

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

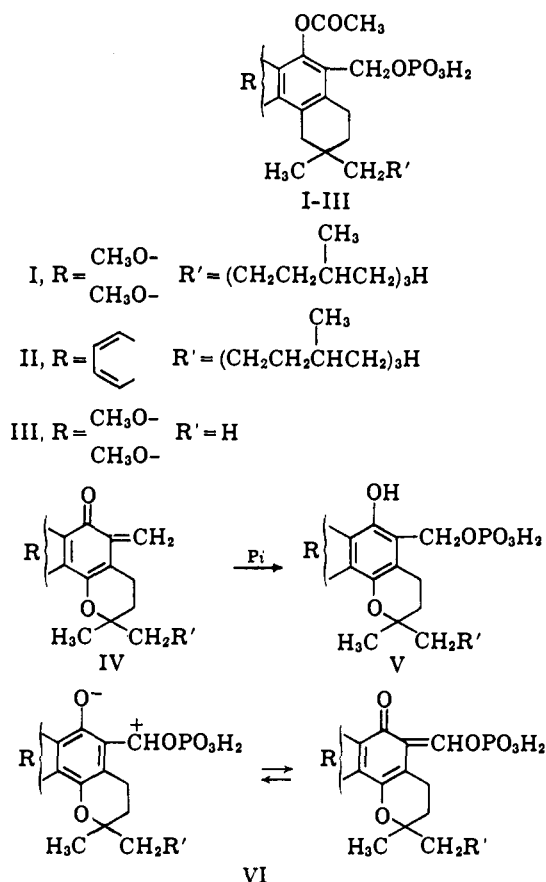
ether. A single such treatment usually sufficed to effect at least 80% exchange of the hydrogen atoms adjacent to the carbonyl group.

## 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,<sup>1</sup> this new structural type of phosphate is more sig-



nificant than the types related to the monophosphate of dihydrocoenzyme Q<sub>10</sub><sup>2</sup> and the 6-chromanyl phosphate of vitamin K<sub>1(20)</sub>.<sup>3</sup> We have considered<sup>1</sup> 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,<sup>4</sup> and an ancillary role for the 5-methyl group has been considered

(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).

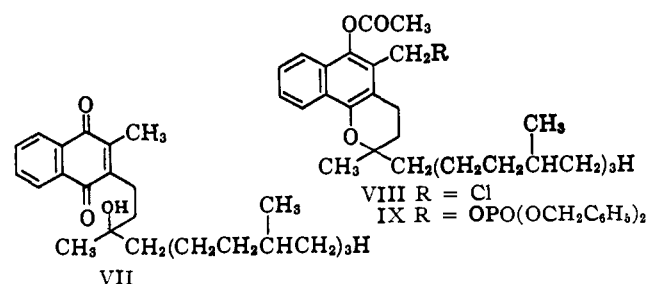
(3) A. F. Wagner, P. E. Wittreich, B. Arison, N. R. Trenner and K. Folkers, *J. Am. Chem. Soc.*, **85**, 1178 (1963).

(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.

by Chmielewska.<sup>5</sup> The biosynthesis of V may occur<sup>1</sup> by addition of  $\text{P}_i$  to the quinone methine IV formed by direct cyclization of the parent 1,4-quinone. The recent interesting paper by Vilkas and Lederer<sup>6</sup> which proposes, on theoretical grounds, addition of  $\text{P}_i$  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.<sup>1</sup>

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<sub>1(20)</sub> and sulfuric acid gave the  $\gamma$ -hydroxyquinone VII;  $\lambda_{\text{max}}^{\text{isooctane}}$  325 m $\mu$  ( $E_1^{1\% \text{cm}}$  58), 273 m $\mu$  ( $E_1^{1\% \text{cm}}$  375), 264 m $\mu$  ( $E_1^{1\% \text{cm}}$  366), 249 m $\mu$  ( $E_1^{1\% \text{cm}}$  398), 244 m $\mu$  ( $E_1^{1\% \text{cm}}$  380);  $\lambda_{\text{max}}^{\text{neat}}$  2.9  $\mu$ , 6.0  $\mu$ ; *Anal.* Found: C, 79.14; H, 10.37. The reaction of VII with acetyl chloride gave the 5-chloromethyl-6-chromanyl acetate VIII:  $\lambda_{\text{max}}^{\text{isooctane}}$  248 m $\mu$  ( $E_1^{1\% \text{cm}}$  707);  $\lambda_{\text{max}}^{\text{neat}}$  5.65  $\mu$ ; *Anal.* Found: C, 74.82; H, 9.59; Cl, 6.26. The n.m.r. spectrum exhibited absorption at 5.45  $\tau$  attributed to  $\text{Ar}-\text{CH}_2-\text{Cl}$  and no absorption at 7.92  $\tau$  characteristic of the  $\text{Ar}-\text{CH}_3$  group. The reaction of VIII with silver dibenzylphosphate gave the corresponding phosphate triester IX;  $\lambda_{\text{max}}^{\text{ethanol}}$  247 m $\mu$  ( $E_1^{1\% \text{cm}}$  497);  $\lambda_{\text{max}}^{\text{neat}}$  2.9-4.0  $\mu$ , 5.65  $\mu$ , 8.3-9.1  $\mu$ , 9.5-10.1  $\mu$ , 14.4  $\mu$ ; *Anal.* Found: C, 73.01; H, 8.09; P, 3.84. The n.m.r. spectrum exhibited absorption at 5.05 and 5.20  $\tau$  characteristic of the  $\text{Ar}-\text{CH}_2-\text{O}$  function. Selective cleavage of the benzyl moieties of the phosphate triester IX yielded the 5-phosphomethyl-6-chromanyl acetate II;  $\lambda_{\text{max}}^{\text{CCl}_4}$  2.9-4.0  $\mu$ , 5.65  $\mu$ , 8.3-9.1  $\mu$ , 9.5-10.0  $\mu$ ;  $\lambda_{\text{max}}^{\text{isooctane}}$  247 m $\mu$  ( $E_1^{1\% \text{cm}}$  506); *Anal.* Found: C, 67.54; H, 8.49; P, 5.00.

