of Robinson and Sugasawa[11] provided (III), identical in mp and optical rotation with (*S*)-(−)-O-methylcryptaustoline iodide.[12]

To a mixture of 500 mg of IV [mp 219—220°, $[\alpha]_D^{25}$ −90.3° (c=1, MeOH)], obtained by quaternization of (*R*)-(−)-laudanosine[13] and 0.1 mg of horseradish peroxidase in 200 ml of H_2O was added 200 ml of 0.02% H_2O_2 over 1 hr while maintaining neutral pH by the addition of 0.1M Et_3N as needed. Acidification with dil HCl followed by concentration to 10 ml afforded on cooling 210 mg (60%)[14] of crystalline (V): mp 80—82°, $[\alpha]_D^{25}$ −40° (c=0.5, H_2O). The absolute configuration of (V) was established by its conversion into the known (*R*)-(−)-glaucine methiodide (VI).[15]

The above transformations[16] show that enzymatic coupling is at least as efficient as chemical methods for the practical preparation of certain types of alkaloids. The studies, which so far have been preliminary in nature, are now being expanded into a thorough investigation with different substrates and enzymes.

11) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, **1932**, 789.
12) G.H. Hughes, E. Ritchie, and W.C. Taylor, *Aust. J. Chem.*, **6**, 315 (1953).
13) A. Pictet and B. Athanescu, *Chem. Ber.*, **33**, 2346 (1900).
14) Optimization of the yield on a smaller scale produced values of 80—90%.
15) J. Go, *Yakugaku Zasshi*, **50**, 933 (1930) [*C. A.*, **25**, 518 (1931)].
16) We gratefully acknowledge the technical assistance of Messrs. S. Roy and J. Van Burik.

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Studies on Ketene and Its Derivatives. LVII.[1] Reaction of Diketene with β-Diketones

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Though the literature contains many references to synthesis of heterocyclic compounds from diketene, the formation of benzene ring system from diketene had not been described. However, in the previous paper of this series[3] we reported that diketene reacted with β-ketoesters such as ethyl acetoacetate in the presence of sodium hydride giving β-resorcinol derivatives such as ethyl orsellinate (V).

The present investigation was undertaken to see if diketene could react with β-diketones such as acetylacetone (Ia), benzoylacetone (Ib), dimedone (Ic) and dibenzoylmethane (Id) in a similar fashion as above to give β-resorcinol derivatives or not.

Concerning this reaction Hamamoto, *et al.*[4] reported that diketene reacted with acetylacetone (Ia) in the presence of acid such as sulfuric acid to give 3-acetyl-2,6-dimethyl-4-pyrone (IV), but did not react in the presence of a basic catalyst such as pyridine to result in the dimerization of diketene to dehydroacetic acid.

In view of the above fact, first we reinvestigated the reaction of acetylacetone (Ia) with diketene, and we found that reaction was affected under a variety of reaction conditions to give different products. When acetylacetone (Ia) was allowed to react with diketene in tetrahydrofuran (THF) in the presence of sodium hydride, colorless crystals of mp 158—159° (II) were obtained. On the other hand, when the reaction was carried out in water in the presence

1) Part LVI: T. Kato and T. Hozumi, *Yakugaku Zasshi*, **93**, 1084 (1973).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kato and T. Hozumi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1574 (1972).
4) K. Hamamoto, T. Isoshima, and M. Yoshioka, *Nippon Kagaku Zasshi*, **79**, 840 (1958).

of either triethylamine or sodium hydroxide as catalyst, the product was a colorless oil of bp 107—112° (IV). On the basis of spectroscopic evidences, compound IV was identified as 3-acetyl-2,6-dimethyl-4-pyrone by the comparison of its infrared (IR) spectrum with that of an authentic sample prepared according to Hamamoto's method.[4]

The IR spectrum of II showed hydroxyl and carbonyl absorptions at 3200 and 1618 cm^{-1}, and the nuclear magnetic resonance (NMR) spectrum indicated the presence of two methyl groups (2.53 and 2.61 ppm), two aromatic ring protons (6.29 ppm), and two OH protons (8.8 and 13.38 ppm).

