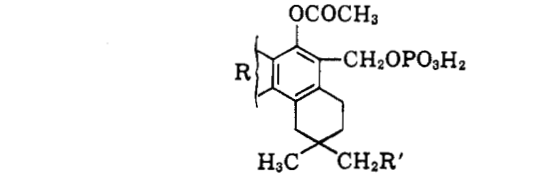
at 70° (heating above 80° caused separation into three phases) for 15 min. in a current of nitrogen, the dioxane distilled under reduced pressure and the product isolated by extraction with ether. A single such treatment usually sufficed to effect at least 80% exchange of the hydrogen atoms adjacent to the carbonyl group.

COMMUNICATIONS TO THE EDITOR

COENZYME Q. XLVII. NEW 5-PHOSPHOMETHYL-6-CHROMANYL DERIVATIVES FROM A NOVEL REACTION OF INTEREST IN OXIDATIVE PHOSPHORYLATION

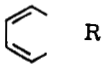
Sir:

The new 5-phosphomethyl derivatives I, II and III of the coenzyme Q and vitamin K groups, which are of current interest in biological oxidative phosphorylation, have been synthesized by a series of steps including a novel cyclization reaction. In view of current concepts,[1] this new structural type of phosphate is more significant than the types related to the monophosphate of dihydrocoenzyme Q_{10}[2] and the 6-chromanyl phosphate of vitamin $K_{1(20)}$.[3] We have considered[1] that the 5-phosphomethyl-6-chromanol type (V) may be enzymically converted by oxidation to the system VI, which would participate in oxidative phosphorylation by generating metaphosphate. The role of metaphosphate has been considered by Todd and co-workers,[4] and an ancillary role for the 5-methyl group has been considered by Chmielewska.[5] The biosynthesis of V may occur[1] by addition of P*i* to the quinone methine IV formed by direct cyclization of the parent 1,4-quinone. The recent interesting paper by Vilkas and Lederer[6] which proposes, on theoretical grounds, addition of P*i* to a quinone methine in the biosynthesis of quinol monophosphates prompts us to report our data in support of such a step in a different mechanism.[1]

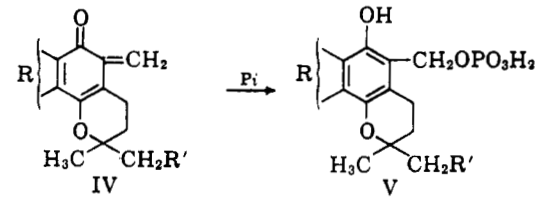


I-III

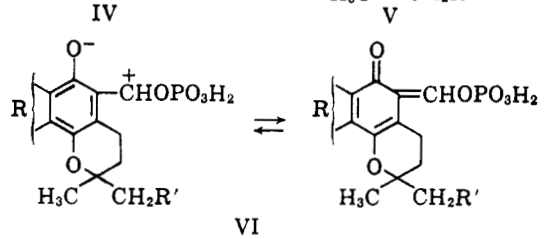
I, R = CH_3O-, CH_3O- R′ = $(CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2)_3H$

II, R =  R′ = $(CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2)_3H$

III, R = CH_3O-, CH_3O- R′ = H



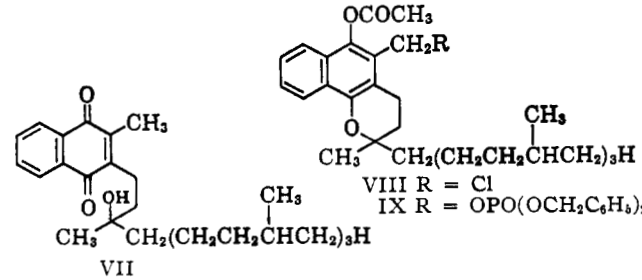
IV V



VI

Several approaches to these 5-phosphomethyl derivatives were explored and the 5-phosphomethyl-6-chromanyl acetates of the desired 5-phosphomethyl-6-chromanols have been synthesized. As an example, syntheses involving corresponding 5-chloromethyl-6-chromanyl acetates are as follows.