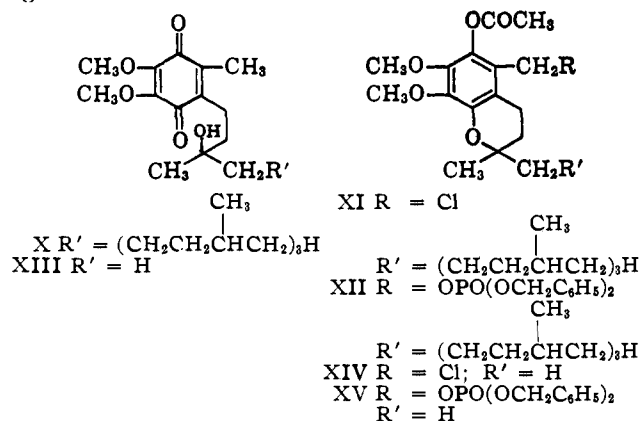


The reaction of the 6-chromanol of hexahydrocoenzyme Q<sub>4</sub> with ferric chloride gave the  $\gamma$ -hydroxyquinone X:  $\lambda_{\text{max}}^{\text{isooctane}}$  276 m $\mu$  ( $E_1^{1\% \text{cm}}$  325);  $\lambda_{\text{max}}^{\text{neat}}$  2.80  $\mu$ , 6.06  $\mu$ , 6.21  $\mu$ , 7.90  $\mu$ , 8.30  $\mu$ , 8.63  $\mu$ ; *Anal.* Found: C, 72.36; H, 10.44. The reaction of X with acetyl chloride gave the 5-chloromethyl-6-chromanyl acetate XI:  $\lambda_{\text{max}}^{\text{isooctane}}$  293 m $\mu$  ( $E_1^{1\% \text{cm}}$  48);  $\lambda_{\text{max}}^{\text{neat}}$  5.64  $\mu$ , 6.30  $\mu$ , 8.30  $\mu$ , 8.99  $\mu$ ; *Anal.* Found: C, 68.80; H, 9.43; Cl, 6.73. The reaction of XI with silver dibenzylphosphate gave the corresponding phosphate triester XII:  $\lambda_{\text{max}}^{\text{isooctane}}$  290 m $\mu$  ( $E_1^{1\% \text{cm}}$  34);  $\lambda_{\text{max}}^{\text{neat}}$  5.64  $\mu$ , 6.30  $\mu$ , 8.30  $\mu$ , 8.99  $\mu$ , 9.9-

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

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

10.1  $\mu$ , 14.35  $\mu$ ; *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-chromanil acetate I:  $\lambda_{\max}^{\text{isooctane}}$  289  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  43);  $\lambda_{\max}^{\text{neat}}$  4.1–4.5  $\mu$ , 5.65  $\mu$ , 6.30  $\mu$ , 8.30  $\mu$ , 8.99  $\mu$ , 9.80  $\mu$ ; *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.



