Diisopropylacetic Anhydride.—A solution of 1.4 g. (0.01 mole) of diisopropylacetic acid[16] and 0.5 g. (0.007 mole) of ethoxyacetylene in 3 ml. of dry ether was held at room temperature for 2 hr. and was then refluxed for 1 hr. Distillation yielded 0.52 g. (39%) of the anhydride, b.p. 105° at 2 mm., n^{20}D 1.4420, and 0.59 g. (42%) of acid.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.1; H, 11.2. Found: C, 70.8, 71.0; H, 10.9, 11.1.

Triisopropylacetic Anhydride.—A solution of 1.9 g. (0.01 mole) of triisopropylacetic acid and 0.5 g. of ethoxyacetylene in 25 ml. of dry ether was refluxed for 5 days. After removal of solvents the residue was recrystallized from petroleum ether, b.p. 90–100°, to yield 1.1 g. (61%) of crude anhydride, m.p. 88–90°, and 0.74 g. (39%) of crude starting acid. Recrystallization of the anhydride from this solvent afforded large hexagonal crystals of triisopropylacetic anhydride, m.p. 92–93°.

Anal. Calcd. for $C_{22}H_{42}O_3$: C, 74.5; H, 11.9. Found: C, 74.8, 74.8; H, 11.7, 11.8.

When a similar reaction was run for 18 hr. only a very small amount of anhydride was formed.

Reaction of Triisopropylacetic Acid.—To 2.2 g. of trifluoroacetic anhydride was added 1.9 g. of triisopropylacetic acid. Within 5 min. the acid dissolved completely and slow evolution of gas occurred. The rate of gas evolution slowed when the reaction mixture was cooled in an ice-bath, but did not stop entirely. On standing at room temperature the color deepened to brown and two layers were visible, the top being colorless. After 1.5 hr. the top layer was separated and washed with water. It readily decolorized permanganate solution and bromine in carbon tetrachloride. The gas evolved did not give a precipitate on passing through barium hydroxide solution and hence was assumed to be carbon monoxide.

When diisopropylacetic acid was treated in a similar way no gas was evolved and no deepening of color was noted. However, no attempt to isolate diisopropylacetic anhydride was made.

When a mixture of triisopropylacetic acid and a large excess of pure thionyl chloride was heated at reflux the acid slowly went into solution. After refluxing for 2 hr. the excess thionyl chloride was evaporated and the residue distilled to yield triisopropylacetyl chloride, b.p. 100–101° at 6 mm., in 95% yield. The distillate solidified to a waxy solid, m.p. 49–52°. This material was used in further work. Recrystallization from petroleum ether, b.p. 65–70°, at −78°, yielded pure acid chloride, m.p. 54.2–55.2° in a sealed tube (infrared absorption at 5.60 μ) but no sample was sent for analysis as it was so unstable in the presence of the slightest trace of moisture.

The addition of 20 ml. of pure absolute methanol to 8.1 g. of triisopropylacetyl chloride at 0° resulted in instantaneous reaction. The reaction mixture separated into two phases. After 1 hr. at room temperature (no gas evolution noticed) distillation afforded 7.2 g. (90%) of methyl triisopropylacetate as a colorless oil, b.p. 91.5–92.5° at 6.5 mm., n^{20}D 1.4518 (infrared absorption, 5.75 μ).

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 72.0; H, 12.1. Found: C, 72.0, 71.7; H, 12.0, 12.1.

A solution of 9.9 g. of triisopropylacetyl chloride in 30 ml. of dry ether was added to a suspension of freshly prepared sodium amide in dry liquid ammonia. After stirring for 30 hr., excess ammonium chloride was added and the ammonia evaporated by gentle warming. Crystallization from benzene–petroleum ether, b.p. 65–70°, yielded 8.3 g. (93%) of triisopropylacetamide, m.p. 141.8–142.8° (infrared absorption, 6.1 μ).

Anal. Calcd. for $C_{11}H_{23}NO$: C, 71.3; H, 12.5; N, 7.6. Found: C, 71.4, 71.6; H, 12.6, 12.4; N, 7.5, 7.6.

In a similar experiment except that only a 3.5-hr. reaction period was used, the yield of amide was 47%. In a similar reaction except that the sodium amide was omitted (reaction time 30 hr.) the yield was 68%.

