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Synthesis of 6-Chloro-3,5-dimethoxyhomophthalic Acid, a Key Intermediate for the Synthesis of Radicicol and Natural Isocoumarin[1]

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6-Chloro-3,5-dimethoxyhomophthalic acid (I) was synthesized as a key intermediate for the synthesis of radicicol and isocoumarins of natural origin, *via* a sequence of reactions including cyclization of 3-(2-chloro-3,5-dimethoxyphenyl)propionic acid (XIV) to 4-chloro-5,7-dimethoxyindan-1-one (XVI) and oxidative decomposition of methyl (4-chloro-2,3-dihydro-5,7-dimethoxy-1-oxo-1H-inden-2-ylidene)hydroxyacetate (XVII) to I as key steps.

Keywords——radicicol; monorden; 6-chloro-3,5-dimethoxyhomophthalic acid; antifungal antibiotic; 5-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin; high resolution MS

Radicicol (synonymous with monorden) is a 14-membered macrolide antibiotic and a potent tranquilizer of remarkably low toxicity.[3] This antifungal antibiotic has been isolated from *Monosporium bonorden*,[3] *Cylindrocarpon radicicola*,[4] and also very recently from *Penicillium luteo-aurantium* by the authors.[5] In this paper we describe the preparation of 6-chloro-3,5-dimethoxyhomophthalic acid (I) as a key intermediate for the synthesis of radicicol. This compound (I) is also a key intermediate for the synthesis of 5-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin, which has been isolated from the fungus *Periconia macrospinosa*[6] but not yet synthesized.

The starting material, 3,5-dimethoxybenzoic acid (II), was prepared by methylation of 3,5-dihydroxybenzoic acid according to the procedure of Suter *et al.*[7] Initially we attempted to chlorinate II by heating with sulfuryl chloride in ethereal or carbon tetrachloride solution. However, no reaction occurred. Thus, compound II was boiled with the same reagent without a solvent. 2,6-Dichloro-3,5-dimethoxybenzoic acid (III) was produced in poor yield, but the monochloro derivative, 2-chloro-3,5-dimethoxybenzoic acid (IV), was not obtained. The positions of the two chlorine atoms on the benzene nucleus in compound III were determined from the ^{13}C-nuclear magnetic resonance (CMR) spectrum, which clearly indicated a symmetrical structure for III. The difficulty of obtaining IV by this reaction may by due to the electron-attracting nature of the carboxyl group in II. Therefore, the carboxyl group in II was converted into alcohol, *i.e.*, 3.5-dimethoxybenzyl alcohol (VI), *via* the ester ethyl 3,5-dimethoxybenzoate (V). The chlorination of VI with sulfuryl chloride gave 2-chloro-3,5-dimethoxybenzyl alcohol (VII) in excellent yield (91%) even at room temperature, with the formation of a very small amount of 2,6-dichloro-3,5-dimethoxybenzyl alcohol (IX) as a by-product. The locations of the two chlorine atoms in IX were again determined from the CMR spectrum. When compound VII was treated with thionyl chloride at room

