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Synthesis of *dl*-Agrimonolide (Constituent of Rhizome of *Agrimonia pilosa* LEDEB)

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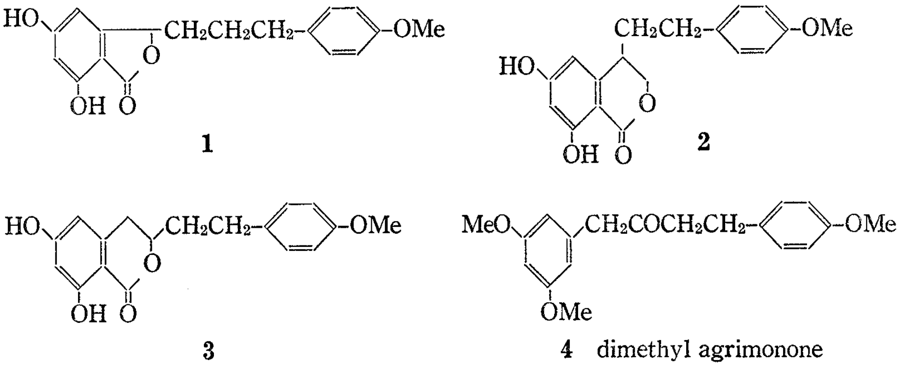
The structure of agrimonolide, isolated as a constituent of *Agrimonia pilosa* LEDEB. in 1958, was confirmed by the synthesis to be 6,8-dihydroxy-3-(*p*-methoxyphenylethyl-3,4-dihydroisocoumarin.

Agrimonolide is a phenolic component of *Agrimonia pilosa* LEDEB., and were reported its isolation and establishment of its structure in 1958.[2] Arakawa[3] subsequently determined its absolute configuration, and its pharmacological action was studied in 1962.[4] In the course of our previous study[2] on the structure of agrimonolide, it was assumed that agrimonolide was not a phthalide derivative (**1**) but a 3,4-dihydroisocoumarin derivative of formula **2** or **3**. However, the synthesis of agrimonolide was not achieved. Therefore, the structure of agrimonolide was established by an indirect means, by the measurement of infrared (IR) absorption spectra of lactone-carbonyl group and the synthesis of dimethylagrimonone which is derived from agrimonolide. IR absorption of lactone-carbonyl group of agrimonolide appeared at 1660 cm^{-1} in a longer wavelength region than that of 7-hydroxyphthalides (1760—1790 cm^{-1}) owing to the strong hydrogen bond between the carbonyl and the neighboring hydroxyl group, and it was rather similar to that of 8-hydroxy-3,4-dihydroisocoumarin (1650—1660 cm^{-1}). 3,5-Dimethoxybenzyl β-(*p*-methoxyphenyl)ethyl ketone (**4**) was synthesized in order to elucidate the correct structure of agrimonolide as formula either **2** or **3**, and its 2,4-dinitrophenylhydrazone agreed with that of dimethylagrimonone derived from agrimonolide. On the basis of these data, the structure of agrimonolide was established as 6,8-dihydroxy-3-[β-(*p*-methoxyphenyl)ethyl]-3,4-dihydroisocoumarin (**3**).



1 **2** **3** **4** dimethyl agrimonone

Fig. 1

An attempt was made to synthesize agrimonolide to confirm its structure, and its synthesis was completed in the present series of work. Route of the synthesis of agrimonolide was restricted since the structure of agrimonolide has a *p*-methoxyphenylethyl group in the 3-position and hydroxyl groups in the 6- and 8-positions of the 3,4-dihydroisocoumarin skeleton.

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[1] Location: *Tsushima-naka, 1-1-1, Okayama, 700, Japan.*
[2] M. Yamato, *Yakugaku Zasshi*, **79**, 1069 (1959).
[3] H. Arakawa, N. Torimoto, and Y. Masui, *Ann. Chem.*, **728**, 152 (1969).
[4] T. Koyama, M. Yamato, and S. Ideguchi, *Kumamoto Pharmaceutical Bulletin*, **5**, 334 (1962).

Recently, Hurd and Shah⁵⁾ reported the synthesis of 2,4-dibenzyloxy-6-(5-benzyloxy-1-penten-1-yl)benzoic acid from dimethyl 3,5-dibenzyloxyhomophthalate and 4-benzyloxybutyraldehyde by the Stobbe-type condensation using sodium hydride in benzene. As a preliminary experiment for the synthesis of agrimonolide 2-(4-phenylbuten-1-yl)benzoic acid (**5**) was synthesized with reference to their report, by the condensation of diethyl homophthalate with phenylpropionaldehyde, followed by hydrolysis and decarboxylation. Cyclization of **5** was attained by using bromine in chloroform and 4-bromo-3-(β-phenylethyl)-3,4-dihydroisocoumarin (**6**) was obtained as colorless needles (Chart 1).

