Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. 7. 4-, 5-, and 6-(Piperidinomethyl)-3-*n*-pentadecylcatechols

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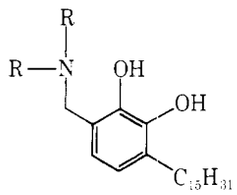
Derivatives of 3-*n*-pentadecylcatechol, the saturated component of poison ivy urushiol, which are substituted in the 6 position of the aromatic ring by various aminomethyl groups, have been found to be toleragens, the most potent being 6-(piperidinomethyl)-3-*n*-pentadecylcatechol (**24**). In order to examine the structural requirements of a toleragen, 4- and 5-(piperidinomethyl)-3-*n*-pentadecylcatechols (**11** and **21**) have been synthesized and isolated as their hydrochloride salts **13** and **23** along with the hydrochloride salt **25** of **24**. The syntheses include as the last step a novel coupled use of boron tribromide and piperidine to effect ether cleavage followed by ammonolysis. In the synthesis of the 5 isomer, an unusual exclusive para substitution of a phenol using the Mannich reaction has been exploited.

Recently, it has been observed that a number of substituted 6-aminomethyl analogues **1** of 3-*n*-pentadecylcatechol (3-PDC) **2** are potent toleragens for poison ivy.[1,2] This observation has inspired the present investigation, which is focused on the synthesis of structural isomers of 6-(piperidinomethyl)-3-*n*-pentadecylcatechol (**24**), the most promising toleragen of those observed. The objective has been to study the effect of the position of substitution on toleragenicity. The synthesis of 4- (**11**) and 5-(piperidinomethyl)-3-*n*-pentadecylcatechol (**21**) in the form of their hydrochloride salts **13** and **23**, respectively, has been achieved. For comparison, 6-(piperidinomethyl)-3-*n*-pentadecylcatechol (**24**) has been resynthesized in the form of its hydrochloride salt **25**.



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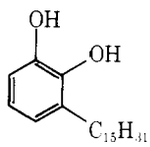

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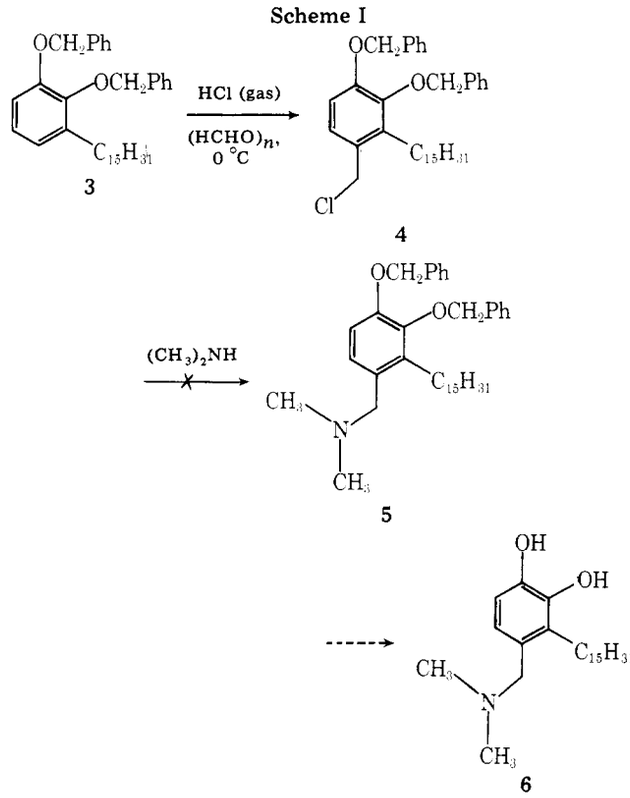
Results and Discussion

The 4 Isomer. The synthesis of 4-(*N,N*-dimethylamino)-methyl-3-*n*-pentadecylcatechol (**6**) was attempted (Scheme I) by Lerner[2] using the dibenzyl ether of 3-PDC. His failure to isolate a product in the ammonolysis step suggested a possible advantage of using a different protective group. In the present investigation, the methyl protective group was chosen as the alternative because of its stability to both acids and bases and because of the better availability of the starting material **8b** than **3**.