1) This work was presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, Aug. 1979, p. 308.
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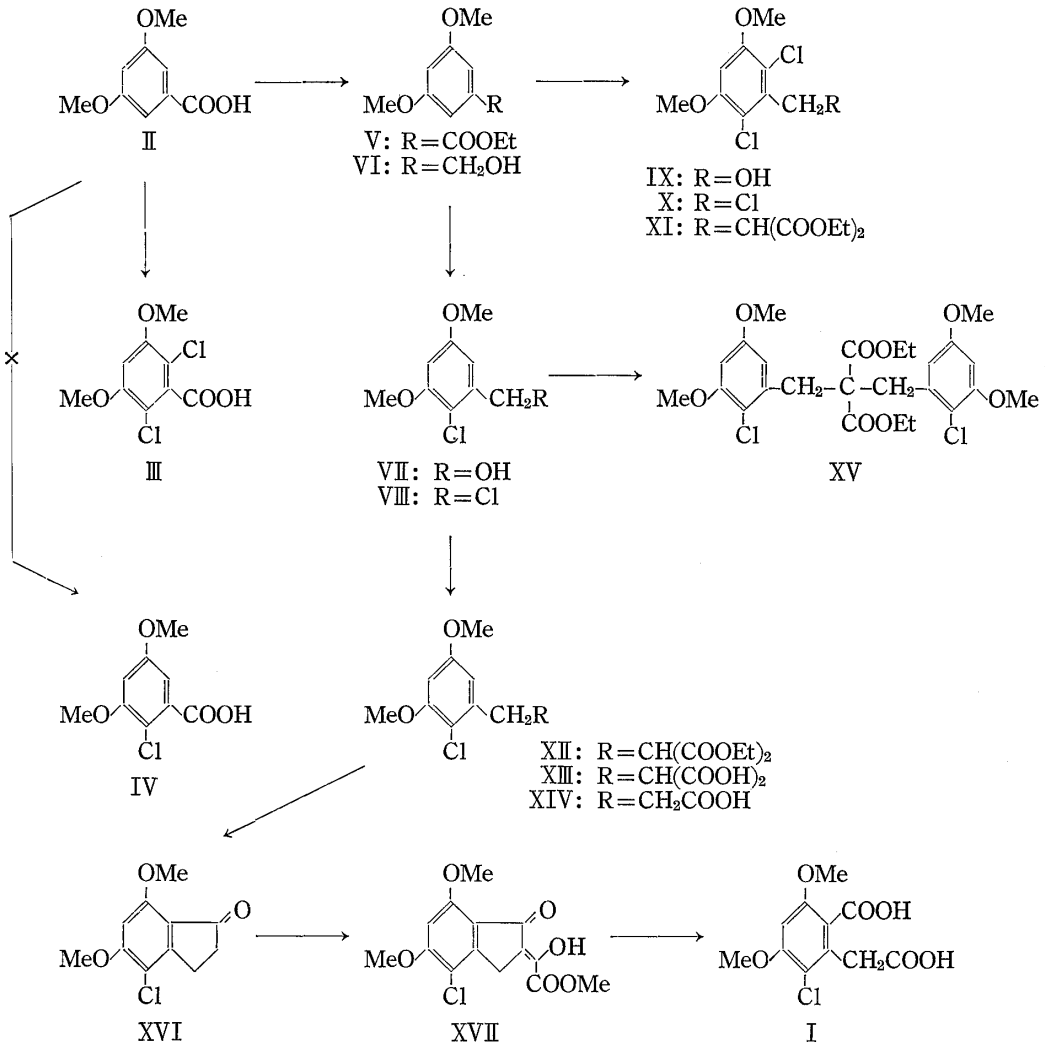

Chart 1

temperature, 2-chloro-3,5-dimethoxybenzyl chloride (VIII) was formed. Since purification of the crude VII containing a small amount of IX by recrystallization is not very easy, the crude VII was mostly used as such for further reactions. For this reason, the main reaction product of VII with thionyl chloride was a mixture of VIII and 2,6-dichloro-3,5-dimethoxybenzyl chloride (X). This mixture, which again proved to be difficult to separate, was reacted with diethyl malonate in the presence of sodium ethoxide. When the reaction mixture was distilled *in vacuo*, diethyl (2-chloro-3,5-dimethoxybenzyl)malonate (XII) and diethyl (2,6-dichloro-3,5-dimethoxybenzyl)malonate (XI) were both obtained as distillates, and diethyl bis(2-chloro-3,5-dimethoxybenzyl)malonate (XV) was obtained from the residue. The structure of XV was determined as follows. It showed three molecular ion peaks in the mass spectrum at *m/e* 528, 530 and 532 with relative intensities of 9, 6 and 1, indicating the presence of two chlorines in the molecule. In the proton nuclear magnetic resonance (PMR) spectrum, it showed a four-proton singlet at δ 3.52 assignable to two equivalent methylenes, and two-proton doublets at δ 6.39 and δ 6.50, assignable to a pair of *meta* coupling aromatic protons, as well as a six-proton triplet at β 1.10 coupled with a four-proton quartet at δ 4.10, arising from two equivalent ethyls, and two six-proton singlets at δ 3.73 and δ 3.84, due to two equivalent methoxyls.

