Synthesis of 2-Multiprenylphenols and 2-Multiprenyl-6-methoxyphenols, Biosynthetic Precursors of the Ubiquinones[1-3]

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The synthesis of 2-multiprenylphenols by three routes has been accomplished. Acid-catalyzed condensation of methyl *p*-hydroxybenzoate with phytol followed by ester hydrolysis and thermal decarboxylation yielded 2-phytylphenol. Isoprenylation of phenol under either acidic or basic conditions yielded 2-geranyl-, 2-farnesyl-, 2-phytyl-, 2-nonaprenyl-(2-solanesyl-), and 2-decaprenylphenol. Isoprenylation of 2-methoxyphenol (guaiacol) produced 2-geranyl-, 2-farnesyl-, 2-phytyl-, 2-nonaprenyl-(2-solanesyl-), and 2-decaprenyl-6-methoxyphenol. Among these compounds achieved synthetically, 2-decaprenylphenol, 2-nonaprenylphenol, and 2-decaprenyl-6-methoxyphenol have previously been isolated from cultures of *R. rubrum* and shown to be biosynthetic precursors of ubiquinone.

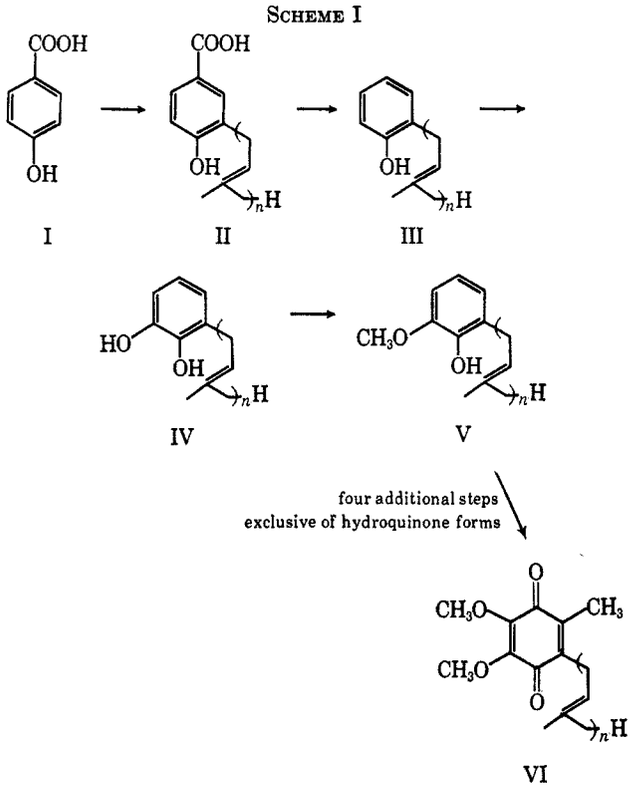
Recent studies of the biosynthesis of ubiquinone (VI) in *Rhodospirillum rubrum* have led to the isolation and identification[4-6] of four new 2-multiprenylphenols (III, n = 4, 9, 10; V, n = 10). Two of these compounds, 2-decaprenylphenol (III, n = 10)[3,4] and 2-decaprenyl-6-methoxyphenol (V, n = 10),[3,5] are precursors of ubiquinone-10 (VI, n = 10) in *R. rubrum;* 2-nonaprenylphenol (III, n = 9) is a precursor of ubiquinone-9 (VI, n = 9), and 2-tetraprenylphenol (III, n = 4) appears to be a precursor of ubiquinone-4 (VI, n = 4), which, however, has not yet been found in nature. Presumably these same biosynthetic intermediates (or appropriate isoprenylogs) function as precursors to the corresponding ubiquinones (VI) in other microorganisms and in mammals. Representative 2-multiprenylphenols (III) and 2-multiprenyl-6-methoxyphenols (V) have now been synthesized for comparison with the natural products and to support extended biological research in this field.

