The Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. II. 4-Methyl-, 5-Methyl-, 6-Methyl-, and 4,5,6-Trimethyl-3-pentadecylcatechol[1]

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Urushiol, the allergenic principle of poison ivy, is an oil composed of four compounds, all having the carbon skeleton of 3-pentadecylcatechol. As part of an investigation of the possible role of the unsubstituted positions on the catechol ring in the allergenic activity of these compounds, a series of ring-methylated homologs of 3-pentadecylcatechol have been synthesized and are being clinically tested. Successful synthetic routes to 4-methyl-, 5-methyl-, 6-methyl-, and 4,5,6-trimethyl-3-pentadecylcatechol are reported.

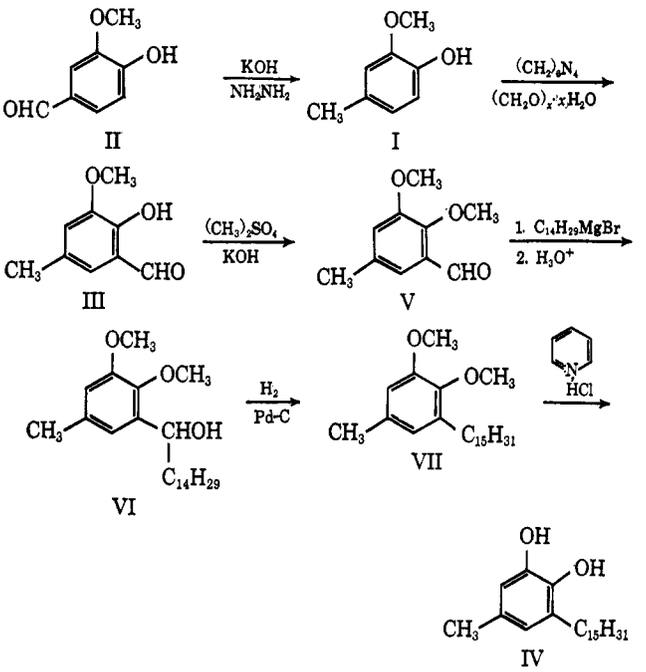
It has been suggested[2] that a critical step in the biochemical mechanism of the poison ivy allergy may be the oxidation of the catecholic components of poison ivy urushiol to the corresponding *o*-benzoquinones. Antigen formation might then occur by reaction of protein nucleophilic groups with the *o*-quinones *via* a 1,4-dipolar addition. Supporting evidence for the above view was obtained by the synthesis and biological testing of 4,5-dimethyl-3-pentadecylcatechol.[2] Preliminary clinical tests revealed that the simultaneous blocking of both the 4 and 5 positions, the normal sites for 1,4 addition to the quinone, resulted in the loss of most, but not all activity. This result made it advisable to synthesize and test other ring-methylated homologs of 3-pentadecylcatechol. Of particular interest were the three monomethyl homologs and the fully substituted compound, 4,5,6-trimethyl-3-pentadecylcatechol.

The 5-Methyl Homolog.—As previously reported,[2] the successful synthesis of 4,5-dimethyl-3-pentadecylcatechol was accomplished by the preparation of 5,6-dimethyl-*o*-vanillin, followed by conversion of that compound into the desired catechol by established means. The most critical steps in this route were the preparation of 4,5-dimethyl guaiacol and its formylation to 5,6-dimethyl-*o*-vanillin. Since the synthesis in good yield of 4-methyl guaiacol (I) from vanillin (II) has been reported in the literature,[3] it appeared that 5-methyl-*o*-vanillin (III) could also be synthesized by formylation and that III could be converted into 5-methyl-3-pentadecylcatechol (IV) by the sequence of reactions shown in Scheme I.

The preparation of 4-methyl guaiacol (I), as reported by Lock,[3] was accomplished in 90% yield by the Wolff–Kishner reduction of vanillin (II). It was found, however, as part of the present investigation, that this reduction could be carried out on a large scale more easily by means of the Huang-Minlon modification of the Wolff–Kishner reaction,[4] which led to a comparable yield (89%). Formylation of compound I was then carried out in strong acid using a mixture of hexamethylenetetramine and paraformaldehyde as the formylating reagent.[5] The reaction proceeded without difficulty to give 5-methyl-*o*-vanillin (III) in about 50% yield, which was comparable with the yield of 5,6-dimethyl-*o*-vanillin obtained in the synthesis of 4,5-dimethyl-3-pentadecylcatechol.[2] Although there were three unsubstituted sites on the guaiacol ring at which formylation might have occurred, only the desired product would have been the result of formylation *ortho* to the free hydroxyl, whereas the other possible products would have resulted from *meta* substitution. Nonetheless it seemed prudent to seek confirmation that the formylation reaction had produced the proper vanillin. Since the phenolic hydroxyl of *o*-vanillins should be hydrogen bonded to the adjacent aldehyde carbonyl, it was predicted that the peak in the nmr spectrum for the hydroxyl proton would appear at lower field than the corresponding peaks for *meta* and *para* compounds. In the nmr spectrum of *o*-vanillin the hydroxyl peak is at τ −0.52 to −0.74, depending on concentration, which is downfield from the aldehyde proton peak at τ −0.15. In vanillin (*para*) and isovanillin (*meta*) the hydroxyl peaks at τ 1.25–1.42 and 1.95, respectively, are upfield from the aldehyde proton. The spectrum of III confirmed *ortho* formylation as the hydroxyl and aldehyde proton peaks were found at τ −0.51 and −0.02, respectively.