The diester (XII) was hydrolyzed by the action of alkali to 2-chloro-3,5-dimethoxybenzylmalonic acid (XIII) and was further converted to 4-chloro-5,6-dimethoxyindan-1-

one (XVI) by decarboxylation followed by cyclization with polyphosphoric acid. Compound XVI gave methyl (4-chloro-2,3-dihydro-5,7-dimethoxy-1-oxo-1H-inden-2-ylidene)hydroxyacetate (XVII) on reaction with diethyl oxalate and sodium methoxide according to the procedure of Wagatsuma *et al.*[8] The formation of XVII instead of ethyl (4-chloro-2,3-dihydro-5,7-dimethoxy-1-oxo-1H-inden-2-ylidene)hydroxyacetate may be due to ester exchange on recrystallization of the product from methanol. Supporting this assumption, recrystallization of the pure methyl ester (XVII) from ethanol produced a mixture of the methyl and ethyl esters, as judged from the mass spectrum. Compound XVII was converted to the target compound, 6-chloro-3,5-dimethoxyhomophthalic acid (I), by oxidation with hydrogen peroxide.

The synthesis of natural 5-chloro-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin using compound I as an intermediate has been successfully carried out by the authors, and the details will be published shortly. The synthesis of radicicol is now in progress.

Experimental

Melting points are uncorrected. The IR spectra were taken in KBr pellets in the case of solid samples and by the film method in the case of liquid samples, using a Hitachi 215 grating spectrophotometer. The PMR and CMR spectra were obtained on a JEOL JNM-FX 100 FT NMR spectrometer at 100 and 20.05 MHz respectively, using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-D 300 spectrometer. GLC was carried out on a Shimadzu GC-4CMPF gas chromatograph.

2,6-Dichloro-3,5-dimethoxybenzoic Acid (III)——3,5-Dimethoxybenzoic acid (II) (1.0 g) was gently refluxed in an excess of SO_2Cl_2 for 30 min, then the whole mixture was stirred for two days at room temperature. The precipitate was collected on a filter, washed with ether, and recrystallized from benzene to give colorless needles (0.3 g), mp 201—203°. *Anal.* Calcd for $C_9H_8Cl_2O_4$: C, 42.80; H, 3.60. Found: C, 43.24; H, 3.23. IR ν_{max}^{KBr} cm^{-1}: 2500—3000 and 1718 (COOH). CMR (DMSO) δ: 56.72 (OMe, s), 98.24 (C-4, d), 108.57 (C-2 and 6, s), 135.95 (C-1, s), 154.38 (C-3 and 5, s), 165.10 (COOH). MS *m/e*: 254 (M^+ for $2\times{}^{37}Cl$), 252 (M^+ for ^{35}Cl and ^{37}Cl), 250 (M^+ for $2\times{}^{35}Cl$).

3,5-Dimethoxybenzyl Alcohol (VI)——Ethyl 3,5-dimethoxybenzoate (V) (3.3 g), obtained by esterification of II with EtOH and H_2SO_4, was dissolved in absolute ether (30 ml). After addition of $LiAlH_4$ (0.8 g) in portions, the whole mixture was refluxed for 1 hr. Usual work-up gave crude VI as long colorless needles, mp 45° (lit.[9] 48°). This same compound has been synthesized from II directly using a suspension of $LiAlH_4$ in ether.[9] No purification was necessary before further reaction. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH).

2-Chloro-3,5-dimethoxybenzyl Alcohol (VII) and 2,6-Dichloro-3,5-dimethoxybenzyl Alcohol (IX)——Compound VI (20 g) was dissolved in absolute ether (200 ml) and cooled in ice-salt mixture, then a solution of SO_2Cl_2 (15.95 g) in absolute ether (100 ml) was added and the mixture was stirred for 40 min under ice cooling, then for 10 min at room temperature. The reaction mixture was poured into ice-water (200 ml), stirred well, and the ethereal layer was separated and washed with water, 10% Na_2CO_3 then again with water, and dried over Na_2SO_4. The residual solid obtained after removal of the solvent was heated with pet. ether and divided into soluble and insoluble fractions. The pet. ether-soluble fraction (22 g) was purified by repeated crystallization from hexane to give VII as colorless needles, mp 82° (lit.[10] 82°). This compound (VII) has been prepared by Newman *et al.* from VI by treatment with N-chlorosuccinimide.[10] PMR (in $CDCl_3$) δ: 2.00 (1H, t, J=7 Hz, OH), 3.82 (3H, s, OMe), 3.88 (3H, s, OMe), 4.76 (2H, d, J=7 Hz, $-CH_2-$), 6.46 (1H, d, J=3 Hz, arom.–H), 6.68 (1H, d, J=3 Hz, arom.–H). CMR (in d_6-acetone) δ: 55.72 and 56.42 (3 and 5 OMe, q), 62.00 ($-CH_2-$, t), 98.81 (C-4, d), 104.68 (C-2, d), 111.67 (C-6, s), 142.31 (C-1, s), 156.34 (C-3, s), 160.10 (C-5, s). MS *m/e*: 204 (M^+ for ^{37}Cl), 202 (M^+ for ^{35}Cl). The insoluble fraction (0.5 g) was purified by recrystallization from ether to give IX as colorless needles, mp 138—140°. *Anal.* Calcd for $C_9H_{10}Cl_2O_3$: C, 45.29; H, 4.69. Found: C, 45.80; H, 4.27. IR ν_{max}^{KBr} cm^{-1}: 3450 and 3560 (OH). PMR (in d_6-acetone) δ: 3.95 (6H, s, $2\times$OMe), 4.10 (1H, d, J=6 Hz, OH), 4.89 (2H, d, J=6 Hz, $-CH_2-$), 6.89 (1H, s, arom.–H). CMR (in d_6-acetone) δ: 56.89 (OMe, q), 60.06 ($-CH_2-$, t), 98.34 (C-4, d), 115.78 (C-1, s), 138.44 (C-2 and 6, s), 155.46 (C-3 and 5, s). MS *m/e*: 240 (M^+ for $2\times{}^{37}Cl$), 238 (M^+ for ^{37}Cl and ^{35}Cl), 236 (M^+ for $2\times{}^{35}Cl$).

