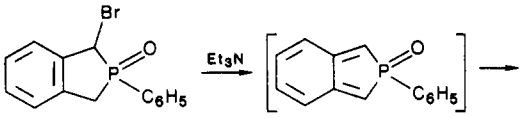
Carbon-Carbon Bond Cleavage during Silane Reductions of the Dimer of 2-Phenylisophosphindole Oxide[1]

Louis D. Quin* and F. Christian Bernhardt

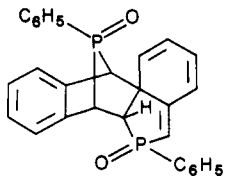
Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received March 11, 1986

When treated with triethylamine, 1-bromo-2-phenylisophosphindoline oxide 1 undergoes dehydrohalogenation to the isophosphindole oxide 2.[2] As is characteristic for monocyclic phosphole oxides, this compound undergoes rapid dimerization to give a single product, which has been assigned structure 3 from ^{1}H NMR spectral studies.[2] Stereochemistry at the phosphorus nuclei was assumed, but not proved, to be the same as found in phosphole oxide dimers.

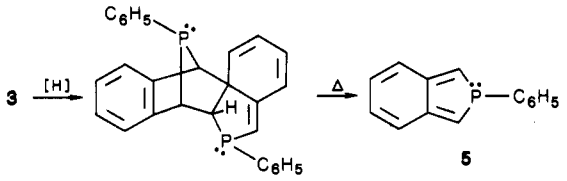


1 2



3

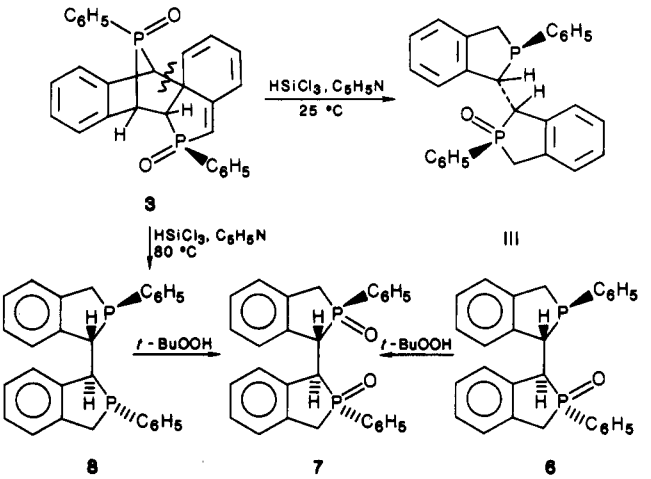
The diphosphine 4 that would be produced by deoxygenation of dimer 3 has never been reported, yet it could be of great value as a precursor of the still-unknown and potentially aromatic (10π-electron) isophosphindole system (5) by thermal retrodimerization as used for forming monocyclic phospholes from their dimers.[3]



4 5

The synthesis of dimer 3 was successfully accomplished as described.[2] We have characterized it more fully by ^{31}P and ^{13}C NMR spectroscopy (Table I), which confirms the assigned structure. Thus, the ^{31}P NMR spectrum consists of a doublet of doublets with the same large three-bond coupling constant (36.6 Hz) as is found in phosphole oxide dimers with endo ring fusion[4] (exo fusion leads to quite small $^3J_{PP}$ values[5]). The ^{13}C NMR spectrum was not fully interpreted in the sp^2 region; the sp^3 region was useful in supporting the stereochemical assignments, however. The three-bond, dihedral angle controlled[6] coupling of the bridging P to the β-carbon of the 2-phospholene moiety (C_e in Table I) is of such size (7.8 Hz) as to be inconsistent with exo ring fusion, where the dihedral angle would be near that of negligible coupling (90°). The two-bond coupling of the bridging P to fusion carbons C_c and C_f is an indicator of configuration at P; the relatively small values (9.8 and 7.3 Hz, respectively) resemble those seen for phosphole oxide dimers with syn orientation of the phosphoryl oxygen to these carbons[4] (11–12 Hz). With the anti oxygen orientation, the values are much larger (18–20 Hz). The stereochemistry of the 2-phospholene P remains unconfirmed.