Ionization Constants of Acids.—The ionization constants listed in Table I were determined by potentiometric titration using a glass electrode, calomel reference electrode and Beckman pH meter, model G, in 50 volume per cent methanol–water at 40°. The ionization constants were calculated by the Henderson equation[20] using $^1/_4$, $^1/_2$ and $^3/_4$ neutralization points. The values thus calculated were accurate to ±0.03 pK unit.

$$pH = pK + \log([A^-]/[HA])$$

The values we obtained (Table I) do not agree too well with the values cited.[10] The system was standardized before and after each titration with 0.05 M phthalate buffer for pH 4.03, 0.05 M phosphate buffer for pH 6.84, and 0.01 M borax buffer for pH 9.07.[21] Sample solutions were prepared by weighing the acid sample directly in the 180-ml. titrating beaker and adding 50.0 ml. of absolute methanol kept in a reservoir in the thermostated bath at 40°. After the acid had dissolved completely, 50.0 ml. of water held at 40° in the same thermostat was added and the titrations were carried out with 0.0967 N carbonate-free methanolic sodium hydroxide solution in a 25-ml. needle valve buret at room temperature.

(20) See S. Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 982.

(21) H. H. Willard, L. L. Merrit and J. A. Dean, "Instrumental Methods of Analysis," D. Van Nostrand Co., Inc., Princeton, N. J., 1958, pp. 447–469.

Synthesis of the New 3,4-Dihydro-2-H-naphtho[1,2-b]pyran-6-yl Phosphate from Vitamin K1(20)[1]

BY ARTHUR F. WAGNER, PAUL E. WITTREICH, BYRON ARISON, NELSON R. TRENNER AND KARL FOLKERS

A role for the 6-chromanyl derivatives of vitamin K in microbial oxidative phosphorylation was suggested on the basis of enzyme studies with a light-inactivated, cell-free extract of *Mycobacterium phlei*. As a part of a program to study such intermediates, 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]-pyran-6-yl phosphate (VIII) and the corresponding acetate V were synthesized from vitamin $K_{1(20)}$. The new reaction of the synthetic sequence is the sodium hydride-catalyzed cyclization of the naphthoquinone derivative to a corresponding 6-chromenyl intermediate.

The effect of certain naphthoquinones on the electron transport and oxidative phosphorylation processes of cellular respiration has been studied in light-inactivated (360 mμ), cell-free extracts of *Mycobacterium phlei*.[2–6] The light-inactivated system is dependent upon the addition of vitamin $K_{1(20)}$ or certain closely related derivatives for the restoration of oxidative phosphorylation. Evidence suggestive of participation by a 6-

chromanol and a 6-chromanyl phosphate in this process was obtained by adding vitamin $K_{1(20)}$ in substrate quantity to the light-inactivated *M. phlei* extract; the biosynthetic intermediates were stabilized by acetylation, and diacetyldihydrovitamin $K_{1(20)}$ and the 6-chromanyl acetate (V) derived from vitamin $K_{1(20)}$ were identified in the reaction mixture on the basis of certain spectral and chromatographic properties.[5,6] In later studies,[7] the 6-chromanyl acetate V was isolated in pure form from the enzymic and acetylated mixture, but it was shown that this acetate may be derived, at least in part, from a non-enzymic cyclization of dihydrovitamin $K_{1(20)}$; whether the chromanol is

(1) Coenzyme Q. XLI.

(2) A. F. Brodie, M. W. Weber and C. T. Gray, *Biochim. et Biophys. Acta*, 25, 448 (1957); (b) A. F. Brodie and B. R. Davis, *Federation Proc.*, 18, 198 (1959).

(3) A. F. Brodie and J. Ballantine, *J. Biol. Chem.*, 235, 226 (1960).

(4) A. F. Brodie and J. Ballantine, *ibid.*, 235, 232 (1960).

(5) P. J. Russell and A. F. Brodie, *Federation Proc.*, 19, 38 (1960).

(6) A. F. Brodie, P. J. Russell and E. Kashet, Abstracts, 137th National Meeting of the American Chemical Society, 1960, p. 25C.