The methylation of the vanillin to give 5-methyl-*o*-veratraldehyde (V) was then carried out in 87% yield using dimethyl sulfate in aqueous potassium hydroxide. The over-all yield to this stage was just about 40%. The remainder of the synthesis was easily accomplished

SCHEME I



(1) This investigation was supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health and by a predoctoral training grant (T1-GM-1130), National Institutes of General Medical Sciences, U. S. Public Health Service, to J. S. B. during 1963–1964.

(2) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **32**, 1084 (1967).

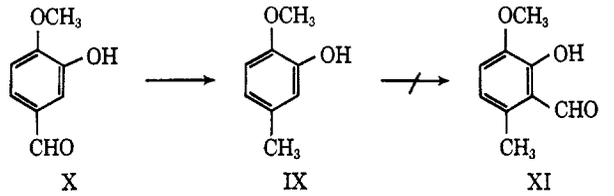
(3) G. Lock, *Monatsh.*, **85**, 802 (1954).

(4) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

(5) Farbenfabriken Bayer A.-G., British Patent 794,885 (May 14, 1958).

without any unusual difficulties in quite satisfactory yield (about 50%). The side chain was introduced by the reaction of V with tetradecylmagnesium bromide to yield the carbinol (VI), which was then directly hydrogenolyzed over palladium-on-charcoal catalyst, without complete purification, to give 5-methyl-3-pentadecyl veratrole (VII). The final step was cleavage of the veratrole (VII) by means of refluxing pyridine hydrochloride[6] to give 5-methyl-3-pentadecylcatechol (IV) in 88% yield and nearly 20% yield overall from vanillin.

The 4-Methyl Homolog.—Since the synthesis of both 4,5-dimethyl- and 5-methyl-3-pentadecylcatechol had been successfully accomplished by similar routes involving the formylation of appropriate guaiacols to give *o*-vanillins, it was assumed that the synthesis of 4-methyl-3-pentadecylcatechol (VIII) could also be carried out in this fashion. Once again employing the Huang-Minlon modification of the Wolff–Kishner reduction, 5-methyl guaiacol (IX) was readily prepared from isovanillin (X) in 96% yield. However, the direct formylation of IX using hexamethylenetetramine and paraformaldehyde repeatedly failed to yield the desired compound (XI). Only a small amount of an uncharacterized amorphous yellow substance could be isolated. Other methods of formylation[7,8] also failed to produce the desired product (XI).

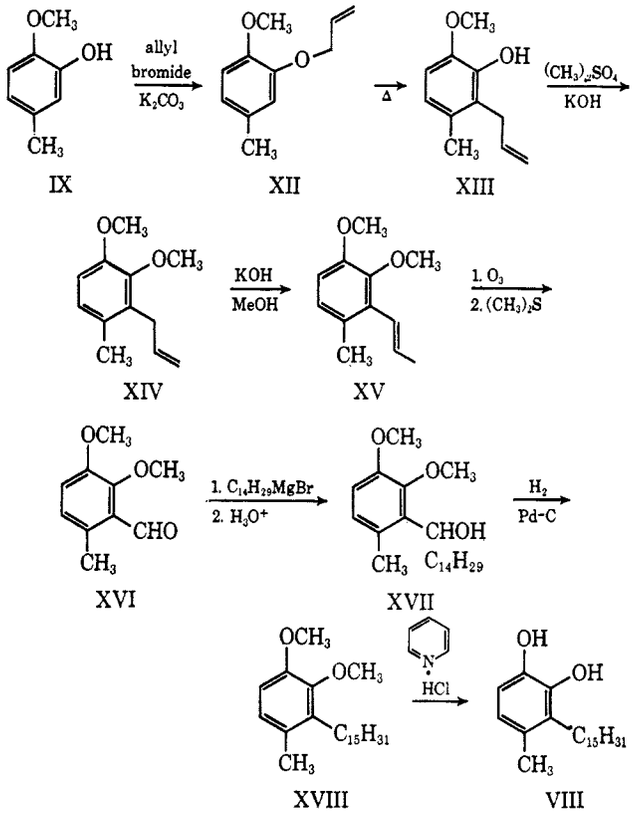


X IX XI

The route by which 4-methyl-3-pentadecylcatechol was finally prepared employed a Claisen rearrangement as a means for introducing useful functionality into the appropriate position of 5-methyl guaiacol (IX).

After conversion of IX into its allyl ether (XII) had been readily accomplished in 92% yield according to the procedure of Allen and Gates,[9] the thermal rearrangement of XII was then carried out by heating the neat liquid to 255° under a nitrogen atmosphere[9] to give 5-methyl-6-allyl guaiacol (XIII) in about 70% yield. Evidence of the successful rearrangement was provided by the shift upfield in the nmr spectrum of the allylic methylene doublet from τ 5.58 to 6.60 and the appearance of the hydroxyl group absorption in the infrared spectrum at 2.80 μ and in the nmr as a sharp singlet at τ 4.33. After methylation of XIII to the corresponding veratrole XIV in 87.5% yield, isomerization of the allyl group to give 4-methyl-3-propenylveratrole (XV) was accomplished by heating the allyl compound under nitrogen with saturated methanolic potassium hydroxide.[10] The most significant feature of the nmr spectrum of the isomerized compound was the complete disappearance of the two-proton allylic methylene doublet at τ 6.60, which was replaced by the three-proton doublet of the new allylic methyl group at τ 8.12. Recovery of the propenyl compound XV was nearly quantitative (96%). Ozonization of XV was carried out in methanolic solution at −30 to −40°, after which reductive decomposition of the ozonide using dimethyl sulfide yielded 6-methyl-*o*-veratraldehyde (XVI) in 82% yield. Vapor phase chromatography of this substance confirmed the absence of any 2′,3′-dimethoxy-6′-methylphenylacetaldehyde, the compound which would have been formed by ozonolysis of any unisomerized 3-allyl-4-methylveratrole (XIV) (Scheme II).

