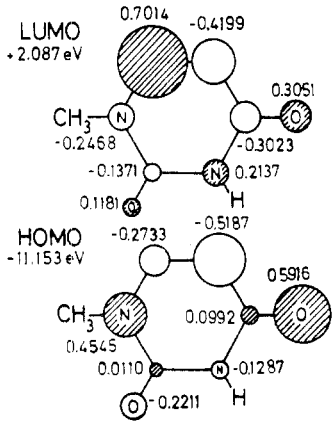

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(18) Polar solvents seemed to promote the formation of **4a** as judged by TLC, but in such a case separation of **3a** and **4a** by the usual crystallization technique was highly difficult. After all, toluene has proved to be most profitable since the products precipitate out of the reaction system and furthermore the yield of **3a** is strikingly high.
(19) Generally, compounds **3** are less polar than compounds **4**.
(20) Analogous effects exerted by a 2',3'-acetal group in the formations of cyclonucleosides have been documented. For example, see a review by L. Goodman, ref 2, pp 186 and 187.
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Structures, Syntheses, and Chemotaxonomic Significance of Some New Acetophenone Derivatives from *Encelia farinosa* Gray

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The resinous exudate of brittle bush (*Encelia farinosa* Gray) contains a number of substituted benzofurans and chromenes. All appear to arise from the biogenic prenylation of resacetophenone. The chromene compounds constitute a remarkable sequence of reduction states of encecalin (**3**) and represent important chemotaxonomic indicators. All the compounds have been characterized on the basis of spectral and chemical methods. A new general synthesis of dimethylchromene derivatives from resorcinol is described.

Brittle bush (*Encelia farinosa* Gray) is an abundant perennial which is indiginous to southern Arizona, growing on rocky slopes at elevations of 1500–3000 ft. It is characterized by a sticky fragrant exudate. This exudate is used by Arizona Indians as an analgesic chewing gum and as an incense. Preliminary investigations of the exudate[1] revealed a number of chromenes and benzofurans derived by prenylated resacetophenone. These two classes of compounds occur almost exlusively in the Compositate family[2] and are valuable in assessing phylogenic relations of genera and species within this family. In light of the possible therapeutic and chemotaxonomic significance of these compounds, we undertook a systematic investigation of *E. farinosa* extracts.

Isolation and Structure Determination

The major constituent of the plant was isolated as optically inactive encecalol ethyl ether (**1**). Although the compound never gave a satisfactory elemental analysis, the molecular ion appeared in the mass spectrum at *m/e* 262, suggesting the composition $C_{16}H_{22}O_3$. This formula was substantiated by the ^{13}C NMR spectrum. That the compound was aromatic was evidenced by the IR spectrum, and an absorption at 1630 cm^{-1} suggested the presence of additonal unsaturation. The 100-MHz ^1H-NMR spectrum of this compound was remarkably simple and displayed the signals characteristic of a dimethylchromene derivative. Singlets at δ 1.33 (6 H) and 3.91 (3 H) corresponded to the *gem*-dimethyl substituents on the chromene ring and to the methoxyl group. The olefinic protons at C-3 and C-4 were displayed as an AB pattern of doublets at δ 5.33 and 6.21 (1 H each, J = 10 Hz). The aromatic protons appeared as singlets at δ 6.28 and 7.00, corresponding to the protons at C-8 and C-5. The two aromatic protons and their observed multiplicity indicated a para relationship. These conclusions, in addition to the remaining signals in the NMR spectrum, led to the formulation of encecalol ethyl ether as **1**, a conclusion that was later substantiated by synthesis.

In addition to **1** there was also obtained in a lesser amount a substance structurally very similar (encecalol methyl ether, **2**). The obvious similarity of the racemic **1** and the optically active **2**, coupled

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Table I. ^{1}H NMR Signals for Chromenes 1–6, 12, 13, 18, and 19

	1[a,h]	2[a,i]	3[a,j]	4[a,k]	5[a,l]	6[a,m]	12[b,n]	13[b,o]	18[b,p]	19[b,q]
H-3	d 5.35[c]	d 5.33[c]	d 5.44[c]	d 5.25[c]	d 5.49[c]	t 1.62[d]	t 1.82[d]	d 5.55[c]	d 5.36[d]	d 5.30[c]
H-4	d 6.22[c]	d 6.24[c]	d 6.25[c]	d 6.04[c]	d 6.29[c]	t 2.40[d]	t 2.70[d]	d 6.26[c]	d 6.12[c]	d 6.09[c]
H-5	s 6.96	s 7.00	s 7.44	s 6.53	s 7.09	s 6.60	s 7.40	s 7.28	s 6.98	s 6.90
H-7										
H-8	s 6.25	s 6.28	s 6.25	s 6.07	s 6.35	s 6.09	s 6.15	s 6.30	s 6.23	s 6.10
H-10										
H-11	q 4.58[e]	q 4.72[d]		q 2.44[d]	dd 6.94[f]	q 2.60[d]				q 4.90[d]
H-12	d 1.25[e]	d 1.26[d]	s 2.45	t 1.04[d]	*c* dd 5.59[f]	t 1.04[d]	s 2.50	s 2.56		d 1.30[d]
					t dd 4.94[g]					
H-13,14	s 1.34	s 1.33	s 1.43	s 1.38	s 1.43	s 1.15	s 1.33	s 1.42	s 1.38	s 1.39
OMe	s 3.67	s 3.63	s 3.91	s 3.68	s 3.68	s 3.65			s 3.78	s 3.70
Ar-OH							s 12.00	s 12.36		
R	s 3.14	q 3.31[e]								bs 2.85
		t 1.10[e]								