The reaction of vitamin $K_{1(20)}$ and sulfuric acid gave the γ-hydroxyquinone VII; $\lambda_{max}^{isooctane}$ 325 mμ ($E_{1\,cm.}^{1\%}$ 58), 273 mμ ($E_{1\,cm.}^{1\%}$ 375), 264 mμ ($E_{1\,cm.}^{1\%}$ 366), 249 mμ ($E_{1\,cm.}^{1\%}$ 398), 244 mμ ($E_{1\,cm.}^{1\%}$ 380); λ_{max}^{neat} 2.9 μ, 6.0 μ; *Anal.* Found: C, 79.14; H, 10.37. The reaction of VII with acetyl chloride gave the 5-chloromethyl-6-chromanyl acetate VIII: $\lambda_{max}^{isooctane}$ 248 mμ ($E_{1\,cm.}^{1\%}$ 707); λ_{max}^{neat} 5.65 μ; *Anal.* Found: C, 74.82; H, 9.59; Cl, 6.26. The n.m.r. spectrum exhibited absorption at 5.45 τ attributed to Ar–CH_2–Cl and no absorption at 7.92 τ characteristic of the Ar–CH_3 group. The reaction of VIII with silver dibenzylphosphate gave the corresponding phosphate triester IX; $\lambda_{max}^{ethanol}$ 247 mμ ($E_{1\,cm.}^{1\%}$ 497); λ_{max}^{neat} 2.9–4.0 μ, 5.65 μ, 8.3–9.1 μ, 9.5–10.1 μ, 14.4 μ; *Anal.* Found: C, 73.01; H, 8.09; P, 3.84. The n.m.r. spectrum exhibited absorption at 5.05 and 5.20 τ characteristic of the Ar–CH_2–O function. Selective cleavage of the benzyl moieties of the phosphate triester IX yielded the 5-phosphomethyl-6-chromanyl acetate II; $\lambda_{max}^{CCl_4}$ 2.9–4.0 μ, 5.65 μ, 8.3–9.1 μ, 9.5–10.0 μ; $\lambda_{max}^{isooctane}$ 247 mμ ($E_{1\,cm.}^{1\%}$ 506); *Anal.* Found: C, 67.54; H, 8.49; P, 5.00.



VII

VIII R = Cl
IX R = $OPO(OCH_2C_6H_5)_2$

The reaction of the 6-chromanol of hexahydrocoenzyme Q_4 with ferric chloride gave the γ-hydroxyquinone X: $\lambda_{max}^{isooctane}$ 276 mμ ($E_{1\,cm.}^{1\%}$ 325); λ_{max}^{neat} 2.80 μ, 6.06 μ, 6.21 μ, 7.90 μ, 8.30 μ, 8.63 μ; *Anal.* Found: C, 72.36; H, 10.44. The reaction of X with acetyl chloride gave the 5-chloromethyl-6-chromanyl acetate XI: $\lambda_{max}^{isooctane}$ 293 mμ ($E_{1\,cm.}^{1\%}$ 48); λ_{max}^{neat} 5.64 μ, 6.30 μ, 8.30 μ, 8.99 μ; *Anal.* Found: C, 68.80; H, 9.43; Cl, 6.73. The reaction of XI with silver dibenzylphosphate gave the corresponding phosphate triester XII: $\lambda_{max}^{isooctane}$ 290 mμ ($E_{1\,cm.}^{1\%}$ 34); λ_{max}^{neat} 5.64 μ, 6.30 μ, 8.30 μ, 8.99 μ, 9.9–

(1) R. E. Erickson, A. F. Wagner and K. Folkers, *J. Am. Chem. Soc.*, **85**, 1535 (1963).

(2) C. H. Shunk, J. F. McPherson and K. Folkers, *Biochem. Biophys. Res. Commun.*, **6**, 124 (1961).

