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The Synthesis of Some Dimethylpyranocoumarins and Isopropenyldihydrofuranocoumarins

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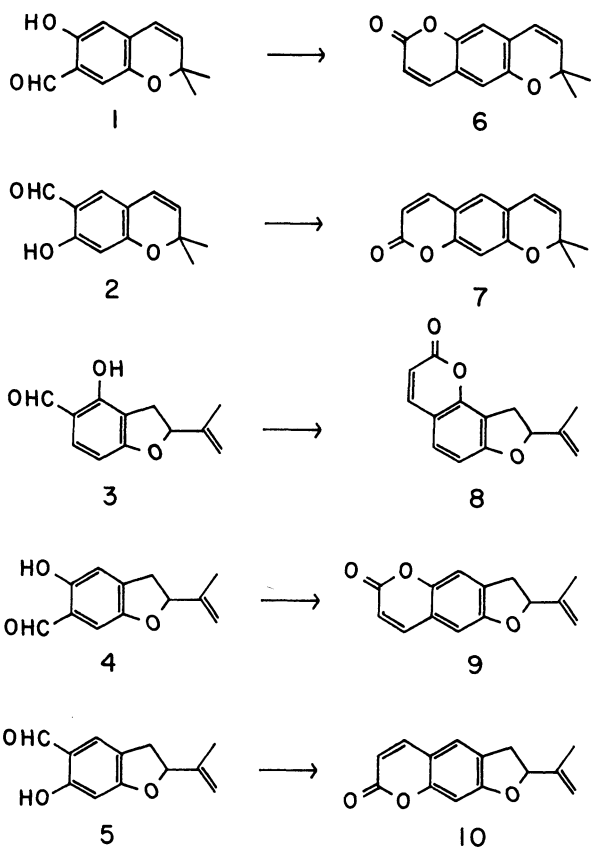
Two pyranocoumarins, 7,7-dimethyl-2(7*H*)-benzo[1,2-*b*:4,5-*b'*]dipyranone and 8,8-dimethyl-2(8*H*)-benzo[1,2-*b*:5,4-*b'*]dipyranone, and three dihydrofuranocoumarins, 2-isopropenyl-1,2-dihydro-8-furo[1,2-*f*][1]benzopyranone, 2-isopropenyl-2,3-dihydro-6-furo[1,2-*e*][1]benzopyranone, and 2-isopropenyl-2,3-dihydro-7-furo[2,1-*e*][1]benzopyranone, were synthesized by an effective pyrone-ring formation in corresponding *o*-hydroxybenzaldehyde derivatives. And, 2-[1-(hydroxymethyl)vinyl]-1,2-dihydro-8-furo[1,2-*f*][1]benzopyranone was also synthesized selenium dioxide oxidation.

Natural xanthyletin[1] is a dimethylpyranocoumarin, and natural ammirin,[2] isoangenomalin,[3] angenomalin,[4] masquin,[5] and majurin[6] are isopropenyldihydrofuranocoumarins. In plants, these tricyclic *O*-heteroaromatic compounds may be prepared by prenylations of 7-hydroxycoumarin followed by cyclizations. We have studied the syntheses of 2,2-dimethyl-2*H*-chromenes and 2-isopropenyl-2,3-dihydrobenzofurans. In this paper we describe a new approach to dimethylpyranocoumarins and isopropenyldihydrofuranocoumarins by a pyrone-ring formation in some *o*-hydroxybenzaldehyde derivatives having 2*H*-chromene and dihydrobenzofuran structures.