2-Chloro-3,5-dimethoxybenzyl Chloride (VIII)——A mixture of VII (2 g), pyridine (0.1 ml), absolute ether (30 ml) and $SOCl_2$ (2.5 g) was stirred at room temperature overnight, then all the liquid portion was evaporated off *in vacuo* and the residual solid was purified by recrystallization from methanol to give VIII

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as colorless needles, mp 87°. Yield 1.9 g. *Anal.* Calcd for $C_9H_{10}Cl_2O_2$: C, 48.89; H, 4.56. Found: C, 49.02; H, 4.77. PMR (in d_6-acetone) δ: 3.83 (3H, s, OMe), 3.90 (3H, s, OMe), 4.74 (2H, s, $-CH_2-$), 6.67 (1H, d, $J=3$ Hz, arom.–H), 6.76 (1H, d, $J=3$ Hz, arom.–H). MS *m/e*: 224 (M^+ for $2\times{}^{37}Cl$), 222 (M^+ for ^{37}Cl and ^{35}Cl), 220 (M^+ for $2\times{}^{35}Cl$).

2,6-Dichloro-3,5-dimethoxybenzyl Chloride (X)——Crude compound VII (containing a small amount of IX) (18 g) was treated with $SOCl_2$ and pyridine as described above. Recrystallization from methanol gave colorless crystals, which were a mixture of VIII with X in a ratio of 94 to 6, as judged by GLC (column, 13% polyethyleneglycol succinate on Diasolid L; carrier gas, N_2; flow rate, 35 ml/min; column temp., 200°; injection temp., 200°): t_R (min) 3.8 (VIII), 10 (X). Separation of X from the mixture was difficult, and its presence was confirmed by high resolution GC–MS spectroscopy: Calcd for $C_9H_9O_2{}^{35}Cl_3$ (M^+ for $3\times{}^{35}Cl$) 253.9670. Observed: M^+, 253.9675.