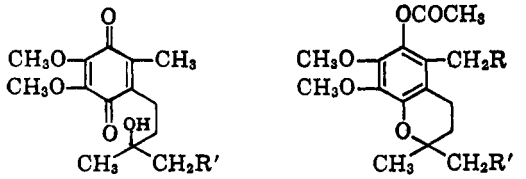
(3) A. F. Wagner, P. E. Wittreich, B. Arison, N. R. Trenner and K. Folkers, *J. Am. Chem. Soc.*, **85**, 1178 (1963).

(4) V. M. Clark, D. W. Hutchinson, G. W. Kirby and A. Todd, *J. Chem. Soc.*, 715 (1961); V. M. Clark, D. W. Hutchinson and A. Todd, *ibid.*, 722 (1961); V. M. Clark and A. Todd, "Quinones In Electron Transport," J. & A. Churchill, Ltd., London, 1961, pp. 190–200.

(5) I. Chmielewska, *Biochem. Biophys. Acta*, **39**, 170 (1960).

(6) M. Vilkas and E. Lederer, *Experientia*, **18**, 546 (1962).

10.1 μ, 14.35 μ; *Anal.* Found: C, 69.62; H, 8.47; P, 3.32; 85% purity based upon elemental analysis and hydrogenation data. Preferential cleavage of the benzyl moieties of the phosphate triester XII yielded the corresponding 5-phosphomethyl-6-chromanyl acetate I: $\lambda_{max}^{isooctane}$ 289 mμ ($E_{1\,cm.}^{1\%}$ 43); λ_{max}^{neat} 4.1–4.5 μ, 5.65 μ, 6.30 μ, 8.30 μ, 8.99 μ, 9.80 μ; *Anal.* Found: C, 60.68; H, 9.00; P, 4.80. The n.m.r. spectra of compounds I and X–XII were in agreement with the assigned structures.



X R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$
XIII R′ = H

XI R = Cl
R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$
XII R = $OPO(OCH_2C_6H_5)_2$
R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$
XIV R = Cl; R′ = H
XV R = $OPO(OCH_2C_6H_5)_2$
R′ = H

The 6-chromanol of coenzyme Q_1 was converted to the corresponding γ-hydroxyquinone XIII by ferric chloride oxidation; $\lambda_{max}^{isooctane}$ 276 mμ ($E_{1\,cm.}^{1\%}$ 588); λ_{max}^{neat} 2.8 μ, 6.1 μ, 6.2 μ, 7.8–7.9 μ; *Anal.* Found: C, 62.40; H, 7.46. When the γ-hydroxyquinone was dissolved in acetyl chloride at room temperature, the 5-chloromethyl-6-chromanyl acetate XIV was formed; m.p. 82–84°; $\lambda_{max}^{isooctane}$ 293 mμ ($E_{1\,cm.}^{1\%}$ 78); λ_{max}^{Nujol} 5.68 μ, 6.35 μ, 8.35 μ, 8.45 μ, 9.0 μ; *Anal.* Found: C, 58.68; H, 6.61; Cl, 10.23, 10.37. The chloromethyl compound on treatment with silver dibenzylphosphate yielded the phosphate triester XV: $\lambda_{max}^{isooctane}$ 291 mμ ($E_{1\,cm.}^{1\%}$ 54); λ_{max}^{neat} 5.6 μ, 6.3 μ, 6.85 μ, 7.8 μ, 8.3 μ, broad 9.8–10.1 μ, 13.4 μ, 14.35 μ. *Anal.* Found: C, 62.48; H, 6.31; P, 5.24. Selective cleavage of the benzyl moieties of the phosphate triester XV yielded the 5-phosphomethyl-6-chromanyl acetate III; potassium salt, $\lambda_{max}^{H_2O}$ 286 mμ ($E_{1\,cm}^{1\%}$ 38.5); λ_{max}^{Nujol} 5.7 μ, 6.3 μ, 8.2 μ, 8.9 μ, 9.8 μ, 10.25 μ, 12.0 μ.

