Synthesis of Phosphalilolidine and Phosphajulolidine

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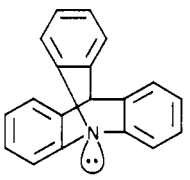
The successful syntheses and characterizations of the novel bicyclic C–P heterocycles 1,1,5,5,8-pentamethylphosphalilolidine (3) and 1,1,6,6,8-pentamethylphosphajulolidine (4) are described. Cyclization of 1-(methyl-*p*-tolylphosphinoyl)-3-methylbutan-2-ol (7) by using polyphosphoric acid at 120 °C produced an inseparable, isomeric mixture (83% yield) of 1,4,4,7- and 1,4,4,6-tetramethylphosphinoline oxides (8 and 9) in ratio of ca. 3:1. This isomerization is rationalized by a mechanism which involves the cationic ipso cyclization followed by migration of the phosphinoyl group. Cyclic voltammetric and UV spectroscopic data suggest that both phosphajulolidine and phosphalilolidine have essentially no n–π interaction between the lone-pair electrons on the phosphorus and the adjacent aromatic π system.

The possibility of conjugation between the nonbonding pair of electrons (n) on a phosphorus atom and an adjacent π system has been the focus of much discussion.[2]

The major difficulty in achieving effective n–π interaction in arylphosphines has been attributed to the fact that, owing to its pyramidal configuration, the orbital of the unshaired pair of electrons on the phosphorus is oriented away from the adjacent π orbitals (Figure 1). Thus, the energetically favorable state of maximum orbital overlap seen in nitrogen compounds (Figure 2) cannot be attained in most acyclic phosphines, wherein the C–P–C bond angels are about 103°.[3] This rationalization is supported by a recent study of a series of triaryl-substituted phosphines by using an infrared spectral technique, which showed that the Hammett σ_R^0 value for *p*-Ph_2P is only –0.08[4]—less than the electron-donating power of a methyl group (–0.17). Likewise, although the average valence angle in aromatic amines is 116°,[5] no n–π interaction was observed for 9-azatriptycene (1), in which the rigid molecular frame prevents the lone pair of electrons on nitrogen from overlapping with the adjacent π system.[6]



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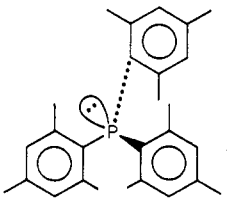
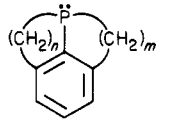


2

The idea of deforming the phosphorus pyramid so that the unshaired pair of electrons on phosphorus can assume more p character and overlap more effectively with an adjacent π orbital has intrigued many chemists. Among the most noteworthy are the studies of Mislow and coworkers,[7] who prepared trimesitylphosphine (2), the most flattened phosphine known, having an average C–P–C angle of 109.7°. This extraordinary expansion of the valence bond angles, most likely due to the nonbonded repulsive interaction among the three bulky mesityl groups, is reflected in a bathochromic shift of its ultraviolet adsorption maximum to 312 nm compared to triphenylphosphine (C–P–C = 103°) with λ_{max} 258 nm.[3] Presumably this is a result of an enhanced n–π interaction brought about by its more planar pyramidal structure.

The effectiveness of enhancing n–π interaction via phosphorus pyramid deformation is diminished, however, by the fact that although the overcrowding indeed forces the valence bonds of phosphine 2 to assume a more planar conformation, it also forces each mesityl group to twist (about 44°)[7] out of the plane formed by the P–C bond and the idealized threefold axis of the PC_3 unit. This deviation of coplanar disposition of the hybrid unshared pair of electrons of the phosphine and the π system of the substituents has been reported to diminish the n–π conjugation energy in proportion to the square of the cosine of the angle of deviation.[8]

To avoid this intrinsic drawback of flattening the phosphorus pyramid by steric compression, we conceived the idea of synthesizing the bicyclic arylphosphine represented by structure A (n, m = 2, 3). We envisaged that

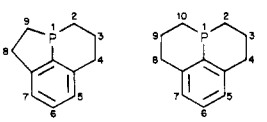


A

by constraining the geometry of the substituents around phosphorus in a fused bicyclic array, the lone pair of electrons on phosphorus may be forced to overlap with the attached aromatic π system, resulting in enhanced n–π interaction without conformational distortion.

This report describes the successful syntheses and characterization of derivatives of two of our proposed bicyclic carbon–phosphorus heterocycles, 1,1,5,5,8-pentamethylphosphalilolidine (3)[9] and 1,1,6,6,8-pentamethylphosphajulolidine (4).[9,10]

(1) Kodak Summer Research Fellow, 1978.
(2) Bochvar, D. A.; Gambaryan, N. P.; Epshtein, L. M. *Russ. Chem. Rev. (Engl. Transl.)* **1976**, *45*, 660. Stepanov, B. I.; Bokanov, A. I.; Svergun, V. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1971**, *41*, 526.
(3) The C–P–C bond angles in triphenylphosphine are 103.57°, 102.07°, and 103.34° (Daly, J. J. *J. Chem. Soc.* **1964**, 3799).
(4) Grindley, T. B.; Johnson, K. F.; Kaack, H.; Katritzky, A. R.; Schiemenz, G. P.; Topsom, R. D. *Aust. J. Chem.* **1975**, *28*, 327.
(5) Tsvetkov, E. N.; Kabachnik, M. I. *Usp. Khim.* **1971**, *40*, 177.
(6) Wittig, G.; Steinhoff, G. *Justus Liebigs Ann. Chem.* **1964**, *676*, 21; Hellwinkel, D.; Schenk, W.; Blaicher, W. *Chem. Ber.* **1978**, *111*, 1798.
(7) Blount, J. F.; Maryanoff, C. A.; Mislow, K. *Tetrahedron Lett.* **1975**, 913.
(8) Tsvetkov, E. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1975**, *45*, 489.
(9) The systematic nomenclature names for phosphalilolidine A (n = 2, m = 3) and phosphajulolidine A (n = m = 3) would be phospholano[3,2,1-*i,j*]tetrahydrophosphinoline and phosphorinano[3,2,1-*i,j*]tetrahydrophosphinoline, respectively. (For reference, see: Mann, F. G. "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth", 2nd ed.; Wiley-Interscience: New York, 1970; p 124.) We feel to name them as nitrogen analogues of lilolidine (Almond, C. Y.; Mann, F. G. *J. Chem. Soc.* **1952**, 1870) and julolidine (Mann, F. G.; Smith, B. B. *J. Chem. Soc.* **1951**, 1898. Pinkus, G. *Chem. Ber.* **1892**, *25*, 2798) is simpler and more descriptive.