(7) A. F. Wagner, P. E. Wittreich, C. H. Hoffman, K. Folkers and A. F. Brodie, *Biochem. Biophys. Research Commun.*, 8, 38 (1962).

I, Vitamin $K_1(20)$ II   III

VI   V   IV

VIII   VII
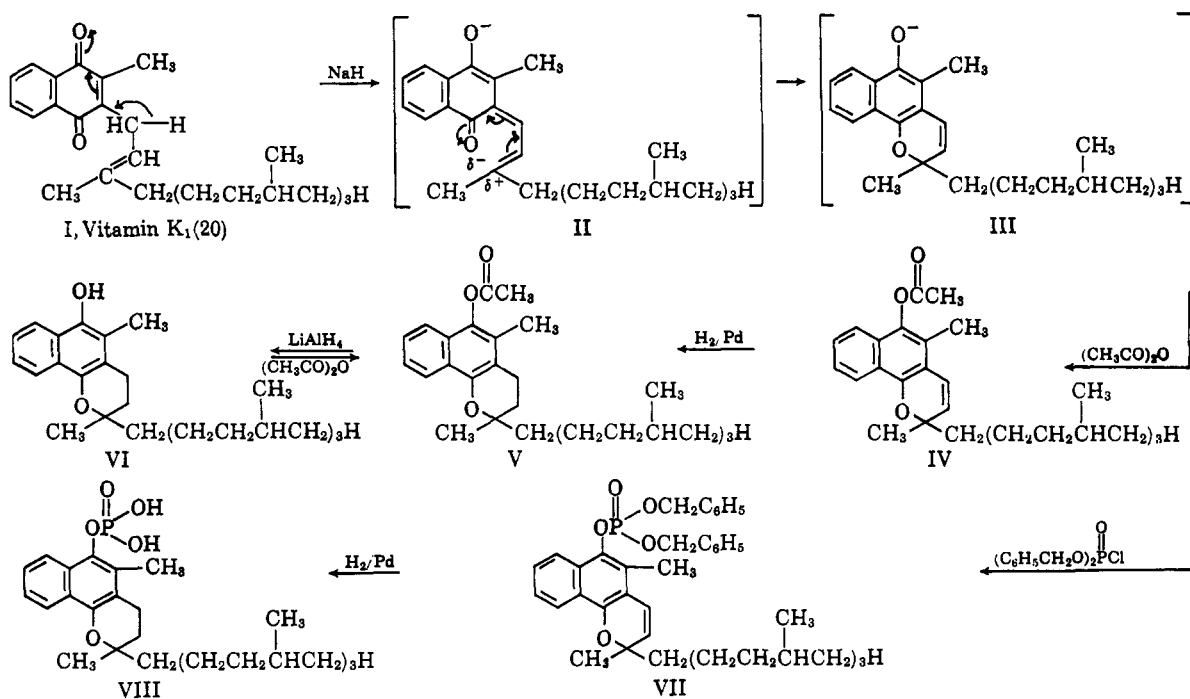
produced enzymically prior to the acetylation step has not been established in a manner to exclude the now recognized artifactual cyclization.

The fact that the only naphthoquinones which seem to restore oxidative phosphorylation in the microbial system are those appropriately substituted to permit the formation of a chroman moiety has also been considered as evidence for the participation of a 6-chromanyl intermediate.[8-10]

In the course of evaluating the validity of participation by 6-chromanyl derivatives of vitamin K in oxidative phosphorylation, it was necessary to synthesize and rigorously characterize the 6-chromanyl acetate and 6-chromanyl phosphate of vitamin $K_{1(20)}$. Authentic specimens of these new compounds were required for comparison with "trapped" intermediates, and to investigate the phosphate transfer reaction associated with a single oxidative step of the electron transport sequence. This paper details the synthesis of the new 6-chromenyl and 6-chromanyl derivatives of vitamin $K_{1(20)}$. The preliminary biological studies with these synthetic derivatives have been published separately.[11]

