SYNTHESIS OF 3-HYDROXY-3-(HYDROXYMETHYL)-5-METHYL-1,2-CYCLOHEXANEDIONE, A HYDROLYTIC PRODUCT OF LEUCOGENENOL*

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ABSTRACT

One of the hydrolytic products of leucogenenol was synthesized, thereby confirming a part of its structure.

The monoethoxy derivative of 5-methyl-1,3-cyclohexanedione was reduced with lithium aluminum hydride to 5-methyl-2-cyclohexen-1-one (**2**), which was then hydroxylated with permanganate, and the product condensed with acetone to yield the 2,3-*O*-isopropylidene derivative (**3**) of 2,3-dihydroxy-5-methylcyclohexanone; this was treated with diazomethane to form the corresponding 3-oxirane (**4**) of the 1,2-isopropylidene acetal of 5-methyl-1,2-cyclohexanediol. The oxirane ring was hydrolyzed in the presence of alkali to yield the 1,2-*O*-isopropylidene derivative of 3-(hydroxymethyl)-5-methyl-1,2,3-cyclohexanetriol, which formed a diacetate and a dibenzoate, both of which showed four compounds in t.l.c. and g.l.c. Two of the components of the diacetates and dibenzoates had the same retention times and R_F values as the corresponding derivatives obtained by the reduction and condensation with acetone of the diacetoxy and dibenzoxy derivatives from the dione isolated from leucogenenol.

In addition, the 1,2-isopropylidene acetal of 3-acetoxy-3-(acetoxymethyl)- and 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol prepared from the dione isolated from leucogenenol had i.r. and n.m.r. spectra that were indistinguishable from the spectra of the corresponding synthetic compounds having the same R_F values. Oxidation, with ammonium vanadate in dilute sulfuric acid, of a mixture of two of the isomers of synthetic 3-acetoxy-3-(acetoxymethyl)- and 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol yielded diones whose i.r. and n.m.r. spectra, and m.p. of the bis(phenylhydrazone) of the benzoxy derivative, were indistinguishable from those of the corresponding derivatives of the dione prepared from leucogenenol.

INTRODUCTION

Leucogenenol, isolated from the metabolic products of *Penicilium gilmanii*[1] and from bovine and human liver[2], increases the maturation rate of the precursors

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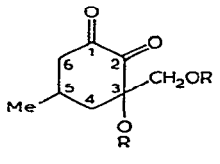
of peripheral leukocytes[3–5]. One of the compounds that leucogenenol, namely, 2-(1,2-dihydroxy-3-methyl-5-oxocyclohexyl)-3,11-dihydroxy-11-(hydroxymethyl)-9-methyl-1-oxa-5-azaspiro[5.5]undeca-2,4-dien-7-one[6], yields on hydrolysis is 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione[6] (**1a**), the structure of which was deduced from its i.r., u.v., and n.m.r. spectra, together with its oxidation with periodate to carbon dioxide, formaldehyde, and 3-methylglutaric acid. In view of the biological importance of leucogenenol, it was of interest to synthesize **1a** for (*a*) comparison with one of the products obtained on hydrolysis of leucogenenol, and (*b*) use as an intermediate for the projected synthesis of leucogenenol.

DISCUSSION

Ethyl crotonate was condensed with ethyl acetoacetate in the presence of sodium as described by Crossley and Renouf[7], to yield 5-methyl-1,3-cyclohexanedione, which was then treated with ethanol in the presence of Amberlyst-15 (H^+) resin to form the monoethoxy derivative; this was reduced with lithium aluminum hydride to 5-methyl-2-cyclohexen-1-one (**2**) as described by Blanchard and Goering[8]. Compound **2** was hydroxylated with permanganate, and the product was condensed with acetone, to yield a mixture of isomers of the 2,3-*O*-isopropylidene derivative of 2,3-dihydroxy-5-methylcyclohexan-1-one (**3**), which was treated with diazomethane[9] to yield the 1,2-isopropylidene acetals of the 3-oxirane (**4**) of the isomers of 1,2-dihydroxy-5-methylcyclohexane having *cis*-hydroxyl groups (DL-*erythro*). The oxirane ring was opened by hydrolysis in the presence of alkali, to yield the 1,2-isopropylidene acetal of the isomers of 3-(hydroxymethyl)-5-methylcyclohexane-1,2,3-triol (**5a**), of which both the diacetate (**5b**) and dibenzoate (**5c**) showed, by g.l.c. and t.l.c., four components from the compounds having *cis*-hydroxyl groups.