We have already reported the acylation of 2,2-dimethyl-2*H*-chromenes[7] and 2-isopropenyl-2,3-dihydrobenzofurans,[8] and have obtained some methoxyl aldehydes by their formylations. Two *o*-hydroxybenzaldehyde derivatives having chromene structures, 6-hydroxy-2,2-dimethyl-2*H*-chromen-7-carbaldehyde (**1**) and 7-hydroxy-2,2-dimethyl-2*H*-chromen-6-carbaldehyde (**2**), were prepared from the corresponding methoxy derivatives by demethylation with magnesium iodide etherate. Two *o*-hydroxybenzaldehydes having dihydrobenzofuran structures, 5-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-6-carbaldehyde (**4**) and 6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**5**), were also prepared by demethylation of the corresponding methoxy derivatives. However, a similar preparation of 4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**3**) was not so effective, since in the cyclization of *m*-methoxyphenol with 1,4-dibromo-2-methyl-2-butene, the 4-methoxy derivative was the minor and the 6-methoxy derivative the major; the formylation of the minor 4-methoxy derivative, furthermore, gave a mixture of 5- and 7-formylated products. Thus, **3** was prepared in another procedure. A cyclization of 1,3-cyclohexanedione with 1,4-dibromo-2-methyl-2-butene gave 2-isopropenyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone (**11**) in 41% yield. The structure of **11** was confirmed by dehydrogenation to 2-isopropenyl-2,3-dihydro-4-benzofuranol (**12**). The methyl ether of **12** was identical with the sample prepared in cyclization of *m*-methoxyphenol with 1,4-dibromo-2-methyl-2-butene.[8] Condensation of **11** with ethyl formate gave 5-hydroxymethylene-2-isopropenyl-2,3,6,7-tetrahydro-4-(5*H*)-benzofuranone (**13**) in 35% yield, which was easily converted by dehydrogenation with DDQ to the desired *o*-hydroxybenzaldehyde **3** in 87% yield. This isopropenyldihydrobenzofuran **3** showed an ABX signal pattern typical in 2-isopropenyl-2,3-dihydrobenzofurans.

Some methods for pyrone-ring formation in *o*-hydroxybenzaldehydes were reported, but they were not so effective. We tried some new pyrone-ring



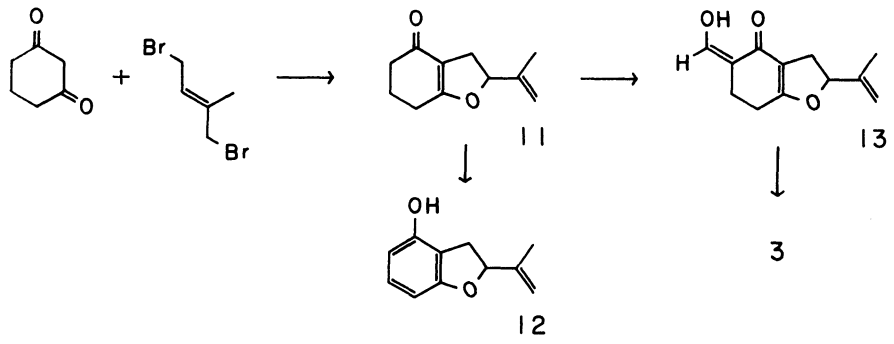


Table 1. The Yields, Some Physical Data, and Elemental Analyses of Dimethylpyranocoumarins and Isopropenyldihydrofurocoumarins

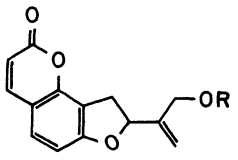
Compound	Yield %	Mp θ_m/°C	IR cm^{-1}	MS (M^+)	Elemental analysis[a] C(%)	H(%)
6	64	157—158	1700	228	73.51	5.46
7	49	133—134.5	1720	228	73.46	5.26
8	46	111—113	1735	228	73.96	5.23
9	63	157—158	1710	228	73.45	5.31
10	18[10]	98—98.5	1720	228	73.68	5.30

a) Calcd data for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%.

