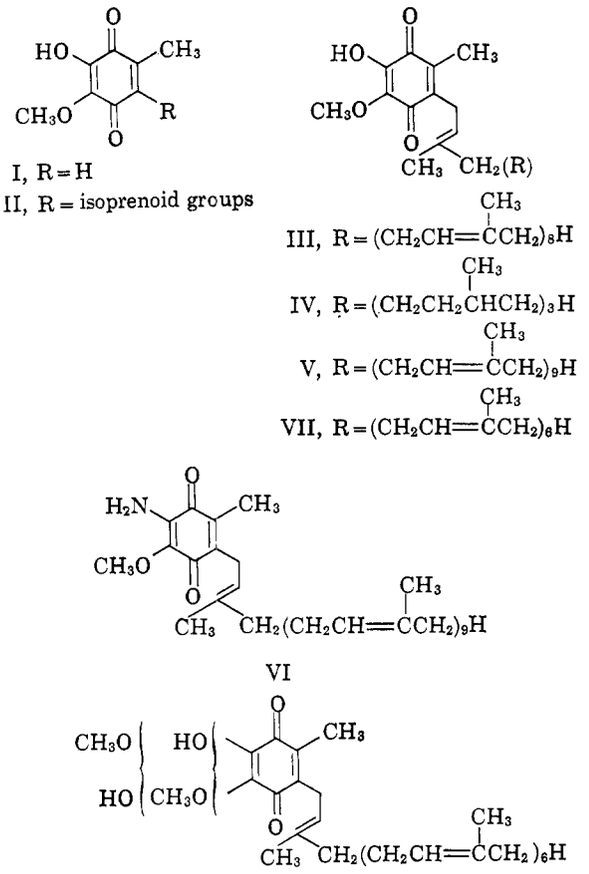
CHART I



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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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]

(1) One of the laboratories of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

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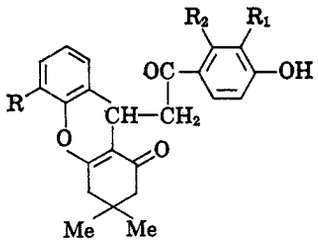
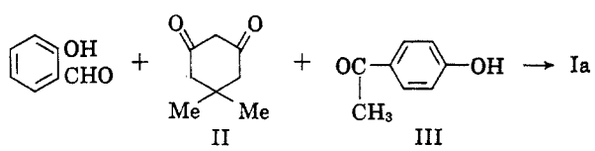


Ia, R = R_1 = R_2 = H
b, R = OMe; R_1 = R_2 = H
c, R = R_2 = H; R_1 = OMe
d, R = OMe; R_1 = H, R_2 = OH

as 9-phenacyl-5-ketotetrahydroxanthene derivatives of type I.

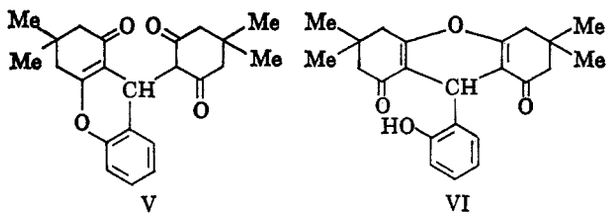
The xanthene derivatives Ia–d have now been synthesized by a facile process which involves sequential condensation of three reactants. Thus, mixtures of equimolecular quantities of salicylaldehyde, 5,5-dimethyl-1,3-cyclohexanedione (II), and 4-hydroxyacetophenone (III) react readily in dilute aqueous acetic acid–hydrochloric acid or ethanolic hydrochloric acid solutions to yield Ia, identical in all respects with the described[2] 4′-hydroxyflavylium chloride–II condensation product. Mixtures of *o*-vanillin, II, and III and of salicylaldehyde, II, and 3-methoxy-4-hydroxy-



II III

acetophenone condense similarly to yield Ib and Ic, respectively. Although crystalline products have not yet been obtained from the reaction of II with 2′-hydroxyflavylium salts, equimolecular mixtures of *o*-vanillin, II, and 2,4-dihydroxyacetophenone give the xanthene derivative Id. The presence of the 2,4-dihydroxyphenacyl grouping in this product was indicated (a) by the formation of a dimethyl ether and (b) by the formation of a monoacetate when acetylated under conditions[3] which do not normally acetylate phenolic groups *ortho* to a carbonyl group.