The optimum conditions for the introduction of only one chloromethyl group into a 3-alkylveratrole were studied using a readily available model compound, 3-*n*-decylveratrole (**8a**), which was prepared using an improvement of the Byck and Dawson[3] procedure (as described in the Experimental Section). Thus, 4-(chloromethyl)-3-*n*-decylveratrole (**9a**) was synthesized from **8a** in 73% yield. Under similar conditions, 4-(chloromethyl)-3-*n*-pentadecylveratrole (**9b**) was obtained from **8b**. The ammonolysis reaction was also found feasible when **9b** was converted to 4-(piperidinomethyl)-3-*n*-pentadecylveratrole (**10**) in 78% yield by reacting it at room temperature in toluene with an excess of piperidine for 24 h.

The unusually high temperature recommended for the cleavage of 3-alkylcatechol methyl ethers[4] posed a serious problem for the heat-sensitive benzylaminocatechols such as **11**. A solution to this problem was found in the use of boron tribromide,[5] an agent which has been found in the present investigation to be extremely effective in the low-temperature cleavage of 3-alkylcatechol methyl ethers. For example, when **8b** was treated with boron tribromide, high-purity 3-PDC was obtained in 90% yield.[6] However, the cleavage reaction could not be done directly on **10** since in an exploratory experiment it was discovered that boron tribromide cleaved *N*-benzylpiperidine even at room temperature.

Scheme I



The final route by which **11** was synthesized is shown in Scheme II. The key step in this route was the use of boron tribromide and piperidine in the same step. In effect, the boron dibromide group (which remains attached to the phenolic oxygen atom after the first step of the cleavage reaction[5]) was exploited as a protective group against the strongly basic piperidine that was added for the ammonolysis. The isolation of the intermediate, 4-(chloromethyl)-3-*n*-pentadecylcatechol, was not attempted because it was reasoned that in the presence of the basic piperidine the unprotected chloromethylphenol would be under conditions equivalent to those used in the benzylation of 3-PDC.[7] Consequently, extensive polymeric benzylation would likely occur if the ether cleavage and the ammonolysis were carried out as two distinct steps.