Scheme I



3 8 7 6

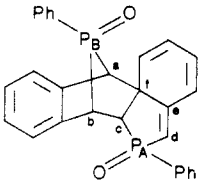
The combination of trichlorosilane and pyridine in refluxing benzene has been found to provide a useful reducing medium for bridged phosphine oxides,[7] and has already been applied successfully to Diels–Alder adducts of isophosphindole oxide 2.[8] However, the only product of the reduction of dimer 3, which was complete, gave a single ^{31}P NMR signal, whose shift of δ −14.9 clearly indicated a tertiary phosphine group. The two different ^{31}P nuclei of expected diphosphine 4 would give vastly different chemical shifts as is well established for phosphole dimers.[7] Sensing that a more complicated reaction than desired had occurred, we repeated the reduction under milder conditions (25 °C), and indeed a different product with two coupled ^{31}P nuclei was obtained. One of the doublets was in the phosphine region (δ −1.8) and one in the phosphine oxide region (δ +53.3, J_{PP} = 24.4 Hz). This product was found by mass spectral analysis to have acquired two hydrogen atoms; one phosphoryl oxygen had been lost as was shown by the ^{31}P NMR analysis. Oxidation of this product gave a different dioxide (δ 53.4) than the starting material. It was then obvious that the trichlorosilane reduction must have accomplished a C–C bond cleavage that created identity of the carbon framework around the two phosphorus atoms; partial reduction left one of these groups as the oxide, thus accounting for the doublet of doublets observed. Identity of the carbon frameworks in the new dioxide was established by the partial reduction to the same monoxide as obtained from the isophosphindole oxide dimer 3 under mild conditions. A reductive cleavage of the bond connecting bridgehead carbon C_a to ring fusion carbon C_f in 3, followed by double bond rearrangements, could give a structure meeting the

(1) Taken from the Doctoral Dissertation of F. Christian Bernhardt, Duke University, 1985. Support of the National Science Foundation through Grants CHE-81-06789 and CHE-84-05826 is gratefully acknowledged.

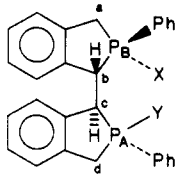
(2) Chan, T. H.; Nwe, K. T. *Tetrahedron* **1975**, *31*, 2537.
(3) Quin, L. D.; Lloyd, J. R.; Caster, K. C. *J. Chem. Soc., Chem. Commun.* **1983**, 1302.
(4) Quin, L. D.; Mesch, K. A.; Bodalski, R.; Pietrusiewicz, K. M. *Org. Magn. Reson.* **1982**, *20*, 83.
(5) Couffignal, R.; Kagan, H. B.; Mathey, F.; Samuel, O.; Santini, C. C. *C. R. Seances Acad. Sci., Ser. C* **1980**, *291*, 29.
(6) Quin, L. D.; Gallagher, M. J.; Cunkle, G. T.; Chesnut, D. B. *J. Am. Chem. Soc.* **1980**, *102*, 3136.
(7) Quin, L. D.; Caster, K. C.; Kisalus, J. C.; Mesch, K. A. *J. Am. Chem. Soc.* **1984**, *106*, 7021.
(8) Quin, L. D.; Bernhardt, F. C. *Magn. Reson. Chem.* **1985**, *23*, 929.

0022-3263/86/1951-3235$01.50/0

Table I. NMR Spectral Data[a] for Dimer 3 and Cleavage Products 6 and 7



3



6, X = lone pair, Y = O
7, X = Y = O

	^{31}P NMR[b]			^{13}C NMR[c]					
compd	δ_{P_A}	δ_{P_B}	J_{PP}, Hz	C_a	C_b	C_c	C_d	C_e	C_f
3	+52.3	+68.3	36.6	58.2	45.8	40.5	*d*	160.4	59.9
				(0)	(1.2)	(76.7)		(21.5)	(14.6)[e]
				[68.4]	[62.5]	[7.3]		[7.8]	[9.8][e]
6	+53.3	−1.8	24.4	31.7	51.1	49.4	33.4		
				(0)	(2.2)	(68.1)	(65.9)		
				[14.3]	[16.4]	[25.3]	[2][f]		
7	+53.4			34.4	44.8	44.8	34.4		
				33.6[g]	32.7[g]	32.7[g]	33.6[g]		

[a] FT, ^{1}H decoupled; $CDCl_3$ solutions. [b] Referenced to 85% H_3PO_4; positive shifts downfield. [c] Referenced to Me_4Si. Given in ppm; *J* values given in Hz. Values in parentheses are J_{CP_A}; values in brackets are J_{CP_B}. [d] Not assigned. [e] May be reversed. [f] Approximate value. [g] Line-spacing in a pseudotriplet.

requirements of identity of the carbon frameworks around the two phosphorus nuclei. The products are shown as structure **8** for the diphosphine and **6** for the monoxide. Both would give the same dioxide (**7**) on oxidation with *tert*-butyl hydroperoxide. These relations are shown in Scheme I.

