The titration was done at 15° using a Radiometer TTTlc titrator and SBR2 titrigraph. The detailed procedure was reported previously.[3] The p*Ka* calculated was practical constant.

Acknowledgement The thermal analysis was carried out at the Instrumental Analysis Center of Application Laboratory, Shimadzu Seisakusho, Ltd. The author wishes to thank Mrs. M. Tsuyama and T. Hattori of the Analysis Center for doing the thermal analysis.

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[3] A. Hanaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 766 (1970).

[Chem. Pharm. Bull. 20(7)1574—1578(1972)]

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Studies on Ketene and Its Derivatives. XLIX.[1] Reaction of Diketene with β-Ketoesters to give Ethyl Orsellinate, Divarate, Olivetol Carboxylate, and Sphaeropherol Carboxylate

TETSUZO KATO and TOYOHARU HOZUMI

Pharmaceutical Institute, Tohoku University[2]

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Diketene reacts easily with an active hydrogen which is attached to a hetero atom such as oxygen or nitrogen to give O-acetoacetyl or N-acetoacetyl derivatives. However, only a few references are available concerning the reaction of diketene with an active hydrogen attached to a carbon atom to give C-acetoacetyl derivative. Hamamoto[3] reported the reaction of diketene with acetylacetone in the presence of an acidic catalyst to give 3-acetyl-2,6-dimethyl-4-pyrone. This reaction suggests that diketene reacts with the active methylene of acetylacetone to give 3-acetyl-pen+an-2,4-dione as an intermediate, which cyclizes to the pyrone derivative. In the previous paper of this series[4] we have reported the reaction of 2-(2-pyridyl)-acetonitrile with diketene to give 2-(2-pyridyl)-2-acetoacetylacetonitrile in good yield.

The objectives of the present paper are twofold—to investigate the activity of diketene toward the active methylene of β-ketoester and establish the simple method of preparation of some metabolites of lichen such as orsellinic acid derivatives.

When ethyl acetoacetate (Ia) was allowed to react with diketene in the presence of sodium hydride in tetrahydrofuran, colorless crystals of mp 131—132°, $C_{10}H_{12}O_4$ (IIa), and a colorless oil of bp 130—131° (4 mmHg), $C_{10}H_{12}O_4$ (IIIa), were obtained in 38% and 7% yield, respectively. Both IIa and IIIa are already known, and characterized as ethyl orsellinate and ethyl 2,6-dimethyl-4-pyrone-3-carboxylate,[5] respectively.

Reaction of IIIa with ammonia afforded ethyl 2,6-dimethyl-4-pyridinol-3-carboxylate (IVa) and ethyl 4-amino-2,6-dimethylpyridine-3-carboxylate (Va). Treatment of Va with nitrous acid gave IVa.

When the reaction was carried out in the presence of triethylamine in place of sodium hydride, both yields of IIa and IIIa decreased. The use of water as a solvent instead of organic solvent such as tetrahydrofuran decreased the yield of IIa but increased that of IIIa.

