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2-METHOXY-4-(*E*-3-METHYLOXIRANYL)PHENYL AND 4-METHOXY-2-(*E*-3-METHYLOXIRANYL)PHENYL 2-ENOATES

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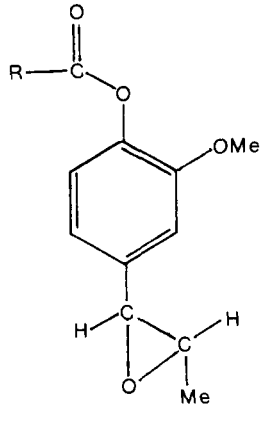
The *E*- and *Z*-2-methyl-2-butenoate esters obtained from the essential oils of *Pimpinella saxifraga* L. (1) and *Ligusticum micronatum* Hort. (2), originally identified as **1a** and **1b**, were recently shown to have the isomeric 4-methoxy-2-(*E*-3-methyloxiranyl)phenyl structures **2a** and **2b** (3,4). These and other 2-enoates of oxiranylphenols are subject to both nucleophilic addition at C-3 of the ester function and nucleophilic substitution at the epoxide carbons, particularly at the benzylic position. They, thus, constitute a so far uninvestigated class of dialkylating agents.

m-Chloroperbenzoic acid has been used to prepare the acetate esters **1** and **2**, R=CH_3, in isolated yields of over



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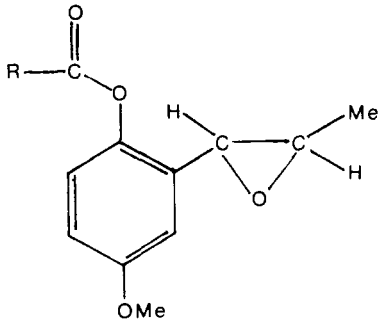

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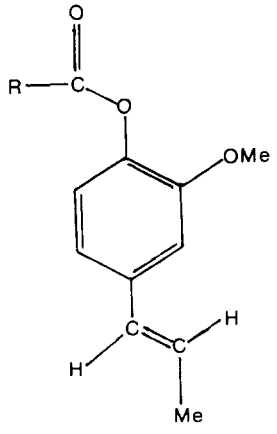

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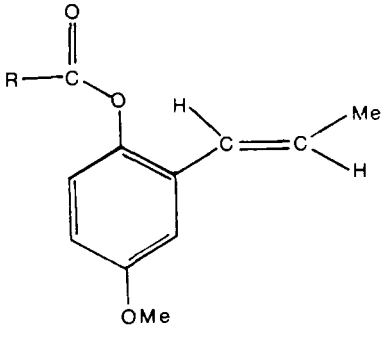

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a R=C(Me)$\overset{E}{=}$CHMe **b** R=C(Me)$\overset{Z}{=}$CHMe **c** R=CH=CHMe

70% from the corresponding (*E*)-1-propenylphenyl esters **3** and **4** (4), and the isobutyrate esters **1** and **2**, R=CH(CH_3)$_2$, have also been prepared by the same route (3). Extension of the use of *m*-chloroperbenzoic acid in the preparation of 2-enoate esters such as **1a** by selective epoxidation seemed feasible because the electrophilic reagent could be expected to show a greater difference in reactivity toward the competing 1-propenyl double bond and the electron-poor double bond of the ester function than it does toward the two double bonds of limonene, i.e., >30:1 (5).