SCHEME II



IX XII XIII XIV XV XVI XVII XVIII VIII

The remainder of the synthesis was carried out by the customary route without difficulty. The reaction of the aldehyde (XVI) with tetradecyl Grignard reagent yielded the carbinol (XVII), which was converted into 4-methyl-3-pentadecylveratrole (XVIII) by hydrogenolysis over palladium-on-carbon catalyst. The combined yield for these two steps was 48%. Finally, pyridine hydrochloride cleavage of the methoxyls gave 4-methyl-3-pentadecylcatechol (VIII) in just over 70% yield. For the entire eight-step synthesis, the yield of VIII from isovanillin was about 15%.

The 6-Methyl Homolog.—The most direct approach to the synthesis of 6-methyl-3-pentadecylcatechol (XIXa) appeared to be the introduction, into the 6 position of 3-pentadecylcatechol, of a functional group which might subsequently be converted into a methyl group, presumably by reduction. One such method was the Mannich reaction which could be used to introduce an N,N-dimethylaminomethylene moiety at the unsubstituted ring site adjacent to the phenolic hydroxyl to yield 6-(N,N-dimethylamino)methyl-3-pentadecylcatechol (XXa). Hydrogenolysis of the benzylic amino group would then be expected to yield XIXa.

(6) E. Wenkert, E. M. Loesser, S. N. Mahaptera, F. Schenker, and E. M. Wilson, *J. Org. Chem.*, **29**, 438 (1964).

(7) A. Russell and L. H. Lockhart, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 463.

(8) J. C. Duff, *J. Chem. Soc.*, 547 (1941).

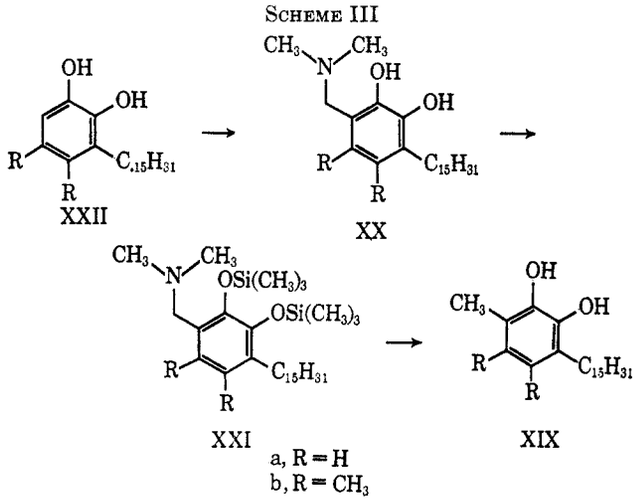
(9) C. F. H. Allen and J. W. Gates, Jr., "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 418.

(10) D. S. Tarbell, *Org. Reactions*, **2**, 1 (1944).

A similar synthesis had already been achieved by Gulati,[11] who converted 3-pentadecylphenol into 6-methyl-3-pentadecylphenol.

The Mannich reaction of 3-pentadecylcatechol with dimethylamine and formaldehyde in ethanol solution led to recovery of XXa in about 89% yield (Scheme III). The structure of this compound was apparent from its nmr spectrum which had a typical AB-type quartet at τ 3.65 for the two adjacent aromatic protons, a singlet for the aminomethylene at τ 6.47, and another singlet at τ 7.70 for the aminomethyl groups in the ratio 1:1:3. The hydroxyls appeared far downfield at τ 1.6, presumably because of hydrogen bonding with the amino nitrogen.

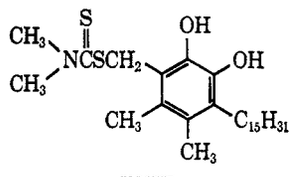
SCHEME III



It was expected that hydrogenolysis of the Mannich base (XXa) would then produce 6-methyl-3-pentadecylcatechol in good yield, but such was not the case. When hydrogenolysis was attempted at 60 psi over Raney nickel or platinum oxide catalysts, there was no observable uptake of hydrogen. When palladium-on-carbon catalyst was used in ethanol, some hydrogenolysis took place, but the yield of 6-methyl-3-pentadecylcatechol was only 12%. Similar difficulties had been encountered by other workers who attempted the preparation of methyl phenols by the hydrogenolysis of phenolic Mannich bases.[12,13] Their solution to this problem was to perform the hydrogenolysis over copper chromite catalyst at elevated temperatures and pressures. While use of these conditions might also have led to the successful preparation of 6-methyl-3-pentadecylcatechol, a less drastic alternative also seemed promising. It was observed that the failure of this reduction to proceed in good yield was in sharp contrast with the hydrogenolysis of N,N-dimethylbenzylamine to toluene, which is rapid with several catalysts and in a variety of solvents. This contrast made it appear that the hydrogen bonding between the amino and hydroxyl groups was in some way largely responsible for the difficulty. Therefore, it seemed that the use of some easily removed hydroxyl protecting group, which could be introduced without altering the N,N-dimethylamino moiety, might facilitate hydrogenolysis. This was accomplished by converting the Mannich base into its bistrimethylsilyl derivative (XXIa) in 76% yield using hexamethyldisilizane in refluxing pyridine.[14] Once the hydroxyls had been derivatized in this manner and could no longer hydrogen bond with the nitrogen atom, hydrogenation proceeded smoothly in absolute ethanol over palladium on charcoal. After completion of the hydrogenation and removal of the catalyst by filtration, hydrolysis of the protecting groups was accomplished by adding water to the ethanolic solution and refluxing. The yield of 6-methyl-3-pentadecylcatechol from the trimethylsilyl derivative of the Mannich base was 78% and the yield, over-all, from 3-pentadecylcatechol was 53%.