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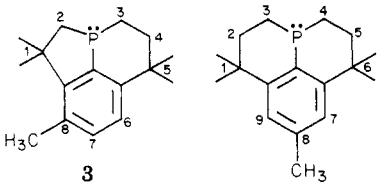


3 4

Results

Synthesis of 1,1,5,5,8-Pentamethylphosphalilolidine (3). Polyphosphoric acid (PPA) has been used extensively in the annulation of phosphorus heterocycles.[11] Using a similar approach which was developed for the synthesis of a related phosphalilolidine oxide,[12] we chose to start from the commercially available dimethyl *p*-tolylphosphine (**5**) bearing a methyl substituent which is to serve later as a latent aldehyde function in connection with another project. The presence of a *p*-methyl group on the benzene ring is expected to also simplify the ^{1}H NMR spectrum in the aromatic region and thus facilitate the monitoring of the annulation reaction by ^{1}H NMR. We chose also to first annulate the six-membered ring onto the phosphine oxide **6** (Scheme I), since this approach would allow the synthesis of a common six-membered monocyclic intermediate, tetrahydrophosphinoline oxide, from which phosphajulolidine **4** can also be prepared by a similar route.

Oxidation of **5** using gaseous oxygen is very slow. The hygroscopic phosphine oxide **6** can be readily prepared, however, by oxidizing **5** with 5% hydrogen peroxide in dichloromethane. Treatment of **6** with 1.2 equiv of *n*-BuLi followed by addition of isobutyraldehyde produced 1-(methyl-*p*-tolylphosphinoyl)-2-methylbutan-2-ol (**7**) in good yield. Cyclization of **7** was best achieved by using freshly prepared PPA, with which it was possible to annulate **7** at a relatively low reaction temperature (120 °C, overnight). However, even under this mild condition, we isolated a pair of isomeric cyclized products in 83% yield as a viscous oil having the expected parent mass peak at *m/e* 222.1159 (M^+ calcd for $C_{13}H_{19}OP$ *m/e* 222.1172). These two isomeric tetrahydrophosphinoline oxides, which cannot be separated by either LC or TLC, also exhibit very similar ^{1}H NMR spectra that are poorly resolved on a 90-MHz NMR instrument. Analysis of the 270-MHz ^{1}H NMR spectrum of this mixture revealed a major isomer (ca. 75%) to which we assigned the structure of **8**, in which the methyl substituent is placed at C-7, meta to the phosphinoyl function. This is based on the characteristic downfield doublet for the C-8 (ortho) proton of **8** at δ 7.58 which couples only to phosphorus, having the typical three-bond vinylic P–H coupling constant of 12.9 Hz.[13] The minor isomer (~25%) is assigned the normal annulated structure **9**, whose C-8 (ortho) proton NMR signal appears as a doublet of doublets (J_{PH} = 12.9 Hz and J_{HH} = 8.1 Hz) downfield at δ 7.65. The large additional spin coupling constant of 8.1 Hz is consistent with the vicinal proton–proton coupling between C-7 and C-8, which is also observed in the ^{1}H NMR spectra of the starting materials **6** and **7**.

The predominant formation of the isomeric tetrahydrophosphinoline oxide **8** during the PPA cyclization of **7** can be rationalized by invoking the ipso ring closure[14] of the carbonium ion B to form the spiro conjugated carbonium ion C (Scheme II). The transition state leading to C, having the developing charge stabilized by both the *p*-methyl substituent and the two allylic functions, is lower

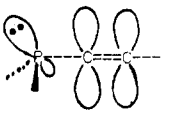


Figure 1. Minimum n–π interaction.

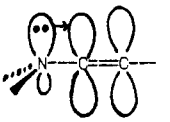
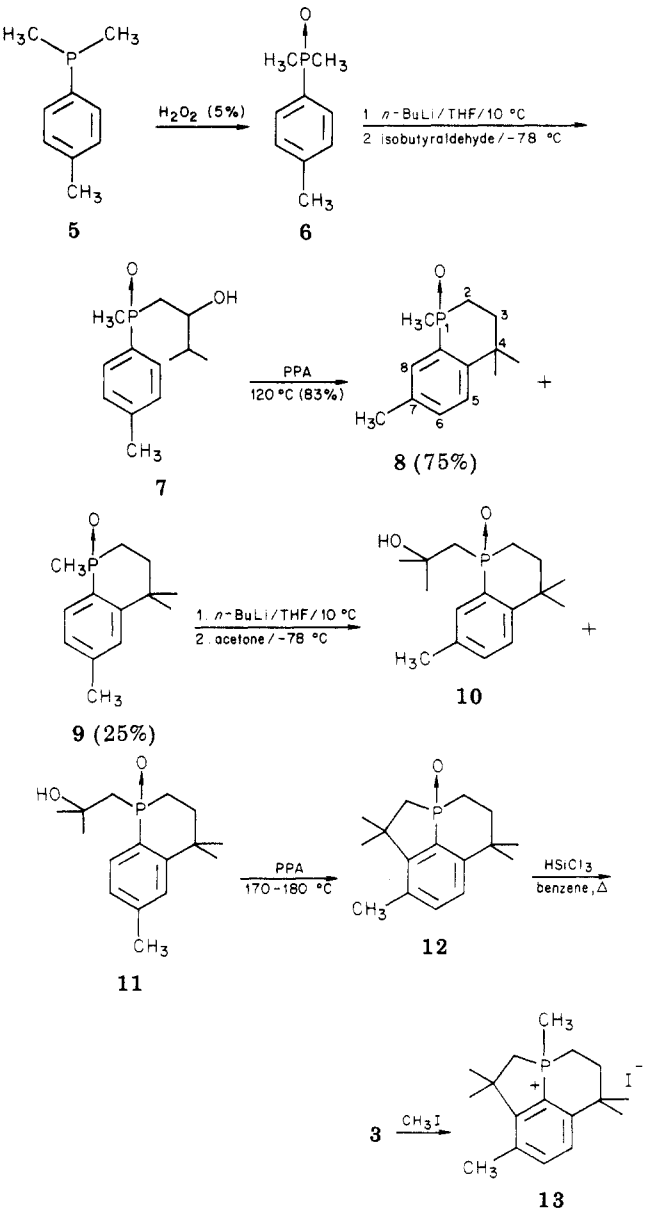


Figure 2. Maximum n–π interaction.

Scheme I



(10) The only member whose derivatives were known in the heterojulolidine family is arsulolidine (Mann, F. G.; Wilkinson, A. J. *J. Chem. Soc.* **1957**, 3336).

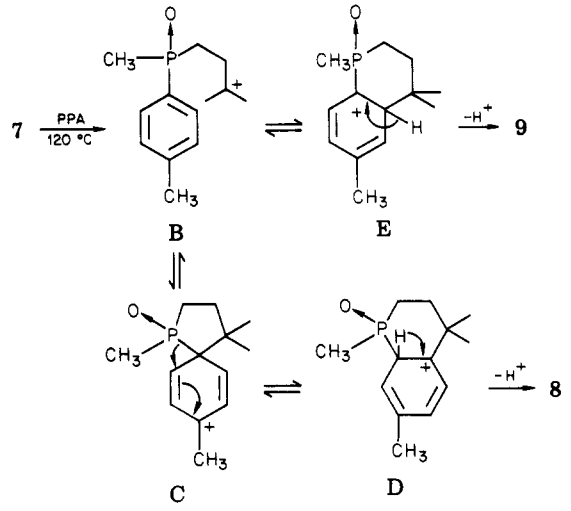
(11) Venkataramu, S. D.; Macdonell, G. D.; Purdum, W. R.; El-Deek, M.; Berlin, K. D. *Chem. Rev.* **1977**, *77*, 121.

