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Intra- and Intermolecular Condensation Reactions of 8-Phenyl-7-octene-2,4,6-trione and 8-Phenyl-2,4,6-octanetrione (Studies on the β-Carbonyl Compounds connected with the β-Polyketides. IV)[1]

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The intramolecular condensation reaction of 8-phenyl-7-octene-2,4,6-trione (**1**) gave **10**, which was subsequently transformed into the aromatic compounds **12** and **15**. On the other hand, the intermolecular condensation reaction of 8-phenyl-2,4,6-octanetrione (**2**) afforded **17** and **18**.

Keywords——β-polyketones; biogenetic-type syntheses; condensation reactions; pyrones; imines; base-catalyzed cyclization; intramolecular Michael reaction

Various syntheses and reactions of protected or unprotected β-polyketones have been reported in connection with biogenetic syntheses of polyketide-derived natural products.[3] The main interest has centered on syntheses of β-polyketones and equivalent compounds, and more recently on the mode of their cyclization.[4] Among others, Birch reported that pinosylvin (**3**), a natural product, could not be prepared from 8-phenyl-7-octene-2,4,6-trione (**1**), whereas dihydropinosylvin (**4**) and the phenol **5** could be generated from 8-phenyl-2,4,6-octanetrione (**2**), a dihydro derivative of **1**, although in low yield.[5]

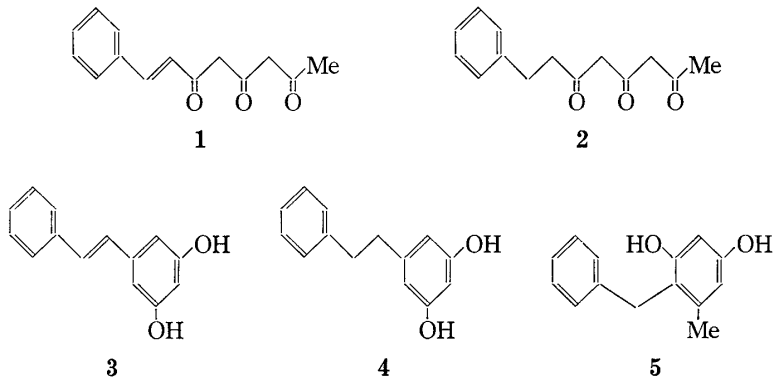

Chart 1

We have investigated the condensation reactions of the triketones **1** and **2** in order to obtain information on the synthesis of natural phenolic compounds in accordance with the biogenetic routes.

1) Part III: N. Takeuchi, H. Nakagawa, M. Kamisato, and S. Tobinaga, *Chem. Pharm. Bull.*, **28**, 2460 (1980).
2) Location: *Tsurumaki, Setagaya-ku, Tokyo, 154, Japan.*
3) T. Money, *Chem. Rev.*, **70**, 553 (1970); Th. M. Harris, C.M. Harris, and K.B. Hindley, "Fortshr. Chem. Org. Naturstoffe," Vol. 31, ed. by W. Herz, H. Grisebach, and G.W. Kirby, Springer Verlag, Inc., Wien, 1974, pp. 217—282.
4) Th. M. Harris, and P.J. Wittek, *J. Amer. Chem. Soc.*, **97**, 3270 (1975); D.A. Grifin, and J. Staunton, *Chem. Commun.*, **1975**, 675; K. Balenovic, and M. Poji, *Tetrahedron Lett.*, **1975**, 3427.
5) A.J. Birch, D.W. Cameron, and R.W. Rickards, *J. Chem. Soc.*, **1960**, 4395.

