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Synthetic Studies on Suberosin and Osthol[1]

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Alternative syntheses of Suberosin (V) as well as Osthol (I) have been described. When the metal salts of 2-hydroxy-4-methoxybenzaldehyde (XI), such as Li, Na, K, Ca and Tl salt, were treated with γ,γ-dimethylallyl bromide in benzene and water, the four compounds, 3-γ,γ-dimethylallyl-2-hydroxy-4-methoxybenzaldehyde (IV), 5-γ,γ-dimethylallyl-2-hydroxy-4-methoxybenzaldehyde (VIII), 2-γ,γ-dimethylallyloxy-4-methoxybenzaldehyde (IX) and 2-γ,γ-dimethylallyl-5-methoxyphenol (X) were obtained.

Furthermore, IX was converted to VIII by the thermal rearrangement of the γ,γ-dimethylallyl group.

In 1934 Späth, *et al.*[3] reported the synthesis of Osthol (I), a naturally occurring-coumarin which posseses the γ,γ-dimethylallyl side chain, by the Parkin condensation reaction of 3-γ,γ-dimethylallyl-2-hydroxy-4-methoxybenzaldehyde (IV) with acetic anhydride. Recent work on the synthesis of Suberosin (V),[4] 7-methoxy-6-γ,γ- dimethylallylcoumarin, was reported. The treatment of 5-γ,γ- dimethylally-2,4-dihydroxybenzaldehyde (XIV) with sodium acetate and acetic anhydride gave 7-acetoxy-6-γ,γ-dimethylallylcoumarin (XIII). Mild alkaline hydrolysis of XIII produced 7-hydroxy-6-γ,γ- dimethylallylcoumarin (XII), whose methylation with diazomethane afforded Suberosin (V).

The synthesis of the intermediates IV and XIV, however, did not proceed satisfactorily under the reaction conditions described. It was described that the sodium salt of 2-hydroxy-4-methoxybenzaldehyde (XI) could be allylated at the 3-position, but the yield of IV was extremely low and the Parkin condensation reaction of IV resulted in very poor yield.

It was suggested that the low yield of IV[3,5] might be due to the side reactions which the allyl group was introduced into several position of XI. In this paper we wish to describe an alternative synthesis of Suberosin (V) and an improved method for preparation of Osthol (I).

Curtin, *et al.*[6] described that in the direct alkylation of the lithium salts of phenol derivatives, the occurrence of the oxygen-alkylation were observed besides the carbon-alkylation.

In order to examine whether the use of other metal salts might lead to increase the carbon-allylation, a series of the following experiments were designed. As shown in Table I, in the allylation of the lithium salt of XI in benzene and water the carbon/oxygen allylation ratios were approximately 74.3/1.8 and 27.8/6.6 respectively. On the other hand, when the sodium salt of XI was used under the same conditions, the ratios were about 42.6/43.8 and 35.5/8.8 respectively.

When the potassium salt of XI was treated, the ratios of about 46.7/34.9 and 37.3/9.1 were respectively observed.

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2) Location: *Nishioji-Hachijo, Minami-ku, Kyoto.*
3) B. Späth and H. Holgen, *Chem. Ber.*, **67**, 264 (1934).
4) *a*) P.W. Austin and T.R. Seshadri, *Indian J. Chem.*, **6**, 412 (1968); *b*) J. Ewing, G.K. Hughes and E. Ritchie, *Australian J. Sci. Research*, **3A**, 342 (1950).
5) D.W. Dreyer, *J. Org. Chem.*, **33**, 3574 (1968).
6) D.Y. Curtin and R.R. Fraser, *J. Am. Chem. Soc.*, **80**, 6016 (1958).