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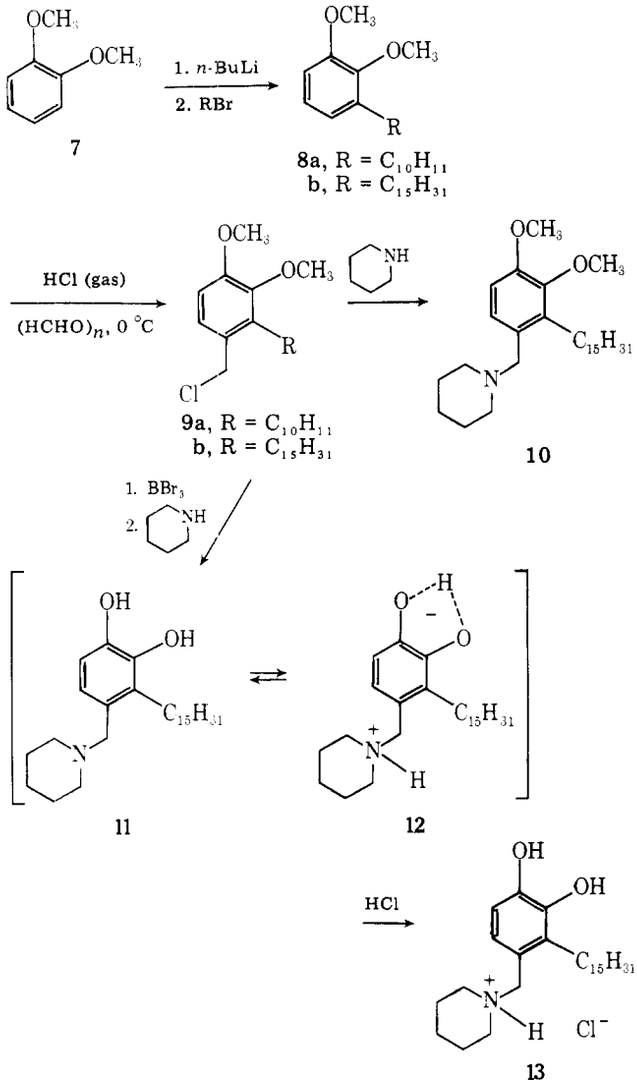
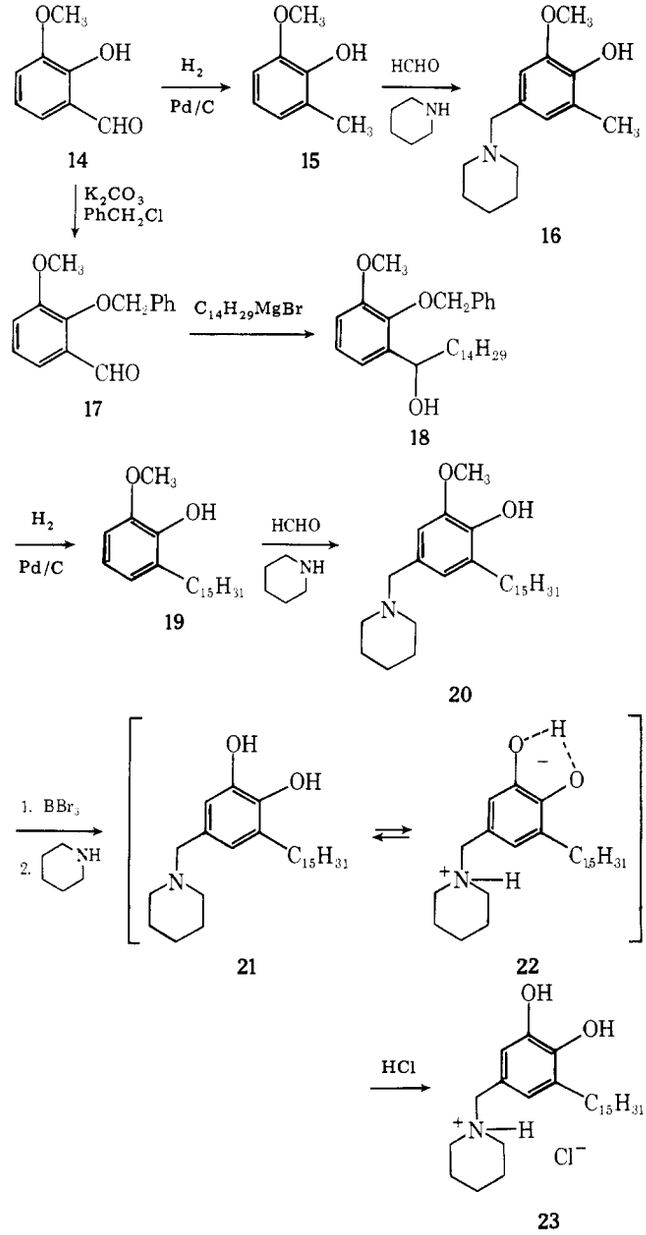
Scheme II



Scheme III



Isolation of the product 11 was complicated by its high sensitivity to air oxidation and its heat-labile property.[6b] Conversion of 11 to its hydrochloride salt 13 provided a means to isolate a pure product. The hydrochloride salt 13 differs from many salts of amines in that it is insoluble in both water and ether, which made it rather simple to isolate. Recrystallization from hot acetone afforded an 89% yield of pure 13 from **9b**.