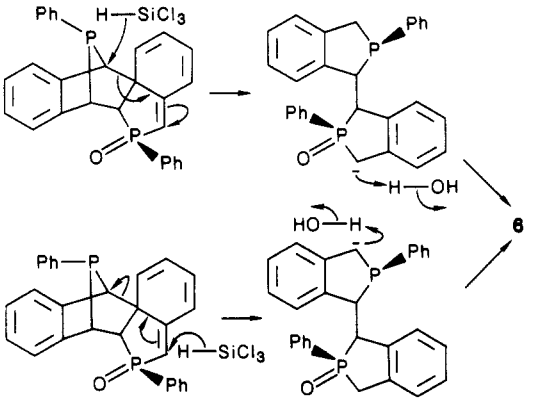
Compounds with the ethylenediphosphorus feature give second-order (AA'X) ^{13}C NMR spectra; a pseudotriplet arises for the connecting carbons from the combination of one-bond and two-bond coupling to the magnetically nonequivalent ^{31}P nuclei.[9] This effect was present in the ^{13}C NMR spectrum (Table I) of dioxide **7**, providing supporting evidence for the proposed structure. The ring carbons joining the two halves of the molecule appeared as a "triplet" at δ 44.8. The other sp^3 carbon in the five-membered ring also gave an AA'X pseudotriplet at δ 34.4; its coupling arises from the large one-bond and small four-bond coupling of the two ^{31}P nuclei. A first-order ^{13}C spectrum would arise from the monoxide **6**, and indeed the carbons of the two different five-membered rings appeared as doublets of doublets. Signal assignments were easily made by using the relations that the phosphine oxide group causes greater deshielding than does the phosphine group and that $^1J_{PC}$ is much larger for the former than the latter.

The stereochemistry at phosphorus shown for products **6–8** is that expected for retention of the features in the starting dimer **3**. The ^{13}C NMR spectral data support these assignments. Thus, in **6** the large coupling (25.3 Hz) of the phosphine ^{31}P to the carbon of attachment in the other ring (through two bonds) arises from the close proximity of the lone pair on phosphorus to this carbon, a well-substantiated effect in stereochemical analysis of cyclic phosphines.[10] This one observation confirms the configuration at the other ^{31}P to be the same, since the AA'X spectrum obtained in the dioxide **8** would only arise from two chemically equivalent ^{31}P nuclei. If one had the opposite configuration, the spectrum would be ABX, and the ^{13}C signal should be a doublet of doublets. The configurations at the ^{31}P nuclei of dimer **3** are therefore confirmed by the structure established for its C–C cleavage product **6**.

(9) For example, see: Carr, S. W.; Colton, R. *Aust. J. Chem.* **1981**, *34*, 35.

(10) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; Wiley-Interscience: New York, 1981; Chapter 6.

Scheme II



The unique feature in dimer **3** that leads to a different result from that obtained with another benzophosphanorbornene[8] seems to be the presence of the five sp^2 carbons in the fused six-membered ring; aromatization by cleavage of a C–C bond could provide a driving force for the process observed. No evidence is presently available that bears on the mechanism of the process, but two possibilities are presented in Scheme II, where it is assumed that deoxygenation of the bridging P precedes the cleavage.

Other silane reducing systems, such as trichlorosilane–triethylamine or phenylsilane, also caused the C–C cleavage and formed some **6**, along with other unidentified products. In no case was the far-downfield ^{31}P NMR signal expected[8] for the bridging P in phosphine **4** ever observed.

Experimental Section

General. NMR spectra were obtained as follows: ^{1}H, IBM NR-80; ^{13}C, JEOL FX-90Q at 22.5 MHz or FX-60 at 15.0 MHz; ^{31}P JEOL FX-90Q at 36.2 MHz. Mass spectra were prepared by the Research Triangle Mass Spectrometry Center. Melting points were taken on a Mel-Temp apparatus and are corrected.

Dimer 3 of 2-Phenylisophosphindole 2-Oxide. 1-Bromo-2-phenylisophosphindoline 2-oxide[2,8] (1.3 g, 4.2 mmol) was reacted with triethylamine (0.51 g, 5.1 mmol) at reflux for 12 h to give the dimer **3** (22%), mp 222 °C dec (lit.[2] mp 216–220 °C dec). The ^{1}H NMR spectrum matched that reported;[2] ^{31}P and ^{13}C NMR data are given in Table I.