Diethyl (2-Chloro-3,5-dimethoxybenzyl)malonate (XII), Diethyl (2,6-Dichloro-3,5-dimethoxybenzyl)-malonate (XI), and Diethyl Bis(2-chloro-3,5-dimethoxybenzyl)malonate (XV)——Na (9.72 g) and then diethyl malonate (63.8 g) were dissolved in absolute EtOH (370 ml), then the crude VIII (containing X) prepared above (87.6 g) was suspended in the solution and refluxed for 3 hr. After removing NaCl by filtration, the EtOH was evaporated off. The residual oil was dissolved in CH_2Cl_2 (800 ml), washed with water, dried over Na_2SO_4 and the solvent was removed. The remaining oil was subjected to distillation *in vacuo* at 3 mmHg. Compound VIII distilled at 125—150°. The fraction that distilled at 160—195° deposited crystals after cooling; these were collected by filtration and purified by recrystallization from MeOH to give XI as colorless prisms (2.5 g), mp 118°. *Anal.* Calcd for $C_{16}H_{20}Cl_2O_5\cdot MeOH$: C, 49.64; H, 5.88. Found: C, 49.41; H, 5.39. IR ν_{max}^{film} cm^{-1}: 1720 (COOEt). PMR (in $CDCl_3$) δ: 1.22 (6H, t, $J=7$ Hz, $-CH_2-C\underline{H}_3$), 3.52—3.76 (3H, m, $-CH_2-C\underline{H}\langle$), 3.89 (6H, s, $2\times$OMe), 4.17 (4H, q, $-C\underline{H}_2-CH_3$), 6.48 (1H, s, arom.–H). MS *m/e*: 382 (M^+ for $2\times{}^{37}Cl$), 380 (M^+ for ^{37}Cl and ^{35}Cl), 378 (M^+ for $2\times{}^{35}Cl$). The filtrate, after concentration, gave crude XII (60.4 g): IR ν_{max}^{film} cm^{-1}: 1725 (COOEt) and MS *m/e*: 346 (M^+ for ^{37}Cl), 344 (M^+ for ^{35}Cl). This compound was not further purified but was converted to XIII. The distillation residue was boiled with 10% NaOH (20 ml) for 1 hr, filtered, washed with water, dried and recrystallized from MeOH to give XV as colorless prisms, mp 101°. *Anal.* Calcd for $C_{25}H_{30}Cl_2O_8\cdot MeOH$: C, 55.52; H, 6.27. Found: C, 55.48; H, 5.80. IR ν_{max}^{KBr} cm^{-1}: 1720 (COOEt). PMR (in $CDCl_3$) δ: 1.10 (6H, t, $J=7$ Hz, $-CH_2-C\underline{H}_3$), 3.52 (4H, s, $2\times-CH_2-$), 3.73 (6H, s, $2\times$OMe), 3.84 (6H, s, $2\times$OMe), 4.10 (4H, q, $J=7$ Hz, $-C\underline{H}_2-CH_3$), 6.39 (2H, d, $J=3$ Hz, arom.–H), 6.50 (2H, d, $J=3$ Hz, arom.–H). MS *m/e*: 532 (M^+ for $2\times{}^{37}Cl$), 530 (M^+ for ^{37}Cl and ^{35}Cl), 528 (M^+ for $2\times{}^{35}Cl$).

2-Chloro-3,5-dimethoxybenzylmalonic Acid (XIII)——Compound XII (3.5 g) was mixed with 10% NaOH (50 ml) and gently boiled for 10 hr. The reaction mixture was filtered, acidified to pH 1 with conc. HCl, and the precipitated crystals were collected, and dissolved in aqueous $NaHCO_3$. The solution was filtered, and the filtrate was again acidified to pH 1 with conc. HCl to give crude XIII as a precipitate (2.8 g). It was purified by recrystallization from ethyl acetate to give colorless needles, mp 178°. *Anal.* Calcd for $C_{12}H_{13}ClO_6$: C, 50.00; H, 4.95. Found: C, 49.92; H, 4.53. IR ν_{max}^{KBr} cm^{-1}: 1710 (COOH). PMR (in d_6-acetone) δ: 3.29 (2H, d, $J=7$ Hz, $-C\underline{H}_2-CH\langle$), 3.74 (1H, t, $J=7$ Hz, $-CH_2-C\underline{H}\langle$), 3.78 (3H, s, OMe), 3.87 (3H, s, OMe), 4.5—5.5 (2H, broad, exchangeable with D_2O, COOH), 6.55 (2H, s, arom.–H). CMR (in d_6-acetone) δ: 33.64 (CH_2, t), 51.72 (CH, d), 55.77 and 56.48 (5 and 8 OMe, q), 98.92 (C-4, d), 108.38 (C-6, d), 138.3 (C-1, s), 156.75 (C-5, s), 159.69 (C-3, s), 196.96 (COOH, s). MS *m/e*: 290 (M^+ for ^{37}Cl), 288 (M^+ for ^{35}Cl).

3-(2-Chloro-3,5-dimethoxyphenyl)propionic Acid (XIV)——When compound XIII (6.07 g) was heated in the oil bath, initially kept at 185°, a vigorous effervescence occurred and continued for 10 min. The solid obtained after cooling was recrystallized from ether–hexane to give XIV as colorless plates (4.97 g), mp 106°. *Anal.* Calcd for $C_{11}H_{13}ClO_4$: C, 53.87; H, 5.39. Found: C, 53.99; H, 5.32. IR ν_{max}^{KBr} cm^{-1}: 2400—3000 and 1695 (COOH). PMR (in $CDCl_3$) δ: 2.69 (2H, t, $J=7$ Hz, $-CH_2-C\underline{H}_2-COOH$), 3.06 (2H, t, $J=7$ Hz, $-C\underline{H}_2-CH_2-COOH$), 3.79 (3H, s, OMe), 3.87 (3H, s, OMe), 6.41 (2H, s, arom.–H). MS *m/e*: 246 (M^+ for ^{37}Cl), 244 (M^+ for ^{35}Cl).