[a] CCl_4. [b] $CDCl_3$. [c] J = 10 Hz. [d] J = 7 Hz. [e] J = 6 Hz. [f] J = 10, 17 Hz. [g] J = 17, 2 Hz. [h] Registry no. 69309-15-5. [i] Registry no. 69309-16-6. [j] Registry no. 20628-09-5. [k] Registry no. 69309-17-7. [l] Registry no. 62458-61-1. [m] Registry no. 69309-18-8. [n] Registry no. 31273-58-2. [o] Registry no. 19013-03-7. [p] Registry no. 67015-37-6. [q] Registry no. 69309-19-9.

with the presence of the biologically unlikely ethyl ether substituent[3] of the former, indicated that 1 was an artifact of the isolation procedure[4] and that 2 was in fact the major constituent of the plant. This was later confirmed by treating 2 with ethanol and a trace of acid; the ethyl ether (1) was obtained as the major product.

There was also isolated from the sample plant source another chromene of related constitution. The IR spectrum of this material displayed absorptions at 1678 and 1625 cm^{-1}. The MS indicated a molecular ion at *m/e* 232 and these data, in conjunction with the NMR spectrum (Table I), were accommodated by the assignment of structure 3 for this substance. The structural features embodied in 3 were identical to those of encecalin[5] from *E. californica* and to those of methyleupatorichromene[6] from *Eupatorium glandulosum*; the chromeno ketone 3 had been identified on the basis of spectral and degradative evidence.

In addition to 2 and 3 several other related compounds were identified in *E. farinosa*. Two of these were obtained as a mixture separable only by GC/MS analysis. These compounds were assigned the structures 4 and 5; the latter has been identified[7] as a metabolite of *Flourensia cernua*. Catalytic hydrogenation of this mixture led to a single substance (6-ethyl-7-methoxy-2,2-dimethylchroman, 6) which proved to be identical to the reduction/hydrogenolysis product obtained upon catalytic hydrogenation of 1 or 2.

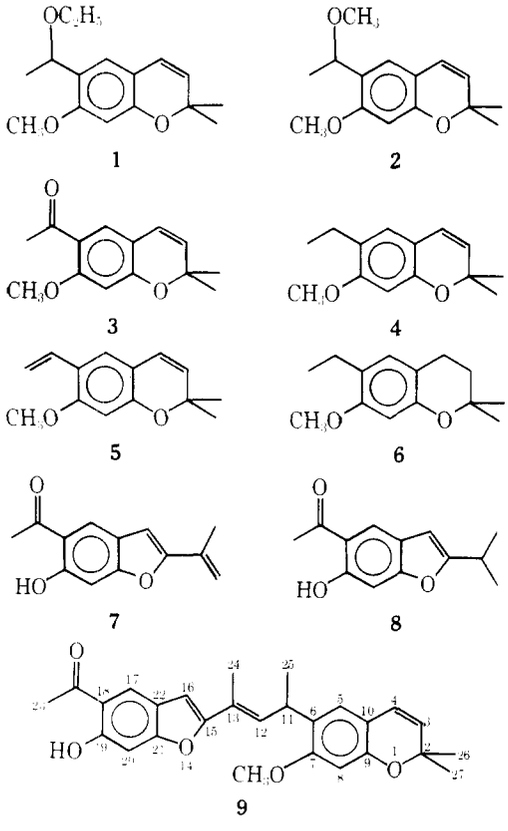
Euparin[8] (7) was identified on the basis of its mp, ^{1}H-NMR spectrum, and the mp of its acetate. Present in the mother liquors obtained from the recrystallization of 7, isodihydroeuparin (8) was identified on the basis of its ^{1}H-NMR spectrum. Satisfactory analytical data were not obtained due to the presence of traces of inseparable 7. Partial hydrogenation of 7 gave rise to signals in the NMR superimposable on those of 8.