(12) Grayson, J. I.; Norrish, H. K.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2556.

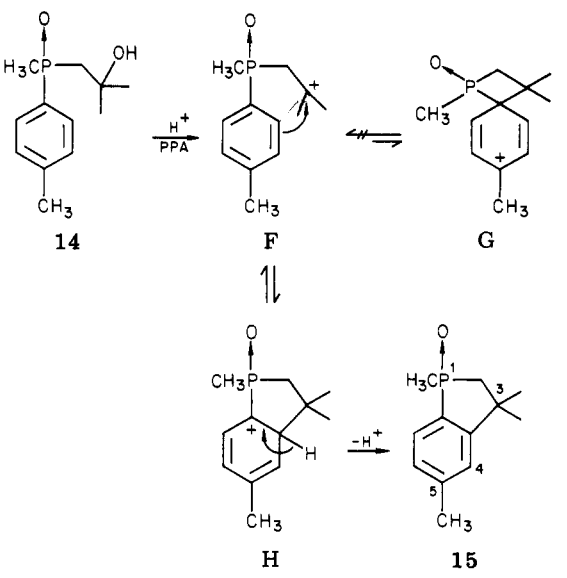
(13) Griffin, C. E. *Tetrahedron* **1964**, *20*, 2399.

(14) Eberson, L.; Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 3506. Trippett, S.; Hawes, W. *J. Chem. Soc. C* **1969**, 1465. Perrin, C.; Skinner, G. *J. Am. Chem. Soc.* **1971**, *93*, 3389.

Scheme II

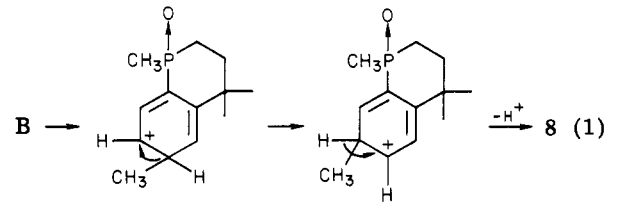


Scheme III



in energy than the normal annulated intermediate carbonium ion E, in which the positive charge is directly adjacent to the electron-withdrawing phosphinoyl function.[12] Migration of the phosphinoyl group to produce the new carbonium ion D is favored by the restoration of the cisoid diene conjugation, which also places the positive charge next to the tertiary alkyl substituent. Loss of a proton to regain aromaticity, forming the isomerized tetrahydrophosphinoline oxide 8, is expected to be facile and irreversible since the proton adjacent to the phosphinoyl function in D is very acidic.

An alternative mechanism involving methyl migration (eq 1)[15] after the ring closure is not likely because it cannot



rationalize the lack of methyl migration observed in the PPA cyclization of 1-(methyl-*p*-tolylphosphinoyl)-2-methylpropan-2-ol (14), from which only the normal annulated 1,3,3,5-tetramethylphosphindoline oxide (15) was obtained in 52% yield. However, the absence of the phosphinoyl migration in the PPA reaction of 14 is consistent with the rationalization that an ipso cyclization[14] of F would involve a four-membered spiro phosphetane intermediate G whose transition-state energy would be too high to compete effectively with the normal annulation pathway involving the carbonium ion H (Scheme III).

Further alkylation of 8 and 9 with *n*-BuLi/THF at ca. 10 °C followed by addition of acetone at −78 °C gave a mixture of 1-(2-hydroxy-2-methylpropyl)-4,4,7-trimethyltetrahydrophosphinoline 1-oxide (10) and its *p*-methyl isomer 11 in the ratio of ca. 4:1. Although the major isomer 10 could be enriched by liquid chromatography over silica gel (ethyl acetate/methanol, 10:1 v/v), this material was best used directly, without further purification, for the subsequent PPA cyclization.

It is noteworthy that the lithiation of phosphine oxides 6 and 8/9 with *n*-BuLi/THF can be done with external ice cooling (ca. 10 °C) under nitrogen. The subsequent reaction with acetone or isobutyraldehyde is best run at a much lower temperature (−78 °C) to minimize the proton-exchange reaction between the lithiated phosphine oxides 16 and the added carbonyl compounds. When 16 was treated dropwise with excess acetone at about 10 °C (ice cooling), most of the starting phosphine oxide 8/9 was recovered along with a large amount of nonphosphorus-containing self-condensation products of acetone.

The final cyclization of 10 could be brought about only at a much higher temperature (170–180 °C) by using freshly prepared PPA. The annulation was followed by observing the disappearance of the characteristic NMR signal of the downfield doublet at δ 7.65 due to the only ortho proton (C-8) of the phenyl ring in 10. From this we were able to isolate a pure isomer to which we assigned the structure of 1,1,5,5,8-pentamethylphosphalilolidine oxide (12). The yield is relatively low (ca. 22% based on the isomeric mixture of 10/11), presumably because of the strain energy to be overcome in forming the bicyclic system.[12]

This phosphalilolidine oxide 12 can be recrystallized from hexanes as a white solid (mp 160.6 °C) and is quite stable in air. Its structure was fully supported by ^{1}H and ^{31}P NMR spectra, high-resolution mass spectra, and elemental analysis. The homogeneity of this material was confirmed by the presence of *only* one ^{31}P signal (^{31}P NMR) at δ 38.86 and one aromatic methyl signal (270-MHz ^{1}H NMR) at δ 2.4. The ^{1}H NMR spectrum of 12 also shows two mutually coupled aromatic protons at δ 7.15 (J_{HH} = 7.9 Hz and J_{PH} = 4.7 Hz) and 7.22 (J_{HH} = 7.9 Hz), which are consistent with the assignments of the C-6 and C-7 protons, respectively. Furthermore, only the C-6 proton is further coupled with phosphorus, with the typical conjugated four-bond coupling constant of ~5 Hz.[12] The large coupling constant between the two protons (J = ~8 Hz) also confirms their vicinal relationship.

The phosphalilolidine 3 was readily prepared in ~82% yield by reduction of 12 by using excess trichlorosilane in benzene at reflux.[16] It is a colorless viscous liquid [bp 133–134 °C (0.8 mm)] with a pungent phosphine odor and is oxidized to the corresponding phosphine oxide 12 on prolonged exposure to air. Like other reactive phosphines, phosphalilolidine 3 reacts readily with methyl iodide to

(15) We thank one of the reviewers for suggesting this alternative mechanism.

(16) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.

give the stable methyl phosphinium salt **13**.