In accordance with this preliminary experiment, agrimonolide was synthesized by the process shown in Chart 2. Diethyl 3,5-dibenzyloxyhomophthalate (**7**) was condensed with *p*-methoxyphenylpropionaldehyde to give 2,4-dibenzyloxy-6-[1-ethoxycarbonyl-4-(*p*-methoxyphenyl)buten-1-yl]benzoic acid (**8**). Hydrolysis and decarboxylation, similarly as in the preliminary experiment, gave 2,4-dibenzyloxy-6-[4-(*p*-methoxyphenyl)buten-1-yl]benzoic acid

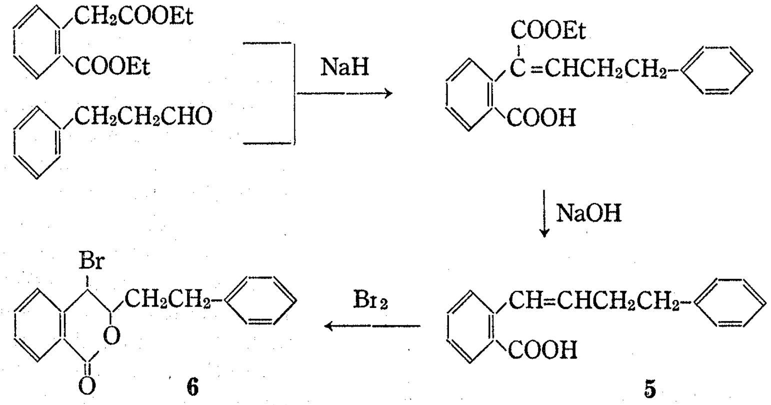

Chart 1

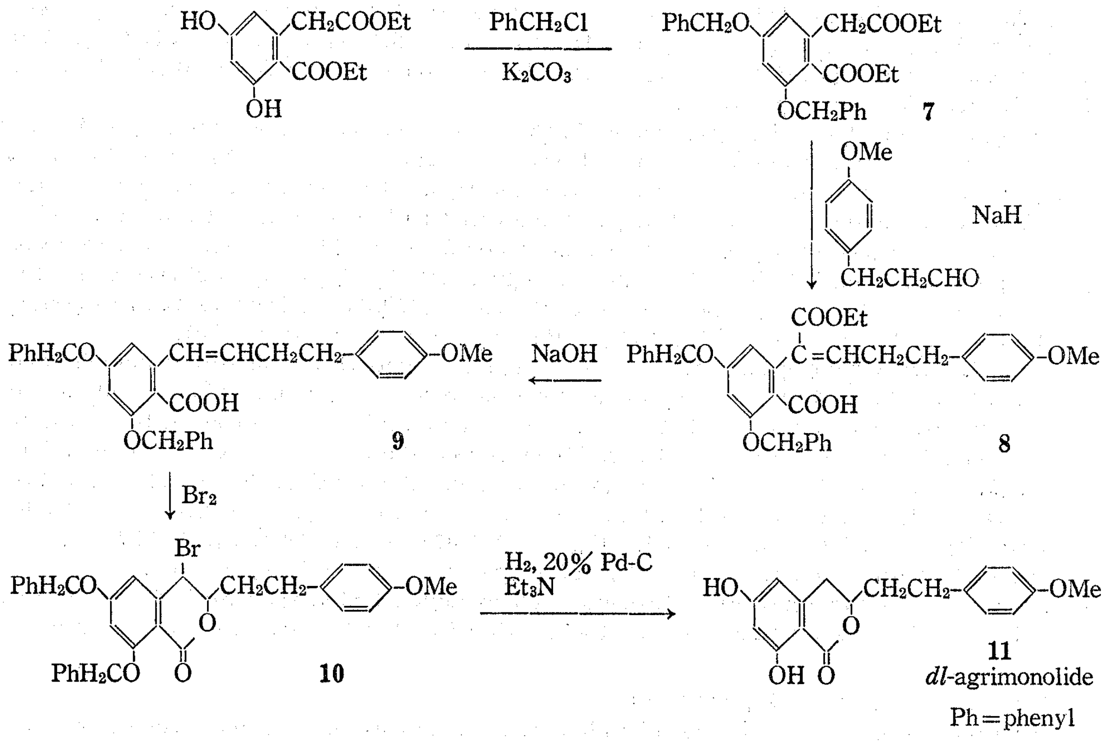

Chart 2

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5) R.N. Hurd and D.H. Shah, *J. Org. Chem.*, 38, 607 (1973).

