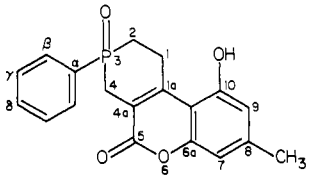
Carbon-Phosphorus Heterocycles. Synthesis of Phosphorus-Containing Cannabinoid Precursors and a Single-Crystal Analysis of 1,2,3,4-Tetrahydro-10-hydroxy-8-*n*-pentyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-Oxide

Jang B. Rampal, K. Darrell Berlin,* Nantelle S. Pantaleo,* Ann McGuffy, and Dick van der Helm*

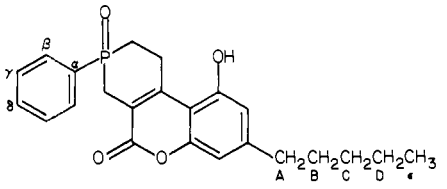
Contribution from the Departments of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078, University of Tulsa, Tulsa, Oklahoma 74104, and University of Oklahoma, Norman, Oklahoma 73109. *Received September 8, 1980*

Abstract: The syntheses of 1,2,3,4-tetrahydro-10-hydroxy-8-methyl- and 1,2,3,4-tetrahydro-10-hydroxy-8-*n*-pentyl-3-phenyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-oxide have been achieved. These precursors of cannabinoid analogues are the first reported in this family of carbon-phosphorus heterocycles. A single-crystal X-ray diffraction analysis of the pentyl derivative confirmed the structure. ^1H, ^{13}C, and ^{31}P NMR analyses are also supportive of the basic assignments for both compounds. An intermediate synthon methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate was analyzed via ^1H, ^{13}C, and ^{31}P NMR spectroscopy and was found to exist primarily in an enol form in solution and had different properties than previously reported.

Considerable activity in the chemistry of cannabinoids,[1] in particular heteroatom-substituted derivatives, in recent years[2] and our interest in carbon-phosphorus heterocycles[3] which are analogues of natural products prompt us to reveal our results on certain phosphorus-containing precursors of cannabinoids. We report herein the synthesis of 1,2,3,4-tetrahydro-10-hydroxy-8-methyl- (**1**) and 1,2,3,4-tetrahydro-10-hydroxy-8-*n*-pentyl-3-phenyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-oxide (**2**).

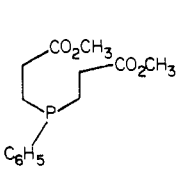


1

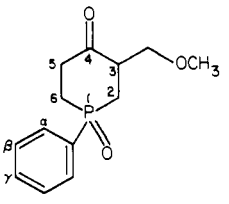


2

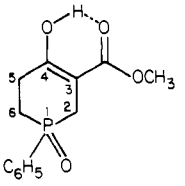
Bis(2-(carbomethoxy)ethyl)phenylphosphine (**3**)[4] was converted



3



4a, X = Lone pair
4b, X = O



5

to methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate (**4a**)[4] which, in crude form, was oxidized with 30% H_2O_2 to give oxide **4b**.[5] Since the physical properties differed significantly for **4b** from those recorded,[5] a careful spectral analysis seemed warranted. IR analysis (KBr pellet) showed a broad band at 3350 cm^{-1} assigned to an O-H stretching frequency of an enol. A small peak at 1725 cm^{-1} also inferred the presence of a carbonyl group. The band at 1639 cm^{-1} was of medium intensity and was supportive of the conjugated double bond present in the enol form.

^1H NMR analysis of **4b** was complex (see Table I) although the protons of the methyl group appeared at δ 3.78. Indeed, the ^{13}C NMR spectrum of **4b** was not simple and the interpretation was best in accord with a very high population of the enol form **5**. In Table I, there are two signals for sp^2-hybridized carbons C(3) and C(4) located at 92.78 ppm ($^2J_{PC}$ = 3.90 Hz) and 172.07 ppm ($^3J_{PC}$ = 9.62 Hz), respectively. The other resonances seem reasonable.[6] The ^{13}C NMR signal pattern did not change for a solution of **4b** in $DCCl_3$ at room temperature down to -70 °C.

* Address correspondence as follows: K.D.B., Okalhoma State University; N.S.P., University of Tulsa; D.v.d.H., University of Oklahoma.

(1) (a) R. Mechoulam, N. K. McCallum, and S. Burstein, *Chem. Rev.*, **76**, 75 (1976); (b) K. Matsumoto, P. Stark, and R. G. Meister, *J. Med Chem.*, **20**, 25 (1977); (c) C. G. Pitt, H. H. Seltzman, Y. Sayed, C. E. Twine, Jr., and D. L. Williams, *Tetrahedron Lett.*, 37 (1978); (d) L. Crombie, W. M. L. Crombie, G. W. Kilbee, and P. Tuchinda, *Tetrahedron Lett.*, 4773 (1979); (e) K. Green, *Curr. Top. Eye Res.* **1**, 175 (1979); (f) M. A. Caolo and F. R. Stermitz, *Tetrahedron*, **35**, 1487 (1979); (g) I. Tamir, R. Mechoulam, and A. Y. Meyer, *J. Med. Chem.*, **23**, 221 (1980). The above citations are not exhaustive but contain references to much of the earlier work and information which proved instructive for our effort.