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[1] XLVIII: T. Kato, N. Katagiri, and N. Minami, *Chem. Pharm. Bull.* (Tokyo), **29**, 1368 (1972).
[2] Location: *Aobayama, Sendai, 980, Japan.*
[3] K. Hamamoto, T. Isoshima, and M. Yoshioka, *Nippon Kagaku Zasshi*, **79**, 840 (1958).
[4] T. Kato and T. Atsumi, *Yakugaku Zasshi*, **87**, 961 (1967).
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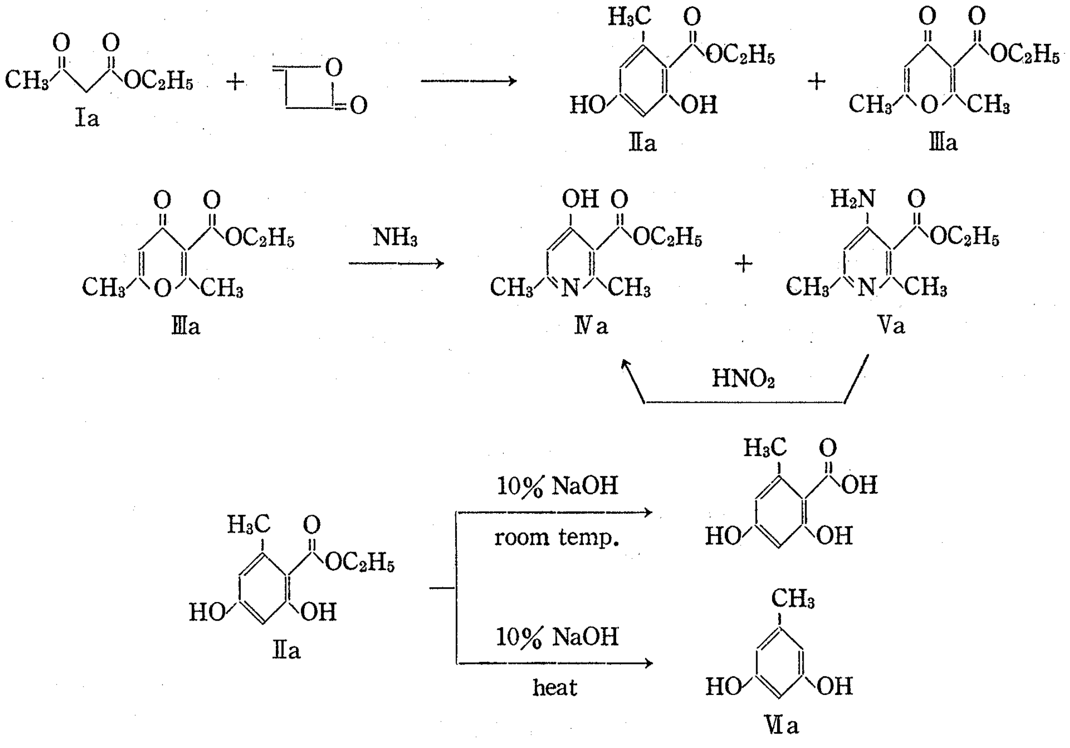
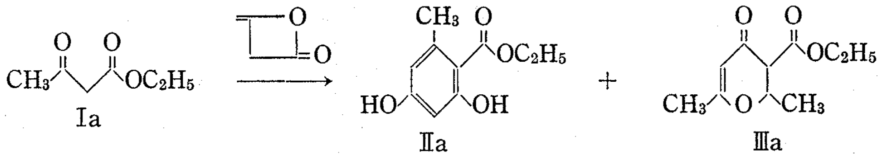


Chart 1

Table I.



Catalyst		Et_3N			KOH			EtONa		NaH
solvent		THF	EtOH	H_2O	THF	EtOH	H_2O	THF	EtOH	THF
Product	IIa	13	trace[a]	0.8	32.2	14.5	5.4	37.2	34.7	38
(%)	IIIa	0.8	trace[a]	35	19.4	3.1	21.7	8.4	2.8	6.9

[a] The products were identified by thin layer chromatography.

The results are summarized in Table I.

Hydrolysis of IIa with 10% sodium hydroxide at room temperature gave rise to orsellinic acid (II: $R=CH_3$, $R'=H$), but heating at reflux resulted in the evolution of carbon dioxide giving 5-methylresorcinol (VIa).

Orsellinic acid is known as a metabolite of lichen. Since its synthetic studies previously reported[6-10] are not always satisfactory in respects of yields, procedures, or starting materials, we have been focusing our attention on further investigations of this reaction. Thus, ethyl β-ketocapronate (Ib) was allowed to react with diketene in the presence of sodium

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[6] K. Hoesh, *Chem. Ber.*, **46**, 886 (1913).

[7] A. Sonn, *Chem. Ber.*, **61**, 926 (1928).

[8] T. Money, I.H. Quereshi, G.B. Webster, and A.I. Scott, *J. Am. Chem. Soc.*, **87**, 3004 (1965).