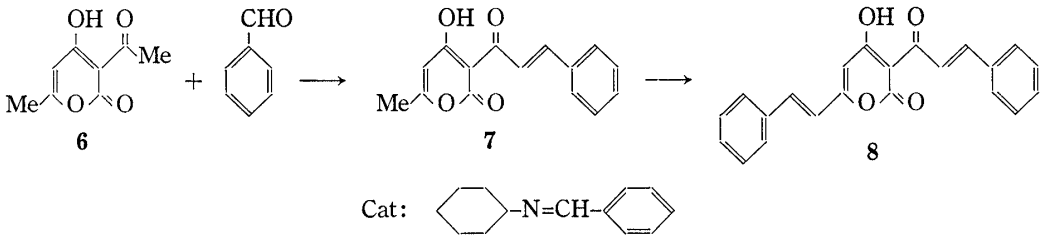

Chart 2

The triketones **1** and **2** were readily prepared by a modification of the procedure of Birch, as described in our previous report.[1,6] Namely, the reaction of benzaldehyde with dehydroacetic acid (**6**) in the presence of a catalytic amount of N-benzylidenecyclohexylamine in toluene at reflux temperature for 24 hr gave a condensation product **7**, mp 128—130°, in 72% yield. Upon further treatment of **7** with benzaldehyde under similar conditions, the bisbenzylidene compound **8**, mp 160—162°, was obtained in 67% yield. Thus, **7** and **8** (triketones in protected form) were prepared in good yields in comparison with the known method.[5] The condensation product **7** was transformed successively into the triketones **1** and **2** according to the procedure of Birch,[5] as shown in Chart 3.

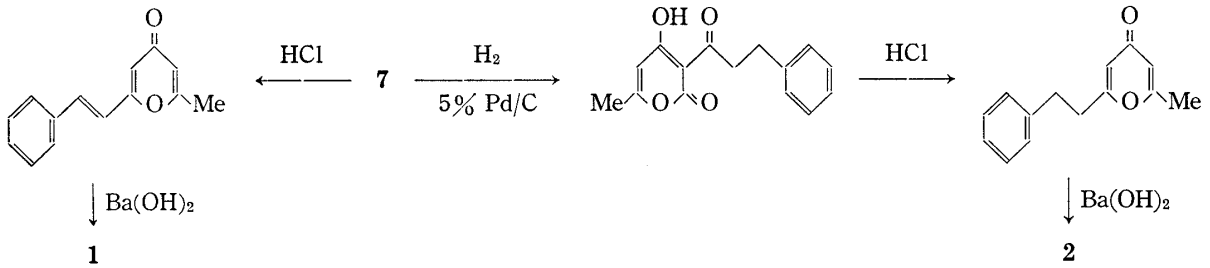

Chart 3

For the purpose mentioned above, self-condensation of the triketone **1** was carried out under various acidic and alkaline conditions. Treatment of the triketone **1** with 10% K_2CO_3–MeOH (1: 1) yielded an acidic product **10** (31%), mp 138—139.5°. The compound **10** was converted to the corresponding methyl ether **11** by treatment with diazomethane, and to the phenol acetate **12** by treatment with Ac_2O–H_2SO_4. The nuclear magnetic resonance (NMR) spectrum of **10** shows the presence of an olefinic proton at 5.53 (1H, s) and an acidic proton centered at 5.83 (1H, m), but the signals of these protons disappeared on addition of D_2O. On the other hand, the NMR spectrum of **11** shows the presence of an olefinic proton at 5.58 (1H, s), which does not disappear in the presence of D_2O. Thus, the condensation product **10** was assigned as 6-acetyl-3-hydroxy-5-phenyl-2-cyclohexenone, formed by intramolecular Michael condensation of the triketone **1**.

The transformation of **10** to aromatic compounds was attempted in order to confirm the structure. When treated with $CuCl_2 \cdot 2H_2O$–LiCl, **10** gave the dichloro compound **13** (63%), which was transformed into the acetate **14** (67%), mp 78—81°, upon treatment with Ac_2O–H_2SO_4. The NMR spectrum of **14** shows the presence of two methylenic protons at 2.76 (1H, q, J=5 Hz, J=18.5 Hz) and 3.52 (1H, q, J=18.5 Hz, J=10 Hz) and one methine proton at 4.28 (1H, q, J=5 Hz, J=10 Hz). On treatment with LiCl in DMF, **14** was converted to the phenol **15** (83%), mp 111—112°, which was transformed into the diacetate **16** (78%), 122—123°, $C_{18}H_{15}ClO_5$, upon treatment with Ac_2O–H_2SO_4. Therefore, the structure of **10** was established by NMR spectral confirmation of the structure of **14** and the above chemical transformations.

6) S. Tobinaga, N. Takeuchi, and H. Nakagawa, *Chem. Commun.*, **1972**, 890.