(**9**). Cyclization of **9** with bromine as in the preliminary experiment gave 4-bromo-6,8-dibenzyloxy-3-[*β*-(*p*-methoxyphenyl)ethyl]-3,4-dihydroisocoumarin (**10**). Although, debromination of **10** was not effected by catalytic reduction over palladium-charcoal catalist in ethanol, addition of triethylamine into the medium promoted reductive debromination[6] and debenzylation simultaneously. *dl*-Agrimonolide (**11**) was obtained as a colorless needles, mp 173°, NMR, IR, and mass spectra of **11** agreed with those of agrimonolide, NMR spectrum of **11** shown in Fig. 2.

Experimental[7]

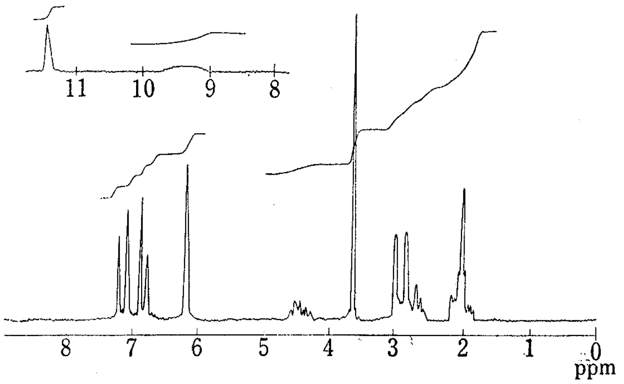

Fig. 2. NMR Spectrum of *dl*-Agrimonolide (Solution in d_6-Acetone)

Synthesis of 2-(4-Phenylbuten-1-yl)benzoic Acid(5)——To a solution of diethyl homophthalate (8.5 g) dissolved in 20 ml of dry benzene and 10 drops of absolute EtOH, 50% NaH (1.45 g) was added while cooling with ice-water and in N_2 atmosphere, and the solution of *β*-phenylpropionaldehyde (4.8 g) in dry benzene was added dropwise to it. After stirring for 3 hr at 30°, 300 ml of H_2O was added, the aqueous phase was separated, and washed with ether, and then acidified with dil. H_2SO_4. The separated solid was extracted with AcOEt and the solvent was washed, dried, and evaporated. The residue was a paste, which was used without further purification. The paste (9 g) was added to 10 ml of a solution of 10% NaOH and heated on a water bath for 1 hr. Further, 40 ml of dimethylformamide was added to the reaction mixture, which was refluxed for 1 hr at 160° in the N_2 atmosphere. When cooled, the reaction mixture was diluted with H_2O, acidified with dil. H_2SO_4, extracted with ether, and the solvent was evaporated. The residue was purified by chromatography over silica gel and eluted with $CHCl_3$ to give 3.1 g (34%) of **5**. It was recrystallized from cyclohexane, mp 99—101°. *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.99; H, 6.41. NMR (solution in $CDCl_3$) δ: 2.35—3.02 (4H, m, $=CH-C\underline{H}_2-C\underline{H}_2$), 5.95—6.47 (1H, m, $-CH=C\underline{H}-CH_2$), 7.10—7.78 (9H, m, aromatic H and $-C\underline{H}=CH-CH_2$), 7.92—8.12 (1H, m, aromatic H), 8.70—9.60 (1H, broad, $COO\underline{H}$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1725 (C=O), 1685 (CH=CH).

4-Bromo-3-(*β*-phenethyl)-3,4-dihydroisocoumarin (6)——To a cooled solution of 0.7 g of **5** dissolved in 10 ml $CHCl_3$ a solution of Br_2 (0.4 g) in 10 ml $CHCl_3$ was added at 0—5°. After stirring for 10 min, the reaction mixture was washed with a solution of 10% $KHCO_3$ and H_2O. The solvent was evaporated and the residue was purified by chromatography over silica gel, eluted with $CHCl_3$ to give 0.2 g of **6**, mp 169—171°, yieled 22%. *Anal.* Calcd. for $C_{17}H_{15}O_2$ Br: C, 67.02; H, 5.06; Found: C, 67.26; H, 5.38. NMR (solution in d_6-acetone) δ: 2.08—2.37 (2H, m, $CH-C\underline{H}_2-CH_2$), 2.66—3.35 (2H, m, $CH_2-C\underline{H}_2-C_6H_5$), 4.25 (1H, d, $J=4$ Hz, $C_{(4)}$-H), 5.12 (1H, m, $C_{(3)}H$), 7.30—7.88 (5H, m, aromatic H), 7.40—7.87 (3H, m, aromatic H), 7.91 (1H, q, $J_1=9$ Hz, $J_2=1$ Hz, $C_{(8)}H$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1718 (C=O). Mass Spectrum *m/e*: 250 (M^+-Br).