(2) (a) H. G. Pars, F. G. Branchelli, J. K. Keller, and R. K. Razdan, *J. Am. Chem. Soc.*, **88**, 3664 (1966); (b) H. G. Pars, F. E. Granchelli, R. K. Razdan, J. K. Keller, D. G. Teoger, F. J. Rosenberg, and L. S. Harris, *J. Med. Chem.*, **19**, 445 (1976); (c) R. K. Razdan, B. Z. Terris, H. G. Pars, N. P. Plotnikoff, P. W. Dodge, A. T. Dren, J. Kyncl, and P. Somani, *ibid.*, **19**, 454 (1976); (d) M. Winn, D. Arendsen, P. Dodge, A. Dren, D. Dunnigan, R. Hallas, K. Hwang, J. Kyncl, Y.-H. Lee, N. Plotnikoff, P. Young, H. Zaugg, H. Dalzell, and R. K. Razdan, *ibid.*, **19**, 461 (1976); (e) R. K. Razdan, G. R. Handrick, H. C. Dalzell, J. F. Howes, M. Winn, N. P. Plotnikoff, P. W. Dodge, and A. T. Dren, *ibid.*, **19**, 552 (1976); (f) R. K. Razdan, B. Z. Terris, G. R. Handrick, H. C. Dalzell, H. G. Pars, J. F. Howes, N. Plotnikoff, P. Dodge, A. Dren, J. Kyncl, E. Shoer, and W. R. Thompson, *ibid.*, **19**, 549 (1976); (g) C.-M. Lee, R. J. Michaels, H. E-Zaugg, A. T. Dren, N. P. Plotnikoff, and P. R. Young, *ibid.*, **20**, 1508 (1977); (h) P. F. Osgood, J. F. Howes, R. K. Razdan, and M. G. Pars, *ibid.*, **21**, 809 (1978).

(3) (a) S. D. Venkataramu, G. D. Macdonell, M. El-Deek, W. R. Purdum, and K. D. Berlin, *Chem. Rev.*, **77**, 121 (1977); (b) R. Fink, D. van der Helm, and K. D. Berlin, *Phosphorus Sulfur*, **8**, 325 (1980), and references therein to previous work.

(4) T. E. Snider and K. D. Berlin, *Org. Prep. Proc. Int.*, 237 (1972).

(5) B. A. Arbuzov, O. A. Erastov, S. N. Ignateva, T. A. Zyablikova, and E. I. Goldfarb, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, **27**, 1339 (1978).

(6) The area of enol-keto tautomerism in carbon-phosphorus heterocycles is relatively new although a recent paper has briefly reviewed certain aspects of the subject; see T. M. Balthazor, *J. Org. Chem.*, **45**, 2519 (1980).

0002-7863/81/1503-2032$01.25/0

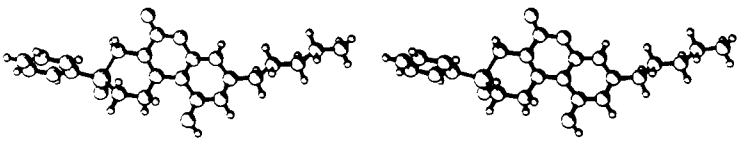


Figure 1. PLUTO[17] drawing of single molecule of 1,2,3,4-tetrahydro-10-hydroxy-8-*n*-pentyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-oxide (**2**).

One ^{31}P signal was observed at +28.95 ppm which indicates the presence of only one isomer.

Treatment of oxide **4b** with 5-methyl- or 5-*n*-pentylresorcinol in the presence of concentrated H_2SO_4 followed by the addition of $Cl_3P{=}O$ gave, after workup, **1** and **2**, respectively, in yields of 43.3% and 38.5%. The C—P heterocycles are the first members to be prepared in this family of heterocyclic cannabinoid precursors. A variety of other conditions were attempted but resulted in lower yields than recorded above.

Although the ^1H NMR spectrum of **1** was very complex, signals for methyl protons occurred at δ 2.24 while the aryl protons H(7) and H(9)[7] appeared as overlapping singlets at about δ 6.40 (see Table I). The ^1H spectrum of **2** was similar except for the additional proton signals for the *n*-pentyl side chain.

The ^{13}C NMR analysis of both **1** and **2** proved interesting. Although **1** was poorly soluble in organic solvents, a spectrum was obtained in Me_2SO-d_6 after 42 h as shown in Table I. In addition to the expected ^{13}C resonances, signals for the aliphatic carbons α [C(2) and C(4)] to the P=O group appeared at 22.89 ppm ($^1J_{PC}$ = 70.0 Hz) and 25.96 ppm ($^1J_{PC}$ = 64.93 Hz). In **1**, since there are no adequate model systems for comparison, we tentatively suggest that the latter resonance is for C(4) which is also α to the double bond. Interestingly also, C(1) had a signal at 25.85 ppm ($^2J_{PC}$ = 5.50 Hz) and was easily distingquished because of the chemical shift and coupling value. We also suggest that the ^{13}C resonance for C(1a) appears at 150.34 ppm ($^3J_{PC}$ = 10.90 Hz) and that for C(4a) appears at 114.82 ppm ($^2J_{PC}$ = 4.95 Hz), both typical shifts for vinyl carbons[8] and J_{PC} coupling values.[9] That the β-carbon in unsaturated six-membered ketones[8c] and lactones[8d] absorbs at lower field than the α-carbon is recognized.[8c,d] We note the larger $^3J_{PCC(4)}$ compared to $^2J_{PC(3)}$ in **4b** in which the assignment of the chemical shift for C(4) is unequivocal. The three-bond coupling to C(5) was somewhat large ($^3J_{PC}$ = 9.0 Hz) and the signal appeared at 160.02 ppm in **1**.

