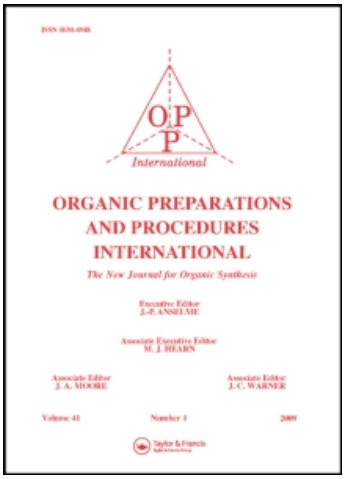

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THE SYNTHESES OF PHENOLIC ANTIOXIDANTS. 1,3,5-TRIS(4-HYDROXYPHENOXYMETHYL)MESITYLENE AND RELATED COMPOUNDS

Luke K. T. Lam[a]; Chester Yee[a]; Ramdas P. Pai[a]; Lee W. Wattenberg[a]
[a] Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota

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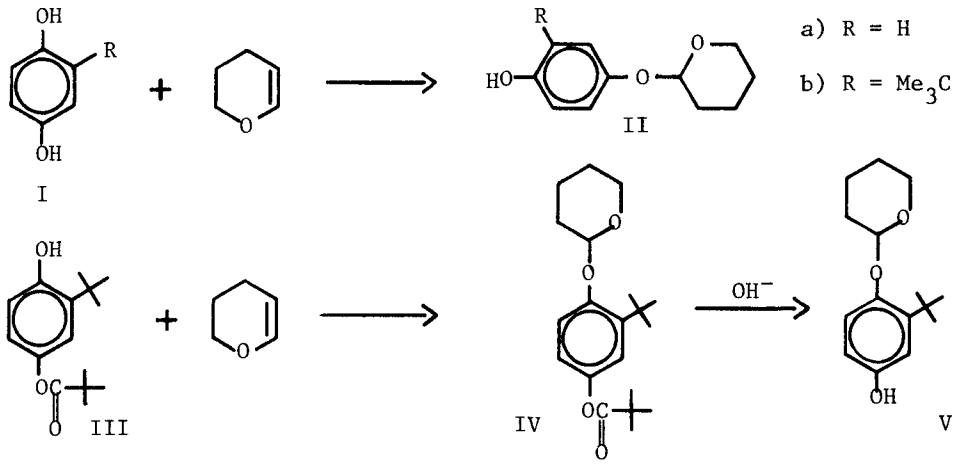
THE SYNTHESES OF PHENOLIC ANTIOXIDANTS. 1,3,5-TRIS(4-HYDROXYPHENOXYMETHYL)MESITYLENE AND RELATED COMPOUNDS

Luke K. T. Lam*, Chester Yee, Ramdas P. Pai

and Lee W. Wattenberg

Department of Laboratory Medicine and Pathology
University of Minnesota Medical School
Minneapolis, Minnesota 55455

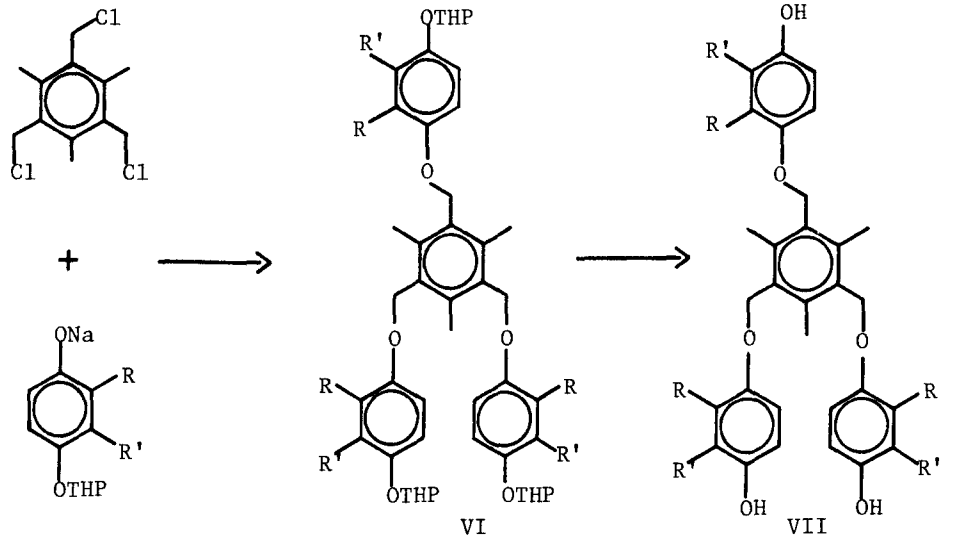
Phenolic antioxidants, such as hydroxyanisole (HA), 2-t-butyl-4-hydroxyanisole (2-BHA) and 3-t-butyl-4-hydroxyanisole (3-BHA), have been found to inhibit chemically induced neoplasia in laboratory animals.[1-4] Efforts have been directed toward the synthesis of new inhibitors with high potency and low toxicity. A series of bulky compounds that contain three phenolic antioxidants attached onto a mesitylene nucleus have been prepared. The phenolic moieties are the active sites for the inhibition