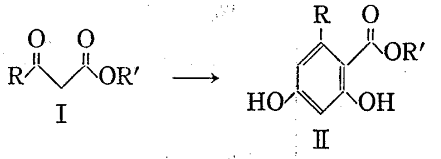
[9] T. Money, J.L. Douglas, and A.T. Scott, *J. Am. Chem. Soc.*, **88**, 624 (1966).

[10] J.M. Harris and R.L. Carney, *J. Am. Chem. Soc.*, **88**, 2053 (1966).

hydride in tetrahydrofuran giving colorless prisms of mp 97—98° (lit.[11] mp 96—97°), which was identical with ethyl divarate (IIb). Similarly, ethyl β-ketocaprylate (Ic) and ethyl β-ketocaprinoate (Id) reacted with diketene to yield ethyl olivetol carboxylate (IIc) and ethyl sphaeropherol carboxylate (IId), respectively. Also, ethyl benzoylacetate (Ie) afforded ethyl 6-phenyl-β-resorcylate (IIe) in 40% yield. Similarly, alkylesters of acetoacetic acid (If—i) gave rise to alkylesters of orsellinic acid. Table II summarizes these reactions.

Hydrolysis of alkyl orsellinate (IIf—i) with 10% sodium hydroxide at room temperature afforded orsellinic acid (II: R=CH_3, R′=H) in approximately same yield (40—50%). Similar treatment of ethyl divarate (IIb) gave rise to free divaric acid (II: R=C_3H_7, R′=H) in a low yield, but the same treatment of IIc and IId did not give the corresponding free acid. Heating of II with alkali afforded the resorcinol derivative (IVa—e) in almost quan-

TABLE II



						IR $\nu_{max}^{CHCl_3}$ cm^{-1}		NMR ($CDCl_3$, TMS, ppm)		Elemental analysis (%)			
										Calcd.		Found	
No	R	R′	Appearance	mp (°C)	Yield (%)	-OH	>C=O	Ringproton	Formula	C	H	C	H
IIa	CH_3	C_2H_5	needles	131—132	38	3600 3260	1645	6.21 6.28 $(J=3\mathrm{H_z})$	$C_{10}H_{12}O_4$	61.21	6.17	60.76	6.37
IIb	n-C_3H_7	C_2H_5	prisms	97— 98	35	3600 3260	1645	6.21 6.28 $(J=3\mathrm{H_z})$	$C_{12}H_{16}O_4$	64.27	7.19	64.16	7.28
IIc	n-C_5H_{11}	C_2H_5	prisms	68	38	3580 3260	1648	6.15 6.20 $(J=3\mathrm{H_z})$	$C_{14}H_{20}O_4$	66.64	7.99	67.09	8.18
IId	n-C_7H_{15}	C_2H_5	plates	63— 64	40	3600 3280	1648	6.17 6.22 $(J=3\mathrm{H_z})$	$C_{16}H_{24}O_4$	68.54	8.63	68.43	8.90
IIe	C_6H_5	C_2H_5	needles	127—128	36	3580 3340	1655	6.26 6.42 $(J=3\mathrm{H_z})$	$C_{15}H_{14}O_4$	69.75	5.46	69.80	5.56
IIf	CH_3	CH_3	prisms	142.5	45	3600 3260	1652	6.2—6.4	$C_9H_{10}O_4$	59.33	5.53	59.05	5.61
IIg	CH_3	$CH(CH_3)_2$	prisms	117—118	47	3600 3260	1645	6.1—6.3	$C_{11}H_{14}O_4$	62.84	6.71	63.06	7.02
IIh	CH_3	$C(CH_3)_3$	needles	158—159	52	3600 3270	1648	6.22 6.29 $(J=3\mathrm{H_z})$	$C_{12}H_{16}O_4$	64.27	7.19	64.15	7.27
IIi	CH_3	$CH_2C_6H_5$	prisms	140—141	51	3600 3270	1648	6.20 6.28 $(J=3\mathrm{H_z})$	$C_{15}H_{14}O_4$	69.75	5.46	69.28	5.49