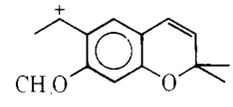
Compounds 2, 4, 5, and 7 were obtained from the woody stems of *E. farinosa*, while 3, 7 and 8 were found in the exudate. One additional substance was also found in trace amounts in the exudate and has been assigned the structure 9 based on spectral data. This compound was optically active and had a molecular ion of 432. Fragmentation ions at 217, 216, and 201 suggested the presence of the dimethylchromene moiety (i) found in the spectra of 1 and 2. The UV absorption spectrum and the green color reaction with $FeCl_3$ indicated the presence of a euparin (7) moiety. Thus, the compound appeared to be a coupling product of euparin (7) and 1 or 2. The nature of the coupling linkage was elucidated by NMR decoupling experiments. Thus, irradiation at 1.39 ppm caused the multiplet at 4.15 ppm to collapse to a broad doublet (J = 10 Hz) indicating vicinal coupling between protons C_{11} and C_{12}. Irradiation at 4.15 ppm caused the collapse of the doublet at 1.39 ppm to a singlet, indicating a coupling between the C_{11} methyl group and the methine proton at C-12 (J = 6 Hz) as in partial structure ii.

The position of the double bond at C_{12}–C_{13} (instead of C_{11}–C_{12}) is not unambiguously established by these data. However, the UV absorption spectrum of 9 is a composite of the UV spectra of euparin (7) and compound 4, and the mass fragmentation ion at 217 reflects the benzylic fragment i. Both of these properties strongly favor the C_{12}–C_{13} double bond assignment.

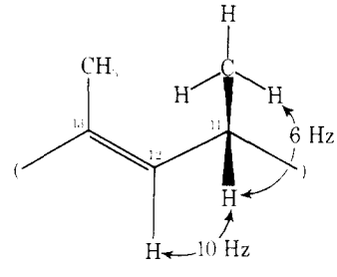
The yellow solid 9 may be seen as a condensation product of 4 and 7; the observed optical activity and occurrence only in the exudate

Chart I. Constituents of *E. furinosa*



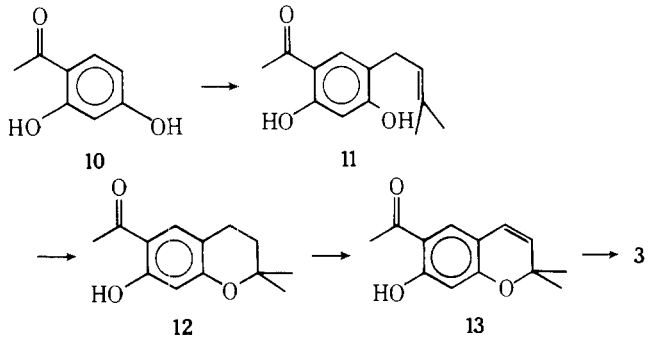


i

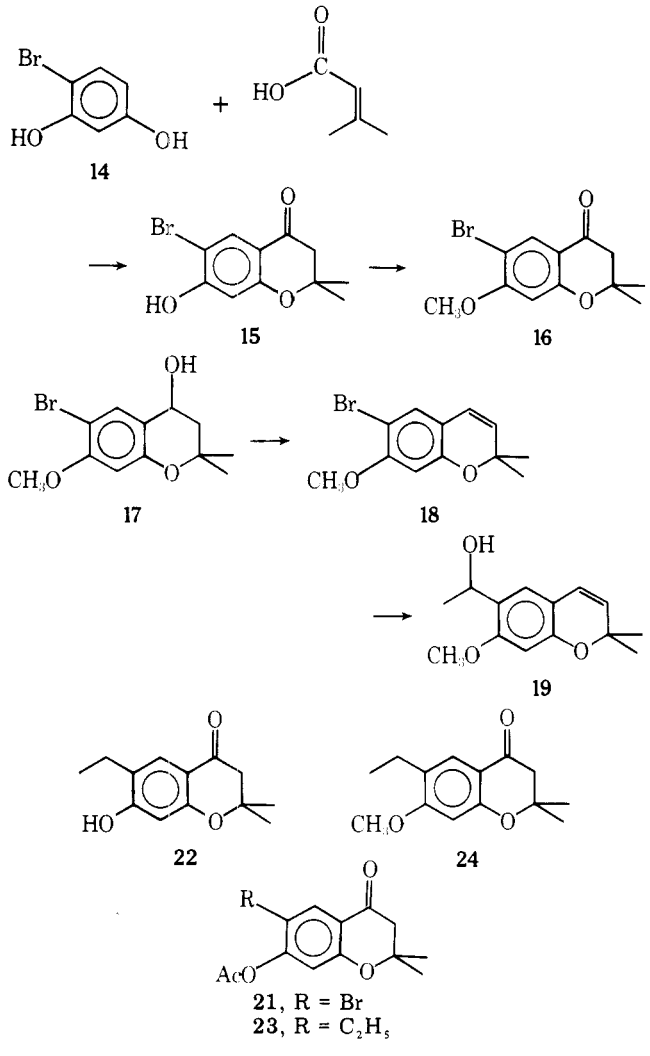


ii

Scheme I. Synthesis of Encecalin



Scheme II. Synthesis of Encecalol



suggests that such a coupling occurred *after secretion* from the plant epidermis.