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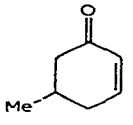

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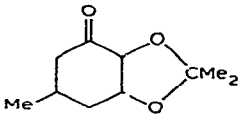

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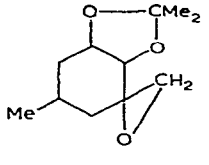

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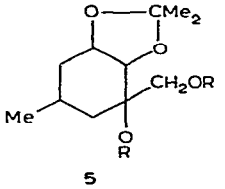

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a, R = H
b, R = Ac
c, R = Bz

For comparison with the synthetic products, the diacetate and the dibenzoate of the 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione isolated from leucogenenol[6] were reduced with sodium borohydride, and the portion of the resulting diols that condensed with acetone (the *cis* diols) was isolated as a mixture of isopro-

pylidene acetals. G.l.c. and t.l.c. showed that the diacetate and the dibenzoate each consisted of two isomers whose retention times and R_F values were the same as those for the corresponding derivatives of the synthetic 3-(hydroxymethyl)-5-methylcyclohexane-1,2,3-triol. The isomers from the synthetic 1,2-isopropylidene acetals of the 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanediol and the 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol were separated by chromatography, and their i.r. and n.m.r. spectra were found indistinguishable from those of the corresponding derivatives prepared from leucogenenol.

The two isomers of the 1,2-isopropylidene acetal of the 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanediol and of the 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol were treated with ammonium vanadate in aqueous sulfuric acid to (*a*) remove the isopropylidene moiety, and (*b*) oxidize the diol liberated to the dione. The i.r. and n.m.r. spectra of the resulting 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanedione and 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanedione were indistinguishable from those of the corresponding derivatives prepared from the 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione isolated from leucogenenol[6]. The results confirm the structure of one of the cyclohexane moieties of leucogenenol.

EXPERIMENTAL

Melting points were determined with a Kofler micro-apparatus and are uncorrected. I.r., n.m.r., and mass spectra were measured with a Beckman IR-8 i.r. spectrometer, Varian A 60 n.m.r. spectrometer, and LKB (Type 9000) gas chromatograph–mass spectrometer, respectively. A P and M Model 700 Laboratory Chromatograph (manufactured by Hewlett-Packard, Avondale, Pa.) was used for gas–liquid chromatography. A coiled-glass column (5 ft × 0.08 in. i. d.) was packed with 3% OV-17 on Gas-Chrom Q (80–100 mesh). Nitrogen was used as the carrier gas, with a flow rate of 40 ml.min^{-1}. Silica gel (Research Specialities Co., Richmont, Calif.) containing zinc silicate (250 mg/30 g) was used for t.l.c.; the developed chromatoplates were examined under ultraviolet light and then after exposure to iodine vapor. Silicic acid (E. Merck, 325 mesh) was used for preparative chromatography.

5-Methyl-2-cyclohexen-1-one (**2**). — Condensation of ethyl crotonate with ethyl acetoacetate in the presence of sodium, as described by Crossley and Renouf[7], yielded 5-methyl-1,3-cyclohexanedione, m.p. 127° (lit.[7] m.p. 128°); δ ($CDCl_3$): 1.15 (3 H, doublet, J 6 Hz, CH_3CH), 2.3 (4 H, multiplet, 2 CH_2), 2.6 (1 H, multiplet, CH_3CH), 3.4 (1 H, singlet, OH), and 5.52 (1 H, singlet, $=CH-$); M^+ *m/e* 126.