The Trimethyl Homolog.—In a similar fashion to the work with the 6-methyl compound, the original plan for the synthesis of 4,5,6-trimethyl-3-pentadecylcatechol (XIXb) called for the conversion of 4,5-dimethyl-3-pentadecylcatechol into the corresponding 6-(N,N-dimethylamino)methyl compound (XXb), followed by appropriate steps to bring about reduction of the Mannich base. Although the Mannich reaction with dimethylamine and formaldehyde led to isolation of XXb, the yield was not high (about 46%). As was expected, hydrogenolysis of the unprotected phenolic Mannich base proved impractical and the bistrimethylsilyl derivative (XXIb) was prepared, but the yield of the silylation reaction was only about 62%. When the hydrogenolysis of this compound was carried out over palladium-on-carbon catalyst, even after 48 hr the yield of the reduction was only 26%, giving an over-all yield from 4,5-dimethyl-3-pentadecylcatechol (XXIIb) of only about 7%. This corresponds to less than a 1% yield from readily available starting materials since the yield in the synthesis of XXIIb was about 13%.

Having found that hydrogenolysis of the amine (XXIb) proceeded so poorly, presumably because of the considerable crowding around the hexasubstituted aromatic ring, it seemed that synthesis of 4,5,6-trimethyl-3-pentadecylcatechol might be better accomplished if it were possible to prepare a similar intermediate which could be converted into XIXb by hydrogenolysis of a more easily broken bond, such as the one between carbon and sulfur. This goal was achieved by the reaction of 4,5-dimethyl-3-pentadecylcatechol with a mixture of carbon disulfide, formaldehyde, and dimethylamine in ethanol to give 6-(N,N-dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIII) in 82% yield.[15] Successful substi-



XXIII

tution for the lone aromatic proton of 4,5-dimethyl-3-pentadecylcatechol was indicated by the absence of a peak in the τ 3–5 region of the nmr spectrum. Desulfurization of XXIII was accomplished using a tenfold excess by weight of Raney nickel W-7 catalyst in reflux-

(11) A. S. Gulati, Ph.D. Dissertation, University of Poona, 1963.

(12) W. T. Caldwell and T. R. Thompson, *J. Amer. Chem. Soc.*, **61**, 765 (1939).

(13) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bills, *J. Org. Chem.*, **26**, 4669 (1961).

(14) S. H. Langer, P. Pantages, and I. Wender, *Chem. Ind.* (London), 1664 (1958).

(15) U. S. Rubber Co., Netherlands Patent Appl. 6,408,883 (Feb 2, (1965).

ing dioxane[16] to give 4,5,6-trimethyl-3-pentadecylcatechol in over 75% yield. Evidence of complete desulfurization was provided by the loss of the thiocarbonyl absorption at 7.65 μ in the infrared spectrum and the presence in the nmr spectrum of a peak at τ 7.92 equivalent to three nuclear methyl groups. This compound was identical with the one obtained by hydrogenolysis of XXIb, but the yield was 62% from 4,5-dimethyl-3-pentadecylcatechol. Thus, the synthesis of the trimethyl homolog *via* the dithiocarbamoyl intermediate resulted in an eightfold improvement in the over-all yield.

Experimental Section[17]

5-Methyl-*o*-vanillin (III).—A mixture of 183.6 g of 4-methylguaiacol (prepared from vanillin in 89% yield by the Huang-Minlon modification of the Wolff–Kishner reduction), 78.6 g of paraformaldehyde, and 78.6 g of hexamethylenetetramine was melted and heated to 110°. To this molten mixture was added 300 ml of glacial acetic acid, followed by slow addition of 150 ml of a 1:1 solution of sulfuric acid and water. Addition of the sulfuric acid caused rapid reflux and considerable darkening of the reaction mixture. The resulting solution was then heated at reflux for 30 min, after which it was poured into 1500 ml of water. This mixture was steam distilled and the product separated from the steam distillate as yellow plates. Recrystallization from ligroin (bp 60–90°) gave 5-methyl-*o*-vanillin as yellow needles, mp 40.0–41.5°. The yield was 110.1 g (49.9%). The significant peaks in the infrared spectrum were hydroxyl at 2.84 μ and carbonyl at 6.00 μ. In the nmr spectrum in acetone solution, the hydroxyl proton produced a sharp singlet at τ −0.51 and the hydrogen on the carbonyl carbon produced a sharp singlet at τ −0.02.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.96; H, 5.97.

5-Methyl-*o*-veratraldehyde (V).—To 110.1 g of melted 5-methyl-*o*-vanillin (III) were simultaneously added 80 g of potassium hydroxide in 175 ml of water and 100 ml of dimethyl sulfate. The mixture was then refluxed for 2.5 hr, after which 500 ml of water was added and the reaction vessel was cooled in an ice bath. The product, which separated as a tan solid, was filtered, washed with water, and then recrystallized from ligroin. The yield of 5-methyl-*o*-veratraldehyde was 104.2 g (87.2%). The hydroxyl peak at 2.84 μ was absent in the spectrum and the carbonyl peak was at 5.85 μ.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.52; H, 6.55.