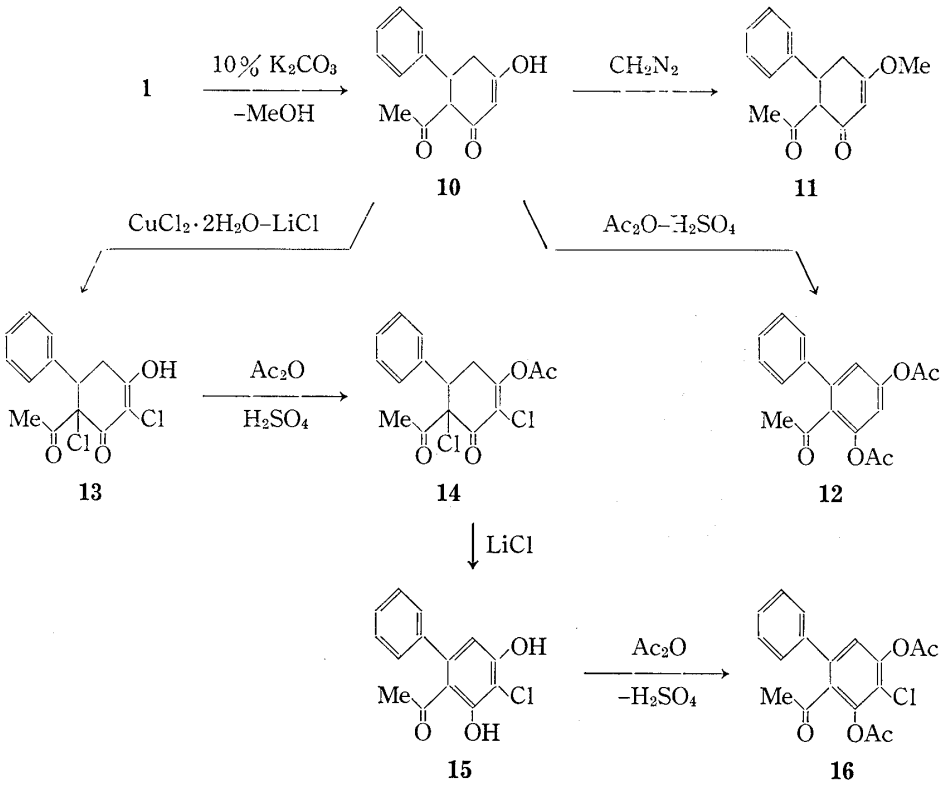

Chart 4

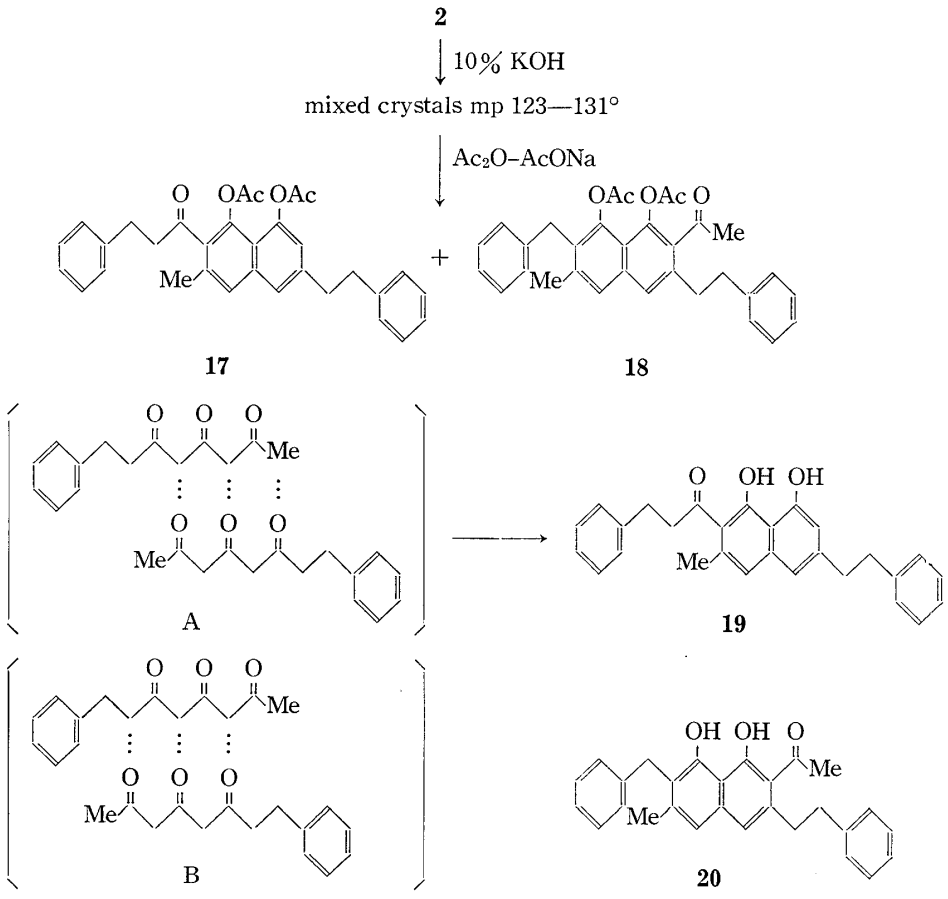

Chart 5

The condensation reaction of the triketone **2** was investigated under various conditions. This compound gave mixed crystals, mp 120—131° in 63% yield, when heating with 10% KOH in MeOH for 2 hr. This mixture could be separated into the acetate **17**, mp 122—123.5°, $C_{32}H_{30}O_5$, MS *m/e* 494 (M^+), and **18**, mp 163—164.5°, $C_{32}H_{30}O_5$, MS *m/e* 494 (M^+), by acetylation with Ac_2O–AcONa followed by column chromatography on silica gel.

Since the analytical data for **17** and **18** show that these compounds are dimeric intermolecular condensation products of the triketone **2**, the reaction may take place *via* bimolecular condensations of **2** in the modes A and B shown in Chart 5, followed by formation of the corresponding intermolecular condensation products **19** and **20**, respectively, with loss of three molecules of H_2O. Therefore, the structures of **17** and **18** were considered to be 3-methyl-6-phenethyl-2-(3-phenylpropionyl)-1,8-naphthalenediol diacetate and 2-acetyl-7-benzyl-6-methyl-3-phenethyl-1,8-naphthalenediol diacetate, respectively, taking into account other physical data.

Summarizing the condensation reactions of the triketone **1** and **2**, **1** gave the intramolecular Michael condensation product **10**, which was transformed into two aromatic compounds, **12** and **15**, and **2** gave the intermolecular condensation products **19** and **20**.

Experimental[7]

