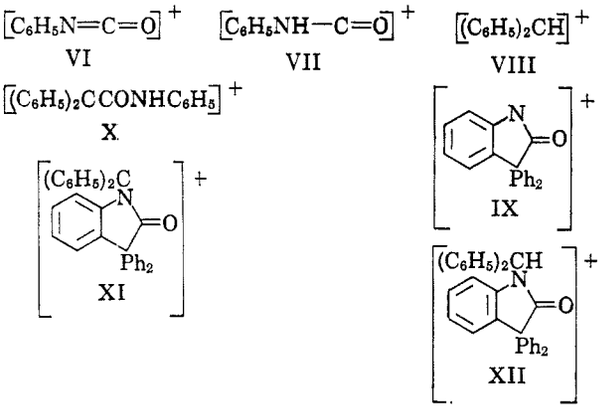
SCHEME II



Reaction of α-Chloro-α,α-diphenyl-N-p-tolylacetamide (Ib)[8] with Sodium Hydride.—The previously described procedure was followed.[1] Recrystallization of the crude reaction product from ethyl acetate gave 5-methyl-3,3-diphenyloxindole (IIIb) (12%): mp 283–283.5° (Kofler); infrared spectrum (Nujol), 3225, 3050, 1710, and 1670 cm^{-1}; ultraviolet spectrum, $\lambda_{max}^{CHCl_3}$ 283 and 260 mμ (log ε 3.27 and 3.75, respectively); nmr spectrum (CF_3COOH), 2.25 ppm (singlet, 3 H), 7.3 ppm (singlet, 3 H), and 7.5 ppm (singlet, 10 H).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.10; H, 5.82; N, 4.63.

Evaporation of the mother liquor from the isolation of IIIb and recrystallization of the residue from acetone gave IIb (23%): mp 249–251° (Kofler); infrared spectrum (Nujol), 3390, 3050, 1725, 1705, 1600, and 1515 cm^{-1}; ultraviolet spectrum ($CHCl_3$), complicated absorption between 300 and 240 mμ with no definite maximum; nmr spectrum ($CDCl_3$), 2.19 ppm (singlet, 3 H), 2.25 ppm (singlet, 3 H), and 6.8–7.8 ppm (complex, 28 H).

Anal. Calcd for $C_{42}H_{34}N_2O_2$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.01; H, 5.63; N, 4.70.

Synthesis of 5-Methyl-3,3-diphenyloxindole (IIIb).—Boron fluoride etherate (30 ml) was added to 1.5 g (4.5 mmoles) of α-chloro-α,α-diphenyl-N-p-tolylacetamide, and the resulting solution was refluxed for 45 min. The solution was then poured into water, and the product was extracted with methylene chloride. Evaporation of the methylene chloride solution gave 1.36 g (98.5%) of 5-methyl-3,3-diphenyloxindole which was recrystallized from ethyl acetate, mp 283–284° (Kofler). The infrared and ultraviolet spectra were identical with those of IIIb.

Saponification of IIa.[2a]—To a solution of 0.2 g (3.5 mmoles) of potassium hydroxide in 10 ml of *n*-amyl alcohol was added 1.0 g (1.75 mmoles) of IIa. The resulting mixture was refluxed for 24 hr, cooled, and poured into benzene. The resulting benzene solution was washed with 1*N* hydrochloric acid and water, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate affording 577 mg (73%) of Va: mp 224–226° (Kofler); infrared spectrum (Nujol), 3050, 1710, and 1605 cm^{-1}; ultraviolet spectrum, λ_{max}^{EtOH} 260 mμ (log ε 3.8).

Synthesis of 1-(Diphenylmethyl)-3,3-diphenyloxindole (Va). — To a suspension of 2.0 g (7.03 mmoles) of 3,3-diphenyloxindole in 20 ml of dry benzene was added 7.03 mmoles of sodium hydride, and the resulting suspension was refluxed under a nitrogen atmosphere with stirring for 30 min. Benzhydryl chloride (7 mmoles) was added, and refluxing was continued for 3 hr. Water was added cautiously, and the layers were separated. The benzene solution was dried over magnesium sulfate and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate giving 1.08 g (34%) of Va, mp 224° (Kofler) (not depressed on admixture with the saponification product). The infrared and ultraviolet spectra were identical with those of Va.