TABLE I. Yield (%) and C/O- Allylation Ratios of the Products by the Allylation of Metal Salts of 2-Hydroxy-4-methoxybenzaldehyde (XI)

Solvents	Benzene						H_2O				
Salts of XI	Li	Na (H_2O)	Na	K (H_2O)	Ca ($\frac{1}{2}H_2O$)	Tl	Li	Na	K	Ca	Tl
Compound IV	35.8	32.0	29.0	37.2	11.0	16.1	7.0	8.0	8.6	0.6	3.8
Compound VIII	38.5	3.3	3.6	—	30.6	1.3	15.4	19.8	21.3	0.6	2.7
Compound IX	1.8	38.5	43.8	34.9	—	63.4	6.6	8.8	9.1	4.0	7.9
Compound X	—	12.1	10.0	9.5	—	2.3	5.4	7.7	7.4	0.4	2.5
Compound *p.s*	6.5	7.3	6.5	8.3	17.8	6.1	2.2	2.8	2.8	0.1	0.4
Recovered XI	17.4	6.8	7.1	10.1	40.6	10.8	63.4	52.9	50.8	93.4	82.7
C-Allyl/O-Allyl	41.3	1.23	0.97	1.34	41.6	0.31	4.21	4.04	4.10	0.40	1.10

XI-M —(Br)→ (IV+VIII)+(IX+X+XI) —GC (sepn.)

(IV+VIII) —TLC (UV)→ IV+VIII

XI/Bromide-1/1 (mol. ratio)
XI/Solvent-1/90 (W/V)
benzene: reflux, 10 hr.
H_2O: room temperature, 12 hr.