Diethyl 3,5-Dibenzyloxyhomophthalate (7)——A mixture of diethyl 3,5-dihydroxyhomophthalate[8] (10 g) and anhyd. K_2CO_3 (20 g) in 150 ml of absolute acetone was refluxed with 20 g of benzyl chloride until the reactant gave a negative reaction to the $FeCl_3$ test. The reaction mixture was cooled, the precipitate was filtered, and the filtrate was concentrated. The residue was recrystallized from EtOH, to 14 g of **7**, mp 61—62°; yield 87.5%. *Anal.* Calcd. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found; C, 72.39; H, 6.26. NMR (solution in $CDCl_3$) δ: 1.23 (3H, t, $J=7$ Hz, $CH_2-C\underline{H}_3$), 1.26 (3H, t, $J=7$ Hz, $CH_2-C\underline{H}_3$), 3.68 (2H, s, CH_2COOEt), 4.13 (2H, q, $J=7$ Hz, $C\underline{H}_2-CH_3$), 4.31 (2H, q, $J=7$ Hz, $C\underline{H}_2-CH_3$), 5.07 (4H, s, $2\times OCH_2C_6H_5$), 6.57 (2H, s, aromatic H), 7.39 (10H, singlet with shoulder, aromatic H). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1730 (C=O), 1694 (C=O).

2,4-Dibenzyloxy-6-[1-ethoxycarbonyl-4-(*p*-methoxyphenyl)buten-1-yl]benzoic Acid (8)——To a solution of 7.5 g of **7**, 1.3 g of 50% NaH, and 3 drops of absolute EtOH in 30 ml of dry benzene, a solution of 5 g of

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6) M.G. Reineck, *J. Org. Chem.*, **29**, 299 (1964).

7) All melting point were measured on a micro-hot stage apparatus and are uncorrected. NMR spectra were obtained on a Hitachi Model R-22 spectrometer at 90 MHz, employing tetramethylsilane as an internal standard. Mass spectra were measured by a Nihon Denshi OI-SG spectrometer.

8) Y. Asahina and H. Nogami, *Yakugaku Zasshi*, **61**, 51 (1940); H. Nogami, *Yakugaku Zasshi*, **61**, 56 (1940); D.S. Jerdan, *J. Chem. Soc.*, **75**, 808 (1899).

β-(p-methoxyphenyl)propionaldehyde[2] dissolved in 10 ml of dry benzene was added and the mixture was treated by the same method as for the synthesis of **5**. A crude product thereby obtained was purified by chromatography over silica gel, eluted with CH_2Cl_2 and recrystallized from ether to 3 g of **8**, mp 129—131°, yield 31.3%. *Anal.* Calcd. for $C_{35}H_{34}O_7$: C, 74.19; H, 6.05. Found: C, 74.29; H, 5.98. NMR (solution in $CDCl_3$) δ: 1.80 (3H, t, $J=7$ Hz, CH_2–$C\underline{H}_3$), 2.00—2.73 (4H, m, $C\underline{H}_2$–$C\underline{H}_2$–C_6H_5), 3.67 (3H, s, OCH_3), 4.13 (2H, q, $J=7$ Hz, $C\underline{H}_2$–CH_3), 4.95 (2H, s, $OC\underline{H}_2C_6H_5$), 5.14 (2H, s, $OCH_2C_6H_5$), 6.25 (1H, d, $J=2.5$ Hz, aromatic H), 6.64 (1H, d, $J=2.5$ Hz, aromatic H), 6.70—7.13 (5H, m, $=C\underline{H}$–CH_2 and aromatic H), 7.38 (10H, singlet with shoulder, $OCH_2C_6H_5 \times 2$). IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1665 (C=O). Mass Spectrum *m/e*: 566 (M^+), 522 (M^+–CO_2), 476 [M^+–(EtO+COOH)].