The isolation and identification of these four new biosynthetic phenols permits the formulation of intermediates II through V in the biosynthesis by *R. rubrum* of ubiquinone (VI) from *p*-hydroxybenzoic acid (I) (see Scheme I). The four additional steps, exclusive of hydroquinone forms, have very recently been elucidated.[7]

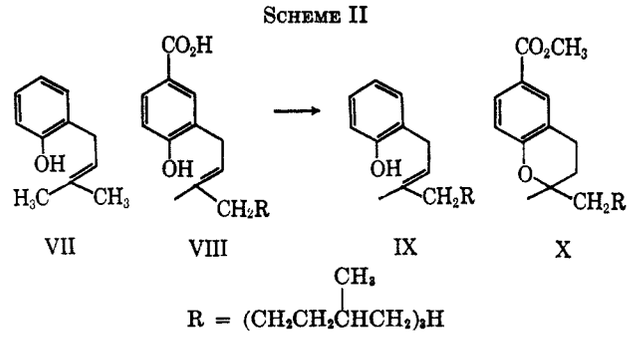
Recently, Isagulyants and Evstafev[8] reported the preparation of 2-(3′-methyl-2′-butenyl)phenol (VII) by the acid-catalyzed reaction of phenol with 3-methylbutene-1, a method not applicable to the synthesis of higher isoprenylogs. A search of the literature failed to reveal other 2-isoprenylphenols (see Scheme II).

The biosynthesis of the 2-multiprenylphenols (III) apparently involves isoprenylation of *p*-hydroxybenzoic acid *ortho* to the hydroxyl function to produce as an intermediate the corresponding 4-hydroxy-3-multiprenylbenzoic acid (II).[5] The lowest isoprenylog of this series, 4-hydroxy-3-(3′-methyl-2′-butenyl)benzoic acid (II, n = 1), is a metabolite of *Streptomyces spheroides*[9] and is incorporated *via* an amide linkage as a moiety in the antibiotic, novobiocin.[10] Initially, a synthetic route to 2-phytylphenol (IX) was developed

SCHEME I



SCHEME II



(1) Coenzyme Q. LXXXII.

(2) Coenzyme Q. LXXIX: C. Hall, M. Wu, F. L. Crane, N. Takahashi, S. Tamura, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **25**, 373, 1966.

(3) The nomenclature used in this paper is based on a recommendation of an IUPAC-IUB Commission of Biochemical Nomenclature in *Biochim. Biophys. Acta*, **107**, 5 (1965).

(4) R. K. Olsen, J. L. Smith, G. D. Daves, Jr., H. W. Moore, K. Folkers, W. W. Parson, and H. Rudney, *J. Am. Chem. Soc.*, **87**, 2298 (1965).

(5) R. K. Olsen, G. D. Daves, Jr., H. W. Moore, K. Folkers, and H. Rudney, *ibid.*, **88**, 2346 (1966).

(6) R. K. Olsen, G. D. Daves, Jr., H. W. Moore, K. Folkers, W. W. Parson, and H. Rudney, *ibid.*, **88**, 5919 (1966).

(7) P. Friis, G. D. Daves, Jr., and K. Folkers, *ibid.*, **88**, 4754 (1966).

(8) V. I. Isagulyants and V. P. Evstafev, *Zh. Organ. Khim.*, **1**, 102 (1965).

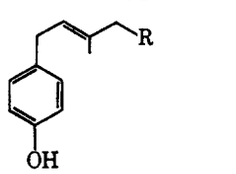
(9) C. H. Shunk, C. H. Stammer, E. A. Kaczka, E. Walton, C. F. Spencer, A. N. Wilson, J. W. Richter, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, **78**, 1770 (1956).

(10) E. A. Kaczka, C. H. Shunk, J. W. Richter, F. J. Wolf, M. M. Gasser, and K. Folkers, *ibid.*, **78**, 4125 (1956).

which utilized this apparent biosynthetic sequence (I → II → III).