This compound (10 g) was dissolved in 1:1 absolute ethanol–benzene (400 ml), Amberlyst-15 (H^+) ion-exchange resin (1 g) was added, and the mixture was boiled overnight under reflux in a Soxhlet extractor, the thimble of which contained anhydrous sodium sulfate (250 g). The mixture was then filtered, the filtrate evaporated to dryness under diminished pressure at 40° (bath temp.), and the residue distilled at 80–83°/0.1 torr to yield 3-ethoxy-5-methyl-2-cyclohexen-1-one (~10 g); δ ($CDCl_3$):

1.15 (3 H, doublet, J 6 Hz, CH_3CH), 1.4 (3 H, triplet, J 8 Hz, CH_3CH_2O–), 2.35 (4 H, multiplet, 2 $-CH_2-$), 2.6 (1 H, multiplet, CH_3CH), 4.0 (2 H, quartet, J 8 Hz, CH_3CH_2O–), and 5.5 (1 H, singlet, =CH–). The m.p. of the monohydrate (from aqueous acetone) was 40° (lit.[7] m.p. 42–43°).

On reduction with lithium aluminum hydride (3 g) in ether (100 ml), this ketone (10 g) yielded, after distillation at 40°/0.1 torr, ~6 g of compound **2**; λ_{max}^{EtOH} 272 nm (log ε, 4.0); δ ($CDCl_3$): 1.15 (3 H, doublet, J 6 Hz, CH_3CH), 2.3 (4 H, multiplet, 2 $-CH_2-$), 2.7 (1 H, multiplet, CH_3CH), 5.7 (1 H, doublet, J 2 Hz, COCH= =CH–), and 6.9 (1 H, quartet, COCH=CH–); M^+ m/e 110; (2,4-dinitrophenyl)-hydrazone, m.p. 150° (lit.[8] m.p. 152°); semicarbazone, m.p. 175° (lit.[8] m.p. 177°).

2,3-O-Isopropylidene derivative (**3**) *of 2,3-dihydroxy-5-methylcyclohexanone.* — A solution of compound **2** (5 g) in 1:1 (v/v) *p*-dioxane–water (20 ml) was cooled to −15°, and a solution of potassium permanganate (7.2 g) in water (275 ml) was added in milliliter quantities during 6 h, while hydroxide ions were continuously neutralized by bubbling carbon dioxide through the solution. The suspension was filtered, the filtrate was evaporated to dryness under diminished pressure at 40° (bath temp.), the residue was dissolved in anhydrous acetone (500 ml), and anhydrous copper(II) sulfate (10 g) was added. After being kept for two days at room temperature with occasional stirring, the mixture was filtered, the filtrate was evaporated to dryness under diminished pressure at 40° (bath temp.), and the product was distilled at 50°/0.05 torr, to yield compound **3**; weight, ~5 g; M^+ m/e 184; δ ($CDCl_3$): 1.15 (3 H, doublet, J 6 Hz, CH_3CH), 1.35 (6 H, 3 singlets, CMe_2), 2.2 (2 H, doublet, J 5 Hz, $-CH_2CO-$), 2.3 (2 H, multiplet, $-CH_2-$), 3.7 (1 H, multiplet, CH_3CH), 3.95 (1 H, doublet, J 7 Hz, CHO–), and 4.2 (1 H, multiplet, CHO–).

Anal. Calc. for $C_{10}H_{16}O_3$: C, 65.3; H, 8.8. Found: C, 65.2; H, 8.6.