Synthesis of 1,1,6,6,8-Pentamethylphosphajulolidine (4). Having successfully prepared the key intermediate 1,4,4,7-tetramethyltetrahydrophosphinoline and 1,4,4,6-tetramethyltetrahydrophosphinoline oxides (**8** and **9**, Scheme I), we synthesized phosphajulolidine **4** similarly according to eq 2. An excess of isobutyraldehyde was added dropwise to a solution of **16** in THF at −78 °C to give a crude diastereoisomeric mixture of **17**. The complex reaction products were purified by preparative liquid chromatography to give a pure sample of a mixture of C-7 methyl and C-6 methyl substituted alcohols **17** in 34% yield. The ^{1}H NMR spectrum of this material is very complicated, owing to the newly generated asymmetric carbon shown by the asterisk in **17**. Nevertheless, by integration over the downfield C-8 proton region, it is possible to estimate the ratio of the C-7 methyl compound [δ 7.6 (d, J_{PH} = 12 Hz)] and the C-6 methyl derivative [δ 7.65 (dd, J_{PH} = 12 Hz and J_{HH} = ~9 Hz)] to be about 1:1. Presumably, the para-substituted (C-6) methyl compound was enriched during the liquid chromatographic purification.

This purified mixture of alcohols **17** was cyclized by PPA, and the annulation was monitored by ^{1}H NMR by following the disappearence of the characteristic C-8 proton at δ 7.6–7.7. Purification of the annulation products by preparative TLC, followed by two recrystallizations from hexanes, produced a *p*-methyl-substituted phosphajulolidine oxide, **18**, in 34% yield as a stable, white solid, mp 145.6 °C. The ^{31}P NMR spectrum shows a single ^{31}P signal at δ 21.75, which is a quintet coupled with four adjacent ring protons with J_{PH} = 17.3 Hz. The ^{1}H NMR spectrum of this material shows only three methyl singlets at δ 1.3 (6 H), 1.53 (6 H), and 2.3 (3 H), which correspond to the two equivalent C-1 and C-6 axial methyls, two equivalent C-1 and C-6 equatorial methyls, and one aromatic methyl, respectively. The position of the methyl substituted at C-8 (para to the phosphinoyl group) was assigned on the basis of the symmetry observed in the ^{1}H NMR spectrum of **18**. Further evidence is provided by the doublet (2 H) observed in the aromatic region at δ 7.0 for the two equivalent meta (C-7 and C-9) protons with the typical phosphorus–hydrogen, conjugated, four-bond coupling constant of J = 3 Hz.

Since examination of the ^{1}H NMR spectrum of the crude cyclization products of **17** does reveal some other signals in the aromatic region which have a splitting pattern similar to that of the meta-substituted phosphalilolidine oxide **12**, we conclude that a small amount of the isomeric phosphajulolidine oxide with (C-7) methyl meta to the phosphinoyl group must have also formed. Presumably, this was removed by preparative TLC during the purification.

Reduction of phosphajulolidine oxide **18** in the same manner as for **12** with trichlorosilane[16] gave the desired phosphajulolidine **4** as a colorless viscous oil [bp 130–132 °C (0.6 mm)] in 85% yield. Like the phosphalilolidine **3**, phosphajulolidine **4** has a strong phosphine odor and is not stable on prolonged exposure to air as it is oxidized to the phosphine oxide **18**. The chemical shifts of the two *gem*-dimethyl singlets being either axial or equatorial on the rigid phosphajulolidine oxide **18** are different, as expected, in the ^{1}H NMR (δ 1.3[17] and 1.53) spectrum. However, upon removal of the oxide, the *gem*-dimethyl groups on the phosphajulolidine **4** become equivalent in the ^{1}H NMR (δ 1.37, s) spectrum recorded at room temperature in $CDCl_3$. In addition, the two sets (C-2/C-5 and C-3/C-4) of the ring CH_2 protons of **4** show up as an almost symmetrical, pseudo-eight-line splitting pattern centered at around δ 1.8, much like a phosphorus-coupled AB quartet.

Discussion

The UV absorption maxima of phosphalilolidine **3** and phosphajulolidine **4** in ethanol are 254 (log ϵ 3.93) and 255 (log ϵ 3.4) nm, respectively. They are comparable to those of diethylphenylphosphine [**19**; λ_{max} (cyclohexane) 255 nm (log ϵ 3.5)] and diethylmesitylphosphine [**20**; λ_{max} (cyclohexane) 260 nm (log ϵ 3.25), 276 (3.21), 284 (3.14)].[2] These data suggest that the n–π interactions in both the phosphalilolidine **3** and phosphajulolidine **4**, if any, must be very weak. This observation is supported by the fact that the corresponding phosphine oxides **12** and **18**, having the electron-withdrawing phosphinoyl group meta and para to the donating methyl group, have slightly longer wavelength adsorptions: λ_{max} (EtOH) 275 nm (log ϵ 3.09) and λ_{max} (EtOH) 274 nm (log ϵ 2.99), 282 (3.05), respectively.

19 (λ_{max} 255 nm)

20 (λ_{max} ~270 nm)

Both phosphalilolidine **3** and phosphajulolidine **4** exhibit irreversible redox potentials at ~E_p = +1.11 and +0.99 V (vs. SCE), respectively. The lack of a reversible cyclic voltammogram in these systems, coupled with the similarity in E_p's with that of triphenylphosphine, further suggests the absence of n-π interactions. Other comparisons with triphenylamine, trimesitylphosphine, triphenylarsine, and triphenylstilbene are made in Table I.

The lack of n–π interaction in the phosphajulolidine **4** may be rationalized by examining its Dreiding stereomodel, which reveals an essentially strain-free and somewhat flexible bonding framework aroung the *pyramidal* phosphorus. There is no reason to expect the phosphorus atom in this environment to flatten from its normal pyramidal configuration. The lack of any significant n–π interaction observed in the phosphalilolidine system **3**, however, is more surprising and difficult to explain. The Dreiding model of **3** clearly shows considerable strain imposed by the fused five-membered C–P heterocyclic ring upon the central phosphorus atom which assumes a normal pyram-

(17) The higher field singlet was assigned the axial methyl. See: Zurcher, R. F. *Helv. Chim. Acta* **1961**, *44*, 1755; Reich, H. J.; Jautelat, M.; Messe, M. T.; Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 7445.