Anal. Calcd for $C_{33}H_{25}NO$: C, 87.77; H, 5.58; N, 3.10. Found: C, 87.69; H, 5.75; N, 2.97.

Saponification of IIb.—The procedure for the saponification of IIa was followed yielding 55% of 1-(diphenylmethyl)-5-methyl-3,3-diphenyloxindole: mp 211–214° (Kofler) (from ethyl acetate); infrared spectrum (Nujol), 3025, 1705, and 1600 cm^{-1}; ultraviolet spectrum, λ_{max}^{EtOH} 262 mμ (log ε 3.8).

(8) C. L. Stevens and J. C. French, *J. Am. Chem. Soc.*, **75**, 657 (1953).

Synthesis of 1-(Diphenylmethyl)-5-methyl-3,3-diphenyloxindole (Vb).—The synthesis was performed in a manner identical with the synthesis of Va yielding 54% of Vb: mp 210–212° (Kofler) (from ethyl acetate); nmr spectrum ($CDCl_3$), 2.25 ppm (singlet, 3H), 7.41 ppm (singlet, 23 H), and 5.5 ppm (Br, 1 H). The infrared and ultraviolet spectra were identical with those of the saponification product of IIb.

Anal. Calcd for $C_{34}H_{27}NO$: C, 87.71; H, 5.85; N, 3.01. Found: C, 87.74; H, 5.94; N, 2.98.

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Synthesis of Coenzyme Q Analogs by Alkylation of Fumigatin[1a]

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The existence of fumigatin (I) in nature and its structural relationship to coenzyme Q provided the initial interest for the synthesis of isoprenoid derivatives of fumigatin by alkylation. Two appropriate coenzyme Q analogs (II) have been synthesized with isoprenoid side chains which are prominent in the coenzyme Q, vitamin E, and vitamin K groups. They are 2-hydroxy-3-methoxy-6-methyl-5-solanesyl-1,4-benzoquinone (III) and 2-hydroxy-3-methoxy-6-methyl-5-phytyl-1,4-benzoquinone (IV). (See Chart I.)

The first structure (V) proposed[2a] for rhodoquinone also supported the interest in the synthetic analogs, III and IV, until very recently when the structure of rhodoquinone was established[2b] as VI.

There is biological interest in the synthetic hydroxyquinones, III–V, etc., since Morimoto and Imada[3,4] and Lester and Fleischer[5] have found that succinoxidase activity is restored to acetone-extracted mitochondria by the photolytic demethylation "product" of coenzyme Q_7. This "product" was presumed to be the hydroxyquinone analog, VII, but new studies have revealed[6] that the "product" is about a 50:50 mixture of both isomers, VIII.

The generic 2-isoprenoidphenols have been reported[7] as precursors to members of the coenzyme Q group. On this basis and other evidence,[8] the biosynthesis of coenzyme Q appears to involve three methylation steps, *i.e.*, the two methoxy groups and the 6-methyl group. The order in these methylations is unknown.

(1) (a) Coenzyme Q. LXIX. (b)Stanford Research Institute, Menlo Park, Calif.

(2) (a) J. Glover and D. R. Threlfall, *Biochem. J.*, **85**, 14P (1962); (b) H. W. Moore and K. Folkers, *J. Am. Chem. Soc.*, **88**, 567 (1966).

(3) H. Morimoto and I. Imada, *Chem. Pharm. Bull.* (Tokyo), **12**, 739 (1964).

(4) I. Imada and H. Morimoto, *ibid.*, **13**, 136 (1965).