Table 2a. NMR Data of Dimethylpyranocoumarins (δ/ppm, J/Hz)

Compound	Me	Olefinic in pyran	Olefinic in pyrone	Aromatic
6	1.4(s)	5.8(d) 6.35(d) J=10	6.3(d) 7.5(d) J=10	6.8(s) 6.9(s)
7	1.4(s)	5.7(d) 6.3(d) J=10	6.2(d) 7.5(d) J=10	6.7(s) 7.0(s)

formation in 2-hydroxy-4-methoxybenzaldehyde, and the corresponding coumarin was obtained in the following three cases: a) heating with acetyl chloride in the presence of DBU at 110—140 °C for 2 h (10%), b) refluxing with *N,N*-dimethylacetamide dimethylacetal in xylene for 30 m (10%), c) refluxing *N,N*-dimethylacetamide dimethylacetal in ether for 6 h (22%). Thus, by pyrone-ring formations with *N,N*-dimethylacetamide dimethylacetal in refluxing ether for 6 h, two chromene derivatives **1,2** were effectively converted to the corresponding pyranocoumarins, 7,7-dimethyl-2(7*H*)-benzo[1,2-*b*:4,5-*b'*]dipyranone (**6**) and 8,8-dimethyl-2(8*H*)-benzo[1,2-*b*:5,4-*b'*]dipyranone (**7**) in 64% and 49% yield. They showed carbonyl absorption at 1700 cm^{-1} (**6**), 1720 cm^{-1} (**7**) in their IR spectra, and new olefinic protons of pyrone-ring at δ 5.8 and 7.5 (**6**), δ 5.7 and 7.5 (**7**) in the ^{1}H NMR spectra. Similar pyrone-ring formations of three dihydrobenzofurans (**3**, **4**, **5**) gave the corresponding furocoumarins, 2-isopropenyl-1,2-dihydro-8-furo[1,2-*f*][1]benzopyranone (**8**), 2-isopropenyl-2,3-dihydro-8-furo[1,2-*e*][1]benzopyranone (**9**), and 2-isopropenyl-2,3-dihydro-7-furo[2,1-*e*][1]benzopyranone (**10**) in 46, 63, and 18%.[9] These furocoumarins showed a carbonyl absorption at 1735 cm^{-1} (**8**), 1710 cm^{-1} (**9**), 1720 cm^{-1} (**10**), and showed the olefinic protons of pyrone-ring at δ 6.2 and 7.6 (**8**), δ 6.3 and 7.6 (**9**), δ 6.2 and 7.6 (**10**). The spectral data of pyrano coumarin **7** were identical with the reported data of natural xanthyletin.[1] Furocoumarins **8**, **10** were also identical with natural majurin,[6] angenomalin,[4] masquin,[5] ammirin,[2] and isoangenomalin,[3] in their spectral data.



14 a) R = Ac
b) R = H

Another furocoumarin having an oxidized isopropenyl graup (**14b**) was also reported as natural sachalinin[10] and discophoridin.[11] We converted **8** to **14b** by oxidation with selenium dioxide. The oxidation of **8** with selenium dioxide in refluxing acetic anhydride for 7 h gave an acetate, 2-[1-(acetoxymethyl)vinyl]-1,2-dihydro-8-furo[1,2-*f*][1]benzopyranone (**14a**), in 18% yield. This acetate **14a**,

Table 2b. NMR Data of Isopropenyldihydrofurocoumarins
(δ/ppm, J/Hz)

Compound	Me	H_A, H_B, H_X in dihydrofuran				Endo-methylene	Olefinic in pyrone		Aromatic	
8	1.8(s)	3.2(dd)	3.5(dd)	5.5(dd)	J_{AB}=16 J_{AX}= 8 J_{BX}=10	5.0(br.s) 5.1(br.s)	6.2(d)	7.6(d) J=10	6.8(d)	7.3(d) J=8
9	1.8(s)	3.2(dd)	3.4(dd)	5.2(dd)	J_{AB}=16 J_{AX}= 8 J_{BX}=10	4.9(br.s) 5.1(br.s)	6.3(d)	7.6(d) J=9	6.8(s)	7.1(s)
10	1.8(s)	3.1(dd)	3.4(dd)	5.3(dd)	J_{AB}=16 J_{AX}= 8 J_{BX}=10	5.0(br.s) 5.1(br.s)	6.2(d)	7.6(d) J=10	6.7(s)	7.2(s)

