6,11-Dihydro-11-hydroxy-6-oxo-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran. A Stable Quinone Hemiketal Related to Vitamin K and of Special Interest Concerning Oxidative Phosphorylation

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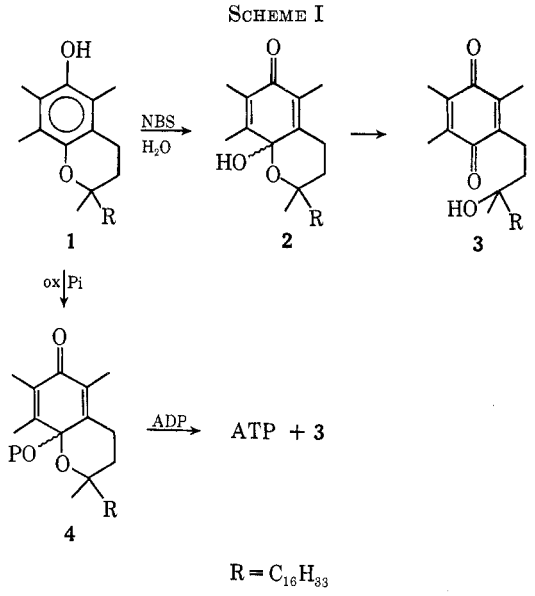
Argentic oxide oxidation of 6-methoxy-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran gives the title compound in 35% yield. The latter is a stable hemiketal of special interest because it is structurally analogous to an intermediate proposed for oxidative phosphorylation. The hemiketal is isolated from an acidic medium and is isomerized only slowly and partially by triethylamine in refluxing benzene. Various attempts to prepare phosphate esters of the ketal hydroxyl function were unsuccessful.

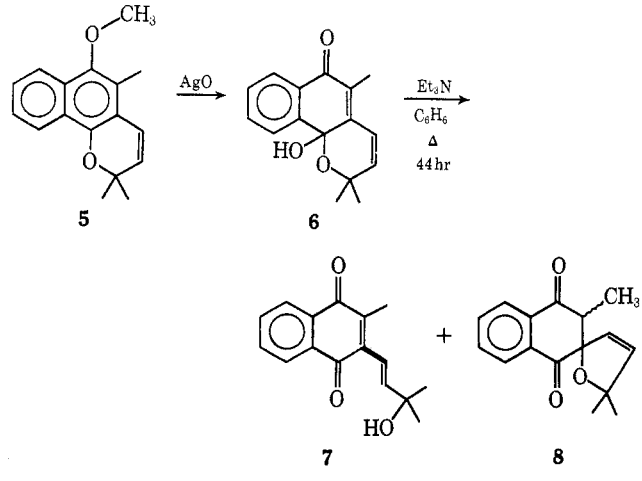
Although the involvement of quinones in oxidative phosphorylation has been decisively demonstrated, the detailed mechanism whereby electron transport (oxidation–reduction or respiration) is coupled to phosphorylation (the conversion of ADP to ATP) remains speculative. Several plausible mechanistic proposals have recently been found inconsistent with the isotope labeling experiments performed in the phylloquinone–*Mycobacterium phlei* system.[1,2] One of the several remaining possibilities consistent with the aforementioned experiments is that proposed by Durckheimer and Cohen (Scheme I).[3] The hemiketal **2** was identified as a

SCHEME I



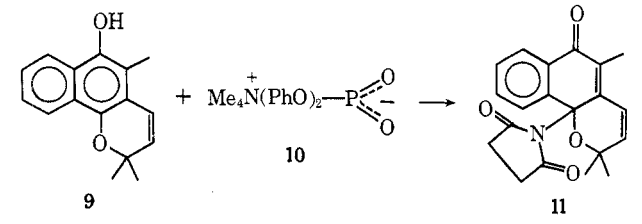
transient intermediate in the NBS oxidation of α-tocopherol (**1**) in the presence of water. The corresponding phosphate (**4**), which might be formed by oxidation of **1** in the presence of inorganic phosphate (P_i), was proposed as an analog of a possible ADP phosphorylating agent, and arguments were advanced in support of this possibility. In this context it is especially interesting that a relatively stable quinone hemiketal (**6**) has been isolated as a product of the oxidation of chromene **5** by argentic oxide (35% yield).[4] The hemiketal is amazingly stable for its structural type, as indicated by its isolation from an acidic aqueous medium and from the fact that long heating with triethylamine in benzene leads to a 27% yield of recovered **6**, along with two other interesting compounds, **7** (10%) and **8** (29%, all isolated yields, Scheme II). The special stability of **6** relative

SCHEME II



to Durckheimer and Cohen's hemiketal may be attributed to the conjugation energy of the pyranyl double bond with the aromatic ring, which could be diminished in the open chain form, and/or to the formation of a naphthoquinone system in the present instance as contrasted to a benzoquinone system in the earlier one. This extraordinary stability provided encouragement for attempts to prepare the phosphate of **6** of interest for oxidative phosphorylation experiments, as mentioned earlier.