In the case of the pentyl analogue **2**, solubility was quite adequate in $DCCl_3$ and a spectrum could be obtained in 15 h. Assignments for the carbon signals paralleled those found in **1** as seen in Table I. Resonances for the side chain were at 35.35, 31.48, 29.90, and 22.46 ppm for the A-, B-, C-, and D-carbons,

$$\underset{A}{Z\text{-}CH_2}\underset{B}{CH_2}\underset{C}{CH_2}\underset{D}{CH_2}CH_3$$

respectively, as similarly found in several tetrahydrocannabinols.[10,11] Suprisingly, a search of the literature did not reveal a single reference to ^{13}C NMR data on the comparable lactone precursors of tetrahydrocannabinols.

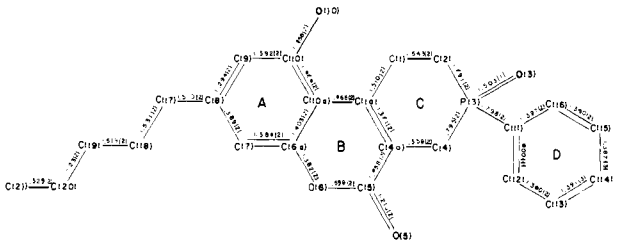


Figure 2. Bond distances as given in Å. Estimated standard deviations for the last digit are given in parentheses.

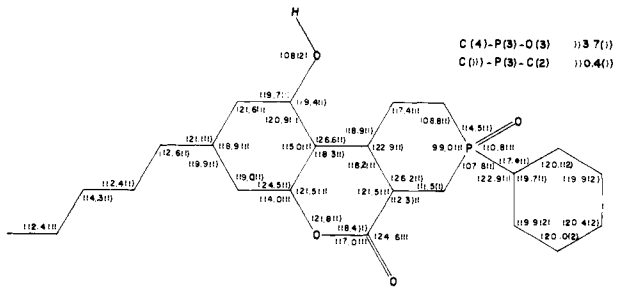


Figure 3. Bond angles are given in degrees. Estimated standard deviations for the last digit are given in parentheses.

Only one ^{13}P NMR signal was detected from solutions ($DCCl_3$) for each compound. Values of +39.23 and +31.54 ppm (from 85% H_3PO_4) for **1** and **2** appear to be typical for six-membered, phosphorus-containing ring systems in which the phosphorus atom is oxidized.[12] In view of the lack of close model systems with which to compare the spectral properties of **1** and **2**, we elected to determine the structure of **2** via a single-crystal analysis using X-ray diffraction techniques to be discussed shortly.

IR analysis of **1** and **2** revealed peaks at 3390 (O—H), 1697 and 1700 (C=O), and 1140 1143 cm^{-1} (P=O) for the two oxides, respectively. These are also typical values to be expected.[13]

Single-Crystal Analysis of 2

To confirm the structures of the molecule synthesized, the single-crystal X-ray analysis of the pentyl derivative **2** was carried out. A stereoview of a single molecule of **2** is shown in Figure 1. Figure 2 shows the bond distances and the numbering scheme, and Figure 3 gives the bond angles. For comparison purposes, we have elected to use data for selected bond distances and angles of *trans*-4-*tert*-butyl-1-phenylphosphorinane (**6**)[12b] and 1-benzyl-2-phenyl-3-hydroxy-4,5-dimethylphosphol-2-one 1-oxide (**7**),[14] two structures previously reported. Final fractional coordinates for the nonhydrogen atoms are available (see supplementary material). Tables of anisotropic temperature factors for the nonhydrogen atoms, positional and isotropic temperature parameters for the hydrogens, and observed and calculated structure factors are also available as supplementry material.

The P–C(sp^3) bond distances in **2** average 1.793 (2) Å, identical with the average PC(sp^3) distance in **6** [1.793 (2) Å], but sig-

(7) These signals are in comparable positions in certain nitrogen analogues; see ref 2a. For ^1H NMR data on synthetic carbocyclic cannabinoids, see ref 1b; K. Matsumoto, P. Stark, and R. G. Meister, *J. Med. Chem.*, **20**, 17 (1977); R. A. Archer, W. B. Blanchard, W. A. Day, D. W. Johnson, E. R. Lavagnino, C. W. Ryan, and J. E. Baldwin, *J. Org. Chem.*, **42**, 2277 (1977).

(8) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press: New York, 1972, Chapter 5. (b) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plas, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973). Analogous piperidines and tetrahydropiperidines are analyzed via ^{13}C NMR spectroscopy in the latter reference. (c) G. C. Levy, R. L. Lichter, and G. L. Nelson, "Carbon-13 NMR Spectroscopy", 2nd ed., Wiley-Interscience, New York, 1980, Chapter 3. (d) W. V. Turner and W. H. Pirkle, *J. Org. Chem.*, **39**, 1935 (1974).