Vitamin $K_{1(20)}$ (I) was converted to the corresponding 6-chromanyl acetate, 3,4-dihydro-2,5-dimethyl-2-(4,8,-12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate (V), by cyclization with sodium hydride,[12] followed by acetylation and catalytic reduction. The cyclization reaction may be interpreted[13] as proceeding by the elimination of a proton from the 1-position of the phytyl side chain and the withdrawal of electrons to the carbonyl oxygen atom at the 1-position of the quinone moiety. The intermediate II is then stabilized by a shift of electrons and bond formation between the carbonyl oxygen atom at the 4-position of the quinone moiety and the quaternary carbon atom of the phytyl

side chain to yield the oxy anion of the 6-chromenol III.[14] Treatment of the reaction mixture with acetic anhydride yielded the 6-chromenyl acetate, 2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate (IV). The 6-chromenyl acetate IV was reduced catalytically to yield the 6-chromanyl acetate, 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate (V).

The 6-chromanol, 3,4-dihydro-2,5-dimethyl-2-(4,8,-12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-ol (VI), was prepared in excellent yield from the corresponding 6-chromanyl acetate V by reductive hydrolysis with lithium aluminum hydride.

The 6-chromanyl phosphate, 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl phosphate (VIII), was synthesized by the cyclization of vitamin $K_{1(20)}$ with sodium hydride, followed by phosphorylation of the oxy anion intermediate III with dibenzyl chlorophosphonate to yield the 6-chromenyl derivative, O,O-dibenzyl O-{2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl} phosphate (VII). Catalytic hydrogenation of the 6-chromenyl ester VII over palladium resulted in reduction of the 3,4-double bond and cleavage of the benzyl moieties to yield the 6-chromanyl phosphate VIII, which was obtained in crystalline form.

Since these syntheses were undertaken to provide authentic specimens for studies on enzymic oxidative phosphorylation, the compounds were rigorously purified and characterized. Spectral data provided the most critical criteria of purity and identity. In the ultraviolet, the 6-chromenyl derivatives are characterized by absorption maxima in the 265- and 275-mμ regions; the 6-chromanyl derivatives are characterized by an absorption maximum in the 245-mμ region.

Nuclear magnetic resonance spectroscopy proved to be an indispensable criterion of structure and purity for these 6-chromenyl and 6-chromanyl derivatives.[15-21]

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(13) This mechanism is similar to that proposed by J. Links, Biochim. et Biophys. Acta, 38, 193 (1960), for the isomerization of coenzyme Q₁₀ to ubichromenol on alumina.

(14) D. McHale and J. Green (Chem. Ind. (London), 1867 (1962)) have just reported that vitamin K₁(₂₀) in refluxing pyridine is converted into a product which shows a typical chromenol spectrum, and a positive Emmerie and Engel reaction, but was not otherwise characterized.

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TABLE I

SPECTRUM OF VITAMIN $K_{1\,(20)}$ (I) IN CCl_4 AT 40 Mc.

Aromatic H	=CCH₂CH=	=CCH₂CH=	2-CH₃; CH₃ =CC	CHC CH₃C	CCH₃
1.95–2.67 (broad m)	5.12(t)	6.82(d)	8.00; 8.32	8.92 (broad)	9.18(d)

TABLE II

Vit. $K_{1(20)}$ derivative	H₇	H₈, H₉, H₁₀	H₄	H₃	6CH₃C=O	5CH₃	2CH₃	CH—C CH₃—C	C—CH₃
6 Chromenyl acetate in CCl₄, IV	1.97(m)	2.69(m)	3.41 3.56(d)	4.42 4.58(d)	7.67	7.83	8.62	8.85 (broad)	9.15(d)
6-Chromanyl acetate in CCl₄, V	1.97(m)	2.67(m)	7.37(t)	...	7.68	7.94	8.70	8.82 (broad)	9.15(d)
6-Chromanol in CCl₄, VI	2.1(m) (broad)	2.72(m) (broad)	7.37(t)	8.13(t)	..	7.79	8.70	8.80 (broad)	9.15(d)
6-Chromenyl dibenzyl phosphate in CCl₄, VII[a]	2.02(m)	2.8(m)	3.44 3.60(d)	4.41 4.58(d)	..	7.68 7.71(d)	8.62	8.89 (broad)	9.17(d)
6-Chromanyl phosphate in CCl₄ and in (CD₃)₂CO, VIII	2.07(m)	2.77(m)	~7.5 (broad)	...	..	7.97 (broadened)	8.74	8.80 (broad)	9.15(d)
	1.85	2.55(m)	7.20(t)	...	..	7.60 (broadened)	8.60	8.70 (broad)	9.18(d)

[a] The aromatic protons of the benzyl groups occur at 2.85(s) and the methylene protons at 5.02 and 5.16, respectively.