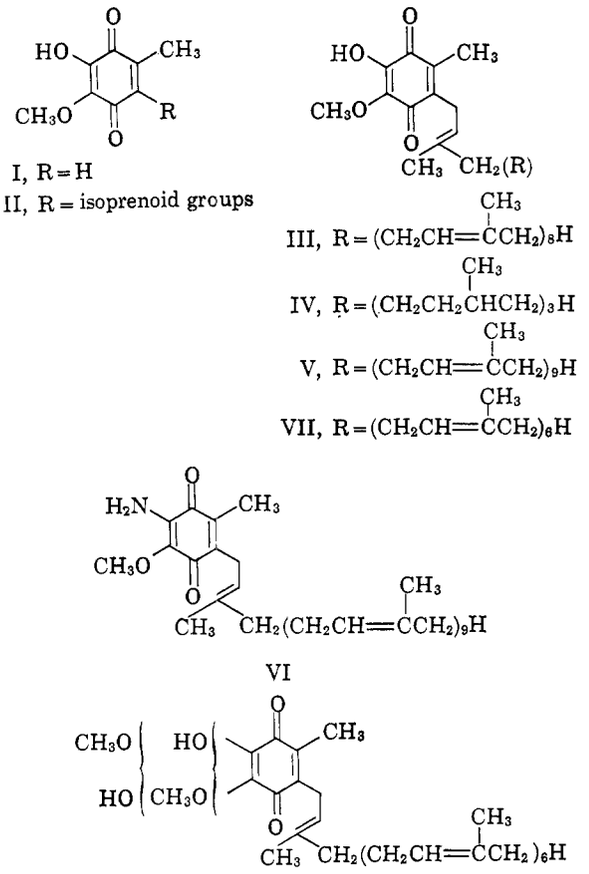
(5) R. L. Lester and S. Fleischer, *Biochim. Biophys. Acta*, **47**, 358 (1961).

(6) H. W. Moore and K. Folkers, *J. Am. Chem. Soc.*, **88**, 564 (1966).

(7) R. K. Olsen, J. L. Smith, G. D. Daves, Jr., H. W. Moore, K. Folkers, W. W. Parson, and H. Rudney, *ibid.*, **88**, 564 (1966).

(8) R. Olson, *Federation Proc.*, **23**, 3393 (1964).

CHART I



The properties and availability of the synthetic analogs, III and IV, may contribute to the elucidation of the mechanism of biosynthesis of coenzyme Q.

The alkylation of the hydroquinone of fumigatin, 4-methoxy-2,3,5-trihydroxytoluene, with solanesol and phytol was based on procedures for the methoxy derivatives.[9-11] The nmr, infrared, and ultraviolet absorption spectra of III and IV are in agreement with the structures.

2-Hydroxy-3-methoxy-6-methyl-5-solanesyl-1,4-benzoquinone (III) was converted to coenzyme Q_9 by methylation with dimethyl sulfate to correlate this hydroquinone with the naturally occurring coenzyme Q_9.

Experimental Section

4-Methoxy-2,3,5-trihydroxytoluene.—3-Hydroxy-4-methoxy-2,-5-toluquinone (fumigatin) (1.0 g) was hydrogenated at room temperature in methanol over Raney nickel catalyst. After 1 equiv of hydrogen had been absorbed, 2 ml of aqueous sulfur dioxide was added. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was extracted with two portions of boiling ether. Concentration of the ether extracts yielded 4-methoxy-2,3,5-trihydroxytoluene as a light brown oil.

2-Hydroxy-3-methoxy-6-methyl-5-solanesyl-1,4-benzoquinone (Solanesylfumigatin).—To the 4-methoxy-2,3,5-trihydroxytoluene obtained from the reduction of 1.0 g of the corresponding quinone and 7.6 g of solanesol (natural source) in 15 ml of dry dioxane, 1.2 ml of boron trifluoride etherate in 5 ml of dioxane was added over a period of 1 hr; the mixture was stirred in a nitrogen atmosphere. After stirring for an additional 2 hr, the solution was diluted with 100 ml of ether and extracted with 5% aqueous sodium bicarbonate. After washing with water, the ethereal solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure, leaving a light brown oil. This was dissolved in 250 ml of benzene and oxidized by stirring with 3.3 g of ferric chloride hexahydrate in 100 ml of water for 3 hr. The layers were separated, and the benzene layer was washed with three portions of water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure, leaving 8.0 g of an orange-red oil, $\lambda_{max}^{isooctane}$ 273 mμ ($E_{1\,cm}^{1\%}$ 28.6).