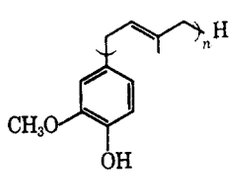
Methyl *p*-hydroxybenzoate was treated with phytol in the presence of boron trifluoride etherate followed by basic hydrolysis of the ester function to yield 4-hydroxy-3-phytylbenzoic acid (VIII). Unambiguous proof of the *ortho* relationship of the phytyl side chain and the hydroxyl function was provided by the formation of 6-carbomethoxy-2-methyl-2-(4′,8′,12′-trimethyltridecyl)chroman (X) upon treatment of the initial reaction product with hot methanolic hydrogen chloride. Thermal decarboxylation of VIII in the presence of calcium oxide yielded 2-phytylphenol (IX).

A direct route to 2-multiprenylphenols (III) was achieved by the direct alkylation of phenol. When a dioxane solution of phytol and a fourfold excess of phenol was treated with boron trifluoride etherate, 2-phytylphenol (IX) was produced along with the *para*-alkylated isomer (XIa). These two isomers were readily separated chromatographically. Acid-catalyzed condensation of phenol with geraniol, farnesol, and solanesol[11] produced the corresponding multiprenylphenols (III, n = 2, 3, 9) together with their *para*-alkylated isomers (XIb, n = 2, 3, 9). Similarly, acid-catalyzed alkylation of 2-methoxyphenol (guaiacol) produced 2-geranyl-6-methoxyphenol (V, n = 2) and 2-farnesyl-6-methoxyphenol (V, n = 3) also together with their *para*-alkylated isomers (XII, n = 2, 3). When 2-methoxyphenol and solanesol[11] were treated with boron trifluoride etherate, the desired 2-nonaprenyl-6-methoxyphenol (V, n = 9) was formed in very low yield (as shown by thin layer chromatography) and only the *para*-alkylated isomer, 4-nonaprenyl-2-methoxyphenol (XII, n = 9) was isolated.



XIa, R = $(CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2)_3H$

b, R = $(CH_2CH{=}\overset{CH_3}{\overset{|}{C}}CH_2)_nH$



XII

Treatment of the sodium derivative of phenol or 2-methoxyphenol with an appropriate multiprenyl bromide produced the desired 2-multiprenylphenol (III) or 2-multiprenyl-6-methoxyphenol (V), respectively, together with the corresponding O-alkylated isomer.[12] No *para*-alkylated isomers were formed. This procedure proved to be preferable especially for the preparation of the higher isoprenylogs, *i.e.*, III, V (n = 9, 10).

The 2-multiprenylphenols (III) and 2-multiprenyl-6-methoxyphenols (V) were readily characterized by spectral methods. The ultraviolet spectra (Table I) of the 2-multiprenylphenols (III) and of the 2-multiprenyl-6-methoxyphenols (V) as well as of their *para*-multiprenyl isomers (XI and XII) correspond closely to the ultraviolet spectra of model compounds. Both

TABLE I

ULTRAVIOLET ABSORPTION FOR 2-MULTIPRENYLPHENOLS AND RELATED COMPOUNDS

Compd	λ_{max}^{hexane}, mμ
Phenol	
2-Phytyl (IX)	273, 278
4-Phytyl (XIa)	270, 273, 276, 278, 285
2-Geranyl (III, n = 2)	272, 279
4-Geranyl (XIb, n = 2)	271, 274, 276, 279, 286
2-Farnesyl (III, n = 3)	272, 279
4-Farnesyl (XIb, n = 3)	271, 274, 276, 279, 286
2-Nonaprenyl (III, n = 9)	273, 278
2-Decaprenyl (III, n = 10)	273, 278
6-Methoxyphenol	
2-Phytyl	273, 279
2-Geranyl (V, n = 2)	273, 279
2-Farnesyl (V, n = 3)	273, 279
2-Nonaprenyl (V, n = 9)	273, 279
2-Decaprenyl (V, n = 10)	273, 279
2-Methoxyphenol	
4-Geranyl (XII, n = 2)	278, 282, 287
4-Farnesyl (XII, n = 3)	278, 282, 288