The n.m.r. spectra of the subject compounds are summarized in Tables I and II in which the data are arranged so that every observed resonance band is indicated beneath the proton-containing function which gives rise to it. In general, these data are straightforward. Since the sole double bond of the vitamin $K_{1(20)}$ side chain shifts into conjugation with those of the aromatic moiety on cyclization to the corresponding chromenol, the changes in the n.m.r. spectrum are unmistakable, especially with regard to the olefinic protons at the 3- and 4-positions and the protons of the methyl groups at the 2- and 5-positions. These data leave no doubt concerning the structures of the compounds.

Experimental

2,5-Dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho-[1,2-b]pyran-6-yl Acetate (IV).—A mixture of 2 g. of vitamin $K_{1(20)}$ (I), 1 g. of 54% sodium hydride dispersion and 50 ml. of benzene was refluxed for 2 hr. under a nitrogen atmosphere. The reaction mixture was cooled and 0.5 ml. of acetic anhydride was added. After about 1 hr., 1.3 g. of acetic acid was added dropwise and the reaction mixture was stirred and then filtered. The filtrate was concentrated, and the residual oil was dissolved in Skellysolve B and adsorbed on silica gel. The column was developed with Skellysolve B and the product was eluted with Skellysolve B containing 1% ether to yield 1 g. of 2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate, (IV), $\lambda_{max}^{isooctane}$ 266 mμ ($E_{1\,cm}^{1\%}$ 646), 276 mμ ($E_{1\,cm}^{1\%}$ 830).

Anal. Calcd. for $C_{33}H_{48}O_3$ (492.71): C, 80.44; H, 9.83. Found: C, 80.16; H, 9.67.

3,4-Dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl Acetate (V).—A solution of 123 mg. of 2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho [1,2-b]-pyran-6-yl acetate (IV) in 15 ml. of methanol was reduced over 100 mg. of 10% Pd-on-Darco. When the reduction was complete, the catalyst was removed by filtration, and the filtrate was concentrated to yield 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate (V), $\lambda_{max}^{isooctane}$ 245 mμ ($E_{1\,cm}^{1\%}$ 815).

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Anal. Calcd. for $C_{33}H_{50}O_3$ (494.73): C, 80.11; H, 10.19. Found: C, 80.20; H, 9.90.

3,4-Dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-ol (VI).—A solution of 85 mg. of 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate (V) in 5 ml. of anhydrous ether was refluxed with 7 mg. of lithium aluminum hydride for 1 hr. The reaction mixture was cooled and the excess lithium aluminum hydride was decomposed by the addition of a few drops of ethyl acetate. The mixture was acidified by the dropwise addition of 2.5 N HCl, and a few ml. of water was added. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. About 70 mg. of 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]-pyran-6-ol (VI) was obtained as a colorless oil, $\lambda_{max}^{CCl_4}$ 2.76, 2.95 μ; $\lambda_{max}^{isooctane}$ 249 mμ ($E_{1\,cm}^{1\%}$ 853), 324 mμ ($E_{1\,cm}^{1\%}$ 128), 338 mμ ($E_{1\,cm}^{1\%}$ 131).

Acetylation of 3,4-Dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-ol.—Forty milligrams of 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-ol (VI) was dissolved in 0.5 ml. of anhydrous pyridine and 0.5 ml. of acetic anhydride. After several hours, the reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel. The product was eluted from the column with Skellysolve B containing 1% ether. In this manner, 14 mg. of 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl acetate (V) was obtained; the identity of this product and that obtained directly from vitamin $K_{1(20)}$ was established by a comparison of spectral data.