showed a new acetoxyl methyl signal at δ 2.0 and a new methylene signal at δ 4.7 in the ^{1}H NMR spectrum. This acetate was easily converted to 2-[1-(hydroxymethyl)vinyl]-1,2-dihydro-8-furo[1,2-*f*][1]benzopyranone (**14b**) in 70% yield by refluxing with 20% potassium hydroxide ethanolic solution for 1 h. This alcohol **14b** showed a hydroxyl absorption at 3400 cm^{-1}, and showed a methylene signal at δ 4.3. The spectral data were identical with those of natural discophoridin.[11]

Experimental

The melting and boiling points were uncorrected (in boiling points: 1 mmHg=133.322 Pa). The IR spectra were measured on a Hitachi 260-50 spectrometer in a liquid film or a KBr disk, and the UV spectra were taken on a Hitachi 220A spectrophotometer in an ethanolic solution. The ^{1}H NMR spectra were recorded on a JEOL PMX-60Si or FX-90Q NMR spectrometer, and the mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer.

Preparation of 1 and 2. By a procedure reported in the demethylation of dihydrobenzofurans,[8] 6-hydroxy-2,2-dimethyl-2*H*-chromen-7-carbaldehyde (**1**) and 7-hydroxy-2,2-dimethyl-2*H*-chromen-6-carbaldehyde (**2**) were prepared from the corresponding methoxyl derivatives[7] in 79 and 70% yield. **1**; mp 96.5—98 °C (from hexane). IR (KBr) 1650 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.4 (6H, s), 5.9 (1H, d, J=10 Hz), 6.4 (1H, d, J=10 Hz), 6.6 (1H, s), 7.0 (1H, s), 10.0 (1H, s), 10.8 (1H, s). Found: C, 70.68; H, 5.91%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. MS *m/z* 204 (M^+). **2**; mp 97.5—98.5 °C (from hexane). IR (KBr) 1630 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.4 (6H, s), 5.5 (1H, d, J=10 Hz), 6.2 (1H, d, J=10 Hz), 6.2 (1H, s), 7.0 (1H, s), 9.6 (1H, s), 12.9 (1H, s). Found: C, 70.49; H, 5.87%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. MS *m/z* 204 (M^+).

Cyclization of 1,3-Cyclohexanedione with 1,4-Dibromo-2-methyl-2-butene. To a solution of 1,3-cyclohexanedione (20.0 g, 179 mmol) and 1,4-dibromo-2-methyl-2-butene (40.3 g, 177 mmol) in dry acetone (250 ml) was added anhydrous potassium carbonate (74.0 g); the mixture was stirred for 8 h under refluxing. After removing the acetone, the mixture was diluted with water and extracted with ether. The ether layer was washed with 5% sodium hydroxide solution and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removing the ether, the residue was distilled under reduced pressure. The fractions boiling at 144—156 °C/17 mmHg were re-distilled to give 2-isopropenyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone (**11**) as fractions boiling at 145—157 °C 16 mmHg (12.8 g, 41%). **11**; IR (neat) 1630 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.8 (3H, s), 2.0—3.2 (8H, m), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.2 (1H, broad t, J=10 Hz). Found: C, 73.97; H, 7.78%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%. MS *m/z* 178 (M^+), 163, 150.