In addition to the above compounds found in the extracts of *E. farinosa*, the following substances were determined by GLC analysis of the steam distillate: borneol, 1,8-cineole, α-pinene, and euparin.

The structures of chromenes **1–4** were verified by independent synthesis from resorcinol. Encecalin (**3**), which has defied synthesis in the past,[9] has now been successfully prepared from resacetophenone (**10**). Acid-catalyzed prenylation[10] of **10** and separation of the resulting product mixture gave **11**, which was cyclized to **12** by brief warming in ethanolic HCl. Dehydrogenation[11] induced by DDQ converted **12** to **13** (eupatoriochromene), which, upon methylation, yielded **3**. This synthetic material was identical in every respect to the natural product. Encecalin was also prepared by an alternate synthesis, which proved to be a more versatile route since it led directly to compounds **1**, **2**, and **19** in high yields. Compound **19** has recently been reported in *F. cernua*.[7]

This alternate synthesis began with 4-bromoresorcinol[12] (**14**) which, upon PPA-catalyzed cyclization[13] with senecioic acid, was converted to **15**. Methylation gave **16** which, upon reduction and dehydration, afforded **18**. Attempts to prepare the organomagnesium compound from **18** were not realized, even with active magnesium.[14] Metalation of **18** with *n*-butyllithium led to the lithium salt; hydroxyalkylation of this salt with acetaldehyde led to **19** in good yield. Oxidation of **19** with active manganese dioxide led to **3**, while conversion of **19** to the sodium salt with sodium hydride followed by treatment with the appropriate alkyl halide cleanly gave **1** and **2**.

Chromene **4** was prepared in a similar fashion. Thus, the condensation of 4-ethylresorcinol and senecioic acid gave the chromanone **22**. Methylation afforded **24**, which after treatment as above yielded **4**.

Biogenetic and Chemotaxonomic Significance

The co-occurrence of **3** and all of its reduced states (**2**,**4**,**5**) in *E. farinosa* is unique. At the time their structures were established, these were the only chromenes of this class known in nature. The co-occurrence of **5** and **19** in *F. cernua* is interesting, since this closely related plant also grows in the southwestern United States, is resinous, and is used by the native population in folk medicine.

Compounds **1–5**, **7**, and **8** are thought to arise from the alkylation of **20** (methyl ether of **10**) by DMAPP, followed by cyclization to the chromene and benzofuran structures.[15] Further modification leads to compounds of the type **1–5** or **7** and **8**; these compounds have also come to be known as aromatic hemiterpenes.[16]

The closely related *E. farinosa*, *F. cernua* and *F. resinosa* appear to be the only known sources of acetophenone-derived metabolites in which the acetyl moiety of resacetophenone (or its equivalent) has suffered further chemical modification. The detection of **8** in *E. farinosa* marks the first occurrence in nature of a 5-acetylbenzofuran in which the 2-isopropenyl substituent has undergone reduction.

It appears that reductive modification of these acetophenone derivatives may complement tribal and subtribal delineations within the large *Compositae*.

Experimental Section

Petroleum ether refers to a fraction boiling at 30–60 °C. Silica gel (60–200 mesh, Baker) was employed for column chromatography. TLC was performed with silica gel plates. Melting points were observed in capillary tubes and are uncorrected, as are boiling points. NMR and IR spectra were determined on the Varian Associates T-60, HA-100 and Beckman Model 137 instruments, respectively. Mass spectra were recorded on a Hewlett Packard Model 5930 quadrupole mass spectrometer. GC/MS analyses were performed with the HP-5930 mass spectrometer equipped with a Hewlett Packard Model 5700A GC, employing a column of 9% OV-101 on Chromosorb P, $\frac{1}{8}$ in. × 6 ft. Optical rotations were measured at the Hg green line (547 nm) on a Zeiss Old 4 polarimeter.

Extraction of Plant Material. *Encelia farinosa* Gray was collected in the lower Santa Catalina mountains at the peak of the flowering stage (March, 1975). Leaves and new growth were separated from woody stems and the latter was air dried and ground to a powder. The extraction of 4300 g of plant with 95% ethanol (Soxhlet) and removal of solvent yielded a tarry residue. Extraction of this tar was carried out by agitation with petroleum ether. After repeating the process three times, the combined extracts were dried, treated with charcoal, and filtered with the aid of celite and the solvent evaporated to give 48.3 g of a yellow oil. This oil was chromatographed over 800 g of silica gel with petroleum ether (fractions 1–53) and benzene (fractions 54–70). Fractions (200 mL) were collected. Fraction 53 gave 750 mg of **7**, fractions 54–55 yielded 4 g of **1**, and fractions 56–60 afforded 2 g of **2**. Since TLC showed that the tarry residue from the above extraction still contained chromenes, the tar was taken up in $CHCl_3$, dried, and distilled to yield a dark yellow oil (3 g). Chromatography over 100 g of silica gel with hexane–benzene led to two fractions. The first was a mixture of **4** and **5** (66 mg). The second gave an additional 200 mg of **7**. The gummy exudate of *E. farinosa* was collected by scraping it from woody stems, 11.5 g being so obtained. Dissolution in benzene, removal of debris, and evaporation of solvent left 10 g of a gummy oil which was chromatographed over silica gel (400 g) with benzene (fractions 1–148) and $CHCl_3$ (fractions 149–360). Fractions 50–148 afforded a mixture of **7**, **8**, and **9** which was further

separated to give 39 mg of 7 (for a total of 989 mg of this compound from the plant), 20 mg of 8, and 10 mg of 9. Fractions 149–250 yielded 250 mg of 3.