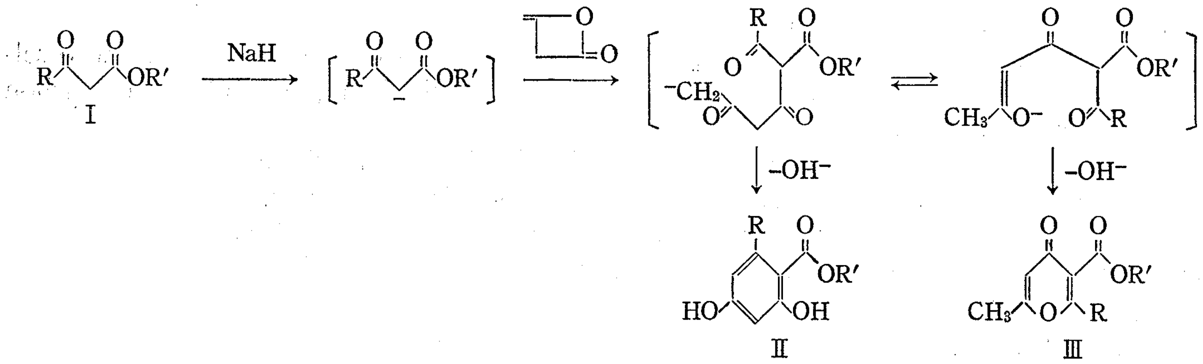


Chart 2

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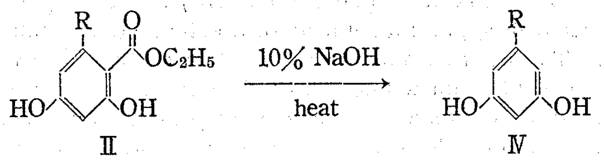
[11] F. Fujikawa, *Yakugaku Zasshi*, **61**, 325 (1941).

TABLE III



II	Product IV R	bp (°C/mmHg) mp (°C) (Solvent)	Yield (%)	Formula	Elemental analysis Calcd. C	 H	 Found C	 H
IIa	CH_3	120—125/3	95	$C_7H_8O_2$	67.73	6.50	67.36	6.51
IIb	n-C_3H_7	127—129/3	97	$C_9H_{12}O_2$	71.02	7.95	71.32	7.94
IIc	n-C_5H_{11}	126—129/3	96	$C_{11}H_{16}O_2$	72.55	8.95	72.81	8.94
IId	n-C_7H_{15}	128—131/3	97	$C_{13}H_{20}O_2$	74.96	9.68	74.63	9.59
IIe	C_6H_5	159 (benzene)	95	$C_{12}H_{10}O_2$	77.40	5.41	77.64	5.72

titative yield. Table III summarizes the hydrolysis of II to give rise to IV.

Though the details of the mechanism is obscure for the present, a likely pathway is shown in Chart 2. Thus, the first stage of this reaction might well involve the C-acetoacetylation of the active methylene of β-ketoesters, followed by the ring-closure giving resorcinol derivatives (II) or pyrone derivatives (III).

Experimental

Alkyl Acetoacetate (Ia, If—i)——General Procedure: Diketene (84 g, 1 mole) was added dropwise to the corresponding alcohol (2 mole) in the presence of triethylamine (1 ml) with heating in a water bath at 90°. After the addition had been completed the heating was continued for 1 hr at 90°. The product was purified by vacuum distillation.

Methyl Acetoacetate (If): bp 77—79° (27 mmHg) (lit. bp 73—74° (12 mmHg)),12) Yield, 112 g (97%).

Ethyl Acetoacetate (Ia): bp 86—88° (25 mmHg) (lit. bp 109° (80 mmHg)),13) Yield, 124 g (95%).