the 2-multiprenylphenols (III) and the 2-multiprenyl-6-methoxyphenols (V) show ultraviolet maxima (hexane) at 273 (274) and 278 (279) mμ. 2-Allylphenol[13] and *o*-cresol[14] show λ_{max}^{hexane} at 272 and 279 mμ. The 4-multiprenylphenols (XI) and 2-methoxy-4-multiprenylphenols (XII) have maxima at longer wavelengths [λ_{max}^{hexane} 278 (279) and 286–288 mμ] and exhibit considerably more fine structure (Table I). The spectrum of *p*-cresol[14] is very similar with considerable fine structure with maxima at 279 and 286 mμ (hexane).

The nmr spectra (Table II) contain even more definitive structural information. The differentiation between the 2-multiprenylphenols (III) and their 4-multiprenyl isomers (XI) is readily accomplished by a comparison of the aromatic proton absorptions. The nmr signal due to the aromatic protons of the 2-multiprenylphenols (III) appears as an unresolved multiplet at τ 2.8–3.5, and the 4-multiprenylphenols (XI) show a well-resolved A_2B_2 pattern centered at 3.3. In the spectra of the 2-multiprenyl-6-methoxyphenols (V), the aromatic protons appear as a three-proton singlet rather than a complex multiplet. This feature was first noted in the spectrum of natural 2-decaprenyl-6-methoxyphenol (V, n = 10) isolated from *R. rubrum*.[4,5] The aromatic protons of the isomeric 4-isoprenyl derivatives (XII) appear as a multiplet at τ 3.2–3.6. An interesting feature of the nmr spectra of these multiprenylphenols is the difference in chemical shifts observed for the benzylic methylene protons of the isomeric 2-multiprenyl- (III) and 4-multiprenylphenols (XI). In every case where a comparison is possible, the benzylic doublet for the 4-multiprenyl isomer appears at higher field than the comparable absorption for the 2-multiprenyl isomer. This is also true in the case of the isomeric 2-multiprenyl-6-methoxyphenols (V) and 4-multiprenyl-2-methoxyphenols (XII). Typically, 2-geranyl-6-methoxyphenol (V, n = 2) shows a benzylic doublet at τ 6.68, while the corresponding doublet in the spectrum

(11) R. L. Rowland, P. H. Latimer, and J. A. Giles, *J. Am. Chem. Soc.*, **78**, 4680 (1956).

(12) See N. Kornblum and A. P. Lurie, *ibid.*, **81**, 2705 (1959), for a critical discussion of alkylation of phenols under basic conditions.

(13) T. J. Webb, L. I. Smith, W. A. Bastedo, Jr., H. E. Ungnade, W. W. Prichard, H. H. Hoehn, S. Wawzonek, J. W. Opie, and F. L. Austin, *J. Org. Chem.*, **4**, 389 (1939).

(14) L. Lang, "Absorption Spectra in the Ultraviolet and Visible Region," Vol. 11, Academic Press Inc., New York, N. Y., 1961, pp 139–144.

TABLE II

NMR DATA FOR 2-MULTIPRENYLPHENOLS AND RELATED COMPOUNDS[a]