O,O-Dibenzyl O-{2,5-Dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]-pyran-6-yl} Phosphate (VII).—Two grams of vitamin $K_{1(20)}$ (I) was dissolved in 25 ml. of anhydrous benzene. After the solution was put under a nitrogen atmosphere, 0.5 g. of a 54.5% sodium hydride dispersion was added, and the mixture was refluxed for 2 hr. The solution was cooled to about 0° and a solution of 0.011 mole of dibenzyl chlorophosphonate in 31 ml. of carbon tetrachloride was added. After the reaction mixture was stirred for 1 hr. at room temperature, it was treated with 5% aqueous sodium bicarbonate. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residual oil was dissolved in Skellysolve B and adsorbed on silica gel (100 g.). The column was eluted successively with Skellysolve B, Skellysolve B containing 1% ether, 10% ether and 25% ether. The fraction eluted with 25% ether was adsorbed on silica gel (50 g.) from a Skellysolve B solution, and the column was developed with Skellysolve B. A fraction was eluted with Skellysolve B containing 10% ether to yield 280 mg. of O,O-dibenzyl O-{2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl} phosphate (VII), $\lambda_{max}^{isooctane}$ 266 mμ ($E_{1\,cm}^{1\%}$ 398), 276 mμ ($E_{1\,cm}^{1\%}$ 498); λ_{max}^{neat} 7.82–8.23 μ, 9.4–9.92 μ.

Anal. Calcd. for $C_{45}H_{59}O_5P$ (710.95): C, 76.03; H, 8.37; P, 4.36. Found: C, 76.48; H, 8.60; P, 3.69.

3,4-Dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]pyran-6-yl Phosphate (VIII).—O,O-Dibenzyl O-

{2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho[1,2-b]-pyran-6-yl} phosphate (VII, 452 mg.) was dissolved in 15 ml. of glacial acetic acid and was reduced and debenzylated over 750 mg. of 10% Pd-on-Darco. The theoretical consumption of hydrogen was essentially complete in about 3 hr.; the catalyst was removed by filtration and washed with 10 ml. of glacial acetic acid. The combined filtrate and washings was concentrated *in vacuo*, and a 242-mg. portion of the residual glassy residue was adsorbed on 10 g. of silica gel from Skellysolve B solution. Elution of the column with Skellysolve B gave a purified fraction which on crystallization from petroleum ether yielded 3,4-dihydro-2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-2-H-naphtho-[1,2-b]pyran-6-yl phosphate (VIII), m.p. 146–147.5°; equiv. wt. (50% aqueous acetone) 558 ($pH^{1/2}$ 3.8), 516 ($pH^{1/2}$ 8.6); λ_{max}^{EtOH} 242.5 mμ ($E_{1cm}^{1\%}$ 750), $\lambda_{max}^{CHCl_3}$ 2.8–3.9 μ.

Anal. Calcd. for $C_{31}H_{49}O_5P$ (532.69): C, 69.90; H, 9.27; P, 5.82. Found: C, 69.57; H, 9.12; P, 5.80.

Nuclear Magnetic Resonance Spectroscopy.—All the n.m.r. data were obtained through the use of a Varian Associates model

4300B high resolution spectrometer equipped with superstabilizer and phase detector and operating at 60 megacycles. All spectra were run using 5–10% solutions in carbon tetrachloride placed in a spinning Wilmad precision bore tube. The resonance positions were determined relative to a benzene capillary as an external reference and scaled by the use of side bands[22] generated by a Hewlett–Packard audioösscillator model 200 CD calibrated by frequency counting. The shielding numbers τ were calculated using the equation $\tau = (\Delta\nu/\nu_0) + 3.50$ in which $\Delta\nu$ is the observed resonance displacement from benzene in cycles per second and ν_0 is the spectrometer frequency in megacycles.[23] In the one instance where $(CD_3)_2CO$ was used as a solvent for VIII, the constant used in the above equation was 2.85 instead of 3.50.