Table I. Cyclic Voltammetry Redox Potentials[a,b]

compd	I		II
	E_p	E_o'	E_p of II
phosphalilolidine 3	+1.11		
phosphajulolidine 4	+0.99		
Ph_3N		1.00 ± 0.04	
trimesitylphosphine (2)		0.69	+1.40
Ph_3P	+0.60 ± 0.02		+1.26 ± 0.02
Ph_3As	+0.66		+1.26
Ph_3Sb	+0.58		+0.93
Ph_3Bi			+1.21

[a] Sample concentration 2×10^{-4} M; solvent CH_3CN; supporting electrolyte 0.1 M tetrabutylammonium tetrafluoroborate (TBABF); indicating electrode glassy carbon; reference electrode SCE (saturated aqueous NaCl); bridge solution for SCE CH_3CN/0.1 M TBABF; scan rate 0.1 V/s. [b] Potential values are reported as E_p (in volts) the peak potential of the cyclic voltammogram for irreversible systems, and as E_o' (in volts), the potential midpoint between forward and reverse peaks for reversible systems.

idal configuration. Presumably, some of the strain energy can be alleviated by stretching the central C–P bond without greatly expanding the CPC bond angle and, hence, the flattening of the pyramidal configuration of the phosphorus. The final test of this concept of the deformation of the pyramidal phosphorus will have to await the synthesis of the more strained bicyclic C–P heterocyclic system phospholano[3,2,1-*hi*]phosphindoline A ($n = m = 2$), which remains, to date, as a synthetic challenge.[18]

Experimental Section

^1H NMR spectra were recorded on Varian EM-390 and Bruker WH 270-MHz spectrometers using Me_4Si as internal standard. ^{13}C NMR spectra were recorded on a Bruker spectrometer at 67.89 MHz using Me_4Si as internal standard; the multiplicity was determined by the off-resonance proton decoupling. ^{31}P NMR spectra were recorded on a Bruker NMR spectrometer at 36.43 or 109.29 MHz by using 85% H_3PO_4 as an external reference. Following the IUPAC recommendation, all ^{31}P chemical shifts are reported with a positive sign in the downfield direction and negative upfield from the standard. High-resolution mass spectra were obtained on an AEI MS-902 mass spectrometer. Microanalyses were done by the Analytical Sciences Division, Kodak Research Laboratories. Melting points (uncorrected) were obtained on a Mettler FPI instrument and a Thomas-Hoover capillary melting point apparatus. UV spectra were recorded on a Cary-17 spectrophotometer. High-pressure liquid chromatography was done on a Waters Associates preparative LC/System 500 unit. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer.

Dimethyl-*p*-tolylphosphine Oxide (6). A solution of dimethyl-*p*-tolylphosphine (5;[19] 100 g, 0.66 mol) in dichloromethane was cooled to 5 °C, and 5% hydrogen peroxide (480 mL) was added dropwise. The mixture was stirred for several hours and was then extracted with chloroform, washed with water and brine, and dried over anhydrous magnesium sulfate. Evaporation in vacuo yielded a white solid, which, after recrystallization from hexane, gave 84.5 g (76%) of extremely hygroscopic white needles: ^1H NMR ($CDCl_3$) δ 1.8 (d, J = 14 Hz, 6, PCH_3), 2.5 (s, 3, *p*-CH_3), 7.2–7.8 (m, 4, Ar H).

1-(Methyl-*p*-tolylphosphinoyl)-2-methylpropan-2-ol (14). Dimethyl-*p*-tolylphosphine oxide (6; 20 g, 0.12 mol) and tetrahydrofuran (500 mL) were combined and ice cooled to 10 °C in a modification of the procedure outlined by Grayson.[12] A 2.4 M solution of *n*-butyllithium in hexane (55 mL, 0.13 mol) was syringed into the reaction vessel, and the resulting brown solution was cooled to −78 °C (dry ice and acetone). A 20% solution of acetone in tetrahydrofuran (60 mL, about 0.2 mol) was added until the color of the solution faded to an opaque white; after 30 min of stirring, saturated ammonium chloride solution (500 mL) was added, and the mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with chloroform. The combined organic layers were dried ($MgSO_4$). Rotary evaporation yielded a yellow liquid which crystallized to a white solid upon being allowed to stand. Recrystallization from hexane gave 14.15 g (52%) of white solid: mp 79.2 °C; mass spectrum, m/e 226 (M^+), 168 ($M^+ - C_3H_6OH$), 153 (168 − CH_3); ^1H NMR ($CDCl_3$) δ 1.22 (s, 3, methyl), 1.37 (s, 3, methyl), 1.7 (d, J = 12 Hz, 3, PCH_3), 2.2 (d, J = 9 Hz, 2, PCH_2), 2.35 (s, 3, *p*-CH_3), 4.6 (s, 1, OH), 7.25 (dd, J_{HH} = 9 Hz, J_{PH} = 3 Hz, 2, Ar H_{ortho}), 7.55 (dd, J_{PH} = 12 Hz, J_{HH} = 9 Hz, 2, Ar H_{meta}).

Anal. Calcd for $C_{12}H_{19}O_2P$: C, 63.7; H, 8.5; P, 13.7. Found: C, 63.9; H, 8.3; P, 13.8.

1,3,3,5-Tetramethylphosphindoline 1-Oxide (15). A 10% solution of phosphorus pentoxide in commercial grade polyphosphoric acid was heated to 165 °C with vigorous stirring. The alcohol 14 (9.33 g, 41 mmol) was added, and the mixture was stirred at 175 °C for 3.5 h. The mixture was allowed to cool to 100 °C and poured into ice–water. The dichloromethane extracts of the aqueous reaction mixture were washed with water, sodium bicarbonate solution, and again with water, dried over $MgSO_4$, and rotary evaporated, leaving a brown liquid. Recrystallization from hexane yielded 2.18 g (25%) of brown, faceted crystals: high-resolution mass spectrum, m/e 208.1024 (calcd for $C_{12}H_{17}OP$ 208.1015); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3, methyl), 1.44 (s, 3, methyl), 1.7 (d, J = 12 Hz, 3, PCH_3), 2.12 (q, J_{PH} = 12 Hz, J_{HH} = 7 Hz, 1, PCH ring), 2.16 (q, J_{PH} = 10.5 Hz, J_{HH} = 7.5 Hz, 1, PCH ring), 2.35 (s, 3, *p*-CH_3), 7.0–7.2 (m, 2, Ar H_{meta}), 7.5 (t, J_{PH} = 9 Hz, J_{HH} = 9 Hz, 1, Ar H_{ortho}).

Anal. Calcd for $C_{12}H_{17}OP$: C, 69.2; H, 8.3; P, 14.9. Found: C, 69.0; H, 8.6; P, 15.3.

1-(Methyl-*p*-tolylphosphinoyl)-3-methylbutan-2-ol (7). A solution of dimethyl-*p*-tolylphosphine oxide (6; 20.0 g, 119 mmol) in THF was cooled to 10 °C, and a 2.4 M solution of *n*-butyllithium (55 mL, 131 mmol) was added with a syringe, producing an orange solution. This was cooled with dry ice/acetone to −78 °C, and freshly distilled isobutyraldehyde (8.57 g, 119 mmol) in THF was added dropwise. The solution was allowed to equilibrate to room temperature, and saturated aqueous ammonium chloride (400 mL) was added. The aqueous layer was separated and extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate and rotary evaporated, yielding 32.64 g of a yellow liquid which crystallized on being allowed to stand. An analytical sample was obtained by recrystallization from hexane to give the pure product as white crystals: mp 67–70 °C; high-resolution mass spectrum, m/e 239.1211 (M^+) (calcd for $C_{13}H_{21}O_2P$ 239.1200); ^1H NMR ($CDCl_3$) δ 0.7–1.0 (m, 6, methyl), 1.75 (d, J = 12 Hz, 3, PCH_3), 1.6–2.1 (m, 3, methylene and methine), 2.35 (s, 3, *p*-CH_3), 3.6–3.8 (m, 1, CHOH), 4.4 (br s, 1, OH), 7.26 (dd, J_{HH} = 7.5 Hz, J_{PH} = 3 Hz, 2, Ar H_{meta}), 7.58 (dd, J_{PH} = 12 Hz, J_{HH} = 9 Hz, 2, Ar H_{ortho}).

