COENZYME Q. XVIII. 7,8-DIMETHOXY-2,5-DIMETHYL-2-(4',8',12'-TRIMETHYLTRIDECYL)-6-CHROMANOL.

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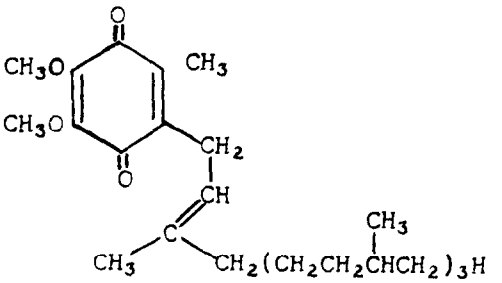
Received May 24, 1960

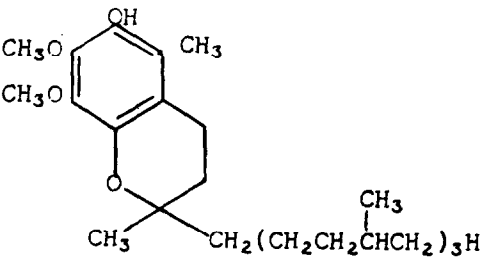
Hexahydro-coenzyme Q_4 (I) (Shunk et al., 1958) has been converted into 7,8-dimethoxy-2,5-dimethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol (II), which is a chromanol of unambiguous structure related to the coenzyme Q series. It has been considered (Dallam and Taylor, 1959; Russell and Brodie, 1960) that such dimethoxy-chromanols may have a role in mammalian oxidative phosphorylation, and may correspond to the possible role of the "naphthotocopherol" in the vitamin K field for oxidative phosphorylation in mycobacteria. Previously, the preparation of the chromanol (III) was studied (Bouman et al., 1958), but the characterization presented did not fully differentiate possible products in the reaction mixtures.

Other attempts (Laidman et al., 1960) to prepare the chromanol (III) from coenzyme Q_{10} (ubiquinone-50) gave materials with unexpected properties; this was believed to be due to reduction and cyclization of the side chain.

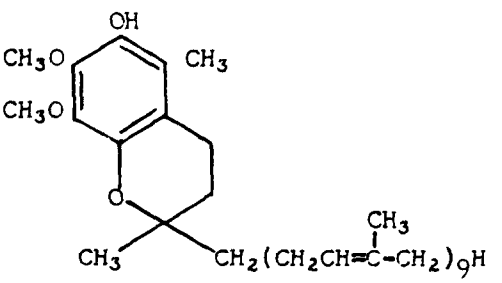
We have examined the reaction of coenzyme Q_{10} with certain reagents in the interest of converting it to the chromanol III. When coenzyme Q_{10} was treated with excess stannous chloride in acetic acid at reflux temperature, reduction to the hydroquinone and cyclization to a chromanol evidently occurred. Other changes also took place. The NMR spectrum showed the isoprenoid side chain