Heating of II in 10% hydrochloric acid at reflux afforded 5-methylresorcinol (III), which was confirmed by the comparison of its IR spectrum with that of an authentic sample prepared from ethyl orsellinate (V).[3]

Based on these data described above, 6-acetyl-5-methylresorcinol is uniquely given for the structure of II.

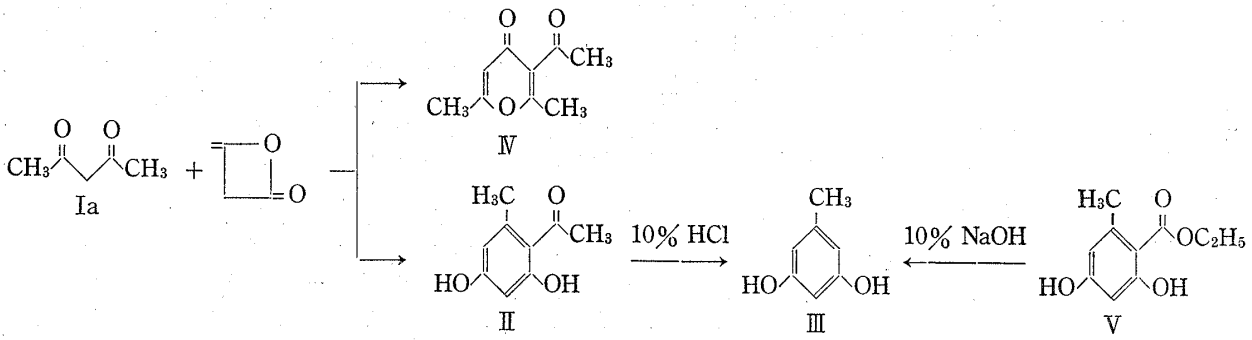

Chart 1

In the reaction of benzoylacetone (Ib), no analogous product of β-resorcinol derivative could be obtained, however, the reaction in water resulted in the formation of 3-acetyl-6-methyl-2-phenyl-4-pyrone (VI) and 3-benzoyl-2,6-dimethyl-4-pyrone (VII) in the ratio of 1: 3. NMR and IR spectra suggested both structures of VI and VII being γ-pyrone derivatives. Mass spectrum of VII showed molecular ion peak of *m/e* 228 and fragment peaks on *m/e* 151 ($M-C_6H_5$) and 105 ($C_6H_5CO^+$), while that of VI showed characteristic peaks of *m/e* 213 ($M-CH_3$) and 185 ($M-COCH_3$) besides *m/e* 228 (M^+).

On the basis of spectroscopic data mentioned above, VI and VII were assigned as 3-acetyl-6-methyl-2-phenyl-4-pyrone and 3-benzoyl-2,6-dimethyl-4-pyrone, respectively.

When dimedone (Ic) was allowed to react with diketene in the presence of sodium hydride, colorless prisms (VIII) of mp 60—61° were obtained in 33% yield. Use of triethylamine or sodium hydroxide instead of sodium hydride in this reaction decreased yield of VIII (less than 5% yield).

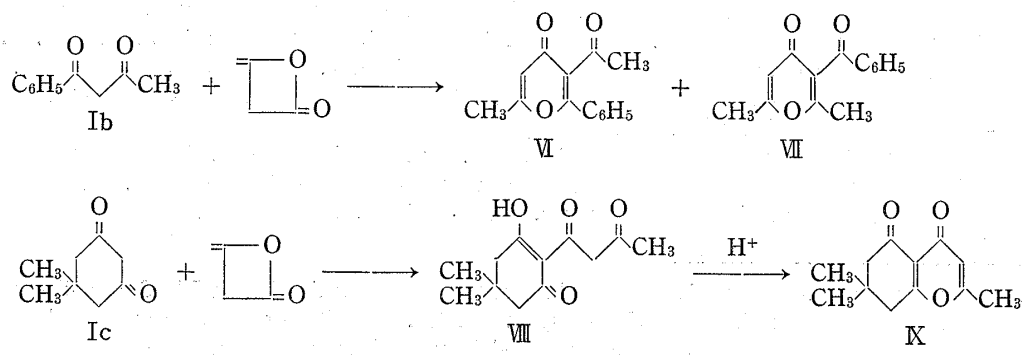

Chart 2

Compound VIII showed characteristic deep purple color by the ferric chloride test. 2-Acetoacetyl-5,5-dimethyl-3-hydroxy-2-hexenone was given for the structure of VIII on the basis of spectroscopic and analytical evidences.