Anal. Calcd for $C_{13}H_{20}O_2P$: P, 12.9. Found: P, 12.6.

1,4,4,7-Tetramethyltetrahydrophosphinoline Oxide (8) and 1,4,4,6-Tetramethyltetrahydrophosphinoline Oxide (9). Polyphosphoric acid (PPA) was freshly prepared by addition of phosphorus pentoxide (800 g) to 85% reagent-grade phosphoric acid (380 mL) at 100–105 °C. When the P_2O_5 dissolved, the solution was heated to 120 °C, and the crude alcohol 7 (20.56 g, 85.6 mmol) was added, producing a cloudy orange mixture. This was stirred overnight at 120 °C and then poured into 1 L of ice–water; ^1H NMR and TLC showed that no starting material remained. The aqueous solution was decanted from tar which had appeared, extracted with CH_2Cl_2, washed with $NaHCO_3$ solution and water, and evaporated, yielding 15.7 g (83%) of a yellow oil containing the desired products 8 [^1H NMR (270 MHz) δ 1.0–1.4 (m, 2, C-3 methylene), 1.33 (s, 3, C-4 methyl), 1.35 (s, 3, C-4 methyl), 1.65 (d, J_{PH} = 12.5 Hz, 3, PCH_3), 1.8–2.3 (m, 2, C-2 methylene), 2.35 (s, 3, $ArCH_3$), 7.26 (dd, J_{HH} = 8 Hz, $J_{PH} \simeq$ 1.5 Hz, partially buried, 1, C-6 Ar H), 7.32 (dd, J_{HH} = 8 Hz, J_{PH} = 5.5 Hz, partially buried, 1, C-5 Ar H), 7.58 (d, J = 12.9 Hz, 1, C-8 Ar H)] and 9 (minor isomer) [^1H NMR δ 1.35, 1.36 (2 s, 6, nonequivalent C-4 methyls), 1.63 (d, J_{PH} = 12.5 Hz, 3, PCH_3),

(18) Chen, C. H.; Brighty, K. E. *Tetrahedron Lett.* **1980**, 4421.
(19) Purchased from Organometallics, Inc.

2.37 (s, 3, $ArCH_3$), 7.65 (dd, J_{PH} = 12.9 Hz, J_{HH} = 8.1 Hz)] in the ratio of ca. 3:1 (estimated by integration of the ^1H NMR spectrum over the C-8 aromatic protons region at δ 7.58 and 7.65, respectively). An analytical sample of this mixture was obtained by short-path vacuum distillation: bp 65 °C (0.05 mm); high-resolution mass spectrum, m/e 222.1159 (calcd for $C_{13}H_{19}OP$ 222.1172).

Anal. Calcd for $C_{13}H_{19}OP$: P, 13.9. Found: P, 13.5.

1-(2-Hydroxy-2-methylpropyl)-4,4,7-trimethyltetrahydrophosphinoline and 4,4,6-Trimethyltetrahydrophosphinoline 1-Oxides (10 and 11). To a solution of the isomeric mixture of tetrahydrophosphinoline oxides 8 and 9 (3.73 g, 16.8 mmol) in THF at 10 °C was added a 2.6 M solution of *n*-BuLi in hexane (7.1 mL, 18.5 mmol). The mixture was cooled with dry ice/acetone, and a 20% solution of acetone (ca. 2 equiv) in THF was added dropwise. The aqueous layer was separated, extracted (CH_2Cl_2), dried ($MgSO_4$), and evaporated, yielding an orange oil. Preparative LC over silica gel (EtOAc/MeOH, 10:1 v/v) gave 2.83 g (60%) of pure 10 and 11 in a ratio about 4:1 [estimated by integration of the ^1H NMR spectrum over the C-8 aromatic proton region at δ 7.65 (d, J_{PH} = 12 Hz) and δ 7.72 (dd, J_{PH} = 12 Hz, J_{HH} = 9 Hz), respectively] as a white solid: mp 120–130 °C; high-resolution mass spectrum, m/e 280.1591 (calcd for $C_{16}H_{25}O_2P$ 280.1591).

Anal. Calcd for $C_{16}H_{25}O_2P$: C, 68.5; H, 9.0; P, 11.0. Found: C, 68.3; H, 9.4; P, 10.7.

1,1,5,5,8-Pentamethylphosphalilolidine Oxide (12). Polyphosphoric acid was freshly prepared by addition of P_2O_5 (250 g) in portions to reagent-grade phosphoric acid (120 mL) at 110–120 °C with vigorous stirring. When most of the P_2O_5 had dissolved, the undissolved chunks of P_2O_5 were picked out, and the temperature was increased to 120 °C. Addition of the alcohols 10 and 11 (2.06 g, 7.3 mmol) produced an orange solution. After the mixture was stirred for 18 h, starting material was still present as indicated by TLC. The temperature was raised to 140 °C for 2 h, to 160 °C for an additional 24 h, and finally to 170–180 °C overnight, as the extent of reaction was followed by TLC and NMR. The reaction mixture was cooled to 100 °C and poured into ice–water. Extraction with chloroform, washing with $NaHCO_3$ solution, drying over $MgSO_4$, and evaporation yielded 1.3 g of a brown solid. The solid was purified by preparative TLC over silica gel (2 mm; EtOAc/MeOH, 10:1), and washing of the plated-off silica gel with EtOAc and extraction of the gel for 8 h in a Soxhlet extractor (EtOAc) produced 0.42 g (22%) of the desired product: mp 160.6 °C (hexanes); high-resolution mass spectrum, m/e 262.1477 (calcd for $C_{16}H_{23}OP$ 262.1485); UV (EtOH) 275 nm (log ϵ 3.09); ^1H NMR ($CDCl_3$) δ 1.21 (s, 3, C-5 methyl), 1.49 (s, 3, C-5 methyl), 1.53 (d, J_{PH} = 2 Hz, 3, C-1 methyl), 1.66 (s, 3, C-1 methyl), 1.8–2.3 (m, 6, ring methylenes), 2.42 (s, 3, $ArCH_3$), 7.15 (dd, J_{PH} = 4.7 Hz, J_{HH} = 7.9 Hz, 1, C-6 Ar H), 7.22 (d, J_{HH} = 7.9 Hz, 1, C-7 Ar H); ^{31}P NMR ($CDCl_3$) δ +38.86 (s).

Anal. Calcd for $C_{16}H_{23}OP$: C, 73.3; H, 8.8; P, 11.8. Found: C, 73.0; H, 9.2; P, 12.0.