4-Chloro-5,7-dimethoxyindan-1-one (XVI)——When a mixture of XIV (200 mg) and 105% polyphosphoric acid (6.0 g) was heated at 90° for 2 hr with good agitation, compound XV was obtained as a purple-colored solution. After heating for another 2 hr at 110° the reaction mixture was poured into ice-water (30 ml), the pH was adjusted to 7 with alkali, and the solution was extracted with benzene (50 ml). The benzene solution was washed with alkali then water, dried over Na_2SO_4, decolorized with charcoal, and the solvent was removed by evaporation. The residual solid was recrystallized from MeOH to give XVI as colorless needles (120 mg), mp 212°. *Anal.* Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.86. Found: C, 58.72; H, 5.34. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). PMR (in $CDCl_3$) δ: 2.67 (2H, t, $J=6$ Hz, $-C\underline{H}_2-CH_2-CO-$), 2.97 (2H, t, $J=6$ Hz, $-CH_2-C\underline{H}_2-CO-$), 3.97 (3H, s, OMe), 4.00 (3H, s, OMe), 6.38 (1H, s, arom.–H). MS *m/e*: 228 (M^+ for ^{37}Cl), 226 (M^+ for ^{35}Cl).

Methyl (4-Chloro-2,3-dihydro-5,7-dimethoxy-1-oxo-1H-inden-2-ylidene)hydroxyacetate (XVII)——Sodium (138 mg) was dissolved in MeOH (250 mg), and benzene (4 ml) was added to this solution. Compound XVI (452 mg) was added in portions with good stirring, then diethyl oxalate (0.2 ml) was added as a single aliquot and the mixture was stirred overnight at room temperature. Next, 5% HCl was added under ice cooling to the residue obtained after removal of the solvent, to give a final pH of 1.0. The precipitate that

deposited was collected on a filter, washed with 5% HCl, then with water, and dried. The solid thus obtained was crystallized from MeOH to give XVII as yellow needles (590 mg), mp 184°. *Anal.* Calcd for $C_{14}H_{13}ClO_6$: C, 53.77; H, 4.19. Found: C, 53.99; H, 4.81. IR ν_{max}^{KBr} cm^{-1}: 1728 (ester C=O), 1660 (chelated C=O). PMR (in $CDCl_3$) δ: 3.90 (2H, s, $-CH_2-$), 3.95 (3H, s, COOMe), 4.02 (6H, s, 2×OMe), 6.43 (1H, s, arom.–H). MS *m/e*: 314 (M^+ for ^{37}Cl), 312 (M^+ for ^{35}Cl).

6-Chloro-3,5-dimethoxyhomophthalic Acid (I)——A solution of XVII (1.0 g) and KOH (0.7 g) in water (15 ml) was cooled to 5—10°, and 35% H_2O_2 (3 g) was added. The mixture was stirred at this temperature for 6 hr. When the temperature was gradually raised to 50°, vigorous frothing occurred. After stirring for a further 2 hr at this temperature, the mixture was filtered, and the filtrate was acidified with conc. HCl. The crystals that precipitated were collected by filtration, and the filtrate was extracted 4 times with AcOEt (30 ml). The combined precipitated and extracted crystals (0.55 g) were purified by recrystallization from CH_2Cl_2 to give I as colorless microcrystals, mp 215—225° (dec.). *Anal.* Calcd for $C_{11}H_{11}ClO_6$: C, 48.08; H, 4.01. Found: C, 48.54; H, 4.22. IR ν_{max}^{KBr} cm^{-1}: 2500—3000, 1700 (COOH). PMR (in d_6-acetone) δ: 3.89 (3H, s, OMe), 3.90 (2H, s, $-CH_2-$), 3.96 (3H, s, OMe), 6.81 (1H, s, arom.–H). MS *m/e*: 276 (M^+ for ^{37}Cl), 274 (M^+ for ^{35}Cl).

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