Reaction of Dimer 3 with Phenylsilane. To 15 mL of dry benzene was added dimer **3** (0.060 g, 0.13 mmol) and phenylsilane

(0.072 g, 0.66 mmol). The reaction mixture was refluxed for 68 h and then stirred at room temperature for 24 h. The solvent was removed in vacuo. The ^{31}P NMR ($CDCl_3$) spectrum of the solid residue contained signals for the biisophosphindoline **8**, δ −12.4, the biisophosphindoline monoxide **6**, δ −1.81 and +53.1 (d, $^3J_{PP}$ = 24.4 Hz) and an upfield signal at δ −60.6, which on proton coupling had J_{PH} = 175.8 Hz and was presumed to be that of a secondary phosphine not further examined.

1-[1-(2-Phenyl)isophosphindolinyl]-2-phenylisophosphindoline 2-Oxide (6). To 100 mL of dry benzene was added pyridine (1.797 g, 13.26 mmol) and trichlorosilane (0.599 g, 4.42 mmol) under N_2 at 0 °C. After 20 min dimer **3** (0.400 g, 0.884 mmol) was added to the mixture. The mixture was stirred for 48 h under N_2 and then cooled in an ice–water bath while being hydrolyzed with 30 mL of 30% NaOH. The aqueous layer was separated and extracted with two 20-mL portions of benzene. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The light yellow oil was dissolved in 5 mL of chloroform and a small amount of silica gel was added to the solution. After being stirred for 10 min the solution was filtered and concentrated to give 0.164 g of **6** (44.1%) as an oil not readily crystallizing. ^{31}P and ^{13}C NMR data are given in Table I. Anal. Calcd for $C_{28}H_{24}OP_2$: *m/z* 438.1303. Found: *m/z* 438.1306.

2,2′-Diphenyl-1,1′-biisophosphindoline 2,2′-Dioxide (7). To compound **6** (0.164 g, 0.374 mmol) in 0.3 mL of $CDCl_3$ was added an excess of *tert*-butyl hydroperoxide. The ^{31}P NMR spectrum (δ +53.4) indicated a quantitative conversion of **6** to the dioxide **7** as an oil not readily crystallizing. ^{13}C NMR data are given in Table I. Anal. Calcd for $C_{28}H_{24}O_2P_2$: *m/z* 454.1252. Found: *m/z* 454.1253.

Registry No. **1**, 102979-51-1; **3**, 102979-52-2; **6**, 102979-53-3; **7**, 102979-54-4; **8**, 102979-55-5; phenylsilane, 694-53-1; trichlorosilane, 10025-78-2.

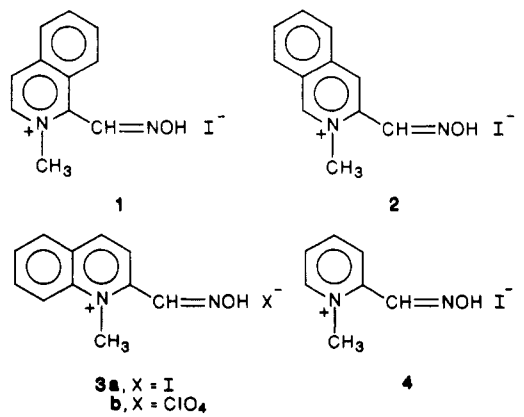
Quinoline-2-aldoxime Methiodide

Donald T. Witiak* and S. Ananthan

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210-1205

Received February 25, 1986

Samples of 3,4-, 4,5- and 5,6-benzannelated analogues **1–3** of 2-pyridinealdoxime methiodide (2-PAM; **4**) were desired to assess regiostructure–activity relationships of hydrophobic areas near the anionic site of the enzyme acetylcholinesterase. Enhanced hydrophobic binding in

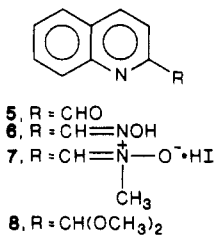


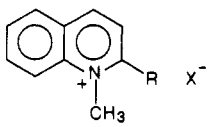
an appropriate analogue may provide for greater efficacy in the displacement of covalently bonded organophosphates from the enzyme. Isoquinoline quaternary salt **2** is unknown; **1** is known, but synthetic methodologies have not been described,[1] and the pharmaceutically desirable quinoline quaternary iodide **3a** has not been reported. The quaternary perchlorate salt **3b** has been described as an intermediate for the synthesis of monomethine cyanine dyes.[2] Several methods for the synthesis of **3a** are compared in this article.