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A Study of the Hydrolysis of Phosphoramides. II. Solvolysis of Phosphoramidic Acid and Comparison with Phosphate Esters[1]

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The solvolysis of phosphoramidic acid ($NH_2PO_3H_2$) in water and various solvent mixtures has been investigated. Our studies of the solvolysis of aromatic phosphoramides and phosphate esters have been extended. The pH *vs.* hydrolysis rate curve (Fig. 1) (pH 2–8) for phosphoramidic acid, in water and methanol–water mixture (50%), is described by the rate equation (1), $k_{obsd} = k_h(H)(M_0) + k_0(M_0) + k_1(M_1)$, where M_0 and M_1 are the mole fractions of the neutral and singly negatively charged species (monoanion) and k_h, k_0 and k_1 are their associated specific rate constants for the particular medium. The variation in product composition, monoalkyl phosphate/phosphoric acid, derived from the solvolysis of both phosphoramidic and N-(p-chlorophenyl)-amidophosphoric acid in various ethanol and methanol–water mixtures over the acidity range 3 M HCl to pH 7 (Fig. 2) has been investigated and correlated with the solvolysis of the ionic species present. For the monoanionic species the ratio alkyl phosphate/phosphoric acid is significantly larger than the ratio alcohol/water present in the reacton mixture. In the case of phosphoramidic acid the two-term bimolecular rate equation (2), $k_{obsd} = k_{H_2O}(H_2O) + k_{CH_3OH}(CH_3OH)$, correctly predicts the rate and product composition for the solvolysis in methanol–water mixture (0–60%). Similar studies with the simple aromatic phosphate esters, monophenyl and mono-p-nitrophenyl phosphate, show that the ratio monomethyl phosphate/phosphoric acid is very nearly the same as the ratio methanol/water in the reaction mixture, while for ethanol–water mixtures it is smaller. The solvolysis of phosphoramides is catalyzed by heterocyclic tertiary nitrogenous base (pyridine, nicotinic acid); that of phosphate esters is not. The strict steric requirement imposed on the base as exemplified by the absence of catalysis with 2-methylpyridine, is noted and the catalytic constant for a number of bases has been evaluated. These observations, coupled with other considerations presented in the text, strongly favor the conclusion that the solvolysis of the monoanionic species of phosphoramides is bimolecular in nature proceeding by way of direct attack of the solvent (H_2O, CH_3OH) on the phosphorus. On the other hand, as has been postulated by many investigators, in the solvolysis of the monoanionic species of simple phosphate esters metaphosphoric acid is formed. Evidence is presented supporting the contention that the zwitterion of the monoanionic species of the phosphoramides is the reactive form. Again in the solvolysis of the neutral species, its zwitterion appears to be the reactive form. The acid-catalyzed solvolysis of phosphoramidic and N-(p-chlorophenyl)-amidophosphoric acid proceed by different mechanisms. The results of product distribution studies in methanol and ethanol–water mixtures support the view that the protonated species of N-(p-chlorophenyl)-phosphoramidic acid decomposes unimolecularly to give metaphosphoric acid, while the solvolysis of phosphoramidic acid is bimolecular involving preferential attack by water.

Introduction

We have reported[2] on the solvolysis of a few aromatic monoamidophosphoric acid derivatives. The evident structural similarity between these compounds and simple monoalkyl and aryl phosphates suggested that for their respective monoanions $(RNHPO_3H)^-$ and $(ROPO_3H)^-$, the same mechanism obtained in the cleavage of the N–P and O–P bonds. It has been reported,[3] however, that heterocyclic tertiary nitrogenous bases, *e.g.*, pyridine and imidazole, catalyze the hydrolysis of phosphoramidic acid $NH_2PO_3H_2(PA)$,[4] the simplest monoamidophosphate. No base catalysis, as reported herein, was noted with aryl phosphates. The possibility that the solvolysis of amidophosphates may proceed by direct attack of the solvent molecule

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(3) T. Rathlev and T. Rosenberg, *Arch. Biochem. Biophys.*, **65**, 319 (1956).
(4) The following abbreviations are used: PA, phosphoramidic acid; ClPhPA, N-(p-chlorophenyl)-amidophosphoric acid.

on the phosphorus, and metaphosphoric acid need not be formed, was indicated. Of particular significance in this connection is the broad body of evidence[5a,b,6,7] strongly favoring the view that in the hydrolysis of the monoanion of simple phosphate esters the unstable hypothetical monomeric metaphosphoric acid is formed and cleavage of the O–P bond (although involving hydrogen bonded intermediates with solvent)[5a,b] does not proceed by direct attack of solvent on the phosphorus atom. The evidence does not necessarily exclude the aforementioned alternate interpretation.[6–8] To gain a better understanding of the hydrolysis of amidophosphates as well as phosphate esters, a study

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