(9) S. I. Featherman, S. O. Lee, and L. D. Quin, *J. Org. Chem.*, **39**, 2899 (1974); S. D. Venkataramu, K. D. Berlin, S. E. Ealick, J. R. Baker, S. Nichols, and D. van der Helm, *Phosphorus Sulfur*, **78** 133 (1979) and references therein.

(10) B. L. Hawkins and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1027 (1973).

(11) E. Wenkert, D. W. Cochran, F. M. Schell, R. A. Archer, and K. Matsumoto, *Experientia*, **28**, 250 (1972).

(12) To compare with the ^{31}P NMR signal in other fused systems, see: (a) G. D. Macdonell, S. D. Venkataramu, M. El-Deek, and K. D. Berlin, *J. Org. Chem.*, **41**, 1403 (1976); (b) G. D. Macdonell, K. D. Berlin, J. R. Baker, S. E. Ealick, D. van der Helm, and K. L. Marsi, *J. Am. Chem. Soc.*, **100**, 4535 (1978). For ^{31}P NMR analysis on simple phosphorinane 1-oxides, see (c) L. D. Quin and S. O. Lee, *J. Org. Chem.*, **43**, 1424 (1978).

(13) For leading references to phosphorinanes and spectral analysis thereof, see ref 3a.

(14) D. van der Helm, D. M. Washecheck, J. E. Burks, and S. E. Ealick, *Acta Crystallogr., Sect. B*, **B32**, 659 (1976).

Table I. Spectral Properties of 1, 2, and 4b.

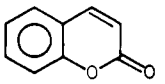
compd	IR,[a] cm^{-1}	^{1}H NMR,[b,c] δ (J, Hz)	^{13}C NMR,[b,c] ppm (J_{PC}, Hz)	^{31}P NMR[c,d]
1	3390, 1697 1144	2.24 (s, 3 H, CH_3) 2.30–4.30 (m, 6 H, H(1), H(2), H(4)) 6.39, 6.42[e] (2 s, 2 H, H(7), H(9)) 7.45–8.10 (m, 5 H, ArH) 10.67 (s, 1 H, OH)	C(1), *25.85*[f] (5.50) C(1a), *150.34* (10.90) C(2), *22.89* (70.00) C(4), *25.96* (64.93) C(4a), *114.82* (4.95) C(5), *160.02* (9.00) C(6a), 155.59; C(7), 108.28 C(8), 142.19; C(9), 105.69 C(10), 152.61; C(10a), 112.42 C(α), *130.37* (101.00) C(β), *129.67* (7.20) C(γ), *128.65* (10.00) C(δ), 133.73 C(ε), 20.80	+39.23
2	3390, 1700 1143	0.87 (t, 3 H, CH_3, $J = 7$) 1.12–1.80 (m, 6 H, H(α), H(β), H(γ), H(δ)) 6.36, 6.39[e] (2 s, 2 H, H(7), H(9)) 7.45–8.04 (m, 5 H, Ar-H) 10.64 (s, 1 H, OH)	C(1), *26.84* (6.05) C(1a), *149.53* (12.37) C(2), *23.49* (66.92) C(4), *26.40* (67.88) C(4a), *112.99* (3.83) C(5), *160.98* (10.22) C(6a), 155.76; C(7), 107.35 C(8), 147.41; C(9), 106.16 C(10), 152.49; C(10a), 111.97 C(α), *129.87* (104.24) C(β), *130.27* (9.64) C(γ), *128.93* (12.41) C(δ), *132.64* (2.71) C(ε), 14.03 C(A), 35.35; C(B), 31.48[g] C(C), 29.90;[g] C(D), 22.46	+31.54
4b	3350, 1725 1640	2.02–3.20 (m, 5 H ring CH_2 and CH) 3.78 (s, 3 H, CH_3) 7.40–8.15 (m, 5 H Ar-H)	C(2), *24.82* (67.05) C(3), *92.78* (3.90) C(4), *172.07* (9.62) C(5), *26.94* (6.46) C(6), *24.07* (66.31) C(7), *171.73* (11.82) C(8), 51.97 C(α), *131.87* (98.55) C(β), *129.87* (9.45) C(γ), *128.66* (11.72) C(δ), *132.03* (2.28)	+28.95

[a] KBr pellets. [b] Ppm from $(CH_3)_4Si$. Average values are italic. [c] Solvent was $DCCl_3$, except for 1 which was dissolved in Me_2SO-d_6. [d] Ppm from 85% H_3PO_4. [e] These singlets overlapped extensively and only the very tops of the signals were discernable. [f] All italic shift values are averages for doublets. [g] These signals may be interchanged.[10,11]

nificantly shorter than that in **7** [average = 1.821 (2) Å]. Likewise, **2** and **6** have similar P–C(sp^2) distances [1.798 (2) and 1.805 (2) Å, respectively], but the P–C_6H_5 distance in **2** is longer than the P–C(sp^2) distance in **7** by 0.022 Å. The overall result is that there is very little difference between the P–C(sp^3) and P–C(sp^2) bond distances in **2**. Since a large number of factors including hybridization, charge, valency, and steric factors influence P–C bond lengths in heterocyclic compounds, they are difficult to correlate with certainty.