Encecalol Ethyl Ether (1). The yellow, oily compound had bp 103–105 °C (0.05 mm). Although homogeneous to TLC, 1 did not give satisfactory microanalysis: NMR (Table I); IR (neat) 1630, 1600, 1500, and 1280 cm^{-1}; MS *m/e* (rel intensity) 262 (M^+, 17), 247 (M − 15, base), 217 (83), 203 (36), 201 (64). Catalytic hydrogenation led cleanly to 6 (NMR, Table I).

Encecalol Methyl Ether (2). The yellow oil has bp 109–110 °C (0.15 mm). Like 1, no acceptable analysis was obtained: NMR (Table I); IR (neat) 1630, 1600, 1500, and 1270 cm^{-1}; MS *m/e* 248 (M^+, 15), 233 (M − 15, base), 203 (17), 201 (6); $[\alpha]^{547}_{22}$ −6.11 (*c* 0.0157, $CHCl_3$). Hydrogenation gave 6.

Encecalin (3): yellow, viscous oil; bp 135–137 °C, 0.11 mm (lit.[5] bp 123 °C, 0.05 mm); NMR (Table I); IR (neat) 1678, 1625, 1601, and 1500 cm^{-1}; MS *m/e* 232 (M^+, 9), 217 (M − 15, base). The compound gave an oxime, crystallized with difficulty from alcohol, mp 136–137 °C (lit.[5] mp 140 °C).

6-Ethyl- and 6-Vinyl-7-Methoxy-2,2-Dimethylchromenes (4 and 5). Each component identified by GC/MS analysis: NMR (Table I); IR (neat) 1630, 1604, 1500, and 1280 cm^{-1}. Compound **4**: MS *m/e* 218 (M^+, 12), 203 (M − 15, base), 91 (13), 77 (9). Compound **5**: MS *m/e* 216 (M^+, 15), 201 (M − 15, base). Physical constants for pure **4** are detailed below.

Euparin (7). Crystallized from $CHCl_3$-pentane, the yellow needles had mp 116 °C (lit.[8] mp 117–118 °C). The compound gave a green color with ferric chloride: NMR ($CDCl_3$) δ 12.13 (s, 1 H, OH), 7.90 (s, 1 H, H-4), 6.95 (s, 1 H, H-7), 6.52 (bs, 1 H, H-3), 5.76 (bs, 1 H, H-12), 5.20 (bs, 1 H, H-12), 2.70 (s, 3 H, H-14), and 2.10 (bs, 3 H, H-11); UV λ_{max} ($CHCl_3$) 240 (ε 21 000), 266 (ε 30 000), 293 (ε 13 000), 304 (ε 11 000); IR (CCl_4) 3500, 1680, 1600, and 1500 cm^{-1}; MS *m/e* 218 (M^+, 10), 203 (M − 15, base). Euparin acetate, prepared in the usual way, obtained white prisms from hexane, mp 78–79 °C (lit.[9] mp 80 °C). The mother liquors from certain crystallizations of 7 contained considerable amounts of 8, which was further purified to give yellow needles, mp 188–120 °C. Analytical data were unavailable since the material could not be freed of traces of 7: NMR ($CDCl_3$) δ 12.01 (s, 1 H, OH), 7.90 (s, 1 H, H-4), 6.95 (s, 1 H, H-7), 6.25 (bs, 1 H, H-3), 3.15 (sep, 1 H, H-10), 2.70 (s, 3 H, H-14), and 1.40 (d, 6 H, H-11, 12).

2-[2-(6-Acetyl-7-hydroxybenzofuranyl)]-4-[6-(7-methoxy-2,2-dimethylbenzo-1-pyranyl)]-pent-2-ene (9): yellow needles from hexane; mp 130–140 °C; UV λ_{max} ($CHCl_3$) 240 (ε 33 000), 267 (ε 37 000), 297 (ε 23 000), 312 (ε 20 000); IR (CCl_4) 3500, 1689, 1640, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 12.21 (s, 1 H, OH), 7.81 (s, 1 H, H-17), 6.95 (s, 1 H, H-20), 6.90 (s, 1 H, H-5), 6.26–6.45 (m, 4 H, H-4, H-8, H-12, H-16), 5.43 (d, *J* = 10 Hz, 1 H, H-3), 4.15 (dq, *J* = 6, 10 Hz, 1 H, H-11), 3.82 (s, 3 H, OMe), 2.61 (s, 3 H, H-23), 2.04 (bs, 3 H, H-24), 1.42 (s, 6 H, H-26, H-27), and 1.39 (d, *J* = 6 Hz, 3 H, H-25); MS *m/e* 432 (M^+, 15), 417 (M − 15, base), 201 (39); $[\alpha]^{547}_{22}$ −2.72 (*c* 0.0011, $CHCl_3$). The compound gave a green color with ferric chloride.