Dehydrogenation of 11 to 12. To a solution of **11** (379 mg, 2.13 mmol) in toluene (20 ml) was added 2,3-dichloro-5,6-dicycano-1,4-benzoquinone (DDQ) (490 mg, 2.16 mmol); the mixture was refluxed for 15 h. After removing of the precipitates by filtration, the filtrate was diluted with benzene and then extracted with 5% sodium hydroxide solution. The alkaline solution was acidified with 10% hydrochloric acid and re-extracted with benzene. The benzene layer was washed with saturated sodium chloride

Table 3. The UV Spectral Data of Dimethylpyranocoumarins and Isopropenyldihydrofurocoumarins

Compound	λ_{max}/nm (log ε)
6	248(4.13) 298(4.17) 308sh(4.14) 370(3.95)
7	222.5(4.38) 263(4.29) 300(3.76) 345(4.12)
8	249(3.54) 259(3.58) 325(4.18)
9	229(4.37) 251(3.86) 259(3.85) 281(4.01) 345(3.89)
10	222(4.08) 245(3.65) 256(3.57) 297sh(3.83) 332.5(4.26)
14a	248.5(3.51) 258.5(3.53) 324.5(4.10)
14b	248.5(3.45) 258(3.49) 325(4.15)

solution and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified on a silica-gel column with benzene eluents to give 2-isopropenyl-2,3-dihydro-4-benzofuranol (**12**)(132 mg, 35%); bp 190—210 °C/15 mmHg (bath temp). IR (neat) 3450 cm^{-1}. ^{1}H NMR (CCl_4) 1.8 (3H, s), 3.0 (1H, dd, J=16 and 8 Hz), 3.2 (1H, dd, J=16 and 9 Hz), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.1 (1H, dd, J=9 and 8 Hz), 5.4 (1H, broad s), 6.2 (1H, d, J=8 Hz), 6.3 (1H, d, J=8 Hz), 6.9 (1H, t, J=8 Hz). MS m/z 176 (M^+), 161. This phenol **12** was labile for its probable partial autooxidation. In the IR spectra, its methyl ether was identical with the sample prepared from *m*-methexyphenol.[8]

Condensation of 11 with Ethyl Formate. To a suspension of sodium hydride (0.43 g, 18 mmol) in dry benzene (50 ml) was added ethyl formate (5.32 g, 71.8 mmol), carefully. Then, 2-isopropenyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone (**11**) (3.19 g, 17.0 mmol) was added under refluxing, and the mixture was refluxed for 2 h. After cooling, the mixture was treated with 5% sodium hydroxide solution. The alkaline aqueous layer collected was washed with benzene and acidified with 10% hydrochloric acid, and then re-extracted with ether. The ether layer was washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the ether, the residue was distilled to give 5-hydroxymethylene-2-isopropenyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone (**13**) (1.29 g, 35%); bp 140—200 °C/23 mmHg. IR (neat) 1635 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.8 (3H, s), 2.5 (4H, broad s), 2.7 (1H, dd, J=16 and 8 Hz), 2.9 (1H, dd, J=16 and 9 Hz), 4.8 (1H, broad s), 5.0 (1H, broad s), 5.2 (1H, dd, J=9 and 8 Hz), 7.0 (1H, broad s). UV (EtOH) 271 (log ε 4.66), 315 nm (sh). MS m/z 206 (M^+), 191, 178, 163. Found: C, 69.96; H, 6.65%. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84%.

Dehydrogenation of 13 to 3. By a procedure described above in dehydrogenation of **11** to **12**, **13** (3.01 g, 14.6 mmol) was dehydrogenated with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (3.31 g, 14.6 mmol) to give a crude phenol, which was purified with a silica-gel column with hexane–ethyl aceteate (1:1) eluents. 4-Hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**3**) (2.59 g, 87%); bp 170—180 °C/20 mmHg (bath temp.). IR (neat) 1645 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.8 (3H, s), 3.0 (1H, dd, J=16 and 8 Hz), 3.3 (1H, dd, J=16 and 9 Hz), 4.9 (1H, broad s), 5.1 (1H, broad s), 5.3 (1H, dd, J=9 and 8 Hz), 6.4 (1H, d, J=9 Hz), 7.3 (1H, d, J=9 Hz), 9.7 (1H, s), 11.5 (1H, s). UV (EtOH) 235 (log ε 3.89), 242 (sh), 291 nm (4.25). MS m/z 204 (M^+), 189. Found: C, 70.81; H, 5.99%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. The methyl ether derived from **3** by methylation with dimethyl sulfate was identical with the sample from formylation of 2-isopropenyl-4-methoxy-2,3-dihydrobenzofuran.[8]

