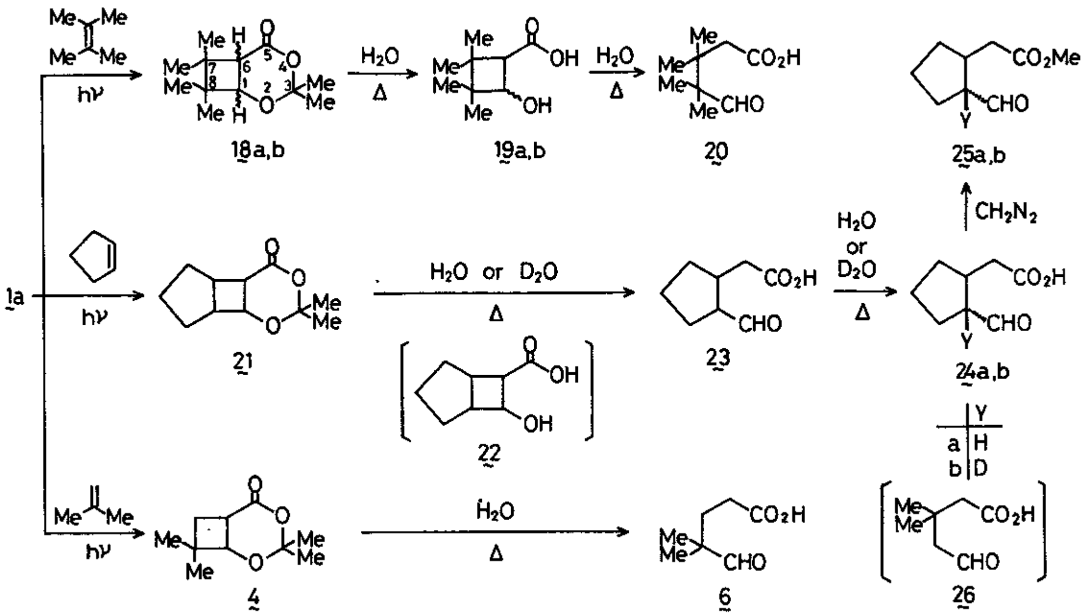
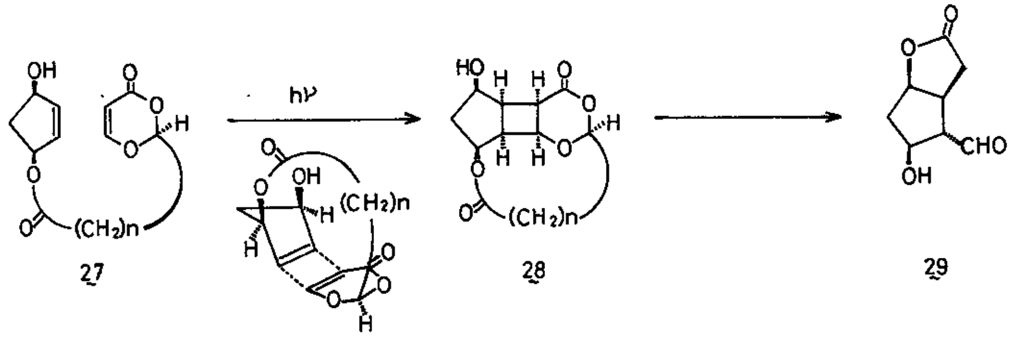
Table I. Yields and Melting Points [Boiling Points] of 5,6-Unsubstituted 1,3-Dioxin-4-ones (1)

	R_1	R_2	Mp [Bp (mmHg)] (°C)	Yield (%)
a	Me	Me	[59 (4)]	67
b	$-(CH_2)_5-$		40-42	67
c	$-(CH_2)_4-$		[47 (0.2)]	49
d	H	n-heptyl	[75 (0.001)]	75