M: metals, GC: 5% SE-52, TLC: Silica gel-G, *n*-hexane 8: 1 acetone, UV: 280 mμ

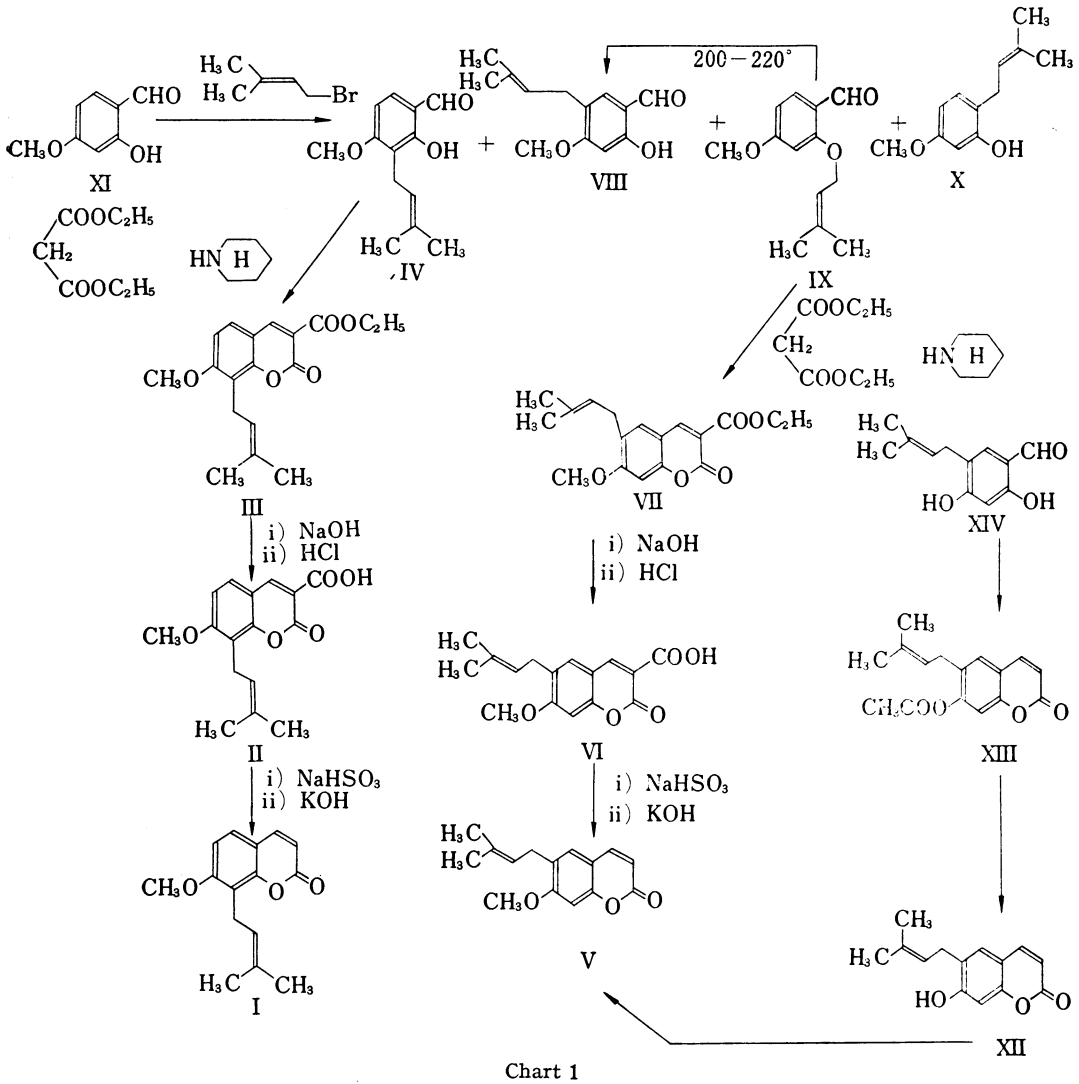

Chart 1

In the case of the lithium salt, the two compounds IV (bp 132°/0.5 mmHg, mp 49—50°) and VIII (bp 125°/0.4 mmHg) were isolated from the carbon-allylated fraction. The compound VIII gave a semicarbazone of mp 215°.

The compound VIII could be also derived by the thermal rearrangement of 2-γ,γ-dimethylallyloxy-4-methoxybenzaldehyde (IX). In the nuclear magnetic resonance (NMR, 60 MHz) spectrum of VIII, a pair of singlets at δ 1.73 and δ 1.68 (3H each, J=1.0 Hz) were attributable to the two methyl groups of the dimethylallyl side chain. A doublet at δ 3.15 (2H, J=7.5 Hz) and a multiplet at δ 5.2 (1H, J=7.5 Hz, J=1.5 Hz) could be assigned to the protons of the methylene and ethylene group of the side chain respectively.

Another pair of singlets at δ 7.1 (1H) and δ 6.3 (1H) corresponded to protons at the 3 and 6 position. This assignment suggested that the compound VIII was 5-γ,γ-dimethylallyl-2-hydroxy-4-methoxybenzaldehyde.

This structure was confirmed as described later by the coumarin condensation.

A Knoevenabel condensation reaction of VIII with diethyl malonate afforded the coumarin derivative (VII), mp 129°, in fairly good yield.

VII, upon hydrolysis, gave the coumarin carboxylic acid (VI), mp 191°, which on decarboxylation produced the compound (V), mp 88°, as colorless crystals. All physical properties of the compound V were in full agreement with those of natural Suberosin cited in the literature.[4] Reaction of IV with diethyl malonate, in the presence of pyridine, produced compound (III), mp 113°.

Alkaline hydrolysis of III afforded its free acid (II), mp 183.5°. Decarboxylation of II by heating in the presence of $NaHSO_3$ gave Osthol (I), mp 83°. The ultraviolet (UV), infrared (IR) and NMR spectra of I were identical with those of the authentic sample.

When alkali metal salts of XI were refluxed with γ,γ-dimethylallyl bromide, another additional compound (X) slightly soluble in alkaline solution was isolated from the reaction mixture as a minor product. The IR spectrum indicated that the absorption band due to aldehydic carbonyl group present in XI disappeared in the compound X. In the NMR spectrum of X, the signals at δ 3.27 (2H, doublet, J=6.5 Hz), δ 1.75 (6H, doublet, J=1.5 Hz) and δ 3.74 (3H, singlet) indicated the presence of the γ,γ-dimethylallyl group and one methoxy group respectively.

These observations suggested that the compound X was 2-γ,γ-dimethylallyl-5-methoxyphenol. The structure was further confirmed by synthesis of authentic sample from 3-methoxyphenol.