3-Cinnamoyl-4-hydroxy-6-methyl-2H-2-pyranone (**7**)——A mixture of dehydroacetic acid **6** (10 g), benzaldehyde (7.8 g) and N-benzylidenecyclohexylamine (0.5 g) in ab. toluene (50 ml) was heated under reflux with water separation by means of a Dean-Stark trap. After reflux for 24 hr, the mixture was allowed to stand at room temperature. The separated crystals were collected and recrystallized from ethyl acetate to yield 11 g (72%) of **7** as yellow crystals, mp 128—130°. IR ν_{max}^{KBr} cm^{-1}: 1725, and 1625. NMR ($CDCl_3$) δ: 2.26 (3H, s, $-CH_3$), 6.00 (1H, s, olefinic H), 7.60 (5H, m, aromatic H×5), 8.01 (1H, d, J=20 Hz, olefinic H), 8.42 (1H, d, J=20 Hz, olefinic H), and 18.00 (1H, s, –OH). Compound **7** was shown to be identical with an authentic sample synthesized by the method of Birch.[5]

3-Cinnamoyl-4-hydroxy-6-styryl-2H-2-pyranone (**8**)——A mixture of **7** (5 g), benzaldehyde (3.9 g) and N-benzylidenecyclohexylamine (3.65 g) in ab. toluene (40 ml) was heated under reflux with water separation by means of a Dean-Stark trap. After reflux for 12 hr, the mixture was allowed to stand at room temperature. The separated crystals were collected and recrystallized from ethyl acetate to yield 4.5 g (67%) of **8** as yellow crystals, mp 160—162°. *Anal.* Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.98. Found: C, 76.81; H, 4.62. IR ν_{max}^{KBr} cm^{-1}: 1715, 1618, and 1590. NMR ($CDCl_3$) δ: 6.16 (1H, s, olefinic H), 6.62 (1H, d, J=16 Hz, olefinic H), 7.66 (10H, m, aromatic H×10), 7.80 (1H, d, J=11 Hz, olefinic H), 8.25 (1H, d, J=11 Hz, olefinic H), 8.50 (1H, d, J=16 Hz, olefinic H), and 18.00 (1H, s, –OH, D_2O-exchangeable).