The oxygen atom O(3) is in an axial position relative to the phosphorus-containing ring as is the oxygen atom in **6**. However, the P–O distance in **2** of 1.503 (1) Å is appreciably longer than in **6** [1.483 (2) Å] and more closely parallels the P–O distance in **7** [1.505 (2) Å]. It is also longer than the value of 1.48 Å determined by electron diffraction for trimethylphosphine oxide.[15]

The central, aromatic portion of the molecule **2** [ring A = C(6a), C(7)–C(10), and C(10a); ring B = C(1a), C(4a), C(5), O(6), C(6a), and C(10a)] can be most readily compared to the structure of coumarin (**8**).[16] As in **8**, the C(1a)–C(4a) bond is



8

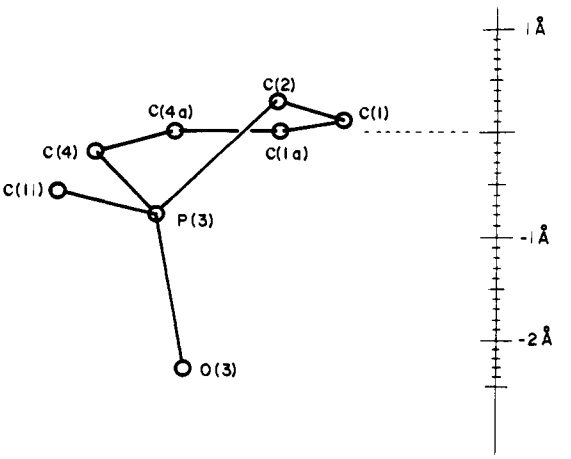


Figure 4. The phosphorus-containing ring showing the derivatives of the atoms from the plane of the aromatic portion of the molecule.

a fairly localized double bond while the C(10a)–C(1a) and C(4a)–C(5) bond distances are significantly larger than 1.40 Å in both compounds. The A ring in both compounds is essentially aromatic although the C(10)–C(10a) bond distance in **2** of 1.424 (2) Å is appreciably longer than the other bonds in the ring and

(15) H. K. Wang, *Acta Chem. Scand.*, **19**, 879 (1965).
(16) E. Gavuzzo, F. Mazza, and E. Giglio, *Acta Crystallogr., Sect. B*, **B30**, 1351 (1974).
(17) S. Motherwell, PLUTO, University Chemical Laboratory, Cambridge, England.

the corresponding bond in **8** [1.390 (5) Å]. The average C–C bond distance around both rings of **2** is 1.409 (27) Å, larger by 0.018 Å than the average C–C carbon distance in coumarin.

The bond angles in **2** and **8** are similar. The C(10a)–C(6a)–C(7) angle is larger than 120° while the O(6)–C(6a)–C(7) angle is smaller than 120° in both compounds. Likewise, the C(4)–C(5)–O(5) angle in coumarin of 125.6 (3)° is comparable to that found in **2** [124.6 (1)°].

The A and B rings taken together are planar with an average distance from the plane of 0.016 Å. The conformation of the phosphorus-containing ring is shown in Figure 4 which illustrates the deviations of the atoms from the plane through rings A and B. The planes formed by the alkyl chain [C(8), C(17)–C(21)] and the phenyl group [C(11)–C(16)] are approximately perpendicualr to the central plane as indicated by the angles between the planes and the central plane of 80.6 and 86.1°, respectively.

As in compound **7**, the oxygen atom O(3) is involved in a hydrogen bond with the hydroxyl group of a symmetry-related molecule. The O(3)–O(10) intermolecular distance is 2.651 (2) Å in **2**, somewhat longer than the corresponding distance in **7** of 2.595 Å. The H(10)–O(10) distance is 0.89 (3) Å, the O(3)···H(10) distance is 1.76 (3) Å, and the O(3)–H(10)–O(10) angle is 176 (2)°, where O(10) and H(10) have been transformed by $-x, 1-y, -z$.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. The ^1H, ^{13}C, and ^{31}P NMR data were obtained on a Varian XL-100(15) NMR spectrometer equipped with Nicolet TT-100 PFT accessory operating at 100.1 MHz with tetramethylsilane (Me_4Si) as internal standard for ^1H NMR, at 25.2 MHz with Me_4Si as internal standard for ^{13}C NMR, and at 40.5 MHz (with 85% H_3PO_4 as external standard) for ^{31}P NMR. The ^{13}C and ^{31}P NMR spectra were obtained by operating in the FT mode utilizing broad-band proton decoupling. Mass spectral data were collected on a CEC Model 21-110B HR mass spectrometer. Infrared spectral data were obtained on a Beckmann IR-5A unit. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Preparation of Bis(2-(carbomethoxy)ethyl)phenylphosphine (3). Phenylphosphine (10 g, 0.09 mol) was dissolved in acetonitrile (10 mL). To this stirred solution was added potassium hydroxide (1 mL, 10 N) and freshly distilled methyl acrylate (15.5 g, 0.18 mol), dropwise, under N_2. During the addition, the temperature was maintained at 20–35 °C by controlling the drop rate of the ester and by using an ice bath. After the addition was completed, the mixture was heated (45–50 °C) for 8 h. The resulting mixture was cooled to room temperature, washed with 2 × 10-mL portions of saturated aqueous NaCl solution, and then dried (Na_2SO_4). Distillation gave **3** boiling at 160–170 °C (0.5 mm) (lit.[4] 158–160 °C (0.51 mm)); 16 g 62.4%).