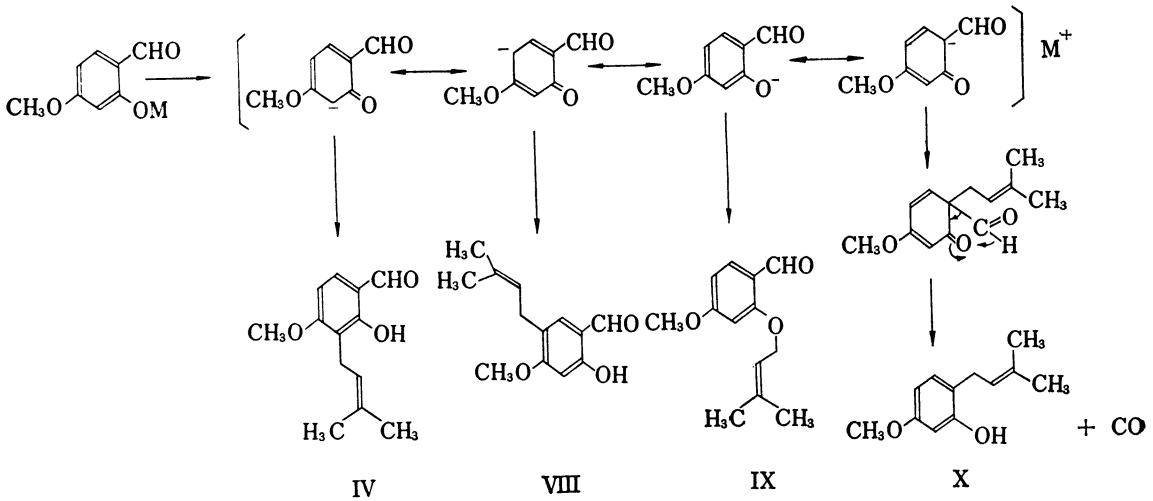

Chart 2

It seems likely that the formation of four compounds, IV, VIII, IX and X by the allylation of XI might be due to the contribution of the canonical structures as shown in Chart 2.

Treatment of IV and X with formic acid afforded 2,2-dimethyl-8-formyl-5-methoxychroman (XVI), mp 109.5° and 2,2-dimethyl-7-methoxychroman (XV), bp 120°/2.5 mmHg respectively.

Experimental[7]

Salts of 2-Hydroxy-4-methoxybenzaldehyde——i) An aqueous solution of $LiOH \cdot H_2O$ (4.2 g) was added slowly to a chilled solution of 2-hydroxy-4-methoxybenzaldehyde (15.2 g) in MeOH (40 ml) with stirring. The crystalline product was filtered rapidly from the reaction mixture, washed with a small amount of MeOH and dried overnight at room temperature to give hydrated lithium salt of XI (12.5 g). By further drying at 160° for 8 hr *in vacuo*, anhydrous lithium salt of XI was obtained.

Sodium, calcium, thallium ,and potassium salt were obtained by the following procedure.

ii) Sodium powder prepared from 1.32 g of sodium metal according to the usual procedure was added to a solution of XI (8.73 g) in benzene (20 ml) and refluxed for 10 hr with stirring. After the sodium powder disappeared, this solution was used for the reaction with γ,γ-dimethylallyl bromide in benzene.

iii) A solution of XI (15.2 g) in ether (100 ml) was added to a suspension of $Ca(OH)_2$ (3.71 g) in water (200 ml), and shaken in a separating funnel for 15 hr.

Then, crystals were collected by suction, washed with water and ether and dried to give 13.6 g (85%) of calcium salt of XI according to the same manner as i).

iv) A solution of TlOEt (22 g) in benzene (30 ml) was added to a chilled solution of XI (14.75 g) in benzene (200 ml) with stirring, and yellow crystalline product was obtained. Recrystallization from MeOH gave 19.5 g of thallium salt of XI, 173—175°.

γ,γ-Dimethylallyl Bromide——γ,γ-Dimethylallyl bromide was prepared from isoprene (100 g) and HBr according to the method of previous papers,[8] bp 46—49°/32—33 mmHg, yield 186 g, 85%.