Isopropyl Acetoacetate (Ig): bp 86° (22 mmHg) (lit. bp 74—77° (15 mmHg)),13) Yield, 130 g (90%).

tert-Butyl Acetoacetate (Ih): bp 94—96° (35 mmHg) (lit. bp 82° (15 mmHg)),14) Yield, 142 g (90%).

Benzyl Acetoacetate (Ii): bp 129—133° (5 mmHg) (lit. bp 162—164° (16 mmHg)),13) Yield, 152 g (79%).

Alkyl 6-Substituted-β-resorcylate (II)——General Procedure: To a solution of β-ketoester (I, 0.02 mole) in tetrahydrofuran (THF, 20 ml) was added sodium hydride (52.9% oil, 1.02 g, 0.02 mole) with continuous stirring and cooling, and a solution of diketene (1.68 g, 0.02 mole) in THF (20 ml) was added dropwise to the mixture at −5—0°. The reaction mixture was stirred for 1 hr at the same temperature, and the stirring was continued for additional 1 hr at room temperature. The mixture was neutralized with 10% HCl, and extracted with ether. The ether soluble fraction was dried over Na_2SO_4, filtered, and the filtrate was evaporated to give a brown oily substance, which was purified by silica gel chromatography. Petroleum ether (bp 30—35°) and the mixture of petroleum ether–ether (8: 1) were used as solvents. From the petroleum ether–ether effluent, a crystalline product was obtained. Purification by recrystallization from n-hexane afforded II. Table II shows the summary of this reaction.

Ethyl 2,6-Dimethyl-4-pyrone-3-carboxylate (IIIa)——1) To the mixture of ethyl acetoacetate (Ia, 2.6 g, 0.02 mole) and triethylamine (2.02 g, 0.02 mole) in H_2O (40 ml) was added diketene (1.68 g, 0.02 mole) dropwise at −5—0°, and the mixture was stirred for 1 hr. The stirring was continued for additional 1 hr at room temperature. The reaction mixture was neutralized with 10% HCl, and was extracted with ether. The ether soluble fraction was dried over Na_2SO_4, and condensed to give a residue, which was purified by silica gel chromatography. The mixture of petroleum ether–ether (8: 1) was used as a solvent. The eluent was condensed and the resulting oily residue was purified by vacuum distillation to afford an oil of bp 130—131° (4 mmHg) (lit. bp 150° (3 mmHg)).5) Yield, 1.37 g (35%). *Anal.* Calcd. for $C_{10}H_{12}O_4$ (IIIa): C, 61.21;

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12) J.W. Brühl, *J. Prakt. Chem.*, **50**, 127 (1894).
13) J.C. Shivers, M.L. Dillon, and C.R. Hauser, *J. Am. Chem. Soc.*, **69**, 119 (1943).
14) W.B. Renfrow and G.B. Walker, *J. Am. Chem. Soc.*, **70**, 3957 (1948).

H, 6.17. Found: C, 61.69; H, 6.41.

2) To the solution of ethyl acetoacetate (2.6 g, 0.02 mole) in EtOH (20 ml) was added KOH (1.12 g, 0.02 mole) with stirring and ice-cooling, and a solution of diketene (1.68 g, 0.02 mole) in EtOH (20 ml) was added dropwise at −5—0°. The mixture was stirred for 1 hr at the same temperature, and the stirring was continued for additional 1 hr at room temperature. The mixture was neutralized with 10% HCl, and evaporated to give an oily residue, to which was added H_2O (10 ml), and extracted with ether. The ether fraction was dried over Na_2SO_4, and condensed. The resulting residue was purified by silica gel chromatography. The mixture of petroleum ether–ether was used as an eluent. From the petroleum ether–ether (8:1) effluent, a crystalline product was obtained. Purification by recrystallization from *n*-hexane afforded IIa. Yield, 0.57 g (14.5%). From the petroleum ether–ether (1:1) effluent, an oily product was obtained, which was purified by distillation to give IIIa, bp 120—130° (3 mmHg). Yield, 0.12 g (3.1%).