Expected selectivity was first tested and realized with the crotonate esters **3c** and **4c** which were prepared from crotonyl chloride and the sodium phenolates in THF. Epoxidation gave **1c** and **2c** cleanly in isolated yields of 95 and 89%. The (*E*)-2-methyl-2-butenoate (tiglate) esters **1a-4a** were prepared similarly from commercial tiglic acid. The (*Z*)-2-methyl-2-butenoic (angelic) acid needed for the remaining esters was synthesized from the commercial 15% (*E*): 85% (*Z*) mixture of 2-bromobutene by an extension of Neumann and Seebach's method (6), which involves stereospecific lithiation with *t*-butyllithium at −110°, followed by carbonation. The angelic acid-rich mixture was neutralized with alcoholic KOH; the salt that resulted was dried and treated with oxalyl chloride, and the crude acid chloride was used directly. The angelates **3b** and **4b** were separated from the isomeric tiglates by chromatography on Si gel. The ir, ms, ^{1}H-, and ^{13}C-nmr spectra of the synthetic angelate were indistinguishable from those of (+)-**2b** obtained from *Pimpinella diversifolia* (4).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were taken with a Buchi melting point apparatus and are corrected. Boiling points are uncorrected. Product purity was determined with a Varian 3700 gas chromatograph controlled by a CDS 111 microprocessor; a 50-m×0.24-mm i.d. fused silica column coated with bonded methyl (5% phenyl) was used with an FID with He as carrier gas at 13 psi. A 25-cm×9-mm 10μ Chromasil column was used for semipreparative hplc; the mobile phase was hexane-Et_2O (75:25). Si gel, 230-400 mesh, from Sigma Chemical Co. was used as the stationary phase for column chromatography. Ir spectra were obtained with a Beckman Acculab 4 using thin film for liquids and KBr pellets for solids. ^{13}C- and ^{1}H-nmr spectra were obtained with NT-200 and NT-360 spectrometers at the University of California, Davis, NMR Facility. High resolution eims at 70 eV were obtained with a VG Analytical ZAB-HS mass spectrometer at the Mass Spectrometry Laboratory, University of California, Davis. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley. 2-Methoxy-4-(*E*-1-propenyl)phenol was obtained by fractional distillation of commercial isoeugenol from Aldrich Chemical Company. 4-Methoxy-2-(*E*-1-propenyl)phenol was prepared as described earlier (4).

PREPARATION OF OXIRANYLPHENYL ESTERS **1** AND **2**.—A solution of 10 mmol of the phenyl ester **3** or **4** in 30 ml CH_2Cl_2 was placed in a dried, 100-ml, three-neck flask equipped with a magnetic stirring bar and fitted with a thermometer and a 60-ml addition funnel protected with a $CaCl_2$ drying tube. The flask was cooled with an ice-salt bath, and when the temperature of the ester solution reached 0°, 11 mmoles of *m*-chloroperbenzoic acid (ca. 85% purity, Aldrich Chemical Co.) in 30 ml CH_2Cl_2 was added dropwise with stirring. After the addition, the stirred mixture was maintained at ca. 2° for 3 h and then allowed to warm to room temperature. The progress of the reaction was monitored by following the disappearance of **1** or **2** on a Si gel tlc plate using hexane-Et_2O (70:30) as the developer; reactions were usually complete within 12 h. The reaction mixture was filtered, and the precipitate was washed with 20 ml CH_2Cl_2. The filtrates were combined, washed successively with saturated $NaHCO_3$ solution (1×15 ml), saturated NaCl (2×15 ml), 10% Na_2SO_3 (2×15 ml), saturated $NaHCO_3$ (2×15 ml) and saturated NaCl (2×15 ml), and dried with $MgSO_4$. Filtration followed by removal of the solvent with a Rotovap at 40-45° gave the crude epoxidation product, which was purified by chromatography on Si gel with hexane-Et_2O (80:20). In all cases, the Rf of the product was less than that of the starting ester. The products were 90-99% pure. When necessary, final purification was done by semipreparative hplc. Liquid products were not subjected to distillation. Yields and properties of the products are given in Tables 1 and 2.

PREPARATION OF (*E*)-1-PROPENYLPHENYL ESTERS **3** AND **4**.—Anhydrous THF (25 ml) was added to a dried, 100-ml, three-neck flask

TABLE 1. Oxiranylphenyl Esters and (1-Propenyl)phenyl Esters Prepared

Product	Yield[a] [%]	mp or (bp/torr)	Molecular formula[b]	ms *m/z*, obs. (*m/z*, calc.)	ir ν[cm^{-1}]
1a	78		$C_{15}H_{18}O_4$	262.1205 (262.1205)	1760, 1670
1b	83	37-39°	$C_{15}H_{18}O_4$	262.1190 (262.1205)	1750, 1660
1c	95	54-56°	$C_{14}H_{16}O_4$	248.1037 (248.1049)	1760, 1660
2a	81		$C_{15}H_{18}O_4$	262.1214 (262.1205)	1750, 1670
2b	79		$C_{15}H_{18}O_4$	262.1206 (262.1205)	1750, 1660
2c	89	63-64°	$C_{14}H_{16}O_4$	248.1042 (248.1049)	1760, 1670
3a	81	50-51°	$C_{15}H_{18}O_3$	246.1262 (246.1256)	1730, 1660
3b	51	114-115°/0.1	$C_{15}H_{18}O_3$	246.1262 (246.1256)	1750, 1660
3c	82	68-69°	$C_{14}H_{16}O_3$	232.1100 (232.1100)	1760, 1670
4a	95	118-120°/0.08	$C_{15}H_{18}O_3$	246.1257 (246.1256)	1740, 1660
4b	73	112-113°/0.1	$C_{15}H_{18}O_3$	246.1273 (246.1256)	1750, 1660
4c	92	114-116°/0.08	$C_{14}H_{16}O_3$	232.1104 (232.1100)	1750, 1670