5-Methyl-3-(1′-hydroxy)pentadecylveratrole (VI).—To a solution of tetradecylmagnesium bromide in 150 ml of anhydrous ether prepared in the usual manner from 3.8 g of magnesium metal and 41.6 g of 1-bromotetradecane was added 18.0 g of the above 5-methyl-*o*-veratraldehyde in 100 ml of ether. The reaction mixture was heated at reflux for 18 hr under a nitrogen atmosphere and then was cooled in an ice bath and hydrolyzed by addition of 150 ml of 10% sulfuric acid. After separating the two phases, the aqueous layer was washed with 200 ml of ether, and the combined ether solutions were dried over magnesium sulfate. Removal of solvent gave a yellow oil which was dissolved in boiling 95% ethanol. On chilling of the ethanolic solution, octacosane precipitated as silvery plates and was filtered. Solvent was again removed to give 36 g of crude 5-methyl-3-(1′-hydroxy)-pentadecylveratrole as a yellow oil. This material was used in the next step without further purification.

5-Methyl-3-pentadecylveratrole (VII).—The crude 5-methyl-3-(1′-hydroxy)pentadecylveratrole obtained in the previous step was dissolved in 100 ml of ethyl acetate to which was added 5 drops of sulfuric acid and 0.35 g of 10% palladium-on-charcoal catalyst. Hydrogenation was carried out in a Parr shaker at approximately 60° and at an initial hydrogen pressure of 60 psi. Hydrogenation was continued for 24 hr and then the solution was allowed to cool and was diluted with 200 ml of ether. After the catalyst had been removed by filtration, the solvent was evaporated and vacuum distillation of the residual oil was carried out at 0.4-mm pressure to give 20.3 g (56.2%) of 5-methyl-3-pentadecylveratrole as a colorless oil (bp 206–209°). On cooling, the oil formed a white solid which was recrystallized from an ethanol–acetone mixture (mp 35.2–36.2°). The nmr spectrum of this compound consisted of a two-proton singlet at τ 3.61 (aromatic H), a six-proton singlet at τ 6.30 ($-OCH_3$), and a three-proton singlet at τ 7.80 (nuclear $-CH_3$), as well as the characteristic peaks for the pentadecyl side chain. In the infrared, the low intensity peaks indicative of a 1,2,3,5-tetrasubstituted benzene appeared at 5.15, 5.25, and 5.80 μ.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.51; H, 11.44.

5-Methyl-3-pentadecylcatechol (IV).—A solution of 50 g of 5-methyl-3-pentadecylveratrole (VII) in 250 g of pyridine was heated at reflux, and dry hydrogen chloride gas was bubbled through the refluxing solution. In approximately 1 hr all of the pyridine had been converted into pyridine hydrochloride, and the temperature of the reaction mixture rose to about 220°. After refluxing at that temperature for 2.5 hr, the solution was allowed to cool and 250 ml of ether was added as well. The layers were then separated, the aqueous layer was extracted with two 250-ml portions of ether, and the combined ether solutions were washed with two 200-ml portions of water. After treatment with decolorizing charcoal and drying over magnesium sulfate, the solvent was removed *in vacuo* to give a white solid. After recrystallization from ligroin, the yield of 5-methyl-3-pentadecylcatechol (mp 74.5–76.0°) was 41.2 g (89.5%). The significant peak in the infrared spectrum of this compound was that for the hydroxyl groups at 2.85 μ.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 78.95; H, 10.98.

5-Methylguaiacol Allyl Ether (XII).—To a solution of 41.4 g of 5-methylguaiacol (IX) (prepared from isovanillin in 96% yield by the Huang-Minlon modification of the Wolff–Kishner reduction) in 75 ml of acetone was added 42 g of anhydrous potassium carbonate and 40 g of allyl bromide. The mixture was refluxed with rapid stirring for 8 hr, after which 200 ml of water was added. As soon as all solids had dissolved, the phases were separated and the aqueous layer was extracted with two 100-ml portions of ether. The organic solutions were then combined, washed with two 100-ml portions of 10% sodium hydroxide, and dried over anhydrous potassium carbonate. After evaporating the solvent, the residual oil was distilled at 10 mm to yield 49.2 g (92%) of 5-methylguaiacol allyl ether as a colorless oil, bp 128–132°. The infrared spectrum contained no peak for hydroxyl and had a new peak at ~10.6 μ. The following peaks appeared in the nmr spectrum: singlet (3) at τ 3.37 (aromatic H); multiplet (1) at τ 3.7–4.3 ($-CH_2CH{=}CH_2$); multiplet (2) at τ 4.5–5.0 ($-CH_2CH{=}CH_2$); doublet (2) at τ 5.58 ($-CH_2CH{=}CH_2$); singlet (3) at τ 6.33 ($-OCH_3$); singlet (3) at τ 7.80 (nuclear $-CH_3$).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.92.

5-Methyl-6-allylguaiacol (XIII).—Using an oil bath set at 235°, 48.0 g of the above 5-methylguaiacol allyl ether was heated under an inert atmosphere of nitrogen. When the temperature of the liquid reached 210°, slow evolution of bubbles began. At 225° rapid reflux started, the internal temperature rose quickly to 255°, and the bath was removed. When the temperature began to fall, heating was resumed and the temperature of the liquid was kept at 245° for 1 hr. After cooling to room temperature, 100 ml of ether was added, and the ethereal solution was extracted with three 100-ml portions of 10% sodium hydroxide. The alkaline solution was then acidified with hydrochloric acid and extracted with two 150-ml portions of ether. These were combined, dried over magnesium sulfate, and concentrated to give a clear, brown oil. Distillation of that oil at 10 mm yielded 33.4 g (69.5%) of 5-methyl-6-allyl guaiacol as a colorless oil, bp 135–142°. In the infrared, there was now a hydroxyl peak at 2.80 μ and a peak at 10.4 μ. In the 5–6-μ region, low intensity peaks appeared at ~5.4 and ~5.8 μ, with the shorter wavelength peak the more intense of the two. In the nmr, the allylic methylene doublet was shifted upfield to τ 6.60 and there was a sharp singlet at τ 4.33 (–OH).

(16) G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962).