The 6-chromanol of coenzyme Q<sub>1</sub> was converted to the corresponding  $\gamma$ -hydroxyquinone XIII by ferric chloride oxidation;  $\lambda_{\max}^{\text{isooctane}}$  276  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  588);  $\lambda_{\max}^{\text{neat}}$  2.8  $\mu$ , 6.1  $\mu$ , 6.2  $\mu$ , 7.8–7.9  $\mu$ ; *Anal.* Found: C, 62.40; H, 7.46. When the  $\gamma$ -hydroxyquinone was dissolved in acetyl chloride at room temperature, the 5-chloromethyl-6-chromanil acetate XIV was formed; m.p. 82–84°;  $\lambda_{\max}^{\text{isooctane}}$  293  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  78);  $\lambda_{\max}^{\text{Nujol}}$  5.68  $\mu$ , 6.35  $\mu$ , 8.35  $\mu$ , 8.45  $\mu$ , 9.0  $\mu$ ; *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:  $\lambda_{\max}^{\text{isooctane}}$  291  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  54);  $\lambda_{\max}^{\text{neat}}$  5.6  $\mu$ , 6.3  $\mu$ , 6.85  $\mu$ , 7.8  $\mu$ , 8.3  $\mu$ , broad 9.8–10.1  $\mu$ , 13.4  $\mu$ , 14.35  $\mu$ . *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-chromanil acetate I; potassium salt,  $\lambda_{\max}^{\text{H}_2\text{O}}$  286  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  38.5);  $\lambda_{\max}^{\text{Nujol}}$  5.7  $\mu$ , 6.3  $\mu$ , 8.2  $\mu$ , 8.9  $\mu$ , 9.8  $\mu$ , 10.25  $\mu$ , 12.0  $\mu$ .

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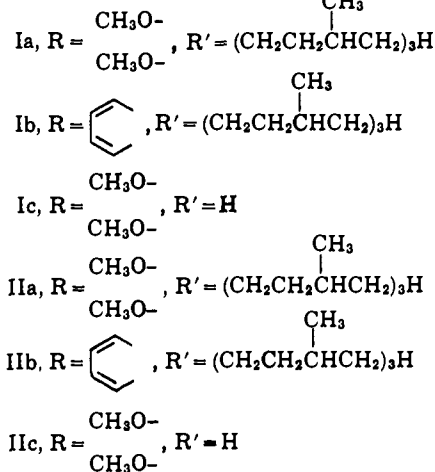
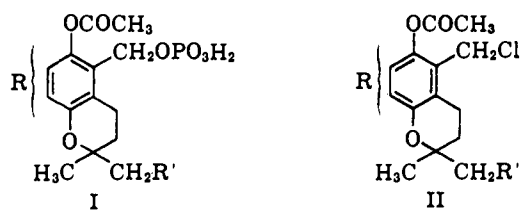
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#### COENZYME Q. XLVIII. DATA ON QUINONE METHINES AS REACTION INTERMEDIATES AND THEIR POSSIBLE ROLE IN OXIDATIVE PHOSPHORYLATION

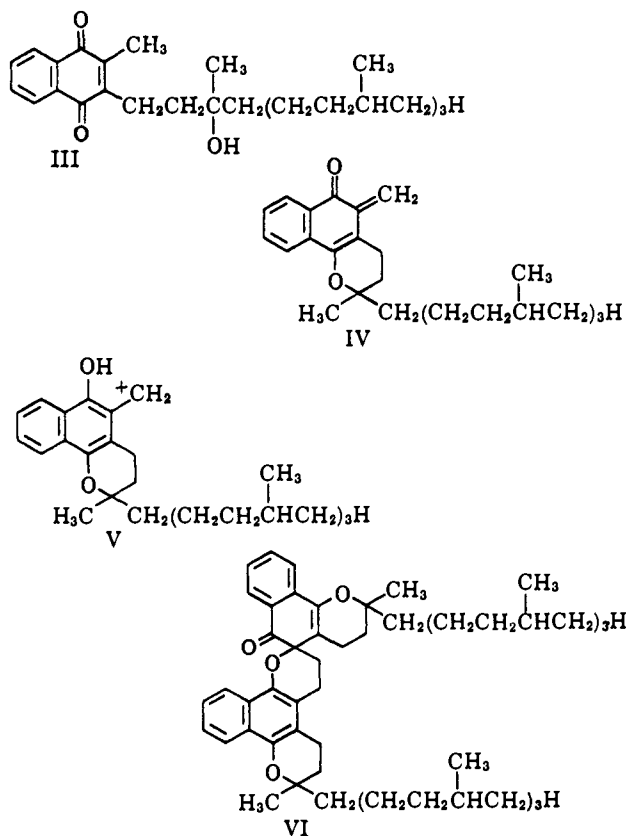
Sir:

Three new phosphomethyl derivatives I in the coenzyme Q and vitamin K groups have been reported.<sup>1</sup> 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.

(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).



The synthesis of the hydroxyquinone III and its reaction with acetyl chloride to form the 5-chloromethyl derivative IIb have been reported.<sup>1</sup> Compound IIb was obtained directly by the reaction of vitamin K<sub>1(20)</sub> with acetyl chloride in the presence of water, strong acids or dihydrovitamin K<sub>1(20)</sub>. 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<sub>1(20)</sub>. Quinone methines are known<sup>2</sup>



(2) For a discussion of quinone methines see: K. Hultsch, *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.