[a]Yields refer to isolated products with satisfactory elemental analyses.
[b]Satisfactory microanalyses were obtained: C±0.13, H±0.12; exceptions **3c**, H-0.20; **4b**, C-0.28.

equipped with a magnetic stirring bar and fitted with a thermometer, a N_2 inlet tube, and a 60-ml addition funnel protected with a $CaCl_2$ tube. NaH (22 mmol) was added to the flask, stirring was started, and the suspension was cooled to 5° with an ice-salt bath. A solution of 20 mmol of the phenol in 15 ml of THF was added dropwise, and, after about 0.5 h, a solution of 22 mmol of the acid chloride in 25 ml THF was added dropwise while maintaining the temperature at 5°. The reaction mixture was allowed to warm to room temperature in 3 h, and it was then poured *with caution* on 200 g of crushed ice. The pH of the aqueous phase was adjusted to ca. 12, and it was extracted with Et_2O (3×75 ml). The Et_2O extracts were combined, washed with saturated NaCl (3×25 ml), and dried with $MgSO_4$. Filtration followed by removal of the solvent with a Rotovap at 40-45° gave the crude ester. Solid esters were purified by crystallization from hexane; liquid esters were chromatographed on Si gel with hexane-Et_2O (80:20) and then distilled at reduced pressure. Yields given in Table 1, together with physical properties, are of esters of analytical purity.

PREPARATION OF ACID CHLORIDES.—Crotonyl chloride was prepared from the commercial acid and benzoyl chloride (7). Tiglyl and angelyl chloride were prepared from the acids by treating their dry potassium salts with oxalyl chloride (8).

Angelic acid was synthesized as an 88:12 mixture with tiglic acid by an extension of a procedure of Neumann and Seebach (6). Freshly distilled commercial 2-bromo-2-butene (85% *Z*; 10.8 g, 0.08 mol) was treated with 0.16 mol of *t*-BuLi at −100° exactly as described (6), and after stirring at −100° for 1 h, the mixture was allowed to warm to −80° in 30 min and then treated with an excess of dry CO_2 gas. The reaction mixture and cooling bath were allowed to warm slowly to room temperature, and the reaction mixture was then added to a separatory funnel containing 100 ml of saturated NaCl solution. The aqueous phase was made acidic with saturated $NaHSO_4$ solution and extracted with CH_2Cl_2 (3×50 ml). The combined extracts were washed with saturated $NaHCO_3$ (3×100 ml), and the combined washings were extracted with CH_2Cl_2, made acidic with saturated $NaHSO_4$, and extracted with CH_2Cl_2 (4×50 ml). The CH_2Cl_2 extracts of the acidic solution were combined, dried ($MgSO_4$), and concentrated with a rotary film evaporator.