Preparation of Methyl 4-Oxo-1-phenyl-3-phosphorinanecarboxylate 1-Oxide (4b). Bis(2-(carbomethoxy)ethyl)phenylphosphine (**3**) (9.4 g, 0.033 mol) dissolved in 50 mL of toluene was added dropwise to a boiling solution of sodium methoxide (1.8 g, 0.03 mol) in 150 mL of toluene. After the reaction mixture had been boiled (2 h), metallic sodium (0.7 g, 0.033 g-at) was added, and the mixture was boiled for an additional 15 h. After being cooled, this reaction mixture was treated with water (100 mL). The aqueous layer was separated and extracted (3 × 50-mL portions) with $HCCl_3$. Combining extracts with the original organic layer gave a new solution which was dried (Na_2SO_4) and then evaporated to an oily residue. This crude phosphine **4a** (10 g, 0.04 mol) was partially dissolved in acetone (70 mL) and cooled in an ice bath. Dropwise addition of 30% H_2O_2 (9.5 mL, 0.086 mol) to this cooled emulsion (0 °C) of **4a** in acetone over a period of 10 min resulted in the formation of a clear solution. Evaporation of the acetone left a residue which was extracted (3 × 20 mL) with $HCCl_3$. The chloroform solution was washed with 5% aqueous ferrous ammonium sulfate (10 mL). After this chloroform solution was dried (Na_2SO_4), the solvent was evaporated to an oil. Acetone (≃5 mL) was added, and the resulting solutions was treated dropwise with dry pentane (12–15 mL). A small amount of oxide **4b** precipitated. Filtration gave a solution, which upon cooling, deposited 5.67 g (53%) of crystalline **4b**: mp 123–24 °C (lit.[5] 88–89 °C); mass spectrum, m/e 266 (M^+). Anal. Calcd for $C_{13}H_{15}O_4P$: C, 58.64; H, 5.64; P, 11.65. Found: C, 58.78; H, 5.89; P. 11.79. The spectral data are in Table I.

Preparation of 1,2,3,4-Tetrahydro-10-hydroxy-8-methyl-3-phenyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-Oxide (1). Methyl 4-oxo-1-phenyl-3-phosphorinanecarboxylate 1-oxide (**4b**) (0.4 g, 0.0016 mol) was mixed with 0.24 g (0.001 92 mol) of 5-methylresorcinol (Eastman Kodak Co.) and 1 mL of concentrated H_2SO_4 was added dropwise with stirring and cooling (under N_2). At the end of the addition (5 min), the mixture was stirred until it became clear, and then 2.0 mL (0.33 g, 0.0021 mol) of $Cl_3P{=}O$ was added slowly (≃5–10 min). A clear, viscous material formed and was stirred for another 40 h at room temp. This reaction mixture was cooled (0 °C, ice bath) and then neutralized with a slight excess of aqueous sodium bicarbonate (10%). Extraction ($HCCl_3$) gave an organic layer which was washed with water, dried (Na_2SO_4), filtered, and concentrated to afford a thick gum. The gum was taken up in 5 mL of chloroform. This solution was chromatographed on silica gel by using 300 mL of 20:1 $HCCl_3/CH_3OH$ as the solvent system from which a light yellow solid **1** (0.23 g, 43.3%) was obtained. Recrystallization (CH_3OH) of this solid gave an analytically pure sample, mp 308–309 °C. Spectral data are summarized in Table I. Anal. Calcd for $C_{19}H_{17}O_4P$: C, 67.05; H, 5.00; P, 9.11. Found: C, 66.94; H, 5.28; P, 9.08.

Preparation of 1,2,3,4-Tetrahydro-10-hydroxy-8-*n*-pentyl-3-phenyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-Oxide (2). Methyl 4-oxo-1-phenyl-3*H*-phosphorinanecarboxylate 1-oxide (**4b**) (1.4 g, 0.0055 mol) was mixed with 1.2 g (0.0066 mol) of 5-*n*-pentylresorcinol (Aldrich Chemical Co.), and 3.2 mL of concentrated H_2SO_4 was added dropwise with stirring and cooling (under N_2). At the end of addition (10 min), 0.6 mL (0.99 g, 0.0064 mol) of $Cl_3P{=}O$ was added slowly. From this point the procedure paralleled that given above for the preparation of **1**. After chromatography, a thick, orange liquid was obtained. When ether was added, a solid (1 g, 38.5%) resulted. Recrystallization ($HCCl_3/CH_3CO_2C_2H_5$, 1:1) of this solid gave an analytically pure sample of **2**: mp 237–238 °C; mass spectrum, m/e 396 (M^+). Other spectral data are summarized in Table I. Anal. Calcd for $C_{23}H_{25}O_4P$: C, 69.69; H, 6.31; P, 7.83. Found: C, 69.86; H, 6.44; P, 8.20.