The naphthopyranol **9** was oxidized by NBS in the presence of excess tetramethylammonium diphenyl phosphate (**10**). The desired phosphate was not found



among the products, but the novel molecule **11** was. It was considered possible that the phosphate had been formed but had undergone SN1 substitution by succinimide, giving **11**. To reduce the SN1 reactivity of any

(1) S. J. DiMari, C. D. Snyder, and H. Rapoport, *Biochemistry*, **7**, 2301 (1968).
(2) C. D. Snyder and H. Rapoport, *ibid.*, **7**, 2318 (1968).
(3) W. Durckheimer and L. A. Cohen, *J. Amer. Chem. Soc.*, **86**, 4388 (1964).
(4) W. E. Bondinell, C. D. Snyder, and H. Rapoport, *ibid.*, **91**, 6889 (1969).

phosphate formed, the more basic and nucleophilic salt ditetramethylammonium phenyl phosphate was substituted for **10** in a similar reaction. Still, none of the desired product was observed. The methyl group at the 5 position provides a convenient means for decomposition of such phosphates, by elimination. It therefore seems possible that model studies on a suitable unmethylated system might be to more avail.

Experimental Section

Melting points were determined without correction using a Mel-Temp apparatus. Infrared spectral measurements utilized a Beckman IR-5, nmr spectra a Varian A-60 spectrometer, unless otherwise specified. A consolidated Electrodynamics 21-102 spectrometer was used for obtaining mass spectra.

6,11-Dihydro-11-hydroxy-6-oxo-2,2,5-trimethyl-2*H*-naphtho[1,2-*b*]pyran (6).—To a stirred solution of 1.7 g (6.7 mmol) of the chromenol methyl ether **5** dissolved in dioxane (77 ml) and 85% phosphoric acid (7.7 ml) was added 2.5 g (20 mmol) of argentic oxide. After stirring for 2.5 hr at room temperature, the mixture was diluted with 200 ml of water and 100 ml of ether and worked up in the usual way. The ether solvent was evaporated cold, leaving an oil, which crystallized from 10% ether–hexane. There was obtained 0.584 g (35.4% yield) of the hemiketal **6**: mp 128–130° dec; ir ($CDCl_3$) ν 3600, 3400, 1650, 1605, 1340 cm^{-1}; mass spectrum *m/e* 256 (M), 238 (M − H_2O); nmr (10% DMSO-d_6–$CDCl_3$) τ 8.68 (s, 3 H), 8.32 (s, 3 H), 8.0 (s, 3 H), 5.9 (br s, 1 H), 3.74, 3.35 (q, 2 H, J_{AB} = 10.0 Hz), 2.47 (m, 2 H), and 2.04 (m, 2 H). Analytical purity could not be achieved because of the decomposition accompanying attempted recrystallizations.

Triethylamine Experiment.—A solution of 0.194 g (0.759 mmol) of the hemiketal **6** in benzene (20 ml) and triethylamine (0.32 ml, 2.27 mmol, 3 equiv) was refluxed for 44 hr under nitrogen and cooled, and the solvent was evaporated. Crystallization of the resulting gum from 4:1 hexane–ether afforded 52 mg (26.8%) of unreacted **6**. The mother liquor was evaporated cold and chromatographed on Florisil. The combined 1:1 benzene–hexane eluates were evaporated and gave 57 mg (29.4%) of **8** as a yellow gum: ir ($CHCl_3$) ν 1700, 1650, 1600 cm^{-1}; mass spectrum *m/e* 256 (M); nmr ($CDCl_3$, HA-100) τ 8.73 (several sharp lines, 9 H, among which are two doublets at 8.83 and 8.63, J = 7.0 Hz), 6.85 (sextet representing two overlapped quartets, 1 H, J = 7.0 Hz), 4.74 and 4.14 (q, 1 H, J = 6.0 Hz), 4.45 and 4.12 (q, 1 H, J = 6.0 Hz), 2.39 (m, 2 H), and 2.05 (m, 2 H).

The chloroform eluate yielded another gum which crystallized from 1:1 ether–hexane, affording 20 mg (10.3%) of the ring-opened quinone alcohol **7** as a tan solid: mp 81–85°; ir (CS_2) ν 3600, 1665, 1295, 713 cm^{-1}; mass spectrum *m/e* 256 (M); nmr ($CDCl_3$, HA-100) τ 8.55 (s, 6 H), 7.74 (s, 3 H), 3.35 (s, 2 H), 2.35 (m, 2 H), and 1.95 (m, 2 H); nmr (DMSO-d_6, 500 Hz sweep) showed the 3.35 singlet to be a doublet separated by about 1 Hz. The initially formed quinone alcohol must certainly have the cis geometry, but may isomerize by reversible addition of triethylamine to the terminal end of the dienone system. Because of the spectral similarity between **7** and the previously reported trans compound,[5] the assignment of the trans geometry is made, pending further evidence.