The formation of 9-phenacyltetrahydroxanthenes in the above reactions probably involves initial condensation of the aldehyde and II to form a tetrahydroxanthylium salt IV,[4] which in turn condenses with the acetophenone to yield I. The acetophenone component does not react when these condensations are attempted in aqueous acetic acid (without hydrochloric acid), aqueous methanol, or alkaline solutions. Mixtures of salicylaldehyde, II, and III under these conditions give the known[4] salicylaldehyde–5,5-dimethyl-1,3-cyclohexanedione product V or VI. This has been prepared[4] by the alkaline condensation of salicylaldehyde with II and, as indicated,[5,6] its structure is uncertain.[7]



V VI

Experimental Section

5-Keto-7,7-dimethyl-9-(4-hydroxyphenacyl)-5,6,7,8-tetrahydroxanthene (Ia).—A solution of salicylaldehyde (1.22 g), 5,5-dimethyl-1,3-cyclohexanedione (II, 1.40 g), and 4-hydroxyacetophenone (III, 1.36 g) in ethanol (10.0 ml) and concentrated aqueous hydrochloric acid (5.0 ml) was warmed on a steam bath for 20 min and allowed to stand for 4 hr. The crystalline mass which separated was collected and recrystallized from acetone–methanol. Ia separated as colorless glistening needles: 1.23 g; mp and mmp with the 4′-hydroxyflavylium–II condensation product[2] 207°; λ_{max}^{EtOH} 282, 218 mμ; λ_{max}^{NaOEt} 332 mμ.

Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.2; H, 6.12. Found: C, 76.3; H, 6.15.

The **acetate** of the product crystallized from methanol as colorless needles, mp and mmp with the acetate[2] of Ia 125°.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.2; H, 5.98. Found: C, 74.1; H, 5.94.

1-Methoxy-5-keto-7,7-dimethyl-9-(4-hydroxyphenacyl)-5,6,7,8-tetrahydroxanthene (Ib).—A solution of *o*-vanillin (1.52 g), II (1.40 g), and III (1.36 g) in acetic acid (15.0 ml) and 10% aqueous hydrochloric acid (20 ml) was heated on a steam bath for 15 min and allowed to stand overnight. The crystalline product was collected, digested with warm water (50 ml) to remove unreacted II, and recrystallized from acetone–methanol. Ib separated as colorless needles: 1.35 g, mp and mmp with authentic[2] Ib 212–213°, λ_{max}^{EtOH} 282 mμ, λ_{max}^{NaO} 332 mμ.

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16; 1MeO, 7.91. Found: C, 73.4; H, 6.13; MeO, 7.89.

The **oxime** of the product crystallized from aqueous methanol as colorless prisms, mp and mmp with the oxime[2] of Ib 204°, λ_{max}^{EtOH} 263 mμ, λ_{max}^{NaOEt} 290 mμ.

5-Keto-7,7-dimethyl-9-(3-methoxy-4-hydroxyphenacyl)-5,6,7,8-tetrahydroxanthene (Ic).—Salicylaldehyde (1.22 g), II (1.40 g), and 3-methoxy-4-hydroxyacetophenone (1.66 g) condensed in ethanolic hydrochloric acid as described above gave Ic (1.05 g). This crystallized from acetone–methanol as cream-colored prisms: mp and mmp[2] 174°; λ_{max}^{EtOH} 280, 226 mμ; λ_{max}^{NaOEt} 353, 289, 252 mμ.