X-ray Analysis. The compound **2** was recrystallized by slow evaporation from chloroform and formed well-shaped crystals belonging to the triclinic system $P\bar{1}$. The unit-cell dimensions (See Table II) and intensity data were measured at low temperature (138 ± 2 K) on an Enraf-Nonius CAD-4 automated diffractometer.

Table II. Summary of Crystallographic Data for 1,2,3,4-Tetrahydro-10-hydroxy-8-pentyl-3-phenyl-5*H*-phosphorino[3,4-*c*][1]benzopyran-5-one 3-oxide (2)

mol formula	$C_{23}H_{25}O_4P$
mol wt	396.4 g/mol
linear abs coeff	13.75 cm^{-1} (Cu K$\bar{\alpha}$)
d(calcd)	1.357 g/cm^3
space group	$P\bar{1}$
cell dimens (138 ± 2 K)	a = 8.698 (4) Å, b = 13.733 (5) Å, c = 8.335 (2) Å, α = 95.54 (2)°, β = 95.77 (3)°, γ = 79.31 (3)°, V = 970.3 Å^3, Z = 2
no. of reflections	measd 3880
	obsd ($F > 5\sigma_{F_o}$) 3544
final R (all reflections)	0.039
R_ω (all reflections)	0.051

The cell parameters were obtained by a least-squares fit to the $+2\theta$ and -2θ values of 47 well-centered reflections by using Cu Kα_1 (λ = 1.5405 Å) radiation. The intensity data for all reflections with $4° \leq 2\theta \leq 150°$ were measured by using Cu K$\bar{\alpha}$ (λ = 1.5418 Å) radiation and the θ–2θ scan technique. The angular scan width was variable and taken to be (1.00 ± 0.15 tan θ)°. A receiving aperture with a variable width of (3.50 + 0.86 tan θ) mm and a constant height of 6 mm was located at a distance of 173 mm from the crystal. The maximum scan time for a reflection was 90 s. For each reflection, two-thirds of the scan time was spent scanning the peak and one-sixth was spent scanning each of the two backgrounds. During the intensity measurements, the intensities of three standard reflections were monitored after every 4000 s of X-ray exposure time and indicated no appreciable decomposition of the crystal.

A total of 3880 unique reflections were measured of which 336 were considered unobserved having observed structure factors less than $5\sigma(F_o)$. All intensity data were corrected for Lorentz and polarization factors, and numerical absorption corrections were applied (μ = 13.75 cm^{-1}, Cu K$\bar{\alpha}$).

The structure was determined by direct methods using the program SHELX-76.[18] The phases of 551 reflections having a normalized structure factor (E) greater than 1.3 were used to construct E maps. The map with the highest reliability factor (parachor = 1.87) gave the entire structure among the top 29 peaks. The nonhydrogen atoms were refined by least-squares methods in stages with isotropic and anisotropic thermal

(18) G. M. Sheldrick, SHELX-76, University Chemical Laboratory, Cambridge, England, 1976.

parameters. Difference maps were used to locate the hydrogen atoms which were then refined isotropically.

Because of the size of the structure and limitations in computer core space, the least-squares refinements were carried out by a blocked full-matrix method using the computer program SHELX. The scattering factors were taken from the "International Tables for X-ray Crystallography", Vol. 4, pages 99 and 149. The weighting scheme used was $W_F = K/[(\sigma_F)^2 + gF_o^2]$ where $\sigma_F = {}^1/_2[\{\sigma^2 + (0.04P)^2\}/P(Lp)]^{1/2}$, $\sigma = T^{1/2}V$, V = scan speed, T = Pk + 4(R + L), P = [Pk - 2(R + L)]V, Pk = peak height, R = right background, L = left backgound, and Lp = Lorentz and polarization factors. The factors K and g were redetermined after each structure factor calculation and were 0.205 and 0.00161, respectively, after the final cycle of refinement.

The variance was calculated as $V = [M\sum[W_f(|F_o| - |F_c|)^2]/N\sum W_f]^{1/2}$, where N is the number of reflections in a group, M is the total number of reflections, the sum in the numerator is over all reflections in a group, and the sum in the denominator is over all the reflections. An analysis of the variance in terms of the parity of the reflection indices, sin θ, and $[F_o/F_{max}]^{1/2}$ showed no significant variation in V for various ranges of the functions tested. Refinement was terminated when all parameter shifts were less than 0.15 of their corresponding standard deviations. The final value of R for all 3880 reflections was 0.039 and for R_w where $R_w = \sum W_f^{1/2}[|F_o| - |F_c|]/\sum W_f^{1/2}|F_o|$ was 0.051.

Acknowledgment. We gratefully acknowledge partial support of this work by the U.S.P.H.S. National Institutes of Health and the National Cancer Institute, Grants CA 22770 (K.D.B.) and CA 17562 (D.v.d.H.).

Supplementary Material Available: A listing of hydrogen parameters, thermal parameters, and final fractional coordinates for the nonhydrogen atoms and structural factors (16 pages). Ordering information is given on any current masthead page.