Since 2,2,6-trimethyl-1,3-dioxin-4-one (14) was reported to add efficiently to alkenes by irradiation,[11] 5,6-unsubstituted 1,3-dioxin-4-ones (1a-1d) are also expected to add to alkenes under comparable conditions. Actually, irradiation of 1a in hexane in the presence of an excess of tetramethylethylene afforded two 2+2 adducts (18a and 18b)[12] in a ratio of *ca.* 4:1 in 55% yield. The minor adduct (18b)[13] is very labile to moisture and converted to hydroxy acid (19b) even by an attempted recrystallization from hexane-ether. The major adduct (18a) is stable enough to be recrystallized from the same solvent, but gives another hydroxy acid (19a) by short refluxing (30 min) in water. As expected, both hydroxy acids (19a and 19b) gave the same aldehyde acid (20) in almost quantitative yield by prolonged refluxing in water (50 h). Only one kind of adduct (21)[14] was obtained upon photoaddition of 1a to cyclopentene, which was converted as above (reflux in water) to aldehyde acid (24a) showing the aldehyde proton at δ 9.65 as a doublet (J 1.5 Hz). Methylation of 24a by diazomethane in ether gave the ester (25a). The facts that the same ester was obtained directly from 21 as the sole product by refluxing in HCl-methanol as well as the formation of the mono-deuteriated acid (24b) whose aldehyde proton appears at δ 9.68 as a singlet from 21 by refluxing in D_2O show clearly that 24a is the *trans* isomer and formed from the *cis* isomer (23: the initial ring cleavage product of 22) via the epimerization at the carbon atom bearing the carboxaldehyde group. In analogy with an almost exclusive formation of the head-to-tail (H-T) adduct by the photoaddition of 14 to isobutene,[4] the H-T adduct (4) was obtained predominantly from 1a and isobutene.

The H-T structure of 4 was readily verified by its hydrolysis to aldehyde acid (6: oil),[15] whose NMR spectrum showed the aldehyde proton at δ 9.41 as a singlet, thus excluding the alternative structure (26).





It should be noted that the introduction of vicinal carboxaldehyde and acetic acid appendages to a double bond by means of photochemical cycloaddition of 1 to olefins is superior to those reported already, especially in its short steps, high regioselectivity, and mildness of the hydrolysis stage. The previous use of uracil derivatives is hampered by the difficulty of the hydrolysis stage[16,17] of the photoadduct and the use of formyl acetic ester is prohibited by the lack of the ability to add alkenes.[18,19]

Since both 1d-type dioxinone and 2-cyclopentene-*cis*-1,4-diol[20] can now be readily prepared, synthesis of 27 (n: an appropriate integer) should be easy. Synthesis of Corey's lactone (29)[21] *via* 28 is underway.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO model A-102 spectrometer and ^{1}H-NMR spectra on a JEOL model JNM-PMX 60 spectrometer at 60 MHz using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi model M-52G and high-resolution MS on a JEOL JMS-01SG-2 spectrometer. The irradiation source used for photoaddition reactions was Rayonet photochemical reactor lamps (Cat. No. RPR-3000Å). Column chromatography was performed on silica gel (Wakogel C-200).

2,2-Dimethyl-1,3-dioxin-4-one (1a) [General Procedure for the Synthesis of 5,6-Unsubstituted 1,3-Dioxin-4-ones]: To a refluxing toluene solution (300 ml) containing acetone (2.9 g, 50 mmol), was added portionwise a finely powdered formyl Meldrum's acid (2, 8.6 g, 50 mmol).[3] When the addition is complete (2 h), the solution was refluxed for an additional hour. The solvent is removed on a rotary evaporator (the bath temperature should be maintained below 30 °C) and the residual oil is distilled at reduced pressure. Yield, 4.3 g (67%). Bp 59 °C/4 torr. [lit.[2] bp 65 °C (oven temperature for bulb to bulb distillation)/1 torr]. Found: M^+, 128.0483. $C_6H_8O_3$ requires 128.0473. $\nu_{max.}$ ($CHCl_3$) 1730, 1620 cm^{-1}. δ (CCl_4) 1.70 (6H, s, CMe_2), 5.28 (1H, d, *J* 6 Hz, C_5-H), 7.07 (1H, d, *J* 6 Hz, C_6-H).