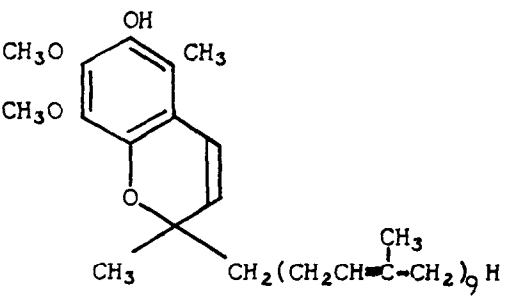
I



II

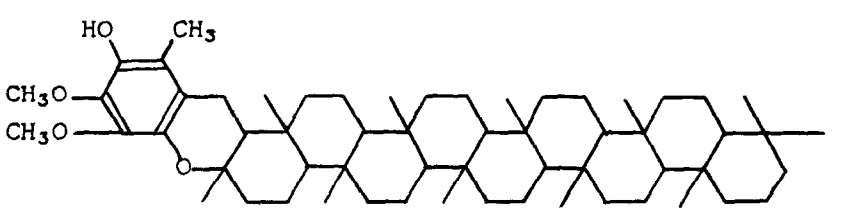


III



IV

to be changed to one which is essentially all paraffinic, because most of the characteristic proton frequencies of the side chain normally present in coenzyme Q_{10} had shifted to typical paraffinic regions (8.7 to 9.2 tau). Treatment of coenzyme Q_{10} hydroquinone with stannic chloride produced a product of similar nature, according to the NMR spectrum. Thus, it appears that condensation rather than reduction of the isoprenoid side chain occurs, and the product may be represented by structure (V), although less completely cyclized products may be present to some degree.



V

It was evident that such reactivity of the isoprenoid side chain of coenzyme Q_{10} could be avoided, if one used hexa-

hydrocoenzyme Q_4 (I). In this molecule, the phytyl side chain possesses only the double bond needed for conversion to the chromanol (II). This chromanol was prepared by refluxing the quinone in acetic acid with excess stannous chloride.

Drs. David Green* and Robert Lester have kindly tested this chromanol (II) and reported that it has no coenzymatic activity when tested by *in vitro* systems for electron transfer which are responsive to members of the coenzyme Q group. Other biological tests of this new chromanol are in progress.

Ubichromenol (IV) has been described by Morton and coworkers (Laidman *et al.*, 1960; Laidman *et al.*, 1959) as a naturally-occurring chromenol of apparent metabolic interest which is related to ubiquinone-50 (coenzyme Q_{10}). Recently, doubts were raised (Links, 1960) concerning the existence of ubichromenol in tissues, because ubiquinone was apparently converted to the chromenol (IV) when passed over alumina, a step used in isolation. Also, the results of Draper and Csallany (in press) indicated that ubichromenol is not a naturally-occurring constituent of animal lipid, but is formed from ubiquinone by cyclization in alkaline solution.

It is obvious that the relation of both these cyclic forms, the chromanol and the chromenol, to coenzyme Q is not a settled one.

Experimental

7,8-Dimethoxy-2,5-dimethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol (II). A solution of 0.755 g. of 2,3-dimethoxy-5-methyl-6-phytylbenzoquinone (Shunk *et al.*, 1958) in 50 ml. of glacial acetic acid was heated to reflux temperature. Solid stannous chloride was added slowly in portions until a total of

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* - David Green, Personal Communication.

0.86 g. had been added. The mixture was then heated at reflux for 30 minutes. The reaction mixture was concentrated under reduced pressure to dryness. The residue was dissolved in petroleum ether and washed several times with water. The petroleum ether solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to leave a brownish-yellow oil; weight 0.685 g., $\lambda_{max.}^{isooctane}$ 293 mμ, $E_{1\ cm.}^{1\%} = 64.4$.

This product was dissolved in isooctane and chromatographed on a column of 50 g. of Florisil (60-100 mesh) packed in isooctane. Fractions were eluted with a mixture of isooctane and 2% diethyl ether. Those fractions (2 through 7 inclusive) having substantial absorption in the ultraviolet (with $\lambda_{max} = 293$ mμ) were collected; the weight of these totaled 0.49 g. Each fraction was distilled in a short-path evaporative apparatus under reduced pressure. Proton magnetic resonance spectra for the fractions were consistent with the proposed structure. The following shielding numbers (tau) (and assignments) were obtained: 4.82 (OH), 6.13, 6.26 (2 different CH_3O-), 7.51 triplet ($CH_2C=$), 7.98 ($CH_3C=$), 8.78 (CH_2C-) and 9.15 doublet (CH_3C-). The method of analysis was that previously described (Erickson et al., 1959). Fraction 3 was analyzed:

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89.

Found : C, 75.43; H, 10.50.

Ultraviolet absorption of fraction 3: $\lambda_{max.}^{isooctane}$ 293 mμ, $E_{1\ cm.}^{1\%} = 81$.

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