(17) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137 Infracord and were measured in carbon tetrachloride solution unless otherwise specified. The nmr spectra were obtained with a Varian A-60 or A-60A spectrometer using tetramethylsilane as an internal standard and carbon tetrachloride as solvent, unless otherwise indicated. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.83; H, 7.91.

3-Allyl-4-methylveratrole (XIV).—To 31.3 g of the above 5-methyl-6-allylguaiacol heated to 100° were added simultaneously 11.2 g of potassium hydroxide in 25 ml of water and 25.2 g of dimethyl sulfate. After the addition was complete, the mixture was refluxed with rapid stirring for 3 hr, then cooled and the layers separated. The aqueous layer was extracted with two 75-ml portions of ether, and the combined organic fractions were dried over magnesium sulfate and the solvent removed *in vacuo* to give a yellow oil. Distillation of this oil at 10 mm yielded 29.5 g (87%) of 3-allyl-4-methylveratrole as a colorless liquid, bp 133–140°. The hydroxyl peak at 2.80 μ was no longer apparent in the infrared. In the nmr the singlet at τ 4.33 was gone, and the two methoxyls appeared as sharp singlets at τ 6.25 and 6.28.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.76; H, 8.28.

3-Propenyl-4-methylveratrole (XV).—Methanol was distilled from a rapidly stirred mixture of 29.0 g of 3-allyl-4-methylveratrole (XIV) and 90 ml of saturated methanolic potassium hydroxide until the temperature of the liquid reached 100°. Distillation was then discontinued, and the mixture was refluxed at 110–120° for 6 hr. It was then cooled, 100 ml of water was added, and the layers were separated. The aqueous phase was extracted with two 75-ml portions of ether, the combined ether extracts were dried over magnesium sulfate, and the solvent was evaporated. Vacuum distillation at 15 mm yielded 27.9 g (96%) of 3-propenyl-4-methylveratrole as a colorless liquid, bp 142–151°. In the nmr the two proton allylic doublet at τ 6.60 was replaced by a three-proton doublet at τ 8.12. There were overlapping multiplets in the τ 3–4 region.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.94; H, 8.38.

6-Methyl-*o*-veratraldehyde (XVI).—A solution of 26.9 g of the above 3-propenyl-4-methylveratrole in 500 ml of methanol was chilled to approximately −40°. A stream of ozone enriched oxygen (2%) was then bubbled through the solution at a rate of 0.08 ft³/min for 1.5 hr, during which time the temperature of the solution was held at −30 to −40°. When the ozonization had been completed, the temperature of the solution was brought to 0°, and the reaction mixture was decanted into an erlenmeyer flask cooled in an ice bath. After rinsing the ozonization vessel with 100 ml of methanol and adding this to the original solution, 10 g of dimethyl sulfide was added, and the mixture was stirred at approximately 0° for 2 hr. Next, the solvent was stripped to leave a residual oil which was suspended in 200 ml of water. This was extracted with three 200-ml portions of ether, the combined ethereal fractions were dried over magnesium sulfate, and the solvent was removed under vacuum. Distillation of the residual oil at 10 mm yielded 20.7 g (82%) of 6-methyl-*o*-veratraldehyde as a pale yellow oil (bp 127–133°). On cooling, the oil became a cream solid which was recrystallized from ligroin as white needles (mp 53.5–54.5°). The significant absorption in the infrared was a carbonyl peak at 5.94 μ. When subjected to vapor phase chromatography on an SE-30 column, the product gave a single sharp peak.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.21; H, 6.62.

4-Methyl-3-(1′-hydroxy)pentadecylveratrole (XVII).—To a solution of tetradecylmagnesium bromide in 150 ml of ether, prepared in the customary fashion from 2.9 g of magnesium metal and 30.5 g of 1-bromotetradecane, was added 18.0 g of the above 6-methyl-*o*-veratraldehyde in 100 ml of ether. The mixture was refluxed for 18 hr, after which it was cooled in an ice bath and then hydrolyzed by addition of 200 ml of 10% sulfuric acid. The layers were separated, the aqueous layer was extracted with 150 ml of ether, and the combined ethereal solutions were dried over magnesium sulfate and then were concentrated to give a yellow liquid. This oil was dissolved in boiling ethanol which was then chilled to precipitate octacosane. After filtering, the solvent was removed to give 35 g of crude 4-methyl-3-(1′-hydroxy)-pentadecylveratrole, which was used in the next step without further purification.

4-Methyl-3-pentadecylveratrole (XVIII).—The above crude 4-methyl-3-(1′-hydroxy)pentadecylveratrole was dissolved in 100 ml of ethyl acetate containing 5 drops of sulfuric acid to which was added 0.35 g of 10% palladium-on-carbon catalyst. This mixture was shaken at about 60° for 48 hr under an initial hydrogen pressure of 60 psi. After that time the solution was diluted with 150 ml of ether, filtered, and washed with 100 ml of 10% sodium bicarbonate, followed by 100 ml of water. After drying with magnesium sulfate, the solvent was evaporated, and the residual oil was distilled at 0.4 mm to yield 17.3 g (48% yield, based on 6-methyl-*o*-veratraldehyde) of 4-methyl-3-pentadecylveratrole as a colorless oil (bp 213–217°). On cooling this oil changed to a white solid, recrystallizable from ethanol–acetone, mp 34.0–35.0°. The significant peaks in the nmr were aromatic H at τ 3.39, methoxyl at τ 6.25, and methyl at τ 7.82.

Anal. Calcd for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.32; H, 11.53.