1-Methoxy-7,7-dimethyl-9-(2,4-dihydroxyphenacyl)-5,6,7,8-tetrahydroxanthene (Id).—A solution of *o*-vanillin (1.52 g), II (1.40 g), and 2,4-dihydroxyacetophenone (1.52 g) in acetic acid (20.0 ml) and 10% aqueous hydrochloric acid (15.0 ml) was heated on a steam bath for 20 min, allowed to stand for 2 hr, diluted with water (10 ml), and refrigerated overnight. The oily product thereby solidified. Recrystallized from acetone–methanol Id separated as cream-colored needles, mp 209–210°, which gave an intense red color with alcoholic ferric chloride: λ_{max}^{EtOH} 282 mμ, λ_{max}^{NaOEt} 340 mμ.

Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.6; H, 5.92; 1MeO, 7.60. Found: C, 70.4; H, 5.98; MeO, 7.62.

Warmed briefly with acetic anhydride and a drop of pyridine, Id formed a **monoacetate**. This crystallized from methanol as colorless prisms, mp 168–169°, which gave an intense red-brown color with alcoholic ferric chloride.

Anal. Calcd for $C_{26}H_{26}O_7$: C, 69.3; H, 5.82; 1CH_3CO, 9.55. Found: C, 69.0; H, 5.86; CH_3CO, 10.4.

Id (0.40 g) was heated under reflux with dimethyl sulfate (2.0 ml), potassium carbonate (6.0 g), and acetone (50 ml) for 2 hr. The mixture was concentrated, diluted with water, and allowed to cool. The solid was collected and recrystallized from

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(7) The product does not give a blue color with Gibbs reagent. Structure VI would be expected to give a positive Gibbs test.

acetone–methanol. The dimethyl derivative of Id separated as colorless, glistening prisms, mp 202°.

Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.5; H, 6.47; 3MeO, 21.3. Found: C, 71.7; H, 6.53; MeO, 21.3.

Salicylaldehyde–5,5-Dimethyl-1,3-cyclohexanedione Condensation Product (V or VI). A.—Condensation of salicylaldehyde (2.8 g) and II (3.5 g) in aqueous KOH as described by Chakravarti, *et al.*,[4] gave V or VI: mp 207–208°, λ_{max}^{EtOH} 268 mμ, λ_{max}^{NaOEt} 285 mμ.

B.—Salicylaldehyde (2.44 g) and II (5.6 g), warmed in acetic acid (30 ml) and water (40 ml) for 30 min, formed a crystalline product. Recrystallized from acetone–methanol, V or VI separated as colorless prisms, 5.8 g, mp and mmp 207–208°.

Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.4; H, 7.15. Found: C, 75.2; H, 7.13.

***o*-Vanillin–5,5-Dimethyl-1,3-cyclohexanedione Condensation Product.** A.—A mixture of *o*-vanillin (1.52 g) and II (2.80 g) condensed in acetic acid (10.0 ml) and water (20 ml) as described above gave a product (3.60 g, mp 226–228°) which crystallized from acetone–methanol as colorless needles: mp 228°, λ_{max}^{EtOH} 268 mμ, λ_{max}^{NaOEt} 284 mμ.

Anal. Calcd for $C_{24}H_{23}O_5$: C, 72.7; H, 7.12; 1MeO, 7.83. Found: C, 72.7; H, 7.17; MeO, 7.94.

B.—A solution of *o*-vanillin (1.52 g), II (1.40 g), and III (1.36 g), condensed similarly in hot aqueous acetic acid, gave only the above *o*-vanillin–II condensation product (1.86 g), mp and mmp 228°.

Acknowledgment.—The author is indebted to L. M. White and Miss G. Secor for elemental analyses.