A New Pyrone-Ring Formation to Coumarin Derivatives. To a solution of *o*-hydroxybenzaldehyde derivatives **1—5** (ca. 5 mmol) in dry ether (20 ml) was added *N,N*-dimethylacetamide dimethylacetal (ca. 10 mmol); and the mixture was refluxed for 6 h under stirring. After cooling, the mixture was treated with 10% hydrochloric acid. The ether layer was collected, and the aqueous layer was extracted with chloroform. The organic layer was washed with a saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After removing the solvents, the two residues from ether and chloroform layers were combined and purified on a short silica-gel column. Pyronocoumarins **6** and **7** were obtained as the fractions eluted with chloroform and recrystallized from benzene. Dihydrofurocoumarins **8**, **9**, **10** were obtained as the fractions eluted with hexane–ethyl acetate (9:1) and recrystallized from cyclohexane. The yields and the spectral data are summarized in Tables 1, 2, and 3.

Oxidation of 8 to 14a with Selenium Dioxide. To a solution of **8** (0.48 g, 2.1mmol) in acetic anhydride (50 ml) was added selenium dioxide (0.25 g, 2.3 mmol); the mixture was refluxed for 7 h with stirring. After cooling, selenium compounds formed were filtered off, and the excess acetic anhydride was removed under reduced pressure. The residue was diluted with chloroform. The chloroform solution was washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified on a short silical-gel column. The fractions eluted with hexane–ethyl acetate (8:2) were collected and recrystallized from hexane–ether to give 2-[1-(acetoxymethyl)vinyl]-1,2-dihydro-8-furo[1,2-*f*][1]-benzopyranone (**14a**) (0.10 g, 18%); mp 77.5—78.5 °C. IR (KBr) 1720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.0 (3H, s), 3.2 (1H, dd, J=16 and 8 Hz), 3.6 (1H, dd, J=16 and 10 Hz), 4.7 (2H, broad s), 5.3 (1H, broad s), 5.4 (1H, broad s), 5.5 (1H, dd, J=10 and 8 Hz), 6.2 (1H, d, J=10 Hz), 6.7 (1H, d, J=8 Hz), 7.4 (1H, d, J=8 Hz), 7.7 (1H, d, J=10 Hz). Found: C, 67.01; H, 4.80%. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93%. MS m/z 286 (M^+), 226, 186. As the fractions eluted with hexane–ethyl acetate (95:5), **8** was recovered in 20%.

Hydrolysis of 14a to 14b. To a solution of **14a** (0.32 g, 1.1 mmol) in ethanol (10 ml) was added 20% potassium hydroxide aqueous solution (15 ml); the mixture was refluxed for 1 h with stirring. After cooling, the mixture was diluted with water and extracted with chloroform. The chloroform layer was washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the chloroform, the residue was crystallized from ethanol to give 2-[1-(hydroxymethyl)vinyl]-1,2-dihy-

dro-8-furo[1,2-*f*][1]benzopyranone (**14b**) (0.19 g, 70%); mp 102—103 °C. IR (KBr) 3400, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.3 (1H, broad s), 3.3 (1H, dd, J=16 and 8 Hz), 3.5 (1H, dd, J=16 and 10 Hz), 4.3 (2H, broad s), 5.3 (2H, broad s), 5.5 (1H, dd, J=10 and 8 Hz), 6.2 (1H, d, J=9 Hz), 6.7 (1H, d, J=9 Hz), 7.2 (1H, d, J=9 Hz), 7.8 (1H, d, J=9 Hz). Found: C, 68.96; H, 5.04%. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95%. MS m/z 248 (M^+), 213, 186.

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