The above material was chromatographed, using 450 g of silica gel as the absorbent. Elution with carbon tetrachloride containing 2% ether yielded solanesol, identified by its infrared spectrum. Elution with carbon tetrachloride containing 4% ether yielded fractions showing ultraviolet absorption at 270 mμ. A fraction was crystallized from petroleum ether (bp 30–60°) at −10°, yielding 0.24 g of reddish crystals, mp 39–42°. Paper chromatography showed that this material was homogeneous: $\lambda_{max}^{isooctane}$ 270.5 ($E_{1cm}^{1\%}$ 116), 277.5 mμ ($E_{1cm}^{1\%}$ 115). The nmr spectrum was found to be in accord with the proposed structure. Absorption bands were observed in carbon tetrachloride solution at τ 4.85 (HC=), 5.88 (CH_3O), 6.91 (d, =CCH_2C=), 8.04 (=CCH_2CH_2C=), 8.27 (CH_3C=, side-chain methyl nearest ring), and 8.43 (CH_3C=, other side-chain methyls).

Anal. Calcd for $C_{53}H_{80}O_4$: C, 81.48; H, 10.32. Found: C, 80.68; H, 10.00.

Conversion of 2-Hydroxy-3-methoxy-6-methyl-5-solanesyl-1,4-benzoquinone into Coenzyme Q_9.—2-Hydroxy-3-methoxy-6-methyl-5-solanesyl-1,4-benzoquinone (25 mg, mp 39–42°), 0.15 ml of dimethyl sulfate, and 0.15 g of anhydrous potassium carbonate in 5 ml of acetone was refluxed for 2.5 hr. The mixture was cooled, diluted with ether, and filtered. Water was added to the resulting solution, and the mixture was kept overnight at room temperature. The layers were separated, and the ether layer was washed with three portions of water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure, yielding 25 mg of a yellow oil. Paper chromatography showed that the oil was a mixture of the starting material and coenzyme Q_9.

2-Hydroxy-3-methoxy-6-methyl-5-phytyl-1,4-benzoquinone (Phytyl Fumigatin).—4-Methoxy-2,3,5-trihydroxytoluene (0.60 g) in 15 ml of dioxane was condensed with excess phytol (3.5 g, natural source) in the presence of 1.3 ml of boron trifluoride etherate by the procedure used in the preparation of the solanesyl analog. After oxidation with ferric chloride, 4.6 g of a red oil was obtained which was chromatographed using 200 g of silica gel as the absorbent. The column was eluted first with 10% ether in isooctane and finally with 25% ether in isooctane. Fractions showing the appropriate ultraviolet absorption were combined and rechromatographed over silica gel. A fraction (40 mg) was eluted with 5% ether in isooctane showing $\lambda_{max}^{isooctane}$ 270 mμ ($E_{1cm}^{1\%}$ 284), 275 mμ ($E_{1cm}^{1\%}$ 282). The nuclear magnetic resonance spectrum was consistent with that expected for 2-hydroxy-3-methoxy-6-methyl-5-phytyl-1,4-benzoquinone.

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(11) M. Kofler, A. Langemann, R. Rüegg, L. H. Chopard-dit-Jean, A. Rayroud, and O. Isler, *Helv. Chim. Acta*, **42**, 1283 (1959).

Anthocyanidins and Related Compounds. IX. The Synthesis of 9-Phenacyl-5-ketotetrahydroxanthenes

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4′-Hydroxyflavylium salts and 5,5-dimethyl-1,3-cyclohexanedione condense in aqueous acid solutions to yield colorless products which, on the basis of their chemical and spectral properties, were formulated[2]

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(2) L. Jurd, *Tetrahedron*, **21**, 3707 (1965).