ARTHUR F. WAGNER
AINO LUSI
CLIFFORD H. SHUNK
BRUCE O. LINN
DONALD E. WOLF
CARL H. HOFFMAN
ROBERT E. ERICKSON
BYRON ARISON
NELSON R. TRENNER
KARL FOLKERS

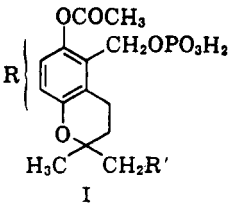
MERCK SHARP & DOHME
RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
RAHWAY, NEW JERSEY

RECEIVED MARCH 30, 1963

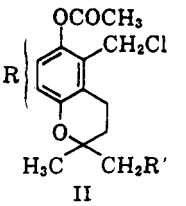
COENZYME Q. XLVIII. DATA ON QUINONE METHINES AS REACTION INTERMEDIATES AND THEIR POSSIBLE ROLE IN OXIDATIVE PHOSPHORYLATION

Sir:

Three new phosphomethyl derivatives I in the coenzyme Q and vitamin K groups have been reported.[1] These phosphates were synthesized from the 5-chloromethyl derivatives II which were derived from the parent quinones. A study of the mechanism of formation of II led to a consideration of quinone methines as intermediates in these reactions. A plausible mechanism involving these reactive intermediates in the biochemical transformations involved in oxidative phosphorylation has evolved.



I



II

Ia, R = 2,3-dimethoxy-5-methyl, R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$

Ib, R = 2-methyl-1,4-benzo, R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$

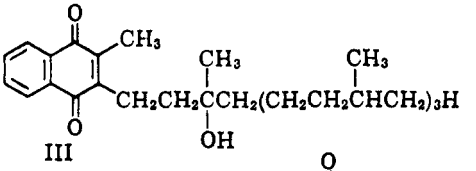
Ic, R = 2,3-dimethoxy-5-methyl, R′ = H

IIa, R = 2,3-dimethoxy-5-methyl, R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$

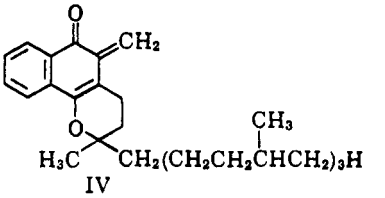
IIb, R = 2-methyl-1,4-benzo, R′ = $(CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_2)_3H$

IIc, R = 2,3-dimethoxy-5-methyl, R′ = H

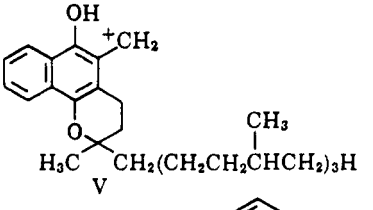
The synthesis of the hydroxyquinone III and its reaction with acetyl chloride to form the 5-chloromethyl derivative IIb have been reported.[1] Compound IIb was obtained directly by the reaction of vitamin $K_{1(20)}$ with acetyl chloride in the presence of water, strong acids or dihydrovitamin $K_{1(20)}$. A reasonable explanation of the formation of IIb involves the 1,4-addition of acetyl chloride to the quinone methine IV, which may be derived from the acid-catalyzed, non-reductive cyclization of vitamin $K_{1(20)}$. Quinone methines are known[2]



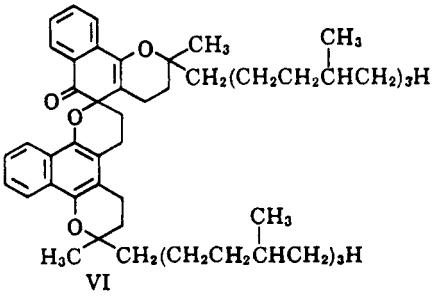
III



IV



V



VI

(1) A. F. Wagner, A. Lusi, C. H. Shunk, B. O. Linn, D. E. Wolf, C. H. Hoffman, R. E. Erickson, B. Arison, N. R. Trenner and K. Folkers, *J. Am. Chem. Soc.*, **85**, 1534 (1963).

(2) For a discussion of quinone methines see: K. Hultzsch, *Angew. Chem.*, **60**, 179 (1948); R. W. Martin, "The Chemistry of Phenolic Resins," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 129, 139–146.