Prenylation of 10. Preparation of 5-Prenyl-2,4-dihydroxyacetophenone (11). To a solution of **10**[17] (15.2 g, 0.1 mol) in 50 mL of 80% HCOOH at 50 °C was added 2-methylbut-3-en-2-ol (Aldrich, 8.6 g, 0.1 mol) over 30 min. After being cooled and stirred for an additional hour, the solution was poured into 300 mL of water and chilled overnight. The crystalline material so obtained was collected by filtration and dissolved in ether. The ether solution was washed with 10% K_2CO_3 and dried and the solvent was removed leaving a red oil. This oily product mixture was chromatographed over silica gel and eluted with benzene–hexane (3:1) to give **11** (7%) as white plates from benzene–hexane: mp 144–145 °C (lit.[18] mp 144 °C); NMR ($CDCl_3$) δ 12.23 (s, 1 H), 7.42 (s, 1 H), 6.20–6.24 (bd, s, 2 H), 5.30 (bt, *J* = 7 Hz, 1 H), 3.35 (bd d, *J* = 7 Hz, 2 H), 2.51 (s, 3 H), and 1.80 (bs, 6 H); IR (CCl_4) 3300, 1670, 1640, 1600, and 1510 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.93; H, 7.29. Found: C, 70.56; H, 7.12.

Cyclization of 11. Preparation of 6-Acetyl-7-hydroxy-2,2-dimethylchroman (12). To 40 mL of alcohol containing 1 mL of concentrated HCl was added 1.5 g (6.8 mmol) of **11**. The solution was warmed for 3 h and cooled and the solvent was removed. The resulting solid was dissolved in ether, washed with 10% $NaHCO_3$ and brine solutions, and dried. Evaporation of solvent and crystallization as above gave 1.3 g (87%) of **12**: mp 117–118 °C (lit.[18] mp 119 °C); NMR (Table I); IR (CCl_4) 3300, 1645, 1500, and 1270 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.93; H, 7.29. Found: C, 70.66; H, 7.19.

Dehydrogenation of 12. Preparation of 6-Acetyl-7-hydroxy-2,2-dimethylchromene (13). In the usual way,[11] the above chroman (500 mg, 2.1 mmol) and DDQ (500 mg) were refluxed in 10 mL of benzene for 1.5 h. The cooled solution was filtered and evaporated to dryness and the resulting yellow solid was chromatographed over silica gel with benzene to give pure **13** as long yellow needles from hexane: mp 76–77 °C (lit.[6] mp 77 °C); NMR (Table I): IR (CCl_4) 3300, 1630, 1600, 1500, and 1280 cm^{-1}; MS *m/e* 218 (M^+, 10), 203 (M − 15, base).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.59; H, 6.42. Found: C, 71.57; H, 6.30.

The acetate of **13** was obtained as colorless needles from hexane, mp 75.5–76.5 °C. This acetate has been reported previously[19] as an oil. Methylation of **13** with methyl sulfate in the usual way gave a material identical in every respect with naturally occurring **3**.

Preparation of 6-Bromo-7-hydroxy-2,2-dimethylchroman-4-one (15). Adapting the method of Bowers,[13] 22.3 g (118 mmol) of **14**[20] and 20 g (200 mmol) of senecioic acid[21] were finely powdered and added to 200 g of PPA at 90 °C. The viscous paste was warmed with stirring until the mixture had become homogeneous and had acquired a yellow color (15 min). After cooling, excess PPA was decomposed by the addition of ice. The mixture was stirred until all the lumps were removed and hydrolysis was complete. The pale yellow solution was extracted with ether and the organic phase was washed with water, 10% $NaHCO_3$, and brine solutions and dried. Removal of solvent gave a solid which was dissolved in alcohol and treated with charcoal. Crystallization from aqueous alcohol gave pure **15** as lustrous plates: mp 206–207 °C; NMR (Table II); IR (Mull) 3300, 1650, 1600, 1500, and 1260 cm^{-1}; MS *m/e* 272 (M + 2), 271 (M + 1), 270 (M^+), 269 (M − 1), 257 (base).

Anal. Calcd for $C_{11}H_{11}O_3Br$ requires: C, 48.73; H, 4.09. Found: C, 48.59; H, 4.23.