Treatment of VIII with sulfuric acid gave colorless needles (IX), mp 121—122° (decomp.), in quantitative yield. Structure of IX was identified as 5-oxo-2,7,7-trimethyl-5,6,7,8-tetrahydrochromone by IR, NMR and analytical data.

The similar reaction of dibenzoylmethane (Id) with diketene resulted in the recovery of starting material quantitatively.

Experimental[5]

Reaction of Diketene with Acetylacetone (Ia)——(1) To a solution of Ia (2.00 g, 0.02 mole) in THF (20 ml) was added sodium hydride (1.02 g, 0.02 mole, in 52.9% mineral oil dispersion) with cooling and a solution of diketene (1.08 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. Stirring was continued for an additional 1 hr at room temperature. The mixture was neutralized with 10% HCl and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and filtered. Removal of the solvent gave a brownish oil, which was purified by silica gel chromatography. Petroleum ether–ether (8: 1) eluted a crystalline product of 5-methyl-6-acetylresorcinol (II), which was recrystallized from benzene to give 0.75 g (20%) of colorless needles, mp 158—159°. *Anal.* Calcd. for $C_9H_{10}O_3$ (II): C, 65.05; H, 6.07. Found: C, 64.98; H, 6.20. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH), 1618 (C=O). NMR (in $CDCl_3-(CD_3)_2CO$) δ: 2.53 (3H, s), 2.61 (3H, s), 6.29 (2H, s), 8.8 (1H, b), 13.38 (1H, s).

(2) To a stirred solution of Ia (2.0 g, 0.02 mole) and triethylamine (2.02 g, 0.02 mole) in H_2O (40 ml) was added dropwise diketene (1.68 g, 0.02 mole) at 5—10°. The mixture was stirred for 1 hr at the same temperature, then for an additional 1 hr at room temperature. The reaction mixture was neutralized with 10% HCl and extracted with ether. The ether layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated. Distillation of the residue gave following fractions: (1) bp 40° (25 mmHg), 0.79 g; (2) bp 107—112° (8 mmHg), 0.77 g (23.2%). Fraction (1) was starting material (Ia) and fraction (2) was 3-acetyl-2,6-dimethyl-4-pyrone (IV), whose IR spectrum was identical in all respects with that of an authentic sample prepared by the method of Hamamoto, *et al.*[4]

When the reaction was carried out in the presence of sodium hydroxide instead of triethylamine, 0.78 g of product IV and 0.68 g of starting material (Ia) were obtained by the same procedure described above.

Deacetylation of II——A solution of II (166 mg) in 10% HCl (5 ml) was refluxed for 2 hr. The solution was extracted with ether, and the ether layer was washed with H_2O and dried over Na_2SO_4. Removal of the solvent followed by distillation gave a colorless viscous oil (III), bp 120—125° (3 mmHg), 0.11 g (89%), which on standing solidified. IR spectrum of III was identical in all respects with that of 5-methylresolcinol.[3]

Reaction of Diketene with Benzoylacetone (Ib)——(1) To a solution of Ib (3.24 g, 0.02 mole) and triethylamine (2.02 g, 0.02 mole) in H_2O (40 ml) was added dropwise diketene (1.68 g, 0.02 mole) at 5—10°. Stirring was continued for 1 hr at 5—10°, then for an additional 1 hr at room temperature. The reaction mixture was neutralized with 10% HCl and extracted with ether. The ether layer was dried over Na_2SO_4 and filtered. The solvent was removed. Distillation of the resulting oil gave 2.89 g of starting material (Ib), bp 103—105° (6 mmHg). The residue was chromatographed on silica gel. Elution with petroleum ether–ether (8: 1) gave Ib (0.16 g), VI and VII. VI was recrystallized from ether–*n*-hexane to give colorless prisms of mp 98—99°. Yield 32 mg (0.9%). Recrystallization of VII from ether–*n*-hexane gave 104 mg (2.9%) of colorless needles, mp 97—98°. *Anal.* Calcd. for $C_{13}H_{12}O_3$ (VI): C, 73.67; H, 5.30. Found: C, 73.52; H, 5.32. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1703, 1658, 1620. NMR (in $CDCl_3$) δ: 2.34 (3H, s), 2.38 (3H, s), 6.21 (1H, s) 7.48 (5H, s). Significant peaks in the mass spectrum of VI besides the parent (intensity 20%) included $C_{12}H_9O_3^+$ ($M-CH_3$, 9.5%), $C_{12}H_9O_2^+$ ($M-COCH_3$, 7.6%). *Anal.* Calcd. for $C_{13}H_{12}O_3$ (VII): C, 73.67; H, 5.30. Found: C, 74.00; H, 5.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1688, 1619. NMR (in $CDCl_3$) δ: 2.20 (3H, s), 2.30 (3H, s), 6.15 (1H, s), 7.38—8.0 (5H, m). Significant mass spectral peaks of VII besides the parent mass ion (13.3%) included $C_7H_7O_3^+$ ($M-C_6H_5$, 6%), $C_6H_5C{\equiv}O^+$ (15.1%).