Repeated attempts to convert 13 to the free base 11 have failed, despite extreme precautionary measures under low temperature and anaerobic conditions. In every case,[6b] only a dark-brown resinous material was obtained. It appears that 4-(piperidinomethyl)-3-*n*-pentadecylcatechol (11) exists largely in the form of the zwitterion **12**. This dipolar ion, being both a benzylamine cation and a phenolate, is susceptible to polymerization via nucleophilic attack of the phenolate ion on the benzylic carbon (Figure 1) or on the trienone which could be formed from the expulsion of piperidine (Figure 2). Such polymerizations are enhanced when the systems are concentrated in an effort to isolate the product.

The 5 Isomer. The direct introduction of a functional group to the 5 position of the aromatic ring of 3-PDC exclusively is developed for the first time in the present investigation. The synthesis of 5-(piperidinomethyl)-3-*n*-pentadecylcatechol (**21**) is shown in Scheme III.

The conversion of *o*-vanillin (14) to 2-benzyloxy-3-methoxybenzaldehyde (17) was accomplished in nearly quantitative yield using the procedure of Merz and Pfäffle.[8] Reaction of 17 with myristyl Grignard reagent, followed directly by hydrogenolysis (compare[9]), gave 3-*n*-pentadecylguaiacol (**19**) in an overall yield of 67%. The crucial step in Scheme III is a special adaptation of the Mannich reaction. This reaction, which normally alkylates at room temperature ortho to the hydroxyl group, has been found in this investigation to result in para alkylation at reflux temperature when blocking groups are situated at both positions ortho to the hydroxyl group. The exploratory experiment using 3-methylguaiacol (**15**) clearly demonstrated that the Mannich reaction at higher temperature results in para alkylation when both of the ortho phenolic positions are occupied. When these conditions were applied to **19**, 5-(piperidinomethyl)-3-*n*-pentadecylguaiacol (**20**) was isolated in 79% yield.

The last step in this reaction sequence uses the same reaction as that for the preparation of **13**. In view of the polymerizing behavior of 11, the hydrochloride salt **23** was isolated directly from the reaction mixture in 87% yield. Surprisingly, this salt **23** is only slightly soluble in water and is appreciably soluble in ether and benzene. It is also an excellent emulsifier, which caused some difficulties in its isolation. Fortunately, it can also be crystallized from hot acetone.

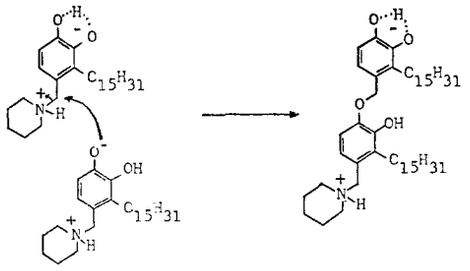


Figure 1. Polymerization via nucleophilic attack of the phenolate ion on the benzylic carbon.

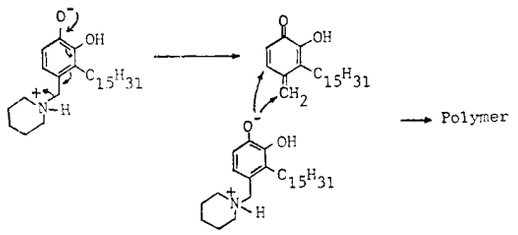
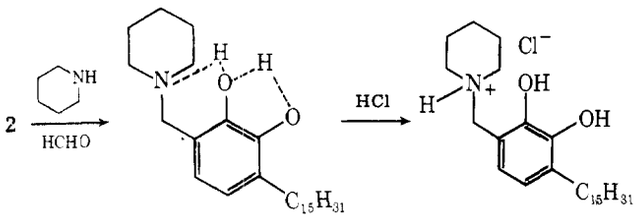


Figure 2. Polymerization via nucleophilic attack of the phenolate ion on the trienone.