Compd	Aromatic	OH	Vinyl	Methoxyl	Benzylic	Alkyl
Phenol						
2-Phytyl (IX)	2.8–3.4 (m 4)	5.15 (s 1)	4.65 (t 1)		6.64 (d 2)	7.8–9.9
4-Phytyl (XIa)	3.32[b]	5.77 (s 1)	4.74 (t 1)		6.78 (d 2)	7.8–9.3
2-Geranyl (III, n = 2)	2.8–3.5 (m 4)	5.24 (s 1)	4.87 (m 2)		6.67 (d 2)	7.8–8.5
2-Farnesyl (III, n = 3)	2.8–3.5 (m 4)	5.23 (s 1)	4.94 (m 3)		6.68 (d 2)	7.8–8.5
2-Nonaprenyl (III, n = 9)	2.8–3.4 (m 4)	5.26 (s 1)	4.94 (m 9)		6.68 (d 2)	7.8–8.5
2-Decaprenyl (III, n = 10)	2.8–3.4 (m 4)	5.25 (s 1)	4.91 (m 10)		6.67 (d 2)	7.8–8.5
6-Methoxyphenol						
2-Phytyl	3.36 (s 3)	4.54 (s 1)	4.70 (t 1)	6.13 (s 3)	6.70 (d 2)	7.8–9.3
2-Geranyl (V, n = 2)	3.39[c] (s 3)	4.57 (s 1)	4.72 (t 1) 4.95 (m 1)	6.16 (s 3)	6.68 (d 2)	7.9–8.5
2-Farnesyl (V, n = 3)	3.39[c] (s 3)	4.58 (s 1)	4.72 (t 1) 4.95 (m 2)	6.16 (s 3)	6.71 (d 2)	7.9–8.5
2-Nonaprenyl (V, n = 9)	3.44 (s 3)	4.63 (s 1)	4.98 (m 9)	6.19 (s 3)	6.75 (d 2)	7.8–8.5
2-Decaprenyl (V, n = 10)	3.37 (s 3)	4.50 (s 1)	4.88 (m 10)	6.08 (s 3)	6.67 (d 2)	7.8–8.5
2-Methoxyphenol						
4-Geranyl (XII, n = 2)	3.2–3.6[c] (m 3)	4.76 (s 1)	4.84 (m 2)	6.17 (s 3)	6.77 (d 2)	7.9–8.5
4-Farnesyl (XII, n = 3)	3.2–3.5[c] (m 3)	4.73 (s 1)	4.88 (m 3)	6.18 (s 3)	6.80 (d 2)	7.9–8.5
4-Nonaprenyl (XII, n = 9)	3.2–3.5 (m 3)	4.64 (s 1)	4.95 (m 9)	6.16 (s 3)	6.78 (d 2)	7.9–8.5
2-Methoxyphenyl phytyl ether	3.30 (s 4)		4.62 (t 1)	6.28 (s 3)	5.60[d] (d 2)	7.8–9.3
2-Methoxyphenyl decaprenyl ether	3.24 (s 4)		4.87 (m 10)	6.15 (s 3)	5.48[d] (d 2)	7.8–8.5

[a] s = singlet; d = doublet; t = triplet; m = multiplet. The number in parentheses is the number of protons. Spectra were obtained using carbon tetrachloride solutions with a Varian Associates HR-60 spectrometer unless otherwise noted. [b] A_2B_2 (δ = 19.9 cps, J = 8.7 cps). [c] Spectrum obtained with a Varian Associates HA-100 spectrometer. [d] Signal for methylene group attached to oxygen.

of 4-geranyl-2-methoxyphenol (XII, n = 2) appears at 6.77. The O-multiprenyl isomers produced in the base-catalyzed multiprenylations are readily recognized by the appearance of a methylene doublet at τ 5.4–5.6, the absence of a signal due to a hydroxyl proton, and consideration of the number of aromatic protons as indicated by integration of the spectrum.

Experimental Section

Materials.—Geraniol, farnesol, and phytol were obtained commercially and were used without purification. Phytyl bromide,[15] solanesyl bromide,[16] and decaprenyl bromide (3,7,11,15,-19,23,27,31,35,39- decamethyltetraconta-2,6,10,14,18,22,26,30,-34,38-decaene 1-bromide)[16] were prepared as previously described.