4-Methyl-3-pentadecylcatechol (VIII).—A solution of 17.3 g of the above 4-methyl-3-pentadecylveratrole in 85 g of pyridine was heated to reflux, and a stream of dry hydrogen chloride gas bubbled through the mixture. After about 1 hr the temperature of the liquid reached 220°. Refluxing was continued at that temperature for 4 hr with the passage of HCl, then the mixture was cooled to 120°, and 100 ml of water was added. After cooling further with an ice bath, 150 ml of ether was added and the layers were separated. The aqueous layer was extracted with 200 ml of ether, and the combined ether layers were treated with decolorizing charcoal and then dried over magnesium sulfate. The solution was concentrated and the residual brown oil was distilled at 0.4 mm to yield 4-methyl-3-pentadecylcatechol as a pale yellow oil (bp 200–203°) which cooled to a white solid. After recrystallization from ligroin, the yield was 11.3 g (70.6%) of white solid, mp 55.0–56.5°.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 79.18; H, 11.51.

6-(N,N-Dimethylamino)methyl-3-pentadecylcatechol (XXa).—A solution of 48 g of 3-pentadecylcatechol in 300 ml of 95% ethanol was chilled in an ice bath and to it was added 42 ml of 25% dimethylamine in water, followed by 18 ml of 37% formaldehyde. After 1 hr, the ice bath was removed and the reaction mixture was stirred at room temperature for 18 hr. During that time a deep violet color developed and considerable solid separated from the solution. This solid was filtered, washed with ice-cold ethanol, and recrystallized from ethanol to give 50.4 g (89.2%) of 6-(N,N-dimethylamino)methyl-3-pentadecylcatechol as cream plates (mp 46.0–46.8°). The significant peaks in the nmr were a quartet at τ 3.65 (aromatic H), a two-proton singlet at τ 6.47 (–N–CH_2), a six-proton singlet at τ 7.70 (–N–CH_3), and a broad two-proton singlet at about τ 1.6 (–OH).

Anal. Calcd for $C_{24}H_{43}NO_2$: C, 76.34; H, 11.48; N, 3.71. Found: C, 75.90; H, 11.39; N, 3.69.

Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-3-pentadecylcatechol (XXIa).—To a solution of 37.7 g of the above 6-(N,N-dimethylamino)methyl-3-pentadecylcatechol in 150 ml of pyridine were added 40 g of hexamethyldisilizane and 10 drops of trimethylchlorosilane.[11] The solution was heated at reflux, causing evolution of ammonia which continued for about 45 min. The solution was then refluxed an additional 1 hr, after which the solvent was removed on the rotary evaporator to give a brown oil. Vacuum distillation of the oil at 0.5 mm yielded 39.6 g (76%) of the product (XXIa) as a colorless liquid, bp 237–243°. The absence of a hydroxyl peak at <3.0 μ in the infrared spectrum indicated complete conversion into the bistrimethylsilyl derivative.

6-Methyl-3-pentadecylcatechol (XIXa). A. By Hydrogenolysis of 6-(N,N-Dimethylamino)methyl-3-pentadecylcatechol (XXa).—A solution of 11.4 g of XXa in 100 ml of absolute ethanol was shaken with 1 g of 10% palladium-on-carbon catalyst at approximately 60° and under an initial hydrogen pressure of 60.2 psi for a total of 48 hr. The solution was then cooled and filtered to remove the catalyst, and the solvent was evaporated to give a dark oil which partially solidified. Recrystallization of this material from ligroin, followed by vacuum sublimation, gave 1.2 g of 6-methyl-3-pentadecylcatechol as a white solid (mp 63.5–64.5°). The yield was 12%. The nmr spectrum of this compound was composed of a sharp two-proton singlet at τ 3.50 (aromatic H), a broad two-proton singlet at τ 4.45 (–OH), and a sharp three-proton singlet at τ 7.80 (nuclear –CH_3), as well as appropriate peaks for the pentadecyl side chain.

B. By Hydrogenolysis of Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-3-pentadecylcatechol (XXIa).—To a solution of 37.7 g of XXIa in 150 ml of absolute ethanol were added 1 g of 10% palladium-on-carbon catalyst and 5 drops of sulfuric acid. The mixture was then hydrogenated on a Parr shaker for 20 hr at approximately 60° at an initial hydrogen pressure of 60 psi. When no further hydrogen uptake could be observed, the reaction

mixture was cooled and filtered. To this was added 25 ml of water, and the solution was refluxed with rapid stirring for 2 hr. The reaction mixture was then poured into 200 ml of water, and the resulting emulsion was extracted with three 100-ml portions of ether. The combined ether solutions were dried over magnesium sulfate, and the solvent was removed to give a dark oil. Vacuum distillation of this material at 0.2 mm yielded a pale yellow oil (bp 200–206°) which cooled to a cream solid. Recrystallization from ligroin gave 18.9 g (78%) of a white solid (mp 62.5–64.5°) which was indistinguishable on the basis of infrared and nmr spectra from the 6-methyl-3-pentadecylcatechol obtained by procedure A, *i.e.*, hydrogenolysis of the unsilylated Mannich base.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 78.73; H, 11.36.

6-(N,N-Dimethylamino)methyl-4,5-dimethyl-3-pentadecylcatechol (XXb).—A solution of 17.4 g of 4,5-dimethyl-3-pentadecylcatechol in 100 ml of 95% ethanol was chilled in an ice bath, and to it was added 14.1 g of dimethylamine (25% in water), followed by 6.3 ml of 37% formaldehyde solution. After 1 hr the ice bath was removed, and the solution was stirred at room temperature for 16 hr. The product separated as a tan solid which was filtered and washed with cold ethanol. After recrystallization from ethanol, 9.4 g (46.5%) of 6-(N,N-dimethylamino)-methyl-4,5-dimethyl-3-pentadecylcatechol was obtained (mp 35.0–37.0°). In the nmr there was a broad two-proton singlet at τ 1.50 (–OH), a two-proton singlet at τ 6.40 ($-N-CH_2-$), a six-proton singlet at τ 7.70 ($-N-CH_3$), and a pair of singlets corresponding to a total of six protons at τ 7.92 and 7.96 (nuclear $-CH_3$), as well as the characteristic peaks for the pentadecyl side chain. There was no peak in the downfield region characteristic of hydrogens on a benzene ring.