8-Phenyl-7-octene-2,4,6-trione (**1**) **and 8-Phenyl-2,4,6-octanetrione** (**2**)——**1** and **2** were prepared from **7** according to the procedure of Birch.[5]

6-Acetyl-3-hydroxy-5-phenyl-2-cyclohexenone (**10**)——A solution of **1** (1 g) in methanol (5 ml) was refluxed on a water bath with 10% K_2CO_3 (5 ml) for 2 hr. The solution was concentrated under a vacuum, acidified with 5% HCl and then extracted with chloroform. The organic layer was extracted with sat. $NaHCO_3$. The aqueous layer was acidified with conc. HCl and then extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 0.31 g (31%) of **10** as colorless crystals, mp 138—139.5°. *Anal.* Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.11; H, 6.12. MS *m/e*: 230 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1724, and 1608. NMR ($CDCl_3$+DMSO-d_6) δ: 2.12 (3H, s, $-COCH_3$), 2.70 (2H, m, $-CH_2-$), 3.43 (1H, m, methine H), 3.76 (1H, m, methine H), 5.53 (1H, s, olefinic H, D_2O-exchangeable), 5.83 (1H, m, –OH, D_2O-exchangeable), and 7.21 (5H, s, aromatic H×5).

6-Acetyl-3-methoxy-5-phenyl-2-cyclohexenone (**11**)——A large excess of an ether solution of diazomethane was added to a solution of **10** (200 mg) in methanol (5 ml), and the mixture was kept at room temperature for 10 min. The solution was concentrated and the residue was purified by preparative TLC (with chloroform as a developing solvent) to yield 95.5 mg (45%) of **11** as a colorless oil. MS *m/e*: 244 (M^+). IR

7) All melting points are uncorrected. IR spectra were recorded with a Hitachi 215 spectrometer, UV spectra with a Hitachi 124 spectrometer, NMR spectra with a Varian T-60 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ soln.), and MS spectra with a Hitachi RMS-4 spectrometer at 70 eV using the direct insertion technique. Elementary analyses were done by Mrs. K. Sasaki, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel G nach Stahl were used for column chromatography and TLC, respectively.

$\nu_{max}^{liq.}$ cm^{-1}: 1718, 1652, and 1608. NMR ($CDCl_3$) δ: 2.15 (3H, s, $-COCH_3$), 2.74 (2H, m, $-CH_2-$), 3.35 (1H, m, methine H), 3.83 (3H, s, $-OCH_3$), 3.86 (1H, m, methine H), 5.58 (1H, s, olefinic H), and 7.37 (5H, s, aromatic H×5).

4-Acetyl-5-phenyl-1,3-benzenediol Diacetate (12)——A solution of **10** (230 mg) in acetic anhydride (5 ml) was treated with 0.2 ml of a mixture of conc. H_2SO_4 (0.2 ml) and acetic anhydride (5 ml), and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. Elution with 50% benzene in chloroform gave 206 mg (66%) of **12** as a colorless oil. MS *m/e*: 312 (M^+). IR $\nu_{max}^{liq.}$ cm^{-1}: 1775, 1692, and 1605. NMR ($CDCl_3$) δ: 1.96 (3H, s, $-COCH_3$), 2.30 (3H, s, $-OCOCH_3$), 2.35 (3H, s, $-OCOCH_3$), 7.04 (1H, d, J=2.2 Hz, aromatic H), 7.13 (1H, d, J=2.2 Hz, aromatic H), and 7.47 (5H, s, aromatic H×5).

6-Acetyl-2,6-dichloro-3-hydroxy-5-phenyl-2-cyclohexenone (13)——A mixture of $CuCl_2 \cdot 2H_2O$ (213.5 mg) and LiCl (22.2 mg) in DMF (1 ml) was heated at 80°, and then **10** (100 mg) was added and the whole was heated at 80° for 3 hr. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with H_2O, dried and concentrated to yield 92 mg (63%) of **13** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1720, 1660, and 1600. The compound **13** was used in the next step without further purification.