Dioxane was refluxed over sodium and distilled prior to use. The boron trifluoride etherate was freshly distilled. Nuclear magnetic resonance (nmr) spectra were obtained on carbon tetrachloride solutions using a Varian HR-60 spectrometer unless otherwise indicated; chemical shifts are in τ units relative to tetramethylsilane as an internal standard. Thin layer chromatographic separations were done in two steps: first, by using 0.3-mm silica gel G plates developed in benzene–chloroform (1:1); second, by using 0.3-mm alumina plates developed in 1.5% acetone in hexane. Bands were detected by spraying with diazotized sulfanilic acid. Using this reagent, 2-multiprenylphenols (III) and 2-multiprenyl-6-methoxyphenols (V) appeared as yellow to orange bands; the isomeric 4-multiprenylphenols (XI) and 4-multiprenyl-2-methoxyphenols (XII) appeared as pink to red bands. The O-multiprenyl isomers produced by base-catalyzed isoprenylation of the appropriate phenol did not react with diazotized sulfanilic acid, but were visualized using permanganate spray reagent. Chromatography on the silica gel system allowed products to be separated from unreacted starting materials and other species present in the reaction mixtures. The isomeric 2- (III, V, IX) and 4-multiprenyl (XI, XII) products produced in the acid-catalyzed reaction were separated by thin layer chromatography on the alumina system described. In each case the 2-multiprenyl isomer appears as the band of higher R_f value. Similarly by thin layer chromatography on alumina the 2-multiprenylphenolic products (III, V, IX) and their corresponding O-multiprenyl isomers were separated. In these cases, the 2-multiprenyl products (III, V, IX) appeared as the band of lower R_f value.

4-Hydroxy-3-phytylbenzoic Acid (VIII).—To a solution of 44.4 g (0.15 mole) of phytol and 38 g (0.25 mole) of methyl p-hydroxybenzoate in 150 ml of dioxane stirred at 50°, was added dropwise 33 ml of boron trifluoride etherate. After 12 hr, the reaction mixture was poured into 300 ml of water and 600 ml of ether. The organic layer was separated, washed with water, and dried. The solvent was removed, the residue was triturated with hexane, and the insoluble material (methyl p-hydroxybenzoate) was removed by filtration. Removal of the hexane gave a residue which was dissolved in 300 ml of 80% aqueous ethanol containing 15 g of potassium hydroxide. The reaction mixture was refluxed for 30 min and then poured into 500 ml of water. The solution was extracted with 200 ml of ether, and the extract was discarded. The aqueous layer was acidified to pH 2 with hydrochloric acid and again extracted with ether. This extract was dried and the solvent was removed to yield 14.4 g of a viscous oil. Chromatography of this oil on 180 g of silicic acid yielded 5.76 g (9%) of 4-hydroxy-3-phytylbenzoic acid (VIII) as a colorless, viscous oil: nmr (CCl_4) broad singlet at τ 1.50 (2 H, COO*H*, O*H*), multiplet at 2.18 (2 H, aromatic), multiplet at 3.21 (1 H, aromatic), triplet at 4.68 (1 H, vinyl, J = 7 cps), doublet at 6.64 (2 H, ArC*H*$_2$, J = 7 cps), multiplet at 7.70–9.30 (36 H, alkyl); infrared (smear) 1665 cm^{-1} (C=O); ultraviolet λ_{max}^{hexane} 258, 285 mμ.

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.9; H, 10.6. Found: C, 77.5; H, 10.8.

6-Carbomethoxy-2-methyl-2-(4′,8′,12′-trimethyltridecyl)chroman (X).—A solution of 0.25 g of 4-hydroxy-3-phytylbenzoic acid (VIII) in 20 ml of methanol containing 2 ml of concentrated hydrochloric acid was heated under reflux for 24 hr. The solvent was removed, the residue was dissolved in ether, and the resulting solution was washed with sodium bicarbonate solution. Evaporation of the dried solvent left 0.23 g of crude product which was further purified by thin layer chromatography to yield 0.17 g (66%) of a colorless, viscous oil: nmr (CCl_4) multiplet at τ 2.34 (2 H, aromatic), multiplet at 3.32 (1 H, aromatic), singlet at 6.20 (3 H, COOC*H*$_3$), triplet at 7.23 (2 H, ArC*H*$_2$, J = 6.7 cps), multiplet at 7.94–9.36 (38 H, alkyl); infrared 1720 cm^{-1} (C=O); ultraviolet λ_{max}^{hexane} 258, 289 mμ.