of the actions of carcinogens and the bulkiness was designed to reduce absorption from the gastrointestinal tract. Lack of absorption would result in high concentrations of the compounds in luminal contents, thus

maximizing potential effectiveness within the alimentary tract. In addition, toxicity would be minimized.

The general synthetic scheme involves protection of one of the hydroxy groups of compounds Ia and Ib with the tetrahydropyranyl ether (THP).[5] The THP ethers of Ia and Ib were prepared by treatment of the corresponding hydroquinones in anhydrous ether with 10% excess of dihydropyran. The desired products were purified by preparative LC. The THP ether of III was synthesized by the reaction of the monopivaloyl ester[6] of III with dihydropyran and subsequent removal of the ester group by saponification. The sodium phenolates of the THP ethers, II and V, were formed by the action of NaH in DMF. Reaction of three equivalents of the



a) R = H, R' = CMe_3 b) R = CMe_3, R' = H c) R = R' = H

sodium phenolates with 1,3,5-trischloromethyl mesitylene in DMF gave the corresponding trisubstituted compounds VI in greater than 90% yield. Hydrochloric acid catalyzed hydrolysis of VI in aqueous THF yielded VII in >70% yield.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-John Mel-Temp apparatus and were uncorrected. Infrared spectra were recorded on a Beckman Acculab V spectrophotometer. NMR spectra were determined with a Varian Associates model HFT-80 MHz spectrometer with tetramethylsilane as internal standard. Mass spectra were taken on an LKB 9000 GC-MS spectrometer at the Gortner Biochemistry Laboratory of the University of Minnesota, St. Paul, MN. Elemental analyses on chemical compounds were done by the M-H-W Laboratories (P.O. Box 15853, Phoenix, AZ 85018).

4-Hydroxyphenoxy tetrahydropyranyl ether IIa. - To a solution of 5.51 g (0.05 mol) of hydroquinone and 5 mg of p-toluenesulfonic acid in 200 mL of anhydrous ether was added dropwise a solution of 4.63 g (0.055 mol) of dihydropyran over a period of 2 hrs at room temperature. The reaction mixture was allowed to stand at room temperature for 24 hrs and was neutralized with solid sodium bicarbonate to pH 6. The excess sodium bicarbonate was removed by filtration and the filtrate was evaporated in vacuo. The crude product was purified by preparative LC on silica gel eluted with petroleum ether-ether (4:1 v/v containing 0.025% acetic acid) mixture. The yield of IIa was 2.62 g (27%), mp. 88-89° (pet ether).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.80; H, 7.16. IR(KBr): 3680-3580 cm^{-1} (-OH), 3040-3010 cm^{-1} (ArH). UV (95% EtOH): 201 nm (log ε 3.88), 224 nm (log ε 3.88), 286 nm (log ε 3.36). NMR($CDCl_3$): δ 1.5-1.99 (m, 6, $(CH_2)_3$), 3.61-3.96 (m, 2, OCH_2), 5.26 (m, 1, OCH), 6.26 (s, 1, OH), 6.58-6.94 (q, 4, ArH). MS (70 eV, m/e (relative intensity)): 194 (2.9), 110 (100.0), 85 (31.8).

3-t-Butyl-4-hydroxyphenoxy tetrahydropyranyl ether (IIb). - Compound Ib was similarly treated with dihydropyran to give IIb in 41% yield, mp. 100-101° (pet ether).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.15; H, 8.88. IR(KBr): 3680-3580 cm^{-1} (-OH), 3040-3010 cm^{-1} (ArH). UV (95% EtOH): 202 nm (log ε 4.19), 226 nm (log ε 3.76), 286 nm (log ε 3.45). NMR($CDCl_3$):

δ 1.36 (s, 9, CMe_3), 1.61-1.90 (m, 6, $(CH_2)_3$), 3.62-3.64 (m, 2, OCH_2), 4.64 (s, 1, OH), 5.25 (m, 1, OCH), 6.58-6.96 (m, 3, ArH). MS (70 eV, m/e (relative intensity)): 250 (2.3), 166 (100.0), 151 (100.0), 123 (18.7), 85 (42.4).