Scheme IV



24 25

The 6 Isomer. The synthesis of 6-(piperidinomethyl)-3-*n*-pentadecylcatechol hydrochloride (**25**) (shown in Scheme IV) was accomplished simply by mixing the free base **24** with dilute hydrochloric acid. Synthesis of **24** was accomplished via an application of the Mannich reaction[10,11] to 3-PDC as reported by Lerner.[2]

Experimental Section

Melting points were taken in open capillary tubes using a Thomas-Hoover capillary melting-point apparatus and are uncorrected. The IR spectra were recorded on a Jasco IRA-1 diffraction grating IR spectrophotometer and were measured in CCl_4 solution unless otherwise specified. The NMR spectra were obtained with a Varian T-60 spectrometer using CCl_4 as solvent, unless otherwise indicated. Chemical shifts, δ, are expressed in ppm relative to internal tetramethylsilane. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Mass spectra were obtained on a Finnigan 3300 quadrapole mass spectrometer. Anhydrous $MgSO_4$ was used as the drying agent. Air-free water was prepared by purging distilled water with nitrogen. Additional information about the experimental observations is given in the thesis of G. P. Ng.[6b]

3-*n*-Decylveratrole (8a). To a solution of 104 g (0.750 mol) of veratrole (**7**) in 440 mL of tetrahydrofuran (THF) at 0 °C under a nitrogen atmosphere was added, with stirring, 367 mL (0.500 mol) of a solution of 1.36 M *n*-butyllithium[12] in anhydrous ether during 30 min. The mixture was stirred at 0 °C for 2 h. A solution of 55.3 g (0.250 mol) of 1-bromodecane[13] in 55 mL of THF was then added. The mixture was refluxed for 4 h, cooled to room temperature, and then hydrolyzed with 300 mL of 10% HCl. The layers were separated. The aqueous layer was extracted with ether. The combined organic solution was washed with 10% aqueous NaOH and brine. The solution was dried and the solvents were evaporated. Vacuum distillation yielded 51.0 g (73%) of **8a** as a colorless liquid: bp 139–140 °C (0.50 mm); NMR δ 6.67 (m, 3 H), 3.75 (s, 6 H), 2.58 (t, 2 H), 1.25 (s, 16 H), 0.90 (t, 3 H); IR no -OH peak.

4-(Chloromethyl)-3-*n*-decylveratrole (9a). A mixture of 15.9 g (0.0570 mol) of **8a**, 64 mL of benzene, 64 mL of glacial acetic acid, and 10.3 g (0.340 mol) of paraformaldehyde[13] was cooled to 0 °C. Dry HCl gas was passed into the mixture rapidly with stirring. When the mixture had become clear, the reaction was continued for 2 h at 0 °C. Then the mixture was poured onto ice and diluted with ether. The layers were separated, and the organic layer was washed with water, saturated aqueous bicarbonate, and brine. After the solution was dried, the solvents were evaporated, leaving a red oily liquid. Vacuum distillation of this liquid yielded 13.6 g (73%) of **9a** as a colorless liquid: bp 167–170 °C (0.50 mm); NMR δ 6.77 (q, 2 H), 4.50 (s, 2 H), 3.77 (s, 6 H), 2.65 (t, 2 H), 1.25 (s, 16 H), 0.90 (t, 3 H); IR no -OH peak.

4-(Chloromethyl)-3-*n*-pentadecylveratrole (9b). Using a mixture of 20.9 g (0.0600 mol) of **8b**, 85 mL of benzene, 85 mL of glacial acetic acid, and 10.0 g (0.333 mol) of paraformaldehyde, a procedure similar to that used for **9a** was followed. The faint yellow oil obtained after the workup solidified on standing. Recrystallization from hexanes yielded in several crops 18.6 g (78%) of **9b** as a white amorphous powder: mp 47.0–49.0 °C; NMR δ 6.77 (q, 2 H), 4.47 (s, 2 H), 3.78 (s, 6 H), 2.60 (t, 2 H), 1.25 (s, 26 H), 0.90 (t, 3 H); IR no -OH peak.