Anal. Calcd for $C_{25}H_{47}NO_2$: C, 76.98; H, 11.68; N, 3.45. Found: C, 77.34; H, 11.48; N, 3.59.

Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-4,5-di-methyl-3-pentadecylcatechol (XXIb).—To a solution of 9.4 g of the above 6-(N,N-dimethylamino)methyl-4,5-dimethyl-3-pentadecylcatechol in 50 ml of pyridine were added 8 g of hexamethyldisilizane and 5 drops of trimethylchlorosilane. This reaction mixture was refluxed for 2.5 hr, after which the solvent was removed under vacuum to give a brown oil. Vacuum distillation of this material at 0.4 mm yielded 8.5 g (62.5%) of the bistrimethylsilyl compound (XXIb) as a clear, colorless oil (bp 205–214°). The absence of a hydroxyl peak in the infrared spectrum at $<3.0\ \mu$ indicated that trimethylsilylation was complete.

6-(N,N-Dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIII).—To a solution of 34.8 g of 4,5-dimethyl-3-pentadecylcatechol in 200 ml of 95% ethanol was added 8.3 g of carbon disulfide, 8.5 g of 37% formaldehyde, and 18.9 g of 25% dimethylamine. The resulting solution was refluxed for 2.5 hr, during which time considerable turbidity developed, and was then chilled in an ice bath to precipitate 6-(N,N-dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol. Recrystallization from ethanol–acetone gave a cream solid, mp 71.0–73.0°. The yield was 39.5 g (82%). In the infrared there was a peak for C=S at 7.65 μ. The significant peaks in the nmr were a two-proton singlet at τ 5.50 ($-S-CH_2-$), a pair of singlets equal to six protons at τ 6.66 and 6.84 ($-N-CH_3$), and a six-proton singlet at τ 7.95 (nuclear $-CH_3$).

Anal. Calcd for $C_{27}H_{47}NO_2S_2$: C, 67.31; H, 9.83; N, 2.91; S, 13.31. Found: C, 67.78; H, 9.96; N, 2.72; S, 13.07.

4,5,6-Trimethyl-3-pentadecylcatechol (XIXb). A. By Hydrogenolysis of 6-(N,N-Dimethyldithiocarbamoyl)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIII).—A solution of 36.1 g of the above XXIII in 1200 ml of anhydrous dioxane was refluxed for 16 hr with Raney nickel W-7 catalyst prepared from 361 g of Raney nickel alloy.[18] The reaction mixture was then cooled and filtered to give a green solution to which was added 750 ml of ether. This solution was shaken with 750 ml of 5% aqueous hydrochloric acid, bleaching the organic layer to an orange color. The phases were then separated, and the aqueous layer was washed with 500 ml of ether. The organic portions were combined, dried over magnesium sulfate, and concentrated to give a red-brown oil. Vacuum distillation at 0.2–0.3-mm pressure yielded 20.5 g (75.7%) of 4,5,6-trimethyl-3-pentadecylcatechol as a colorless liquid (bp 210–223°), which rapidly gave a white solid (mp 78.0–79.0°) on cooling. The infrared spectrum of this compound lacked the thiocarbonyl peak at 7.65 μ. In the nmr the only peaks other than those for the pentadecyl side chain were a broad two-proton singlet at τ 6.49 (–OH) and a nine-proton singlet at τ 7.92 (nuclear $-CH_3$).

Anal. Calcd for $C_{25}H_{42}O_2$: C, 79.50; H, 11.68. Found: C, 79.59; H, 11.71.

B. By Hydrogenolysis of Bistrimethylsilyl-6-(N,N-dimethylamino)methyl-4,5-dimethyl-3-pentadecylcatechol (XXIb).—To a solution of 8.5 g of (XXIb) in 100 ml of absolute ethanol were added 0.85 g of 10% palladium-on-carbon catalyst and 5 drops of sulfuric acid, and the mixture was hydrogenated at approximately 60° at an initial hydrogen pressure of 60 psi. After 48 hr the reaction mixture was cooled and filtered and to it was added 10 ml of water. This solution was refluxed for 2 hr and then was poured into 150 ml of water and 100 ml of ether. After the layers had been separated, the aqueous phase was washed with two 100-ml portions of ether, and the combined ether solutions were dried over magnesium sulfate. Solvent was then removed, and the residual oil was distilled at 0.5 mm. The yellow distillate (bp 225–237°) solidified on cooling to give a tan solid. After recrystallization from ligroin 1.2 g (26%) of 4,5,6-trimethyl-3-pentadecylcatechol (mp 77.0–79.0°) was isolated. This material was identical in infrared and nmr spectra with the product obtained by procedure A.

Registry No.—III, 7452-10-0; IV, 16273-08-8; V, 5701-86-0; VII, 16273-09-9; VIII, 16273-11-3; XII, 16273-12-4; XIII, 16273-13-5; XIV, 16273-14-6; XV, 16273-15-7; XVI, 16273-16-8; XVIII, 16273-17-9; XIXa, 16273-18-0; XIXb, 16273-19-1; XXa, 16273-29-3; XXb, 16273-21-5; XXIa, 16273-23-7; XXIb, 16273-25-9; XXIII, 16273-27-1.

(18) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 176.