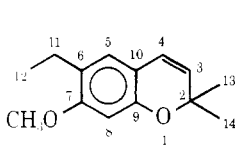
Acetate, prepared in the usual way, gave white needles from hexane: mp 89.5–90.5 °C; NMR (Table II).

Methylation of 15. Preparation of 6-Bromo-7-methoxy-2,2-dimethylchroman-4-one (16). Chromanone **15** was methylated in the usual way with dimethyl sulfate to afford the methoxy ketone **16** as white cubelets from hexane (89%): mp 96–97 °C; NMR (Table II); IR (CCl_4) 1675, 1600, 1500, and 1270 cm^{-1}; MS *m/e* 286 (M + 2), 284 (M^+), 271, 269 (M − 15, base), 231, 229.

Anal. Calcd for $C_{12}H_{13}O_3Br$ requires: C, 50.73; H, 4.26. Found: C, 50.70; H, 4.59.

Generation of 17. Preparation of 6-Bromo-7-methoxy-2,2-dimethylchromene (18). To a slurry of $LiAlH_4$ (1.33 g, 35 mmol) in dry ether (200 mL) was added dropwise with stirring a solution of **16** (18.8 g, 66 mmol) in 200 mL of ether at a rate such that gentle reflux was maintained. When the addition was complete, the mixture was stirred for 1 h, the excess hydride was destroyed by the addition of moist ether, and the organic phase was decanted from residual lithium salts. The organic solution was dried and the solvent removed to afford crude **17** which was not further characterized but carried directly into the next step. Thus, the crude **17** was dissolved in 70 mL of benzene and added dropwise to a stirred solution of $POCl_3$ (6.4 mL, 70 mmol)

Table II. ^1H NMR Signals for Chromanones 15, 16, and 21–24[a]



	15[b,g]	16[d,h]	21[c,i]	22[b,j]	23[c,k]	24[c,l]
H-3	2.73	2.50	2.65	2.68	2.66	2.63
H-5	7.85	7.75	8.05	7.95	6.75	7.60
H-8	6.58	6.22	6.70	6.60	6.61	6.28
H-11				q 2.78[f]	q 2.50[f]	q 2.54[f]
H-12				t 1.25[f]	t 1.18[f]	t 1.07[f]
H-13,14	1.48	1.41	1.43	1.35	1.41	1.44
OH	*e*			*e*		
OMe		3.82				3.81
OAc			2.35		2.30	

[a] Singlet multiplicity unless otherwise noted. [b] Acetone-d_6. [c] $CDCl_3$. [d] Exchanged with solvent. [e] Detected on offset scan. [f] *J* = 6 Hz. [g] Registry no. 50544-78-0. [h] Registry no. 69309-20-2. [i] Registry no. 69309-21-3. [j] Registry no. 69309-22-4. [k] Registry no. 69309-23-5. [l] Registry no. 69309-24-6.

in dry pyridine (40 mL). After the addition was complete, the solution was refluxed for 1 h, cooled, and poured onto ice. The phases were separated and the aqueous phase extracted with ether. The combined organic phases were washed with 10% HCl, 10% $NaHCO_3$, and brine solutions and dried. Evaporation of solvent left a yellow oil which gave, upon distillation, a colorless oil, bp 115–116 °C (0.11 mm). The yield of **18** was 70% (12.3 g). Upon standing, the oil solidified as white prisms: mp 47–48 °C; NMR (Table I); IR (CCl_4) 1630, 1600, 1500, and 1280 cm^{-1}; MS *m/e* 270 (M + 2), 268 (M^+), 255, 253 (M − 15, base).

Anal. $C_{12}H_{13}O_3Br$ requires: C, 53.75; H, 4.51. Found: C, 53.73; H, 4.88.

Catalytic hydrogenation gave the dihydro compound whose properties were identical with literature[22] values.

Preparation of 6-(1-Hydroxyethyl)-7-methoxy-2,2-dimethylchromene (Encecalol, 19). In a flask equipped with a N_2 atmosphere, magnetic stirrer, septum, and provision for cooling was placed 15 mL of dry, olefin-free hexane and dry TMEDA (1.05 mL, 7 mmol). The flask was cooled to 0 °C and *n*-butyllithium (1. 6 M in hexane, 4.3 mL, 7 mmol) was added. To the resulting clear solution was added **18** (1.5 g, 5 mmol) in 15 mL of hexane. The Li salt precipitated almost immediately, and the heterogeneous mixture was allowed to warm to ambient temperature and was stirred for 30 min. After chilling to 0 °C, a twofold excess of freshly distilled acetaldehyde (0.56 mL) in hexane (5 mL) was introduced and the resulting mixture was stirred 2 h. The Li salts were decomposed by the addition of 10% HCl and the mixture was poured into water and extracted with ether. The ether extracts were washed with water, 10% $NaHCO_3$, and brine solutions and dried. Removal of solvent left 1.2 g of a yellow oil, which was chromatographed over 50 g of silica gel with $CHCl_3$ to afford 723 mg (57%) of **19** as a viscous, yellow oil: NMR (Table I); IR (neat) 3400, 1630, 1610, 1500, and 1290 cm^{-1}; MS *m/e* 234 (M^+), 219 (M − 15), 201 (M − 15 − H_2O, base). These values are in good agreement with those reported[8] for natural **19**.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.82; H, 7.69. Found: C, 72.10; H, 7.55.