4-(Piperidinomethyl)-3-*n*-pentadecylveratrole (10). To 118 mL (1.19 mol) of piperidine was added, with stirring, a solution of 15.0 g (0.0378 mol) of **9b** in 50 mL of toluene. A white precipitate of high melting point appeared within seconds. The mixture was stirred at room temperature for 24 h. It was then shaken with excess 10% aqueous NaOH. The aqueous layer was extracted with ether. The combined organic solution was washed with brine and then dried. After removal of the solvents, the yellow oily liquid was subjected to vacuum distillation to yield 13.2 g (78%) of **10** as a yellow oil: bp 217–218 °C (0.15 mm); NMR δ 6.65 (q, 2 H), 3.76 (s, 6 H), 3.24 (s, 2 H), 2.58 (t, 2 H), 2.25 (m, 4 H), 1.45 (br s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed the M^+ peak at *m/e* 445.

The Boron Tribromide Cleavage of *N*-Benzylpiperidine. To a solution of 2.14 g (0.00854 mol) of boron tribromide[14] in 7.6 mL of methylene chloride at −77 °C was added a solution of 1.01 g (0.00574 mol) of a solution of *N*-benzylpiperidine (prepared according to Schotten[15]) in 20 mL of methylene chloride, with rapid stirring. The mixture was allowed to warm up to room temperature slowly over 24 h. The mixture was hydrolyzed with water, diluted with ether, and then shaken with excess 2 N HCl. The layers were separated. The ether layer was washed with 2 N HCl, dried, and distilled at 50 °C (15 mm). A yellow liquid identified as benzyl bromide was left. In a control experiment, where boron tribromide was replaced by methylene chloride, no residue remained after the evaporation of the solvents.

4-(Piperidinomethyl)-3-*n*-pentadecylcatechol Hydrochloride (13). To a solution of 20.0 g (0.0800 mol) of boron tribromide in 50 mL of benzene under a dry nitrogen atmosphere was added, with rapid stirring, a solution of 14.0 g (0.0350 mol) of **9b** in 300 mL of benzene during 30 min. The mixture was stirred at room temperature for 24 h. A solution of 105 g (1.23 mol) of piperidine in 125 mL of benzene was added. The mixture was again stirred at room temperature for 24 h and then 180 mL of air-free water was added. The mixture was transferred to a separatory funnel under nitrogen. The layers were separated and the organic layer was treated with an ice-cold solution of 3 N HCl. The resulting fine white precipitate was filtered and recrystallized from hot acetone to yield, in several crops, 14.1 g (89%) of **13** as a white powdery solid: mp 99.0–100.0 °C; NMR ($CDCl_3$) δ 10.26 (s, 1 H), 9.22 (s, 1 H), 7.14 (q, 2 H), 6.48 (s, 1 H), 4.15 (s, 2 H), 3.38 (br t, 2 H), 2.78 (m, 4 H), 1.90 (s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed a small M^+ peak at *m/e* 417.

Anal. Calcd for $C_{27}H_{48}ClNO_2$: C, 71.41; H, 10.65; Cl, 7.81; N, 3.08. Found: C, 71.29; H, 10.72; Cl, 7.82; N, 3.15.