Reaction of the Salt of XI with γ,γ-Dimethylallyl Bromide——i) To a refluxing mixture of lithium salt of XI (10 g) and benzene (100 ml) was added γ,γ-dimethylallyl bromide (9.43 g) at such a rate that 2 hr would be required and additional stirring was continued under refluxing for 8 hr. After removal of benzene the residue was extracted with ether, ether fraction was separated, washed with water and dried over Na_2SO_4. By removal of ether, reddish-brown oil (8.6 g) was obtained. Furthermore, this oily residue was dissolved in benzene (172 ml) and treated by the same manner as above, 5.95 g of oily residue (XVII) was obtained. The starting material (XI) which remained in the alkaline solution was recovered (2.65 g) by this treatment. According to the above-mentioned procedure, sodium, potassium, calcium and thallium salts of XI were reacted respectively with γ,γ-dimethylallyl bromide in benzene.

ii) XI (10 g) was added to a solution of $LiOH \cdot H_2O$ (2.8 g) in water (100 ml) with being stirred at room temperature for 8 hr, and then γ,γ-dimethylallyl bromide (10 g) was added to this solution with stirring at such a rate that 1 hr would be required.

Additional stirring was continued at room temperature for 12 hr and the reaction mixture was extracted with ether (150 ml).

Ether layer was separated and the aqueous layer was extracted with additional ether (100 ml), then ether solution was collected and washed with water and dried over Na_2SO_4.

After removal of ether, 11.05 g of oily residue was obtained.

This oily residue was dissolved in benzene (200 ml), washed with 5% Na_2CO_3 solution (150 ml × 5) and water, and 4.4 g of oily residue (XVIII) was obtained by removal of benzene. From the aqueous portion, the starting aldehyde (XI) was recovered by the same manner as method of i). According to the same procedure as above, other salts of XI were reacted respectively in the aqueous solution. Form oily residue of i) and ii), IV, VIII, IX, and X were separated by the following manner.

For instance, 150 ml of ether was added to the oily residue (35.3 g) which was obtained by the reaction of potassium salt of IX with γ,γ-dimethylallyl bromide and extracted with 5% KOH aqueous solution (150 ml × 14). Ether layer was dried over Na_2SO_4 and removal of ether afforded 18.3 g of oily residue.

Distillation of the oily residue afforded 13.7 g of crude IX, bp 146—152°/4.5 mmHg. *n*-Hexane (15 ml) was added to crude IX and cooled to give 9.5 g of IX as fine solid, mp 41—42°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.95; H, 7.28. IX gave a semicarbazone, mp 173—174°. KOH aqueous solution was acidified with 10% HCl aqueous solution and extracted with

7) All melting points are not corrected.

8) *a*) D.A. Shirly, "Preparation of Organic Intermediates," John and Wiley Sons Inc., 1951, p. 51; *b*) H. Staudinger, W. Kreis, and W. Schilt, *Herv. Chim. Acta*, **5**, 743 (1922).

ether, and ether was evaporated to give 15 g of residue. This residue was dissolved in 50 ml of MeOH and mixed with a MeOH solution of NaOMe (2.9 g), then concentrated under reduced pressure and ether was added. In this procedure IV and VIII were precipitated as their Na salts. Ether layer was concentrated and a MeOH solution of NaOMe was added to it again and Na salts of IV and VIII were further separated by the procedure as above described. Ether layer was concentrated to give oily residue.

In column chromatography of the residue on silica gel (80 g), X was eluted with a mixture of *n*-hexane and acetone (8: 1).

The fractions of eluate which gave single spot were collected and 3.8 g of residue was obtained by removal of solvents.

Distillation of residue afforded 0.6 g of X, bp 130°/1.1 mmHg. *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.44; H, 8.90. Na salts of IV and VIII which obtained by the treating of NaOMe were collected and dissolved in 10% aqueous solution, then extracted with ether. Ether layer was washed with water and dried over Na_2SO_4 and ether was evaporated to give 10.5 g of residue. According to a column chromatographic procedure as above mentioned, IV and VIII were separated from the residue.