1,1,5,5,8-Pentamethylphosphalilolidine (3). To a solution of 1.3 g (4.96 mmol) of the crude phosphalilolidine oxide 12 in 10 mL of benzene was added ca. 6 mL of trichlorosilane under nitrogen. The solution was refluxed for 5 h, cooled with ice, and decomposed by dropwise addition of 100 mL of 25% NaOH. The organic layer was separated, and the aqueous solution was extracted with ether. The combined organic extracts were washed with brine until neutral, dried ($MgSO_4$), and concentrated on a Rotavap to give 1.3 g of a brown oil. Short-path distillation under vacuum gave 1 g (82%) of 3 as a colorless liquid: bp 133–134 °C (0.8 mm); high-resolution mass spectrum, m/e 246.1499 (M^+) (calcd for $C_{16}H_{23}P$ 246.1485); UV (EtOH) 254 nm (log ϵ 3.93); ^1H NMR ($CDCl_3$) δ 1.4 (s, 6, C-5 *gem*-dimethyl), 1.5 (s, 3, C-1 methyl), 1.58 (s, 3, C-1 methyl), 1–2.3 (m, 6, ring methylenes), 2.4 (s, 3, $ArCH_3$), 6.9 (d, J_{HH} = 7.9 Hz, 1, C-7, Ar H), 7.02 (dd, J_{PH} = 3 Hz, J_{HH} = 7.9 Hz, 1, C-6 Ar H); ^{31}P NMR ($CDCl_3$) δ −42.27 (s).

Anal. Calcd for $C_{16}H_{23}P$: C, 78.0; H, 9.4. Found: C, 77.8; H, 9.8.

***p*-Methyl-1,1,5,5,8-pentamethylphosphalilolidinium Iodide (13).** To a solution of 200 mg (0.81 mmol) of 3 in toluene (5 mL) was added 6 mL of methyl iodide. The homogeneous solution was stirred at ambient temperature overnight and stripped of solvent on a Rotavap to give a white solid. This was recrystallized from methylene chloride and hexanes to give 230 mg (73%) of pure 13: mp 257.6 °C dec; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3, C-5 methyl), 1.4 (s, 3, C-5 methyl), 1.65 (s, 3, C-1 methyl), 1.68 (d, J = 3.4 Hz, 3, C-1 methyl), 2.1–2.35 (m, 2, C-4 methylene), 2.48 (s, 3, $ArCH_3$), 2.68 (m, 1, C-3 proton), 2.88 (t, J = 16 Hz, 1, C-2 proton), 3.42 (dd, J = 16 Hz, J = 10 Hz, 1, C-2 proton), 3.52 (m, 1, C-3 proton), 5.36 (d, J = 5.5 Hz, 1, PCH_3), 7.38 (dd, J_{HH} = 8 Hz, J_{PH} = 5.5 Hz, 1, C-6 Ar H), 7.48 (d, J_{HH} = 8 Hz, 1, C-7 Ar H); ^{31}P NMR ($CDCl_3$) δ +23.4 (s).

Anal. Calcd for $C_{17}H_{26}PI$: C, 52.6; H, 6.7; P, 8.0. Found: C, 52.8; H, 7.0; P, 8.0.

1-(2-Hydroxy-3-methylbutyl)-4,4,6-trimethyl- and -4,4,7-trimethyltetrahydrophosphinoline Oxides (17). A solution of the tetrahydrophosphinoline oxides mixture 8 and 9 (8.2 g, 0.037 mol) in dry THF was cooled to 10 °C with ice. A 2.4 M solution (16.8 mL, 1.2 equiv) of *n*-BuLi in hexane was added, and the solution was stirred for 40 min. Freshly distilled isobutyraldehyde (5 g, 0.069 mol) in dry THF was added dropwise, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 1 h, quenched with ammonium chloride solution, extracted with ether, dried over $MgSO_4$, and evaporated to yield 11.9 g of a brown oil. The oil (11 g) was purified by preparative LC over silica gel (EtOAc/MeOH, 10:1), giving 3.4 g (34%) of a pure isomeric sample as a colorless liquid. The ^1H NMR spectrum of this mixture is very complicated. Integration over the downfield C-8 proton region gives the ratio of the C-7 methyl compound [δ 7.6 (d, J_{PH} = 12 Hz)] and the C-6 methyl compound [δ 7.65 (dd, J_{PH} = 12 Hz, $J_{HH} \simeq$ 9 Hz)] to be ca. 1:1: high-resolution mass spectrum, m/e 294.1724 (calcd for $C_{17}H_{27}PO_2$ 294.1747); ^1H NMR ($CDCl_3$) δ 0.9 (d, 6, J = 6 Hz), 1.1–1.3 (m, 3), 1.35 (s, 3), 1.8–2.2 (m, 5), 2.35 (s, 3), 3.93 (br d, 1, methine proton), 4.94 (br d, 1, OH), 7.1–7.3 (m, 2), 7.65 (m, 1, C-8 proton).

1,1,6,6,8-Pentamethylphosphajulolidine Oxide (18). Polyphosphoric acid was freshly prepared by dissolving P_2O_5 (250 g) in reagent-grade phosphoric acid (120 mL) at 100–105 °C as usual. This was heated to 140–150 °C, the diastereoisomeric alcohols 17 (2.65 g, 0.01 mol) were added, and the resulting orange-brown mixture was stirred at 140–150 °C until (ca. 24 h) the ^1H NMR of a sample showed that the signal at δ ~7.7 due to the ortho (C-8) proton in the aromatic region had disappeared (an indication of completion of annulation). The reaction mixture was poured into 1 L of ice–water. Extraction with chloroform, washing with $NaHCO_3$ solution and water, and evaporation gave 2.1 g of a brown oil. The mixture was purified by preparative TLC (EtOAc/MeOH, 8:1) over silica gel (2 mm); Soxhlet extraction with ethyl acetate gave 950 mg of a partly solidified yellow oil (34%). An analytical sample was obtained by two recrystallizations from hexanes: mp 145.6 °C; high-resolution mass spectrum, m/e (relative intensity) 276.1620 (M^+, 47.54) (calcd for $C_{17}H_{25}OP$ 276.1641), 261.1407 (100, $M^+ - CH_3$), 247.1240 (12.75), 233.1078 (13.05); UV (EtOH) 274 nm (log ϵ 2.99), 282 (3.05); ^1H NMR ($CDCl_3$) δ 1.3 (s, 6, CH_3), 1.53 (s, 6, CH_3), 2.3 (s, 3, $ArCH_3$), 1–2.8 (m, 8), 7.0 (d, J_{PH} = 3 Hz, 2, Ar H); ^{31}P NMR ($CDCl_3$) δ +21.75 (quintet, J = 17.3 Hz).

Anal. Calcd for $C_{17}H_{25}OP$: C, 73.9; H, 9.1; P, 11.2. Found: C, 73.6, H, 9.3; P, 11.1.