3-Methylguaiacol (15). A mixture of 30.0 g (0.200 mol) of *o*-vanillin[16] (**14**), 60 mL of ethyl acetate containing six drops of concentrated sulfuric acid, and 1.00 g of 10% palladium on charcoal[14] catalyst was hydrogenated at an initial hydrogen pressure of 60 psi at room temperature for 8 h. The catalyst was filtered off and the filtrate was washed with saturated aqueous bicarbonate until the pH of the aqueous layer remained at 8. It was then dried, and the solvents were evaporated, leaving a clear, brown liquid which solidified in the freezer. Recrystallization from hot hexane yielded as the first crop 16.7 g (60%) of **15** in the form of white needles: mp 41.4–42.8 °C (lit.[17] mp 41–42 °C); NMR δ 6.60 (m, 3 H), 5.66 (s, 1 H), 3.73 (s, 3 H), 2.21 (s, 3 H); IR 3575 cm^{-1} (strong and sharp, -OH), no carbonyl peak.

5-(Piperidinomethyl)-3-methylguaiacol (16). To a solution of 15.0 g (0.109 mol) of **15** in 43 mL of piperidine at 0 °C was added, with stirring, 30.2 g (0.377 mol) of 37% aqueous formaldehyde. The mixture was stirred at room temperature for 1 h and refluxed gently for 2 h. It was diluted with water and ether. The layers were separated. The aqueous layer was extracted with ether. The combined ethereal so-

lution was washed with brine and dried. The solvent was evaporated, leaving a red liquid. Vacuum distillation of the red liquid yielded as the second fraction 15.6 g (61%) of **16** as an extremely viscous yellow liquid: bp 132–135 °C (0.25 mm); NMR δ 6.73 (s, 1 H), 6.62 (s, 1 H), 6.55 (s, 1 H), 3.62 (s, 3 H), 3.25 (s, 2 H), 2.33 (m, 4 H), 2.19 (s, 3 H), 1.50 (m, 6 H).

3-*n*-Pentadecylguaiacol (19). A solution of myristyl Grignard reagent in anhydrous ether was prepared from 51.62 g (0.186 mol) of 1-bromotetradecane[18] and 4.93 g (0.203 mol) of Mg turnings, each in 60 mL of anhydrous ether, and with a crystal of iodine as a catalyst. A 41.0-g (0.169 mol) sample of 2-benzyloxy-3-methoxybenzaldehyde (**17**), prepared according to Merz and Pfäffle,[8] was dissolved in 80 mL of anhydrous ether and added to the Grignard reagent under a nitrogen atmosphere, with stirring and ice-bath cooling to control the reflux. The mixture was then refluxed for 4 h and then cooled to 0 °C. Aqueous 10% HCl (200 mL) was added. After dilution with ether, the layers were separated. The ethereal layer was washed with saturated aqueous bicarbonate. The solvent was evaporated, leaving a yellow oil which was dissolved in 250 mL of hot 95% ethanol and chilled in an ice bath to precipitate hydrocarbon waxes. The waxes were filtered off by gravity and the ethanol was evaporated to give 71 g of the crude carbinol **18** as a viscous yellow-orange oil. The carbinol was hydrogenated in 142 mL of ethyl acetate containing 14 drops of concentrated sulfuric acid and 3.0 g of 10% palladium on charcoal catalyst at an initial hydrogen pressure of 60 psi at room temperature for 24 h. After the usual workup, vacuum distillation of the crude product yielded 37.6 g (67%) of **19** as a white solid: mp 40–44 °C; bp 183–186 °C (0.20 mm). A recrystallization from hexane gave pure 3-*n*-pentadecylguaiacol (**19**): mp 45.5–46.5 °C (lit.[9] mp 46.5–46.8 °C); NMR δ 6.61 (m, 3 H), 5.48 (s, 1 H), 3.80 (s, 3 H), 2.58 (t, 3 H), 1.25 (s, 26 H), 0.90 (s, 3 H).