IV was obtained as fine crystals, bp 131—132°/0.5 mmHg, mp 49.5—50.5°. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.99; H, 7.27. IV gave a semicarbazone, mp 214—215°. VIII was obtained as oily product, bp 125—128°/0.4 mmHg. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.16; H, 7.26. VIII gave a semicarbazone, mp 215—216°.

These products IV, VIII, IX, and X were also detectable by a TLC and a GC technique (Table I).

Preparation of 5-γ,γ-Dimethylallyl-2-hydroxy-4-methoxybenzaldehyde (VIII) by Thermal Rearrangement of 2-γ,γ-Dimethylallyloxy-4-methoxybenzaldehyde (IX)——IX (1 g) was dissolved in N,N-dimethylaniline (5 g), and heated at 200—220° for 5 hr. The reaction mixture was cooled and extracted with ether, ether layer was separated from the mixture, washed with 10% HCl aqueous solution and water, dried over Na_2SO_4 and ether was evaporated. Oily residue was distilled under reduced pressure to give 0.72 g of VIII, bp 124—125°/0.4 mmHg. It gave a semicarbazone, mp 215—216°.

2-γ,γ-Dimethylallyloxy-5-methoxybenzaldehyde (IX)——A mixture of XI (7.6 g), γ,γ-dimethylallyl bromide (7.8 g), acetone (30 ml) and anhydrous K_2CO_3 (7.6 g) was refluxed for 4 hr.

After the reaction mixture was concentrated under reduced pressure, extracted with ether and water. Ether layer was separated from aqueous layer, washed with 5% KOH aqueous solution and water, then ether layer was dried over Na_2SO_4 and ether was removed to give 10.5 g of oily residue. Distillation of the oily residue afforded 8.7 g (79.2%) of IX as fine solid, bp 148—150°/1.0 mmHg, mp 41—42°. NMR ($CDCl_3$), δ: 10.25 (1H, s, CHO), 7.68 (1H, m, J=9 Hz, J=1.5 Hz, phenyl), 6.42 (1H, m, J=9 Hz, J=2 Hz, phenyl), 6.37 (1H, d, J=1.5 Hz, phenyl), 5.47 (1H, m, J=6.5 Hz, J=1.5 Hz, -CH=), 4.58 (2H, d, J=6 Hz, $-CH_2-$), 3.82 (3H, s, OCH_3), 1.78—1.76 (6H, d, s, J=1.5 Hz, $=C\langle^{CH_3}_{CH_3}$).

2-γ,γ-Dimethylallyl-5-methoxyphenol (X)——A solution of MeONa (0.6 g) in MeOH was added to a solution of 3-methoxyphenol (1.24 g) in MeOH. After removal of MeOH, the residue was dried *in vacuo*, and dissolved in anhydrous benzene (20 ml). To this refluxing solution was added slowly γ,γ-dimethylallyl bromide (1.49 g) with stirring. After refluxing for 8 hr with stirring, the reaction mixture was cooled and water was added in order to remove the inorganic salts. Benzene layer was treated according to the same procedure as above to give X, bp 130°/1.1 mmHg, yield 0.15 g (8%). *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.44; H, 8.60. NMR ($CDCl_3$) δ: 6.97 (1H, d, J=9 Hz, phenyl) 6.42 (2H, m, phenyl), 5.28 (2H, m, -OH, $-CH=C\langle^{CH_3}_{CH_3}$), 3.74 (3H, s, OCH_3), 3.27 (2H, d, J=6.5 Hz, $-CH_2-$), 1.75 (6H, d, J=6.5 Hz, $=C\langle^{CH_3}_{CH_3}$).

2,2-Dimethyl-7-methoxychroman (XV)——A solution of X (0.5 g) and formic acid (1.0 g) in benzene (10 ml) was refluxed for 15 hr. After the reaction mixture was cooled, washed with water, 10% KOH aqueous solution (20 ml×2) and water. Benzene layer was separated from the mixture, and dried over Na_2SO_4 and benzene was evaporated to give 0.49 g (98%) of oily residue.