Etherification of 19. Preparation of 6-(1-Methoxyethyl)-7-methoxy-2,2-dimethylchromene (Encecalol Methyl Ether, 2). Alcohol **19** (200 mg, 0.86 mmol) was added to a suspension of sodium hydride (62 mg, 50% dispersion, 1.3 mmol) in 15 mL of dry dimethoxyethane. The solution was refluxed under N_2 for 1 h to insure salt formation. At the end of this time excess MeI (0.75 mL) was added and the mixture was refluxed for an additional 6 h. To the cool solution was added water to destroy excess hydride and the solvent was removed under reduced pressure. The residue was dissolved in ether, washed with water and brine, and dried. Removal of solvent and chromatography over silica gel with benzene afforded the methyl ether **2** (159 mg, 75%) as a yellow oil, bp 107–109 °C (0.1 mm), identical with the naturally derived **2**.

Anal. Calcd fro $C_{15}H_{19}O_3$: C, 72.90; H, 7.69. Found: C, 73.10, H, 7.81.

In an identical fashion **1** was prepared from **19** in 70% yield. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.31; H, 8.39. Found: C, 73.41; H, 8.36.

Oxidation of 19. Preparation of 6-Acetyl-7-methoxy-2,2-dimethylchromene (Encecalin, 3). To a solution of **19** (300 mg, 1.2 mmol) in petroleum ether was added an equal weight of active manganese dioxide.[23] The suspension was stirred for 2 h at room temperature and filtered and the solvent was evaporated to give a golden oil. Chromatography over silica gel with $CHCl_3$ gave 250 mg (84%) of **3** identical with the synthetic material prepared above and the natural product.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.44; H, 6.89. Found: C, 72.35; H, 6.96.

Preparation of 6-Ethyl-7-hydroxy-2,2-dimethylchroman-4-one (22). The chromanone was prepared as outlined above from 5 g (36.2 mmol) of 4-ethylresorcinol[24] and senecioic acid (5 g, 50 mmol). The solid material so obtained was crystallized from aqueous alcohol to give pure **22** as pale tan plates, mp 175–176 °C, in 35% yield. The yield was reduced at the expense of the formation of a considerable amount of base-insoluble tar. The ketone gave a brown color with ferric chloride: NMR (Table II); IR (CCl_4) 3300, 1660, 1600, 1500, and 1260 cm^{-1}; MS *m/e* 220 (M^+), 205 (M − 15, base), 165.

Anal. $C_{13}H_{16}O_3$ requires: C, 70.93; H, 7.27. Found: C, 70.80; H, 7.51.

Acetate **23** obtained as colorless needles from hexane: mp 69.5–70.5 °C; NMR (Table II).

Methylation of 22. Preparation of 6-Ethyl-7-methoxy-2,2-dimethylchroman-4-one (24). The methyl ether was prepared as above from **22** in 85% yield: colorless needles from hexane; mp 78–79 °C; NMR (Table II); IR (CCl_4) 1680, 1600, 1500, and 1250 cm^{-1}; MS *m/e* 234 (M^+), 219 (M − 15, base), 178 (M − 56).

Anal. $C_{14}H_{18}O_3$ requires: C, 71.82; H, 7.69. Found: C, 72.10; H, 7.75.

Preparation of 6-Ethyl-7-methoxy-2,2-dimethylchromene (4). As in the previous preparation, **24** was subjected to reduction and dehydration to give 675 mg (75%) of the desired **4** as a pale tan oil: bp 115–116 °C (0.1 mm), identical with natural **4**; NMR (Table I); UV λ_{max} ($CHCl_3$) 240 (ε 15 000), 280 (ε 6600 infl.), 290 (ε 6700), 311 (ε 7700), 324 (7000); IR (CCl_4) 1630, 1605, 1500, and 1280 cm^{-1}; MS *m/e* 218 (M^+), 203 (M − 15, base), 91, 77.

Anal. $C_{14}H_{18}O_2$ requires: C, 77.09; H, 8.25. Found: C, 76.95; H, 8.32.

Registry No.—**3** oxime, 23840-18-8; **7**, 532-48-9; **7** acetate, 69309-25-7; **8**, 5207-55-6; **9**, 69309-26-8; **10**, 89-84-9; **11**, 28437-37-8; **13** acetate, 19013-04-8; **14**, 6626-15-9; **15** acetate, 69309-27-9; **17**, 69439-75-4; 2-methylbut-3-en-2-ol, 115-18-4; senecioic acid, 541-47-9; 4-ethylresorcinol, 2896-60-8.

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