Three analogs (1b, 1c, and 1d) were also synthesized according essentially to the above modified procedure all in satisfactory yields (see Table I). In these cases, however, 5 molar equivalent (to 2) of a ketone or aldehyde was used. Synthesis of 1b-1d and other 5,6-unsubstituted 1,3-dioxin-4-ones will be reported in detail elsewhere.[22]

General Procedure for the Photoaddition of 1a to Alkenes: Irradiation was performed using Rayonet photochemical reactor with RPR-3000Å lamps (quartz vessel) as light source. Typically the alkene and 1a were present in 10:1 molar ratio. The concentration of 1a was 0.1 M with irradiation times of 12 h. Prior to irradiation, argon was passed through the reaction mixture for about 10 min.

The Formation of the Photoadducts of 1a with Tetramethylethylene and Their Hydrolysis: A solution of hexane (20 ml) containing 1a (0.256 g, 2 mmol) and tetramethylethylene (1.68 g, 20 mmol) was irradiated for 12 h. After concentration *in vacuo*, oily residue was stored in a refrigirator overnight. After addition of a small amount of pentane, a deposited crystalline (18b) was collected, mp 136-138 °C. Yield, 0.045 g (11%). An analytical sample (mp 141-142 °C) was recrystallized from diethyl ether. Found: C, 67.57; H, 9.46. $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%; $\nu_{max.}$ ($CHCl_3$) 1730, 1710 cm^{-1}. δ ($CDCl_3$) 0.97, 1.05 (each 6H, s, 2xMe) 1.58, 1.65 (each 3H, s, C_3-Me), 2.80 (1H, d, *J* 9 Hz, C_6-H), 4.23 (1H, d, *J* 9 Hz, C_1-H). The pentane soluble portion was separated by column chromatography (hexane-ether 6:1 v/v) to give the other adduct (18a, 0.185 g, 44%), which was recrystallized from pentane, mp 77-79 °C. Found: C, 67.60; H, 9.62. $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%; $\nu_{max.}$ ($CHCl_3$) 1720 cm^{-1}. δ ($CDCl_3$) 0.98 (3H, s, Me), 1.12 (6H, s, 2xMe), 1.15 (3H, s, Me), 1.53, 1.57 (each 3H, s, C_3-Me), 2.85 (1H, d, *J* 5 Hz, C_6-H), 4.07 (1H, d, *J* 5 Hz, C_1-H).

The major adduct (18a, 0.106 g, 0.5 mmol) was refluxed in water (2 ml) for 30 min. After evaporation of water *in vacuo*, the residual solid was recrystallized from hexane to give a hydroxy acid (19a, 0.070 g, 81%) as colorless needles, mp 102-104 °C. Found: C, 62.35; H, 9.31. $C_9H_{12}O_3$ requires C, 62.76; H, 9.36%; $\nu_{max.}$ ($CHCl_3$) 3460, 2800-2450, 1720 sh cm^{-1}. δ ($CDCl_3$) 1.02, 1.12 (each 6H, s, 2xMe), 3.05 (1H, d, *J* 7 Hz, $C\underline{H}CO_2H$), 4.08 (1H, d, *J* 7 Hz, $C\underline{H}OH$), 7.52 (1H, bs, $CO_2\underline{H}$).