Distillation of the oily residue gave 0.45 g of XV, bp 120°/2.5 mmHg. *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.80. NMR (CCl_4) δ: 6.80 (1H, d, phenyl), 6.25 (2H, m, phenyl), 3.67 (3H, s, $-OCH_3$), 2.65 (2H, t, J=7 Hz, 4-CH_2-), 1.71 (2H, t, J=7 Hz, 3-CH_2-), 1.27 (6H, s, $=C\langle^{CH_3}_{CH_3}$).

2,2-Dimethyl-8-formyl-5-methoxychroman (XVI)——A solution of IV (0.5 g) and formic acid (0.2 g) in benzene (2 ml) was refluxed for 40 hr. The reaction mixture was treated by the same procedure as XV to give XVI, mp 108—109.5° (from MeOH).

Yield, 0.45 g (90%). *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.91; H, 7.28. NMR ($CDCl_3$) δ: 2.63 (2H, t, J=7 Hz, 4-CH_2-), 1.80 (2H, t, J=7 Hz, 3-CH_2-).

3-Ethoxycarbonyl-7-methoxy-6-γ,γ-dimethylallylcoumarin (VII)——A mixture of VIII (3.3 g), diethyl malonate (2.6 g), pyridine (0.3 g), acetic acid (0.07 g) and anhydrous EtOH (6 ml) was refluxed for 4 hr. After cooling, water was added to the reaction mixture and appearing crystals were collected by suction, washed with dil. HCl aqueous solution, water and cold EtOH. Recrystallization from AcOEt gave

3.4 g (93%) of VII, colorless needles, mp 126—129°. *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.22; H, 6.49. IR ν_{max}^{KBr} cm^{-1}: 1748, 1695, 1625.

3-Ethoxycarbonyl-7-methoxy-8-γ,γ-dimethylallylcoumarin (III)——A mixture of IV (4.4 g), diethyl malonate (3.5 g), pyridine (0.2 g), acetic acid (0.04 g) and anhydrous EtOH (15 ml) was refluxed for 4 hr by the same fashion as above to give 4.5 g (90%) of III, colorless needles, mp 110.5—113°. (EtOH). *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.45; H, 6.30. IR ν_{max}^{KBr} cm^{-1}: 1760, 1695, 1605.

6-γ,γ-Dimethylallyl-7-methoxycoumarin (Suberosin, V)——VII (3.3 g) was dissolved in hot EtOH (20 ml) and maintained at 65°. To this solution was added 10% NaOH aqueous solution (10 ml) rapidly. After 10 minutes the reaction mixture was cooled and acidified with 10% HCl aqueous solution.

Appearing crystals were collected by filtration, washed with water and cold EtOH, then dried to give 2.9 g (96%) of crude crystals of 3-carboxy-6-γ,γ-dimethylallyl-7-methoxycoumarin (VI) and recrystallization from AcOEt gave 2.4 g of fine yellowish white plates, mp 189—191°. Then VI was dissolved in a solution of $NaHSO_3$ (5.2 g) in water (21 ml) under refluxing. To this hot solution was added 50% KOH aqueous solutfion (6 ml) rapidly and vigorous boiling was caused. The reaction mixture was cooled and extracted with ether (80 ml × 3). Ether layer was washed with dil. HCl aqueous solution and water and dried over Na_2SO_4. Removal of ether afforded 1.5 g (62.5%) of crude crystals and recrystallization from *n*-hexane–acetone and MeOH gave fine crystals, mp 87—88°. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.61; H, 6.67. IR ν_{max}^{KBr} cm^{-1}: 1725, 1615, 832.

7-Methoxy-8-γ,γ-dimethylallylcoumarin (Osthol I)——According to the same procedure as Suberosin (V), Osthol was obtained from III in a same yield, mp 82—83°. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.25; H, 6.64. IR ν_{max}^{KBr} cm^{-1}: 1718, 1605, 830.

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