1,2-O-Isopropylidene derivative (**4**) *of the 3-oxirane of 5-methyl-1,2-cyclohexanediol.* — A solution of compound **3** (1 g) in ether (10 ml) was cooled to 0°, treated with diazomethane (0.5 g) dissolved in ether (200 ml), and kept overnight[9]. The suspension was then filtered, the filtrate evaporated to dryness, and the product distilled at 50°/0.01 torr, to yield compound **4**; weight ~1 g; M^+ m/e 198; δ ($CDCl_3$): 1.1 (3 H, doublet, J 6 Hz, CH_3CH), 1.4 (6 H, 2 singlets, CMe_2), 2.3 (4 H, multiplet, $-CH_2-$), 2.65 (2 H, singlet, CHO–), 3.5 (1 H, multiplet, CHO–), 3.6 (1 H, multiplet, CH_3CH), and 3.7 (1 H, doublet, CHO–).

Anal. Calc. for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.5; H, 9.2.

1,2-O-Isopropylidene derivative (**5a**) *of 3-(hydroxymethyl)-5-methyl-1,2,3-cyclohexanetriol.* — To a solution of compound **4** (1 g) in a mixture of *p*-dioxane (5 ml) and water (5 ml) was added sodium hydroxide (0.1M, 0.1 ml), and the solution was heated to boiling for ~1 min and then kept overnight at room temperature. The solution was then neutralized with carbon dioxide, the suspension filtered, and the filtrate evaporated to dryness under diminished pressure at 40° (bath temp.). T.l.c. on silica gel with ether showed four components, the isomers of the 1,2-isopropylidene acetals of 3-(hydroxymethyl)-5-methyl-1,2,3-cyclohexanetriol; M^+ m/e 216; δ ($CDCl_3$): 1.1 (3 H, doublet, J 6 Hz, CH_3CH), 1.35 (6 H, 4 singlets, CMe_2), 2.3 (4 H, multiplet,

–CH_2–), 3.5 (2 H, doublet, J 3 Hz, CH_2O–), 3.7 (1 H, multiplet, CH_3CH), 3.95 (1 H, doublet, J 7 Hz, CHO–), and 4.2 (1 H, multiplet, CHO–).

1,2-O-Isopropylidene derivative (**5b**) *of 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanediol.* — Acetic anhydride (0.3 ml) was added to a solution of compound **5a** (0.4 g) in pyridine (0.4 ml), cooled to 0°, and the solution was kept overnight at 4°. The solution was then poured into ice–water (50 ml), made neutral with sodium hydrogen carbonate, and extracted with ten 10-ml portions of dichloromethane. Pyridine was removed from the combined extracts with 50% aqueous cadmium chloride, and the solution was then dried (sodium sulfate), and evaporated to dryness under diminished pressure at 40° (bath temp.), to yield a semicrystalline mass (~1 g). G.l.c. showed the presence of four compounds that appeared at 135, 150, 162, and 170° when the temperature was programmed at 10°/min from 40 to 260°. T.l.c. (silica gel, ether) also showed four compounds; their R_F values were 0.77, 0.60, 0.48, and 0.24. The compounds having R_F 0.77 and 0.60 were separated as one fraction on a column (2 × 20 cm) of silicic acid by using ~50 ml of ether; δ ($CDCl_3$): 1.1 (3 H, doublet, J 6 Hz, CH_3CH), 1.25 (3 H, singlet, CMe_2), 1.35 (3 H, singlet, CMe_2), 2.05 (3 H, singlet, O*Ac*), 2.14 (3 H, singlet, O*Ac*), 2.4 (4 H, multiplet, 2 –CH_2–), 3.75 (1 H, multiplet, CH_3CH), 3.8 (1 H, multiplet, CHO–), 3.9 (1 H, doublet, J 7 Hz, CHO–), and 5.3 (2 H, doublet, J 3 Hz, CH_2O–); ν_{max}^{film} 2959s, 2941s, 2874m, 1745s, 1724m, 1653m, 1608m, 1460w, 1374s, 1250s, 1235s, 1220s, 1205s, 1093m, 1053m, and 952m cm^{-1}.

Anal. Calc. for $C_{15}H_{24}O_6$: C, 60.0; H, 8.0. Found: C, 59.9; H, 8.1.