TABLE 2. NMR Data ($CDCl_3$) for Oxiranylphenyl Esters

Product	^{1}H-nmr[a] δ (ppm)	^{13}C-nmr[b] δ (ppm)
1a	7.11 (q, q, J=7.1, 1.4 Hz, $C_{3'}$-H), 1.95 (m, $C_{2'}$-CH_3, 1.88 (d, q, J=7.1, 1.1 Hz, $C_{4'}H_3$)	165.4 (C=O), 138.8 ($C_{3'}$), 127.4 ($C_{2'}$), 14.7 ($C_{2'}$-CH_3), 12.4 ($C_{4'}H_3$)
1b	6.22 (q, q, J=6.1, 1.6 Hz, $C_{3'}$-H), 2.06 (d, J=6.1 Hz, $C_{4'}H_3$), 2.05 (d, J=1.6 Hz, $C_{2'}$-CH_3)	165.3 (C=O), 139.4 ($C_{3'}$), 126.8 ($C_{2'}$), 20.8, ($C_{2'}$-CH_3), 15.8 ($C_{4'}H_3$)
1c	7.18 (d, q, J=15.5, 6.9 Hz, $C_{3'}$-H), 6.07 (d, q, J=15.5, 1.7 Hz, $C_{2'}$-H), 1.96 (d, d, J=6.9, 1.7 Hz, $C_{4'}H_3$)	163.8 (C=O), 146.6 ($C_{3'}$), 121.3 ($C_{2'}$), 18.4 ($C_{4'}H_3$)
2a	7.13 (q, q, J=7.1, 1.3 Hz, $C_{3'}$-H), 1.96 (m, $C_{2'}$-CH_3), 1.90 (d, q, J=7.1, 0.8 Hz, $C_{4'}H_3$)	165.8 (C=O), 139.0 ($C_{3'}$), 127.4 ($C_{2'}$), 20.7 ($C_{2'}$-CH_3), 16.0 ($C_{4'}H_3$)
2b	6.28 (q, q, J=7.1, 1.6 Hz, $C_{3'}$-H), 2.08 (d, J=7.1 Hz, $C_{4'}H_3$), 2.06 (m, $C_{2'}$-CH_3)	166.1 (C=O), 141.0 ($C_{3'}$), 126.8 ($C_{2'}$), 14.8 ($C_{2'}$-CH_3), 12.4 ($C_{4'}H_3$)
2c	7.20 (d, q, J=15.5, 6.9 Hz, $C_{3'}$-H), 6.07 (d, q, J=15.5, 1.7 Hz, $C_{2'}$-H), 1.98 (d, d, J=6.9, 1.7 Hz, $C_{4'}H_3$)	164.7 (C=O), 147.1 ($C_{3'}$), 121.4 ($C_{2'}$), 18.2 ($C_{4'}H_3$)

[a]Common to **1a-c** (±0.01): δ 7.01 (C_6-H), 6.88 (C_5-H), 6.83 (C_3-H), 3.81 (OCH_3), 3.58 ($C_{1''}$-H), 3.00 ($C_{3''}$-H) and 1.45 ppm ($C_{3''}$-CH_3), $J_{3,5}$ 1.80±0.05 Hz, $J_{5,6}$ 8.07±0.02 Hz, $J_{1''\text{-}3''}$ 2.00±0.02 Hz, $J_{3''\text{-}CH3}$ 5.13±0.02 Hz. Common to **2a-c** (±0.01); δ 6.98 (C_6-H), 6.81 (C_5-H), 6.77 (C_3-H), 3.78 (OCH_3), 3.59 ($C_{1''}$-H), 2.92 ($C_{3''}$-H), 1.39 ppm ($C_{3''}$-CH_3), $J_{3,5}$ 3.05±0.01 Hz, $J_{5,6}$ 8.75±0.01 Hz, $J_{1''\text{-}3''}$ 2.03 ±0.03 Hz, $J_{3'}$-CH_3 5.12 Hz.

[b]Common to **1a-c** (±0.1 unless noted otherwise): δ 151.0 (C_2), 139.2±0.2 (C_1), 136.1 (C_4), 122.4±0.2 (C_6), 117.6 (C_5), 108.7 (C_3), 59.2 and 59.1 ($C_{2''}$ and $C_{3''}$), 55.9 (OCH_3) and 17.9 ppm ($C_{3''}$-CH_3). Common to **2a-c**: δ 157.4±0.2 (C_4), 142.4 (C_1), 131.1±0.2 (C_2), 122.7 (C_6), 114.1±0.2 (C_5), 109.8 (C_3), 58.3 and 55.5 ($C_{2''}$ and $C_{3''}$), 55.3±0.2 (CH_3O) and 17.8 ppm ($C_{3''}$-CH_3).

The residual pale yellow oil weighed 6.2 g, and gc analysis indicated that it was an 8:78:14 mixture of pivalic, angelic, and tiglic acids. This corresponds to a 72% yield of angelic and tiglic acids. The mixture was fractionated with a spinning band column. The fraction with bp <117° was essentially pure pivalic acid. The fraction with bp 117-118° consisted of 88% angelic acid: 12% tiglic acid and was used for preparation of **1b** and **2b**.

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