2-Phytylphenol (IX) *via* Decarboxylation of VIII.—A mixture of 0.25 g of 4-hydroxy-3-phytylbenzoic acid (VIII) and 0.25 g of calcium oxide was heated under reduced pressure (~100 mm) at 280° for 2 hr or until evolution of carbon dioxide ceased. The mixture was cooled and the methylene chloride soluble material was chromatographed on Florisil using hexane as eluent to yield

(15) P. Karrer and B. H. Ringier, *Helv. Chim. Acta*, **22**, 610 (1939).

(16) R. Rüegg, U. Gloor, R. N. Goel, G. Ryser, O. Wiss, and O. Isler, *ibid.*, **42**, 2616 (1959).

0.14 g (63%) of 2-phytylphenol (IX) as a colorless oil. Ultraviolet data appear in Table I; the nmr data are in Table II.

Anal. Calcd for $C_{26}H_{44}O$: C, 83.9; H, 11.8. Found: C, 83.5; H, 11.8.

General Procedures for the Preparation of 2-Multiprenylphenols (III and V). A. Acid-Catalyzed Isoprenylation of Phenol and 2-Methoxyphenol (Guaiacol).—To a solution of 0.02 mole of phenol or 2-methoxyphenol and 0.005 mole of the appropriate multiprenyl alcohol in 25 ml of redistilled dioxane, was added dropwise 1.5 ml of freshly distilled boron trifluoride etherate in 5 ml of dioxane. After a reaction period of 3 to 5 hr, the solution was poured into a mixture of three volumes of water and two volumes of ether. The organic phase was separated, dried, and evaporated. The oily residue was subjected to preparative thin layer chromatography as described. Spectral data for the 2-multiprenylphenols (III, V) and 4-multiprenylphenols (XI, XII) prepared in this way are recorded in Tables I and II.

By this procedure by isoprenylation of phenol were prepared 2-phytylphenol (IX), 2-geranylphenol (III, $n = 2$), 2-farnesylphenol (III, $n = 3$), and 2-nonaprenylphenol (III, $n = 9$). Similarly, by isoprenylation of guaiacol were prepared 2-geranyl-6-methoxyphenol (V, $n = 2$) and 2-farnesyl-6-methoxyphenol (V, $n = 3$). In each case the corresponding 4-multiprenyl isomer (XI, XII) was observed by thin layer chromatography; only those for which spectral data are given in Tables I and II were actually isolated and characterized. In the BF_3-catalyzed reaction of guaiacol with solanesol[16] the desired 2-nonaprenyl-6-methoxyphenol (V, $n = 9$) was present (tlc) in low yield, but was not isolated since the base-catalyzed procedure (see below) had been shown to be superior for the preparation of this compound.

B. Base-Catalyzed Isoprenylation of Phenol and 2-Methoxyphenol (Guaiacol).—A solution of 0.02 mole of phenol or 2-methoxyphenol in 5 ml of anhydrous benzene was added dropwise to a suspension of 0.025 mole of sodium hydride in 15 ml of dry benzene maintained under nitrogen. After 2 hr, a solution of 0.02 mole of the appropriate multiprenyl bromide in 10 ml of anhydrous benzene was added dropwise. After 24 hr, the reaction mixture was washed with water, and the organic phase was dried and evaporated. The residue was subjected to preparative thin layer chromatography as described. Spectral data for the 2-multiprenylphenols (III, V) and multiprenyl phenyl ethers prepared in this way are recorded in Tables I and II.