1,2-O-Isopropylidene derivative (**5c**) *of 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol.* — Benzoyl chloride (0.2 ml) was added to a cooled (0°) solution of compound **5a** (0.5 g) in pyridine (0.5 ml), and the solution was kept overnight at 4°, poured into ice–water (50 ml), made neutral with sodium hydrogen carbonate, and extracted with benzene (10 × 5 ml). The extracts were combined, dried (sodium sulfate), and evaporated to dryness under diminished pressure at 40° (bath temp.), to yield a semicrystalline mass. G.l.c. showed the presence of four compounds that appeared at 120, 190, 200 and 212° when the temperature was programmed at 10°/min from 40 to 260°. T.l.c. on silica gel, with ether, also showed four compounds; their R_F values were 0.86, 0.78, 0.45, and 0.28. The compounds having R_F 0.86 and 0.78 were separated as a single fraction by chromatography on a column (2 × 20 cm) of silicic acid (ether); wt. ~200 mg; δ ($CDCl_3$): 1.1 (3 H, doublet, J 6 Hz, CH_3CH), 1.25 (3 H, singlet, CMe_2), 1.35 (3 H, singlet, CMe_2), 2.4 (4 H, multiplet, 2 –CH_2–), 3.45 (1 H, doublet, CHO–), 3.65 (1 H, multiplet, CHO–), 5.8 (2 H, doublet, J 3 Hz, CH_2O–), 7.5 (5 H, multiplet, Bz), and 8.0 (5 H, multiplet, Bz); ν_{max}^{film} 3067m, 3030m, 2959m, 2924m, 2874m, 1786m, 1724s, 1695sh, 1600m, 1449s, 1316s, 1282s, 1212s, 1176s, 1111s, 1099s, 1070m, 1020m, 952m, and 709s cm^{-1}.

Anal. Calc. for $C_{25}H_{28}O_6$: C, 70.7; H, 6.7. Found: C, 70.1; H, 6.5.

Reduction of the 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanedione from leucogenenol. — The diacetate of the 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione (50 mg) isolated from leucogenenol[6] was dissolved in methyl

alcohol (1 ml), and reduced with sodium borohydride (10 mg) at 0°. After 10 min, the solution was acidified with acetic acid (0.1 ml), and evaporated to dryness under diminished pressure at 40° (bath temp.). The residue was extracted with anhydrous acetone (10 ml), and the extract filtered, the filtrate evaporated to dryness, and the residue redissolved in acetone (20 ml). To the solution was added anhydrous copper(II) sulfate (1 g), and after 4 days at room temperature, the suspension was filtered, the filtrate was evaporated to dryness under diminished pressure, and the residue dissolved in ether (20 ml). The solution was washed with water (2 × 2 ml), dried (sodium sulfate), and passed through a column (2 × 10 cm) of silicic acid (to remove compounds that had not condensed with acetone). The column was washed with ether (50 ml), and this eluate was evaporated to dryness, to yield ~20 mg of the two isomers of the 1,2-isopropylidene acetal of 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanediol. T.l.c. showed two compounds on silica gel (ether) having R_F values of 0.77 and 0.60. The n.m.r. and i.r. spectra were indistinguishable from the corresponding spectra of the mixture of the two isomers that were separated from the synthetic 1,2-isopropylidene acetal of 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanediol, having R_F values of 0.77 and 0.60.

Anal. Calc. for $C_{15}H_{24}O_6$: C, 60.0; H, 8.0. Found: C, 59.9; H, 8.1.

Reduction of the 1-benzoxy-1-(benzoxymethyl)-5-methyl-2,3-cyclohexanedione obtained from leucogenenol. — The dibenzoate of the 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione (50 mg) isolated from leucogenenol[6] was reduced with sodium borohydride, and the product condensed with acetone in the same way as for the diacetate. T.l.c. on silica gel (ether) showed two isomers, having R_F values of 0.86 and 0.78. The mixture had the same i.r. and n.m.r. spectra as the mixture of isomers obtained from the synthetic 1,2-isopropylidene acetal of 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol, having R_F values of 0.86 and 0.78.