2,4-Dibenzyloxy-6-[4-(*p*-methoxyphenyl)buten-1-yl]benzoic Acid (9)——According to the procedure for the synthesis of **5**, a mixture of 16 g of **8** and 10 ml of 10% NaOH in 75 ml of dimethylformamide was refluxed for 2 hr and treated similarly as for the synthesis of **5**, giving 11 g of **9**, as recrystallized from petr. ether–benzene, mp 122—125°, yield, 54.4%. *Anal.* Calcd. for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.98; H, 5.98. NMR (solution in $CDCl_3$) δ: 2.20—2.94 (4H, m, $C\underline{H}_2$–$C\underline{H}_2$), 3.73 (3H, s, OCH_3), 5.03 (2H, s, $OCH_2C_6H_5$), 5.08 (2H, s, $OCH_2C_6H_5$), 6.08 (1H, m, $CH=C\underline{H}$–CH_2), 6.50 (1H, d, $J=3$ Hz, aromatic H), 6.70 (1H, d, $J=3$ Hz, aromatic H), 6.75—7.25 (5H, m, $C\underline{H}=CH$–CH_2 and aromatic H), 7.38 (10H, singlet with shoulder, $OCH_2C_6H_5 \times 2$), 8.60—9.70 (1H, broad, COOH). Mass Spectrum *m/e*: 494 (M^+), 450 (M^+–CO_2), 360 $[C_6H_2(OCH_2C_6H_5)_2(COOH)$-$(CH=CH_2)]^+$. IR ν_{max}^{Nujol} cm^{-1}: 1675 (C=O).

4-Bromo-6,8-dibenzyloxy-3-[β-(*p*-methoxyphenylethyl)]-3,4-dihydroisocoumarin (10)——According to the procedure for the synthesis of **6**, a solution of 0.4 g of Br_2 and 10 ml of $CHCl_3$ was added to a solution of 1 g of **9** in 20 ml of $CHCl_3$, and the mixture was treated similarly as for the synthesis of **6**, to give 0.6 g of **10** which was purified by chromatography over silica gel and eluted with $CHCl_3$; mp 40—43°; yield 43.9%. *Anal.* Calcd. for $C_{32}H_{29}O_5Br$: C, 67.02; H, 5.06. Found: C, 67.26; H, 5.38. NMR (solution in $CDCl_3$) δ: 1.88—3.05 (4H, m, $C\underline{H}_2$–$C\underline{H}_2$–C_6H_5), 3.73 (3H, s, OCH_3), 3.95 (1H, m, $C_{(3)}H$), 5.02 (2H, s, $OCH_2C_6H_5$), 5.23 (2H, s, $OCH_2C_6H_5$), 5.43 (1H, d, $J=6$ Hz, $C_{(4)}H$), 6.55 (2H, d, $J=3$ Hz, aromatic H), 6.62 (2H, d, $J=3$ Hz aromatic H), 6.70—7.24 (4H, m, aromatic H), 7.42 (10H, singlet with shoulder, $OCH_2C_6H_5 \times 2$). Mass Spectrum *m/e*: 574 $(M+2)^+$, 572 (M^+), 492 (M^+–Br). IR ν_{max}^{Nujol} cm^{-1}: 1755 (C=O).

Synthesis of *dl*-Agrimonolide (11)——A solution of 4.3 g of **10** in 160 ml of EtOH and 40 ml of Et_3N was reduced over 20% Pd-C (2.5 g). After the absorption of H_2 was completed, the solvent was evaporated, the residue was dissolved in AcOEt, which was washed with H_2O. The solvent was evaporated and the residue was purified by chromatography over silica gel and eluted with $CHCl_3$ to give 1.2 g of *dl*-agrimonolide, mp 173—174°, as recrystallized from MeOH, yield, 40.4%. *Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.47; H, 5.54. NMR (solution in d_6-acetone) δ: 1.85—2.23 (2H, m, $C\underline{H}_2$–CH_2–C_6H_5), 2.63—3.02 (4H, m, $C_{(4)}H_2$ and CH_2–C_6H_5), 3.73 (3H, s, OCH_3), 4.30—4.72 (1H, m, $C_{(3)}H$), 6.25 (2H, s, aromatic H), 6.78—7.31 (4H, m, aromatic H), 8.97—9.65 (1H, broad, $C_{(6)}$–OH), 11.32 (1H, s, $C_{(8)}$–OH). Mass Spectrum *m/e*: 314 (M^+), 296 (M^+–H_2O), 270 (M^+–CO_2), 193 [M^+–(CH_2–C_6H_4–OCH_3)], 179 [M^+–(CH_2CH_2–C_6H_4–OCH_3)], 147 ($HC^+=CH$–CH_2–C_6H_4–OCH_3). IR ν_{max}^{Nujol} cm^{-1}: 3370 (OH), 1662 (C=O).