Tetrahydroxpyranyl Ether of 3-t-Butyl-4-hydroxyphenyl pivaloate (IV). - To a solution containing 315.1 gm (1.26 mole) of 3-t-butyl-4-hydroxyphenyl pivaloate and 227.2 ml (2.49 mole) of dihydropyran in 500 ml benzene at 55-60°C were added 10 drops of conc. hydrochloric acid. The temperature of the reaction was maintained at 55-60°C for 16 hrs. On cooling, 374.1 g (89%) of white crystals of THP ether of the mono ester, mp. 115-116°, were obtained.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.86; H, 8.98. Found: C, 71.98; H, 9.14. IR(KBr): 3040-3010 cm^{-1} (ArH), 3000-2900 cm^{-1}, 1750-1740 cm^{-1} (-C(=O)-), UV (100% EtOH) 280 nm (log ε 3.31), 272 nm (log ε 3.32), 224 nm (log ε 3.92), 212 nm (log ε 3.89). NMR ($CDCl_3$): δ 1.32 (s, 9, CMe_3) 1.38 (S, 9, CMe_3), 1.54-2.0 (m, 6, $(CH_2)_3$), 3.70-3.72 (m, 2, OCH_2), 5.37 (m, 1, OCHO), 6.86-7.11 (m, 3, ArH). MS (70 eV, m/e (relative intensity)): 334 (0.3), 250 (89.3), 166 (100.0), 85 (82.9).

2-t-Butyl-4-hydroxyphenoxy tetrahydropyranyl ether (V). - A solution containing 374 g (1.12 mol) of IV was saponified with 112 g of potassium hydroxide in 1L 80% aqueous ethanol, yield 228 g (77%) of V, mp. 85-86° (benzene).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.89; H, 8.93. IR(KBr): 3680-3580 cm^{-1} (-OH), 3040-3010 cm^{-1} (ArH), 3000-2945 cm^{-1}, UV (100% EtOH): 204 nm (log ε 3.90), 226 nm (log ε 3.84), 286 nm (log ε 3.50). NMR ($CDCl_3$): δ 1.36 (s, 9, $C(CH_3)_3$), 1.53-1.90 (m, 6, $(CH_2)_3$), 3.69-3.71 (m, 2, OCH_2), 5.25 (s, 1, OH), 5.36 (m, 1, OCHO), 6.49-6.98 (m, 3, ArH). MS (70 eV, m/e (relative intensity)): 250 (1.1), 166 (100.0),

151 (57.1), 123 (17.2), 85 (42.6).

Synthesis of 1,3,5-tris(4-tetrapyranyloxyphenoxymethyl)mesitylene (VI). - To NaH (75 n mol of a 50% suspension in oil), washed three times with pet ether, was added 300 ml DMF. To this mixture, under nitrogen atmosphere, was added dropwise a solution of the phenol II, (69 n mol) in 300 ml DMF over a period of 0.5 hr. The reaction mixture was then heated to 60° and a solution of 1,3,5-tris(chloromethyl)-mesitylene (20 nmol) in 200 ml DMF was added over a period of 1 hr. The temperature of the reaction was maintained at 60° for an additional 2 hrs. The reaction mixture was then cooled and acidified with glacial acetic acid to pH 6.5. The product VI was precipitated with 3L water and dried under reduced pressure. The yield ranged from 90-96%.

VIa, mp.228-229° (ethanol).

Anal. Calcd for $C_{57}H_{78}O_9$: C, 75.46; H, 8.67. Found: C, 75.42; H, 8.79. IR(KBr) 3040-3010 cm^{-1} (ArH), 3000-2940 cm^{-1}. UV ($CHCl_3$): 242 nm (log ε 4.01), 285 nm (log ε 4.22). NMR ($CDCl_3$): δ 1.40 (s, 27, $C(CH_3)_3$), 1.21-1.99 (m, 18, $3x(CH_2)_3$), 2.44 (s, 9, $(CH_3)_3$), 3.61-3.96 (m, 6, $(OCH_2)_3$), 5.03 (s, 6, $ArCH_2$), 5.26 (m, 3, $(OCHO)_3$), 6.63-6.70 (m, 6, ArH), 6.94 (s, 3, ArH). MS (70 eV, m/e (relative intensity)): 739 (2.7), 654 (24.7), 489 (100.0), 325 (100.0), 267 (100.0), 250 (7.3).

VIb, mp. 154-155° (acetone).