3) According to the procedure given for alkyl 6-substituted-β-resorcylate (II), ethyl acetoacetate (Ia, 2.6 g) was allowed to react with diketene (1.68 g) in the presence of sodium hydride in THF. The product was purified by silica gel chromatography. From the petroleum ether–ether (1:1) eluent, IIIa was obtained as a colorless oil of bp 125—130° (3 mmHg). Yield, 0.27 g (6.9%).

Orsellinic Acid (II: R=CH_3, R′=H)——Ethyl orsellinate (IIa, 2.07 g) was dissolved in 10% NaOH (80 ml) and the solution was allowed to stand at room temperature for a week. The solution was acidified with 10% HCl and extracted with ether. The ether soluble layer was washed with H_2O and then with 5% $NaHCO_3$. The $NaHCO_3$ soluble fraction was neutralized with 10% HCl, and extracted with ether. The ether solution was washed with H_2O, dried over Na_2SO_4, evaporated to give a crystalline residue, which was recrystallized from benzene–acetone to colorless needles of mp 176° (decomp.). Yield, 0.84 g (46%). *Anal.* Calcd. for $C_8H_8O_4$ (II: R=CH_3, R′=H): C, 57.14; H, 4.80. Found: C, 57.45; H, 4.88.

Divaric Acid (II: R=*n*-propyl, R′=H)——Ethyl divarate (IIb, 0.2 g) was dissolved in 30% NaOH (10 ml). After allowing to stand for a week at room temperature, the reaction mixture was acidified with 10% HCl. Similar treatment as above afforded colorless needles of mp 169° (decomp.) (benzene–acetone). Yield, 30 mg (17%). From the $NaHCO_3$ insoluble fraction, 0.16 g (80%) of the starting material (IIb) was recovered. *Anal.* Calcd. for $C_{10}H_{12}O_4$ (II: R=*n*-propyl, R′=H): C, 61.21; H, 6.17. Found: C, 60.93; H, 6.14.

5-Substituted Resorcinol (IVa—e)——IIa—e (0.2 g) was dissolved in 10% NaOH (10 ml) and heated at reflux for 30 min. The mixture was acidified with 10% HCl, and was extracted with ether. The ether soluble fraction was washed with H_2O, dried over Na_2SO_4, and evaporated to give an oily residue, which was purified by distillation. The results are summarized in Table III.

Reaction of Ethyl 2,6-Dimethyl-4-pyrone-3-carboxylate (IIIa) with Ammonia——The mixture of IIIa (0.5 g), EtOH (10 ml), and 30% NH_4OH (10 ml) was heated at reflux for 1 hr, and condensed under reduced pressure to give a residue, to which was added ether (10 ml) and was rubbed with a glass rod to give crystals. Recrystallization from acetone afforded colorless needles of mp 168° (IVa), undepressed on admixture with an authentic sample[14] prepared from ethyl 3-aminocrotonate and diketene. Yield, 0.34 g (68%). The filtrate was condensed to give a residue. Purification by recrystallization from *n*-hexane gave colorless needles of mp 103—105°. Yield, 0.14 g (28%). *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$ (Va): C, 61.83; H, 7.27; N, 14.42. Found: C, 62.35; H, 7.45; N, 14.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3360, 1710, 1675. NMR ($CDCl_3$, TMS, ppm): 1.38 (t, 3H), 2.30 (s, 3H), 2.59 (s, 3H), 4.29 (q, 2H), 5.5—6.1 (broad, 2H), 6.13 (s, 1H).

Diazotization of Va——Va (1 g) was dissolved in 2N H_2SO_4 (3 ml) and the solution was cooled in an ice-bath. 2N $NaNO_2$ solution (3 ml) was added and the mixture was stirred for 10 min. After warming on a steam bath for several minutes at 70°, the reaction mixture was extracted with ether and $CHCl_3$. From the ether extract 0.5 g of the starting material (Va) was recovered. The $CHCl_3$ extract was purified by recrystallization from acetone to give colorless needles, mp 168°, whose IR spectrum was identical in every respects with that of the authentic sample of IVa obtained in the above run.

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