By this procedure were prepared 2-phytylphenol (IX), 2-decaprenylphenol (III, $n = 10$), 2-phytyl-6-methoxyphenol, 2-nonaprenyl-6-methoxyphenol (V, $n = 9$), and 2-decaprenyl-6-methoxyphenol (V, $n = 10$). In each case the corresponding O-multiprenyl isomer was shown to be present by thin layer chromatography on alumina as described. Spectral data for these O-multiprenyl derivatives isolated and characterized are recorded in Tables I and II.

Registry No.—III ($n = 2$), 10232-02-7; III ($n = 3$), 10232-03-8; III ($n = 9$), 10248-68-7; III ($n = 10$), 614-92-6; V ($n = 2$), 10232-05-0; V ($n = 3$), 10248-69-8; V ($n = 9$), 10232-06-1; V ($n = 10$), 7762-53-0; VIII, 10232-08-3; IX, 10232-09-4; X, 10232-10-7; XIa, 10232-11-8; XIb ($n = 2$), 10232-12-9; XIb ($n = 3$), 10232-13-0; XII ($n = 2$), 10232-14-1; XII ($n = 3$), 10232-15-2; XII ($n = 9$), 10232-16-3; 2-phytyl-6-methoxyphenol, 10232-17-4; 2-methoxyphenyl phytyl ether, 10232-18-5; 2-methoxyphenyl decaprenyl ether, 10232-19-6.

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The Grignard Addition to Steroidal Cyclic Ketals

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Grignard reagents, in boiling benzene solution, added to steroidal 3-, 17-, and 20-cyclic ketals, effected cleavage of the heterocyclic ring and formation of tertiary glycol ethers.

In a previous communication[1] we described the Grignard addition to cyclic ketals and acetals in boiling benzene solution. The products of such reactions with cyclic ketals are tertiary glycol ethers, and with cyclic acetals the products are secondary glycol ethers. Similar reactions have been reported by Feugeas[2] on cyclic ketals of halogenated saturated ketones, by Zepter[3] on C-20 steroidal ethylene ketals, by Bible[4] on the ethylene ketal of estrone methyl ether, and by Blomberg, *et al.*,[5] and Shostakovskii, *et al.*,[6] on 2-alkyl-1,3-dioxolanes. We wish to report the results of our work in the steroid series.

Ketals, generally, are stable under Grignard reaction conditions.[7] However, their stability is reduced when the reaction is performed in hot benzene instead of ether, which is the usual solvent used for such Grignard reactions,[8] and the heterocyclic ring is cleaved. Thus, by using benzene as a solvent we were able to add Grignard reagents at the C-3, C-17, and C-20 positions of the steroid molecule and concomittantly to open the ketal rings at these positions.

Reaction of cholestan-3-one ethylene ketal (**1**) with methylmagnesium bromide in boiling benzene solution gave two isomeric glycol ethers which were separated by chromatography on alumina and identified as 3β-methyl-3α-(2-hydroxyethoxy)cholestane (**2**), and 3α-methyl-3β-(2-hydroxyethoxy)cholestane (**3**). That **2** was the axial glycol ether and **3** the equatorial glycol ether was determined by the ease of elution of **2** from the chromatographic column and by examination of the

(1) R. A. Mallory, S. Rovinski, and I. Scheer, *Proc. Chem. Soc.*, 416 (1964).
(2) A. Feugeas, *Bull. Soc. Chim. France*, 2568 (1963).
(3) R. Zepter, *J. Prakt. Chem.*, **26**, 174 (1964).
(4) R. H. Bible, Jr., U. S. Patent 3,081,315 (1963); *Chem. Abstr.*, **59**, 10180b (1963).
(5) C. Blomberg, A. O. Vreugdenhil, and T. Homsma, *Rec. Trav. Chim.*, **72**, 355 (1963).
(6) M. F. Shostakovskii, A. S. Atavin, and B. A. Trofinov, *Zh. Obshch. Khim.*, **34**, 2088 (1964).
(7) C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, Chapter I.
(8) According to Zepter[3] Grignard reagents form a complex both with ether and the dioxolane ring. However, when benzene is used as a solvent, the dioxolane ring is free of competition, and it can thus be cleaved.