Anal. Calcd for $C_{57}H_{78}O_9$: C, 75.46; H, 8.67. Found: C, 75.49; H, 8.72. IR(KBr): 3040-3010 cm^{-1} (ArH), 3000-2940 cm^{-1} (CH_3). UV ($CHCl_3$): 242 nm (log ε 4.17), 286 nm (log ε 3.93). NMR ($CDCl_3$): δ 1.21 (s, 27, $C(CH_3)_3$, 1.21-1.99 (m, 18, $(CH_2)_3$), 2.39 (s, 9, $(CH_3)_3$), 3.61-3.96 (m, 6, OCH_2), 5.03 (s, 6, $ArCH_2$), 5.29 (m, 3, OCHO), 6.92 (m, 6, ArH), 6.97 (s, 3, ArH). MS (70 eV, m/e (relative intensity)): 739 (1.2), 654 (15.3), 489 (100.0),

325 (100.0), 267 (78.1), 250 (2.8).

VIc, mp. 171-172° (acetone).

Anal. Calcd for $C_{45}H_{54}O_9$: C, 73.14; H, 7.37. Found: C, 72.94; H, 7.41. IR(KBr) 3040-3010 cm^{-1} (ArH), 3000-2940 cm^{-1} ($-CH_3$). UV ($CHCl_3$): 242 nm (log ε 4.17), 287 nm (log ε 3.88). NMR ($CDCl_3$): δ 1.21-1.99 (m, 18, $(CH_2)_3$), 2.42 (s, 9, $(CH_3)_3$), 3.61-3.96 (m, 6, $(OCH_2)_3$), 5.02 (s, 6, $ArCH_2$), 5.29 (m, 3, OCHO), 6.97 (s, 12, ArH). MS (70 eV, m/e (relative intensity)): 571 (2.9), 486 (47.9), 379 (100.0), 269 (100.0), 159 (100.0), 110 (100.0).

Acid Hydrolysis of VI. - A solution of 0.03 mol of VI in 40 ml 1N HCl and 1.6L of tetrahydrofuran was stirred at RT overnight. The reaction mixture was neutralized with solid sodium bicarbonate to pH 5.6. The excess sodium bicarbonate was then removed by filtration and the solvent evaporated in vacuo. The end product was extracted into 1L of dichloromethane. The dichloromethane extract was washed with H_2O and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo; the yield of VII was 70-90%.

VIIa, mp. 206-207° (toluene).

Anal. Calcd for $C_{42}H_{54}O_6$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.51. IR(KBr) 3685-3580 cm^{-1} (-OH), 3040-3010 cm^{-1} (ArH). UV (100% EtOH) 208 nm (log ε 4.78), 229 nm (log ε 4.23), 290 nm (log ε 3.95). NMR ($CDCl_3$): δ 1.38 (s, 27, $C(CH_3)_3$), 2.43 (s, 9, $(CH_3)_3$), 4.62 (s, 3, OH), 5.00 (s, 6, $ArCH_2O$), 6.63-6.70 (m, 6, ArH), 6.92 (s, 3, ArH). MS (70 eV, m/e (relative intensity)): 654 (1.2), 489 (20.1), 325 (52.8), 267 (28.7) 159 (100.0).

VIIb, mp. 260-262° (dichloromethane).

Anal. Calcd for $C_{42}H_{54}O_6$: C, 77.03; H, 8.31. Found: C, 76.88; H, 8.22. IR(KBr) 3685-3585 cm^{-1} (-OH), 3040-3010 cm^{-1} (ArH). UV (95% EtOH) 208 nm (log ε 5.09), 228 nm (log ε 4.63), 289 nm (log ε 4.00). NMR (DMSO-d_6): δ 0.78 (s, 27, $C(CH_3)_3$), 2.03 (s, 9, $(CH_3)_3$), 4.60 (m, 6, $ArCH_2$), 6.27 (m, 6, ArH), 6.30 (s, 3, ArH), 8.36 (s, 3, OH). MS (70 eV, m/e (relative intensity) 654 (s.1), 488 (100.0), 323 (99.3), 267 (97.0), 159 (72.4).

VIIc, mp. 140-142° (dichloromethane).

Anal. Calcd for $C_{30}H_{30}O_6 \cdot H_2O$: C, 71.41; H, 6.39. Found: C, 71.75; H, 6.94.

IR(KBr) 3685-3585 cm^{-1} (OH), 3040-3010 cm^{-1} ArH. UV (95% EtOH) 207 nm (log ε 4.90), 226 nm (log ε 4.58), 289 nm (log ε 3.78). NMR (DMSO-d_6): δ 2.97 (s, 9, $(CH_3)_3$), 4.66 (s, 6, $ArCH_2$), 6.41 (s, 6, ArH), 6.46 (s, 6, ArH), 8.56 (s, 3, OH). MS (70 eV, m/e (relative intensity)): 486 (3.3), 377 (100.0), 267 (100.0), 157 (49.6), 110 (69.0).

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