Tetramethylammonium *O,O*-Diphenyl Phosphate (10).—To a stirring solution of 0.616 g (4.0 mmol) of tetramethylammonium bromide in 4 ml of water was added 0.927 g (4.0 mmol) of silver(I) oxide. The mixture was stirred for 3 hr, filtered, and washed three times with 1-ml portions of water. Diphenyl phosphate (1.0 g, 4.0 mmol) was added to the filtrate, and the solution was stirred for 12 hr and then evaporated to a solid. This crude product was stirred in acetone, filtered, washed (acetone), and dried. There was obtained 1.17 g (91%) of **10** as a white solid, nmr (DMSO-d_6) τ 6.90 (s, 12 H) and 2.95 (m, 10 H).

NBS Oxidation of 9 in the Presence of 10.—To a stirring solution of 0.24 g (1 mmol) of **9** in acetonitrile (20 ml) was added 1.14 g (3.52 mmol) of tetramethylammonium diphenyl phosphate (**10**) and then 0.18 g (1.0 mmol) of *N*-bromosuccinimide. The mixture was stirred for 0.5 hr at room temperature, filtered under nitrogen, and evaporated cold under reduced pressure to afford a solid. The latter was leached several times with carbon tetrachloride, the washes were evaporated, and the crude solid was chromatographed on Florisil. Elution with 3:1 benzene–chloroform gave a product which formed yellow crystals in 1:1 ether–hexane. There was obtained 32 mg (9.4%) of the succinimidyl derivative **11**: mp 136° (with resolidification); ir ($CHCl_3$) ν 1700, 1650, 1600, 1205 cm^{-1}; mass spectrum *m/e* 239 (M − succinimidyl); nmr (CCl_4, HA-100) τ 8.68 (s, 3 H), 8.52 (s, 3 H), 8.20 (s, 3 H), 7.36 (s, 4 H), 4.59, 4.10 (q, 2 H, J_{AB} = 10.0 Hz), and 2.0 (d, 1 H, J = 8.0 Hz).

Recrystallization from ether–hexane gave **11** as yellow crystals, mp 144–145°.

Anal. Calcd for $C_{20}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.06; H, 5.81; N, 4.40.

Registry No.—**6**, 31819-55-3; **7**, 22268-05-9; **8**, 31819-57-5; **10**, 31819-58-6; **11**, 31883-40-6.

(5) C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 731 (1969).

Neutral and Positively Charged Azonitriles. Decomposition Rates and Efficiencies of Radical Production[1]

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The uncharged azonitrile, 4,4′-azobis-4-cyano-1-methylpiperidine (ACMP), and its monopositive *N*-methyl and dipositive *N,N*′-dimethyl derivatives (MACMP and DACMP) have been synthesized. Their decomposition rates and efficiencies of radical production have been measured in the solvent DMSO and compared with the analogous data for 1,1′-azobis-1-cyanocyclohexane (ACC) and the new compound, 1,1′-azobis-1-cyano-4,4-dimethylcyclohexane (ACDC). The resulting activation parameters follow [azonitrile, ΔH^* (kcal/mol), ΔS^* (eu), ΔF^* (kcal/mol)]: ACMP, 32.6, 10.4, 28.8; MACMP, 31.7, 9.2, 28.4; DACMP, 29.8, 4.6, 28.1; ACC, 32.4, 9.7, 28.9; ACDC, 31.6, 8.6, 28.5. The efficiencies of radical production from ACC, ACDC, and DACMP are *ca.* 0.6, 0.5, and 0.4, respectively. These data are discussed in terms of electrostatic interactions between the positively charged ends of the molecules and the resultant geminate radicals. It is concluded that electrostatic effects are of minimal importance and that rate differences are largely the result of steric and/or solvation effects.

In order to determine whether positively charged geminate radicals possess a significant "cage effect," Hammond studied the thermal decomposition reactions of a pair of azobisisobutyramidines (**1a**, R = H; **1b**, R = $-CH_2-$) and their conjugate acids (**2a** and **2b**).[3] Products were consistent with radical formation (**3** and

(1) Support by the National Science Foundation (GP-8670) is gratefully acknowledged.

(2) NDEA Predoctoral Fellow, 1968–1971.

(3) G. S. Hammond and R. C. Neuman, Jr., *J. Amer. Chem. Soc.*, **85**, 1501 (1963).