3-Acetoxy-6-acetyl-2,6-dichloro-5-phenyl-2-cyclohexenone (14)——A solution of **13** (50 mg) in acetic anhydride (3 ml) was treated with 0.2 ml of a mixture of conc. H_2SO_4 (0.2 ml) and acetic anhydride (5 ml), and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. Chloroform elution gave 38 mg (67%) of **14** as colorless crystals (ether–*n*-hexane), mp 78—81°. MS *m/e*: 340 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1784, 1724, 1692, and 1628. NMR ($CDCl_3$) δ: 2.12 (3H, s, $-COCH_3$), 2.32 (3H, s, $-OCOCH_3$), 2.76 (1H, q, J=5 Hz, J=18.5 Hz, $-CH_2-$), 3.52 (1H, q, J=18.5 Hz, J=10 Hz, $-CH_2-$), 4.29 (1H, q, J=5 Hz, J=10 Hz, methine H), and 7.35 (5H, s, aromatic H×5).

4-Acetyl-2-chloro-5-phenyl-1,3-benzenediol (15)——LiCl (132 mg) was added to a solution of **14** (220 mg) in DMF (2 ml), and the whole was heated for 2 hr at 100°. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was extracted with 10% NaOH. The aqueous layer was acidified with conc. HCl and extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 141 mg (83%) of **15** as colorless crystals, mp 111—112°. MS *m/e*: 262 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1590, and 1560. NMR ($CDCl_3$) δ: 1.85 (3H, s, $-COCH_3$), 6.33 (1H, broad, –OH, D_2O-exchangeable), 6.60 (1H, s, aromatic H), 7.50 (5H, m, aromatic H×5), and 13.50 (1H, s, –OH, D_2O-exchangeable).

4-Acetyl-2-chloro-5-phenyl-1,3-benzenediol Diacetate (16)——A solution of **15** (50 mg) in acetic anhydride (3 ml) was treated with 0.2 ml of a mixture of conc. H_2SO_4 (0.2 ml) and acetic anhydride (5 ml), and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 51.6 mg (78%) of **16** as colorless crystals, mp 122—123°. *Anal.* Calcd for $C_{18}H_{15}ClO_5$: C, 62.34; H, 4.36; Cl, 10.23. Found: C, 62.31; H, 4.49; Cl, 10.13. MS *m/e*: 346 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1779, and 1700. NMR ($CDCl_3$) δ: 1.96 (3H, s, $-COCH_3$), 2.35 (3H, s, $-OCOCH_3$), 2.42 (3H, s, $-OCOCH_3$), 7.21 (1H, s, aromatic H), and 7.48 (5H, s, aromatic H×5).

The Intermolecular Condensation Reaction of 8-Phenyl-2,4,6-octanetrione (2)——A solution of **2** (1 g) in methanol (10 ml) was treated with 10% KOH (10 ml) and the mixture was refluxed on a water bath for 2 hr. The reaction mixture was concentrated under a vacuum. A solution of the residue in H_2O (10 ml) was washed with ether, acidified with 10% HCl and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 560 mg (63%) of mixed crystals, mp 120—131°. Dried AcONa (50 mg) was added to a solution of the mixed crystals (500 mg) in acetic anhydride (5 ml) and the mixture was heated on a water bath for 3 hr. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel chromatography. The first chloroform eluate gave 220 mg (36.5%) of 3-methyl-6-phenethyl-2-(3-phenylpropionyl)-1,8-naphthalenediol diacetate (**17**) as colorless crystals (ether–*n*-hexane), mp 122—123.5°. *Anal.* Calcd for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.82; H, 6.10. MS *m/e*: 494 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1770, and 1710. NMR ($CDCl_3$) δ: 2.10 (3H, s, $-COCH_3$), 2.26 (3H, s, $-CH_3$), 2.33 (3H, s, $-COCH_3$), 3.02 (4H, s, $-CH_2CH_2-$), 3.09 (4H, s, $-CH_2CH_2-$), 7.02 (1H, d, J=1.8 Hz, aromatic H), and 7.50 (2H, m, aromatic H×2). The second chloroform eluate gave 240 mg (39.4%) of 2-acetyl-7-benzyl-6-methyl-3-phenethyl-1,8-naphthalenediol diacetate (**18**) as colorless crystals (ether–*n*-hexane), mp 163—164.5°. *Anal.* Calcd for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.69; H, 6.13. MS *m/e*: 494 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1780, 1770, and 1703. NMR ($CDCl_3$) δ: 2.22 (3H, s, $-COCH_3$), 2.31 (3H, s, $-COCH_3$), 2.42 (3H, s, $-CH_3$), 2.55 (3H, s, $-COCH_3$), 2.93 (4H, m, $-CH_2-CH_2-$), 4.12 (2H, s, $-CH_2-$), and 7.55 (2H, s, aromatic H×2).