(2) The crude product, obtained from Ib (3.24 g, 0.02 mole), diketene (1.68 g, 0.02 mole) and NaOH (0.8 g, 0.02 mole) was purified by the same procedure mentioned in the above run (1). Yields of VII and VI were 106 mg (3%) and 37 mg (1%), respectively. 3.04 g of Ib was recovered.

5) All melting points are uncorrected. Infrared spectra were determined on a JASCO IR-S spectrophotometer, and mass spectra on Hitachi RMU-7 spectrometer. NMR spectra were measured on a Hitachi R-20 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal reference. Abbreviation: s=singlet, d=doublet, m=multiplet, and b=broad.

Reaction of Diketene with Dimedone (Ic)——To a solution of dimedone (2.8 g, 0.02 mole) in THF (30 ml) was added sodium hydride (1.02 g, 0.02 mole, in 52.9% mineral oil dispersion) with cooling and stirring. To the mixture was added dropwise a solution of diketene (1.68 g, 0.02 mole) in THF (10 ml) at 10—15°. Stirring was continued for 1 hr at 5—10°, then for an additional 1 hr at room temperature. The reaction mixture was extracted with $CHCl_3$ after neutralization with 10% HCl. The $CHCl_3$ layer was dried over Na_2SO_4 and filtered. Removal of the solvent gave a viscous oil, which was solidified by addition of a small amount of ether, and filtered. The ether insoluble substance was collected by suction, which was purified by recrystallization from acetone to give Id, 0.74 g. The ether soluble fraction was evaporated, and the resulting solid was recrystallized from *n*-hexane to give colorless prisms (VIII), mp 60—61°, 1.49 g (33.3%). *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 46.72; H, 7.19. Found: C, 64.15; H, 7.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723, 6159, 1610 (sh). NMR (in $CDCl_3$): 1.09 (6H, s), 2.10 ($\frac{6}{11}$ H, s), 2.32 ($4\frac{5}{11}$ H, s), 2.58 (2H, s), 4.01 ($\frac{9}{11}$ H, s), 6.94 ($\frac{2}{11}$ H, s), 13.92 ($\frac{2}{11}$ H, s), 17.10 ($\frac{2}{11}$ H, s), 17.52 ($\frac{9}{11}$ H, s).

5-Oxo-2,7,7-trimethyl-5,6,7,8-tetrahydrochromone (IX)——A solution of VIII (99 mg) and H_2SO_4 (1 mg) in EtOH (3 ml) was warmed on a water bath at 65° for 10 min. The mixture was neutralized with 10% Na_2CO_3 and evaporated under reduced pressure. The residue was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated, and the residue was recrystallized from cyclohexane–benzene to give colorless needles (IX), mp 121—122° (decomp.), 80 mg (89.2%). *Anal.* Calcd. for $C_{12}H_{14}O_3$ (IX): C, 69.88; H, 6.84. Found: C, 69.58; H, 6.90. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1697 (C=O), 1663 (C=O), 1624 (C=C). NMR (in $CDCl_3$-CCl_4) δ: 1.14 (6H, s), 2.27 (3H, s), 2.41 (2H, s), 2.72 (2H, s), 6.14 (1H, s).

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