The other hydroxy acid (19b, mp 170-172 °C) was obtained in a quantitative yield from the minor adduct (18b) merely by prolonged standing of its ether solution in an open vessel. $\nu_{max.}$ ($CHCl_3$) 3500-3100, 2800-2400, 1710 cm^{-1}. δ ($CDCl_3$-CD_3OD 9:1 v/v) 0.98 (6H, s, 2xMe), 1.03 (3H, s, Me), 1.11 (3H, s, Me), 2.73 (1H, d, *J* 9 Hz, $C\underline{H}CO_2H$), 4.09 (1H, d, *J* 9 Hz, $C\underline{H}OH$). Both hydroxy acids gave the same aldehyde acid (20) by prolonged refluxing in water. Thus, for example, the major adduct (18a, 0.106 g, 0.5 mmol) was refluxed in water (2 ml) for 50 h. After evaporation of water *in vacuo*, the solid residue was recrystallized from ether-hexane to give the aldehyde acid (20, mp 84-86 °C). Yield, 0.060 g (70%). Found: C, 62.44; H, 9.44. $C_9H_{16}O_3$ requires C, 62.76; H, 9.36%; $\nu_{max.}$ ($CHCl_3$) 3500-3100, 2850-2400, 1715 cm^{-1}. δ ($CDCl_3$) 1.06, 1.12 (each 6H, s, 2xMe), 2.39 (2H, s, $C\underline{H}_2CO_2H$), 6.25-6.8 (1H, bs, $COO\underline{H}$), 8.0 (1H, s, $C\underline{H}O$).

The Formation of the Photoadduct of 1a with Cyclopentene and Its Hydrolysis: Under the same irradiation conditions as above, the crude product was obtained which by distillation to give a single adduct (21). Yield, 0.211 g (54%). Bp 110-130 °C (oven temperature for bulb to bulb distillation)/0.3 torr. The spectral data were consistent with those of Baldwin *et al.*[7] Found: C, 66.93; H, 7.97. $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%.

The adduct (21, 0.196 g, 1 mmol) was refluxed in water (4 ml) for 12 h. After evaporation of water *in vacuo*, the oily residue was separated by column chromatography (hexane-ether 2:1 v/v) to give the aldehyde acid (24a).[23] Yield, 0.102 g (65%). Found: C, 58.98; H, 7.66. $C_8H_{12}O_3 \cdot 1/3H_2O$ requires C, 59.24; H, 7.87%; $\nu_{max.}$ ($CHCl_3$) 3500, 2750-2500, 1710 cm^{-1}. δ ($CDCl_3$) 1.15-2.2 [6H, m, $(CH_2)_3$], 2.5 (3H, bs, $C\underline{H}_2CO_2H$ and $C\underline{H}CHO$), 8.62 (1H, bs, $CO_2\underline{H}$), 9.65 (1H, d, *J* 1.5 Hz, $C\underline{H}O$).

The Formation of the Photoadduct of 1a with Isobutene and Its Hydrolysis: To a solution of 1a (0.256 g, 2mmol) in hexane (20 ml), isobutene gas was bubbled through for 30 min at room temperature. After the bubbling was terminated, the solution was irradiated as above for 12 h. The residue obtained after evaporation of the solvent *in vacuo* was separated by column chromatography (hexane-ether 3:1 v/v) to give the adduct (4). Yield, 0.170 g (46%). Found: M^+, 184.1107. $C_{10}H_{16}O_3$ requires 184.1098. $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1}. δ ($CDCl_3$) 1.06, 1.16 (each 3H, s, Me), 1.53, 1.63 (each 3H, s, Me), 1.95-2.4 (2H, m, CH_2), 2.7-3.4 (1H, m, C_6-H), 4.23 (1H, d, *J* 6.5 Hz, C_1-H).[24]

This adduct was hydrolyzed in refluxing water (24 h) to give the aldehyde acid (6) in 70% yield. Oil. δ ($CDCl_3$) 1.08 (6H, s, 2xMe), 1.6-2.6 [4H, m, $(CH_2)_2$], 8.3 (1H, bs, $COO\underline{H}$), 9.41 (1H, s, $C\underline{H}O$).[24]

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24. Very small signals probably due to the other isomer are observed in the spectrum.

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