Anal. Calc. for $C_{25}H_{28}O_6$: C, 70.7; H, 6.7. Found: C, 70.5; H, 6.7.

Oxidation of the 1,2-O-isopropylidene derivative (**5b**) *of 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanediol with ammonium vanadate, to 3-acetoxy-3-(acetoxymethyl)-5-methyl-1,2-cyclohexanedione* (**1b**). — The isomers of **5b** having R_F 0.77 and 0.60 (100 mg) were dissolved in a mixture of *p*-dioxane (1 ml) and water (0.5 ml). The isopropylidene group was removed, and the resulting diol oxidized to the dione, by adding to this solution ammonium vanadate (80 mg) dissolved in 0.1M sulfuric acid (20 ml). After 2 h at room temperature, the solution was extracted with dichloromethane (10 × 5 ml); the extracts were combined, shaken with saturated aqueous sodium hydrogen carbonate solution, dried (sodium sulfate), and evaporated to dryness, to yield a semicrystalline mass (~100 mg), whose i.r. and n.m.r. spectra were indistinguishable from those of the diacetate of the 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione isolated from leucogenenol[6]: ν_{max}^{film} 2959m, 2924m, 2874w, 1724s, 1695sh, 1600w, 1429w, 1370m, 1235s, 1212s, and 1163m cm^{-1}; δ ($CDCl_3$): 1.20 (3 H, doublet, J 7 Hz, CH_3CH), 2.02 (3 H, singlet, CO*Ac*), 2.08 (3 H, singlet, CO*Ac*), 2.6 to 4.0 (5 H, multiplet, 2 $-CH_2-$ and CH_3CH), and 4.2 (2 H, singlet, CH_2O-).

Oxidation of the 1,2-O-isopropylidene derivative (**5c**) *of 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanediol with ammonium vanadate, to 3-benzoxy-3-(benzoxymethyl)-5-methyl-1,2-cyclohexanedione* (**1c**). — The isomers of **5c** having R_F values of 0.86 and 0.78 (100 mg) were dissolved in a mixture of *p*-dioxane (2 ml) and water (0.5 ml). The isopropylidene group was removed, and the resulting diol oxidized to the dione, by adding to this solution a solution of ammonium vanadate (60 mg) in 0.1M sulfuric acid (20 ml). After 2 h at room temperature, the solution was extracted with benzene (10 × 5 ml); the extracts were combined, and shaken with saturated aqueous sodium hydrogen carbonate solution, dried (sodium sulfate), and evaporated to dryness, to yield a semicrystalline mass (100 mg) whose i.r. and n.m.r. spectra were indistinguishable from those of the dibenzoate of the 3-hydroxy-3-(hydroxymethyl)-5-methyl-1,2-cyclohexanedione isolated from leucogenenol[6]. Bis(phenylhydrazone), m.p. 164° (lit.[6] m.p. 164°); λ_{max}^{EtOH} 239 nm (ε_{mM} 65), 274 nm (ε_{mM} 45), identical with that of the corresponding derivative prepared from the dione isolated from leucogenenol; δ ($CDCl_3$): 1.2 (3 H, doublet, *J* 7 Hz, CH_3CH), 2.6 to 3.9 (5 H, multiplet, 2 $-CH_2-$ and CH_3 C*H*), 5.4 (2 H, doublet, *J* 3 Hz, CH_2O-), 7.4 (5 H, multiplet, Bz), and 7.9 (5 H, multiplet, Bz); ν_{max}^{film} 2959sh, 2924s, 2857s, 1724s, 1695sh, 1681sh, 1613w, 1449m, 1316w, 1258s, 1212s, 1176m, 1111s, and 706s cm^{-1}.

Anal. Calc. for $C_{22}H_{18}O_6$: C, 58.9; H, 6.5. Found, C, 59.0; H, 6.6.

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