5-(Piperidinomethyl)-3-*n*-pentadecylguaiacol (20). A mixture of 12.537 g (0.0375 mol) of **19**, 14.7 mL (12.6 g; 0.148 mol) of piperidine, and 9.9 mL (10.5 g; 0.13 mol) of 37% formaldehyde was refluxed overnight. The mixture was diluted with water and ether. The aqueous layer was extracted with ether. The combined ethereal layer was washed with brine and dried. The solvent was evaporated and the residual oil was distilled at 110 °C (0.25 mm) to remove low-boiling materials. The crude product was finally purified by molecular distillation at 125 °C (10^{-3} mm) to yield 12.77 g (79%) of **20** as an extremely viscous oil which crystallized on standing in the freezer (−6 °C) for 24 h into a white waxy solid: mp 42.5–45.5 °C; NMR δ 6.68 (s, 1 H), 6.58 (s, 1 H), 6.20 (s, 1 H), 3.72 (s, 3 H), 3.25 (s, 2 H), 2.60 (t, 2 H), 2.33 (m, 4 H), 1.45 (s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H).

5-(Piperidinomethyl)-3-*n*-pentadecylcatechol Hydrochloride (23). Using a solution of 19 g (0.077 mol) of boron tribromide in 50 mL of benzene, a solution of 6.00 g (0.0139 mol) of **20** in 130 mL of benzene, and a solution of 59.3 g (0.695 mol) of piperidine in 70 mL of benzene, the procedure described in the preparation of **13** was followed. After the layers had been separated, the benzene layer was treated with 250 mL of ice-cold 2 N HCl. The resulting emulsion was cautiously[19] reduced until all the benzene was removed. The mixture was then filtered by gravity and then recrystallized from 80 mL of hot acetone to yield 5.52 g (87%) of **23** as white needles: mp 131.5–133.0 °C; NMR ($CDCl_3$) δ 10.20 (s, 1 H), 7.33 (d, 2 H), 6.66 (s, 2 H), 4.02 (s, 2 H), 3.35 (br t, 2 H), 2.59 (m, 6 H), 1.70 (br s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed no observable M^+ peak, which was expected for a heat-sensitive compound of high molecular weight. The fragmentation pattern, however, was very similar to those of **13** and **25**.

Anal. Calcd for $C_{27}H_{48}ClNO_2$: C, 71.41; H, 10.65; Cl, 7.81; N, 3.08. Found: C, 71.37; H, 10.67; Cl, 7.70; N, 3.09.

6-(Piperidinomethyl)-3-*n*-pentadecylcatechol Hydrochloride (25). A solution of 4.20 g (0.0101 mol) of **24** (prepared according to the procedure of Lerner[2]) in 65 mL of ether was shaken with 60 mL (0.060 mol) of ice-cold 1 N HCl. The white precipitate was collected by suction filtration, washed with ether, and recrystallized from 75 mL of hot acetone. A 3.84-g yield (84%) of **25**, mp 83.0–85.0 °C, was collected in several crops as fine, white crystals: NMR ($CDCl_3$) δ 10.10 (s, 1 H), 6.77 (s, 2 H), 6.52 (s, 2 H), 4.21 (s, 2 H), 3.41 (br t, 2 H), 2.60 (m, 6 H), 1.90 (s, 6 H), 1.25 (s, 26 H), 0.90 (t, 3 H). The mass spectrum showed a small M^+ peak at *m/e* 417.

Anal. Calcd for $C_{27}H_{48}ClNO_2$: C, 71.41; H, 10.65; Cl, 7.81; N, 3.08. Found: C, 70.12; H, 10.90; Cl, 7.61; N, 3.02.

Registry No.—**7**, 91-16-7; **8a**, 66495-60-1; **8b**, 7461-75-8; **9a**, 66495-61-2; **9b**, 66495-62-3; **10**, 66495-63-4; **13**, 66495-64-5; **14**, 148-53-8; **15**, 2896-67-5; **16**, 66495-65-6; **17**, 2011-06-5; **18**, 66495-66-7; **19**, 16825-58-4; **20**, 66495-67-8; **23**, 66495-68-9; **24**, 64022-07-7; **25**, 66495-69-0; 1-bromodecane, 112-29-8; piperidine, 110-89-4; 1-bromotetradecane, 112-71-0.

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