Reactions of (Alkylperoxy)cobaloximes in Acidic Aqueous Solutions

James H. Espenson* and Jwu-Ting Chen

Contribution from the Ames Laboratory and Department of Chemistry, Iowa State University, Ames, Iowa 50011. *Received September 15, 1980*

Abstract: Bis(dimethylglyoximato)cobalt(III) complexes containing coordinated alkylperoxy groups have been studied. The compounds examined are (1) $ROOCo(dmgH)_2$(pyridine) complexes with R = isopropyl, 2-butyl, cyclopentyl, benzyl, and isopropyl-d_7 and (2) $(CH_3)_2CHOOCo(dmgH)_2L$ complexes with L = pyridine, piperidine, water, and ammonia. The complexes react with aqueous perchloric acid to form the cobalt(III) product $(H_2O)Co(dmgH)_2L^+$ and a mixture of ketone and hydroperoxide. The organic products are formed in parallel pathways, each by a kinetic equation having the same algebraic form, and are the products of respective oxygen–oxygen and cobalt–oxygen bond cleavage reactions. Kinetic data were determined as a function of $[H^+]$ and, in the case of the 2-butyl complex, temperature. The rate constants for reactant disappearance and of product formation were determined, as was the ratio of ketone to hydroperoxide in the products. An important preequilibrium is the protonation of the oxime oxygens; the equilibrium constant varies in a way which reflects the basicity of the axial ligand L. The kinetic data and other results can be used to formulate a *separate* pathway leading to each product. Hydroperoxide formation is best accounted for by a pathway in which internal proton transfer from H^+ bound to oxime oxygen occurs. Ketone production, on the other hand, shows an appreciable kinetic isotope effect: $k^H/k^D = 8.9 \pm 1.5$, suggesting C–H bond breaking is a major part of the activation process.

Introduction

The title compounds[1] are formed photochemically, either by insertion of oxygen into the cobalt–carbon bond of alkylcobaloximes,[2-7] as in eq 1 (which, for some R groups, also occurs thermally), or by the substitution process[8] of eq 2 (with R = *tert*-butyl or cumyl):

$$RCo(dmgH)_2L + O_2 \xrightarrow{h\nu} ROOCo(dmgH)_2L \quad (1)$$

$$R'Co(dmgH)_2L + 2ROOH \xrightarrow{h\nu} ROOCo(dmgH)_2L + ROOR' \quad (2)$$

The alkylperoxy compounds are isolated—with R representing a wide range of alkyl and aralkyl groups and L a conventional Lewis base such as pyridine (usually)—as stable, red-brown crystals. The formulation given has been thoroughly verified by spectroscopic methods (^1H NMR, UV[7], and IR[2]), as well as by elemental analysis.[2-8] Crystal structures have been determined for the L = pyridine derivatives of compounds with R = 2-phenylethyl[9] and 2-phenyl-2-propyl[8] (or cumyl), verifying that ROO and L occupy trans positions on either side of the planar $Co(dmgH)_2$ unit.

The (alkylperoxy)cobaloximes are subject to decomposition in solution upon prolonged UV irradiation or thermolysis.[10] In addition,[11] solutions in chloroform or carbon tetrachloride react with acids ($HClO_4$ or CF_3COOH), forming hydroperoxide ROOH (eq 3) and (in parallel or perhaps by decomposition[12] of a primary or secondary hydroperoxide) the corresponding ketone or aldehyde.

$$ROOCo(dmgH)_2L + H^+ = ROOH + [Co^{III}(dmgH)_2L]^+ \quad (3)$$

We have found that the (alkylperoxy)cobaloximes also react with acid in aqueous solution. This medium, where the species

(1) Cobaloxime is the trivial name given to bis(dimethylglyoximato)cobalt complexes: Schrauzer, G. N. *Acc. Chem. Res.* **1968**, *1*, 97.
(2) Giannotti, C.; Gaudemer, A.; Fontaine, C. *Tetrahedron Lett.* **1970**, 3209.
(3) Fontaine, C.; Duong, K. N. V.; Merienne, C.; Gaudemer, A.; Giannotti, C. *J. Organomet. Chem.* **1972**, *38*, 167.
(4) Giannotti, C.; Fontaine, C.; Gaudemer, A. *J. Organomet. Chem.* **1972**, *39*, 381.
(5) Giannotti, C.; Septe, B. *J. Organomet. Chem.* **1973**, *52*, C45.
(6) Merienne, C.; Giannotti, C.; Gaudemer, A. *J. Organomet. Chem.* **1973**, *54*, 281.
(7) Giannotti, C.; Fontaine, C.; Septe, B. *J. Organomet. Chem.* **1974**, *71*, 107.
(8) Giannotti, C.; Fontaine, C.; Chiaroni, A.; Riche, C. *J. Organomet. Chem.* **1976**, *113*, 57.
(9) Chiaroni, A.; Pascard-Billy, C. *Bull. Soc. Chim. Fr.* **1973**, *781*.
(10) Giannotti, C.; Fontaine, C. *J. Organomet. Chem.* **1973**, *52*, C41.
(11) Bied-Charreton, C.; Gaudemer, A. *Tetrahedron Lett.* **1976**, 4153.
(12) Deno, N. C.; Billups, W. E.; Kramer, K. E.; Lastomirsky, R. R. *J. Org. Chem.* **1970**, *35*, 3080.

0002-7863/81/1503-2036$01.25/0