Results and Discussion

Quaternization of quinoline-2-carboxaldehyde (**5**) or its oxime **6** would seem to represent a straightforward approach leading to the synthesis of **3a**. Aldehyde **5** is readily prepared by the oxidation of quinaldine[3] or by the hydrolysis of 2-dibromomethylquinoline.[4] The oxime **6** is available from **5**[5] or by reacting hydroxylamine hydrochloride with 2-dibromomethylquinoline (23% yield). However, quaternization of **5** with iodomethane at 60 °C in a pressure bottle for 50 days provides **9** in only 26% yield.[6] Earlier attempts to quaternize oxime **6** were unsuccessful.[7]

Quaternization reactions are known to be accelerated by polar aprotic solvents of high dielectric constant,[8] and nitromethane has been found to be the solvent of choice for quaternizing pyridine aldoximes that are difficult to alkylate.[1,9] However, we observed that methylation of **6** with CH_3I in nitromethane yields the nitrone hydriodide **7** (33% yield) rather than **3a**.[10,11]





9, R = CHO, X = I
10, R = $CH(OCH_3)_2$, X = I
11, R = $CH(OH)_2$, X = I
12, R = CH=NOH, X = I_3
13, R = CH_3, X = I
14, R = CH_3, X = I_3
15, R = $CH=NC_6H_5$, X = I
16, R = $CH=NC_6H_4N(CH_3)_2$-*p*, X = I

Although approaches leading to **3a** via quaternization of **5** or **6** were clearly unsatisfactory, quaternization of

(1) Poziomek, E. J.; Poirier, R. H.; Morin, R. D.; Page, Jr., T. F. *J. Org. Chem.* **1963**, *28*, 1411–1413.
(2) Mee, J. D. *Res. Discl.* **1979**, *No. 182*, 301–303; Chem. Abstr. **1979**, *91*, 159023k.
(3) Kaplan, H. *J. Am. Chem. Soc.* **1941**, *63*, 2654–2655.
(4) Hammick, D. L.; Johnston, E.; Morgan, E. D. *J. Chem. Soc.* **1957**, 5073–5075.
(5) Goodwin, H. A.; Lions, F. *J. Am. Chem. Soc.* **1959**, *81*, 6415–6422.
(6) Steinberg, G. M.; Poziomek, E. J.; Hackley, B. E., Jr. *J. Org. Chem.* **1961**, *26*, 368–371.
(7) (a) Ginsburg, S.; Wilson, I. B. *J. Am. Chem. Soc.* **1957**, *79*, 481–485. (b) Mason, S. F. *J. Chem. Soc.* **1960**, 22–26.
(8) (a) Zoltewicz, J. A.; Deady, L. W. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1978; Vol. 22, pp 71–121. (b) Duffin, G. F. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Lagowski, J. M., Eds.; Academic: New York, 1964; Vol. 3, pp 1–56. (c) Goerdeler, J. In *Methodicum Chimium*; Zymalkowski, F., Ed.; Academic: New York, 1975; Vol. 6, pp 625–636. (d) Auriel, M.; de Hoffman, E. *J. Am. Chem. Soc.* **1975**, *97*, 7433–7437. (e) Abraham, M. H. *J. Chem. Soc., Chem. Commun.* **1969**, 1307–1308.
(9) Profft, E.; Kruger, G. *Wiss. Z.* Tech. *Hochsch. "Carl Schorlemmer" Chem. Leuna-Merseburg* **1959/1960**, *2*, 281–283; *Chem. Abstr.* **1961**, *55*, 1607e.
(10) Details of methylation of **6** yielding **7** and characterization of the free base of **7** by mass spectra analysis and unequivocal synthesis are given as supplementary material.
(11) (a) For a similar observation, see: Hackley, B. E., Jr.; Poziomek, E. J.; Steinberg, G. M.; Mosher, W. A. *J. Org. Chem.* **1962**, *27*, 4220–4222. Methylation of 6-methylpyridine-2-aldoxime yields a nitrone. (b) Methylation of the oxime nitrogen rather than quinoline nitrogen likely reflects steric hindrance by the peri hydrogen at C-8 and the electron-withdrawing (hydroxyimino)methyl group at C-2. For a comparison of quinoline peri hydrogen steric effects with the steric effects of 2-methyl group in pyridine, see: Deady, L. W.; Stillman, D. C. *Aust. J. Chem.* **1976**, *29*, 1745–1748. A (hydroxyimino) methyl group at the 2-position of pyridine (pK_a ~ 5.17) reduces the pK_a to ~3.42–3.63. See ref 7b and: Hanania, G. I. H.; Irvine, D. H. *J. Chem. Soc.* **1962**, 2745–2749. Cecchi, P. *Ric. Sci.* **1958**, *28*, 2526–2531; *Chem. Abstr.* **1959**, *53*, 14650d.

0022-3263/86/1951-3237$01.50/0