Strictamine

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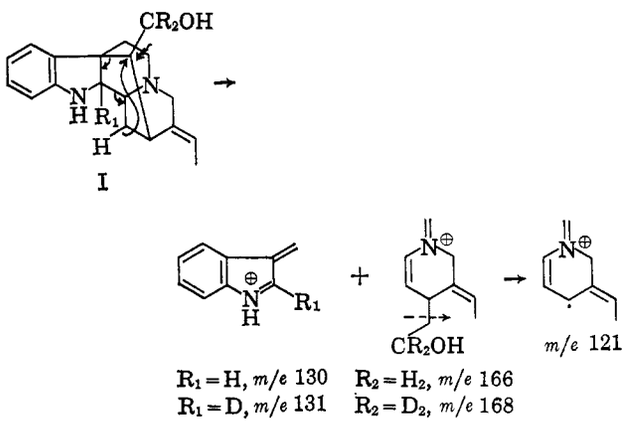
In continuation of earlier work[1,2] on the basic constituents of *Rhazya stricta* Decaisne we had isolated a new alkaloid, mp 110–112° (or 80–83°, hydrate), $[\alpha]^{24}D$ +103°, which was named strictamine. Later it was found that its mass spectrum was identical with that of vincamidine, an alkaloid isolated from *Vinca minor* L. and reported[3] to melt at 78–80° and to possess a composition $C_{20}H_{24}N_2O_3$.

This alkaloid (for which we prefer to retain the name strictamine, because of the similarity of the name vincamidine and vincamedine, an alkaloid of completely unrelated structure[4]) exhibits ultraviolet absorption of the indolenine type: λ_{max}^{EtOH} 213 mμ (log ε 4.37) and 262 mμ (log ε 3.80). Infrared bands at 1740,1630, and 1610 cm^{-1} (in $CHCl_3$) can be assigned to ester, C=N, and C=C groups. The nmr spectrum corroborated some of these conclusions: a complex series of signals between 7.1 and 7.8 ppm indicates four aromatic protons and a singlet at 3.78 ppm (3 H) a methoxy function, while an ethylidene side chain is indicated by the doublet (J = 7 cps, 3 H) at 1.56 ppm, further split (J = 1.5–2 cps) into a quartet (a phenomenon we observed also for other systems possessing an ethylidene side chain). The mass spectrum[5] of the alkaloid is fairly uncharacteristic: a strong molecular ion at m/e 322.1690 requiring the composition $C_{20}H_{22}N_2O_2$ (calcd 322.1681), and prominent peaks due to loss of H and CO_2CH_3 are its distinguishing (but uninformative) features. Most importantly, the spectrum revealed the correct elemental composition and that the two oxygens are present as a carbomethoxy group.

Reduction of strictamine with lithium aluminum hydride and deuteride furnished the first important information on the carbon skeleton of the alkaloid. The product of the hydride reaction showed a molecular ion peak at m/e 296 (322 − 26) corresponding to transformation of an ester to the alcohol and saturation of the C–N double bond. Ultraviolet absorption at 242 and 289 mμ (ε 6040 and 2750) indicated a dihydroindole system; infrared bands at 3610 and 3380 cm^{-1} identified hydroxyl and amino functions, respectively. The mass spectral fragementation pattern was distinguished by strong peaks m/e 166, 144, 143, 136, 130, 122, and 121, which in the case of the deuteride reduction product appeared at m/e 168, 145, 144, 136, 131, 123, 122, and 121. The peaks at m/e 130, 143, and 144 represent indole fragments and their shift by 1 mass unit in the trideuterio derivative indicates incorporation of one deuterium atom into the indole moiety as required by reduction of the indolenine to an indoline. The remaining peaks are best rationalized in terms of the ψ-akuammigine[6,7] type structure I (Scheme I).

SCHEME I



R_1 = H, m/e 130 R_2 = H_2, m/e 166
R_1 = D, m/e 131 R_2 = D_2, m/e 168

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