1,1,6,6,8-Pentamethylphosphajulolidine (4). To a solution of 150 mg (0.54 mmol) of the phosphajulolidine oxide 18 in 6 mL of benzene was added under N_2 ca. 2 mL of trichlorosilane. The solution was refluxed for 4 h, cooled with ice, and decomposed by dropwise addition of 20 mL of 25% aqueous sodium hydroxide. The mixture was extracted twice with ether, and the combined ether extract was washed with brine until neutral, dried ($MgSO_4$), and concentrated on a Rotavap to give 120 mg of 4 (85%). An analytical sample was obtained by short-path vacuum distillation: bp 130–132 °C (0.6 mm); high-resolution mass spectrum, m/e 260.1690 (M^+) (calcd for $C_{17}H_{25}P$ 260.1693); UV (EtOH) 255 nm (log ϵ 3.4); ^1H NMR ($CDCl_3$) δ 1.37 (s, 12, 4 equivalent CH_3), 2.25 (s, 3, $ArCH_3$), 1.1–2.3 (m, 8), 6.98 (d, J_{PH} = 3 Hz, 2, Ar H); ^{31}P NMR ($CDCl_3$) δ −26.32.

Anal. Calcd for $C_{17}H_{25}P$: C, 78.5; H, 9.7. Found: C, 78.9 H, 9.7.

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Registry No. 2, 23897-15-6; 3, 75558-19-9; 4, 75558-20-2; 5, 20676-64-6; 6, 53888-89-4; 7, 75558-21-3; 8, 75558-22-4; 9, 75558-23-5; 10, 75558-24-6; 11, 75558-25-7; 12, 75558-26-8; 13, 75558-27-9; 14, 75558-28-0; 15, 75558-29-1; 17 (isomer 1), 75558-30-4; 17 (isomer 2), 75558-31-5; 18, 75558-32-6; Ph_3N, 603-34-9; Ph_3P, 603-35-0; Ph_3As, 603-32-7; Ph_3Sb, 603-36-1; Ph_3Bi, 603-33-8; acetone, 67-64-1; isobutyraldehyde, 78-84-2.

Vinylogous *N*-Acyliminium Ion Cyclizations: Application to the Synthesis of Depentylperhydrogephyrotoxin

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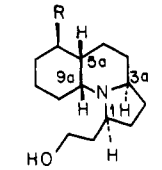
The use of vinylogous *N*-acyliminium ions as olefin cyclization initiators is discussed within the context of a total synthesis of depentylperhydrogephyrotoxin (**2**). It was found that certain *N*-acyliminium and vinylogous *N*-acyliminium ion cyclizations follow a similar stereochemical course.

The structure of gephyrotoxin (**1**), an alkaloid isolated from skin extracts of the neotropical frog *Dendrobates histrionicus*, was recently reported.[1] The inavailability of **1** in more than milligram quantities from the natural source and the interesting pharmacological properties[2] of gephyrotoxin render this structure an attractive target for total synthesis. During the course of studies directed toward the synthesis of **1**, we have examined the stereochemical course of several *N*-acyliminium and vinylogous *N*-acyliminium ion cyclizations.[3,4] This report describes the details of these studies within the context of a synthesis of depentylperhydrogephyrotoxin (**2**).[5]

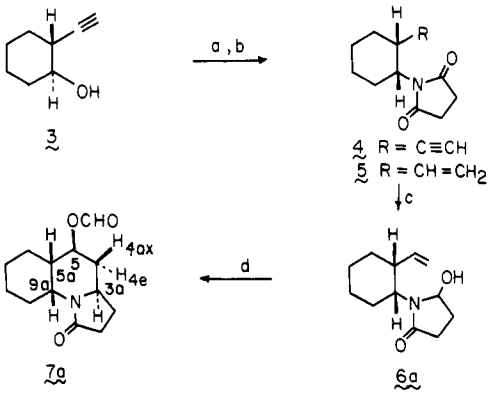


1 R = $CH_2CH_2CH{=}CHC{\equiv}CH$

2 R = H

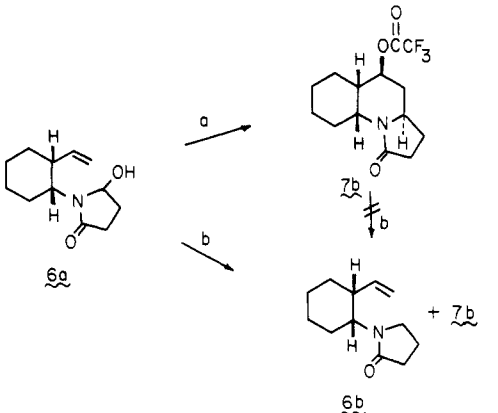
Our initial approach to **2** focused on the preparation of tricyclic lactam **7** via an *N*-acyliminium ion cyclization. The required carbinolamide **6a** was prepared as outlined in Scheme I. Treatment of *trans*-2-ethynylcyclohexanol (**3**) with succinimide under the conditions of Mitsunobu[6] afforded imide **4** in a 59% yield in addition to a 20% yield of *cis*-2-ethynylcyclohexanol.[7] Catalytic hydrogenation of alkyne **4** followed by reduction of the resulting imide **5** with diisobutylaluminum hydride[8] gave **6a** in 63% overall

Scheme I[a]



[a] a, Ph_3P, $EtO_2CN{=}NCO_2Et$, succinimide, THF; b, H_2, $Pd/BaSO_4$, pyr; c, $i\text{-}Bu_2AlH$, toluene; d, 97% HCOOH.

Scheme II[a]



[a] a, CF_3COOH; b, CF_3COOH, Et_3SiH, CH_2Cl_2.

yield. Treatment of **6a** with formic acid gave an 85% yield of a single tricyclic lactam which was assigned structure **7a** on the basis of spectral data.[9,10] In a similar fashion (Scheme II) treatment of **6a** with trifluoroacetic acid gave lactam **7b** in a 62% yield. In the case of the trifluoroacetic

(1) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128.

(2) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163. Daly, J. W.; Mensah-Dwumah, M. *Toxicon* **1978**, *16*, 189.

(3) For an overview of research in the area of acyliminium ion initiated olefin cyclizations, see: Speckamp, W. N. "Stereoselective Synthesis of Natural Products-Workshop Conferences Hoechst"; Bartmann and Winterfeldt, Eds.; Excerpta Medica (Elsevier): Amsterdam, 1979; Vol. 7, p 50. For reference to what is probably vinylogous *N*-acyliminium ion initiated arylation, see: Winterfeldt, E. *Synthesis* **1975**, 617, ref 129.

(4) For stereochemical studies which complement those presented here and elsewhere,[10] see: Maryanoff, B. E.; McComsey, D. F. *Tetrahedron Lett.* **1979**, 3797; Speckamp, W. N.; Nossin, P. M. M. *Ibid.* **1980**, 1991.

(5) For a total synthesis of perhydrogephyrotoxin, see: Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454.

(6) Mitsunobu, D.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(7) The *cis*-2-ethynylcyclohexanol presumably reflects the amount of O-alkylation which occurs during the Mitsunobu reaction.[6]

(8) Winterfeldt, E. *Synthesis* **1975**, 617.

(9) The following critical coupling constants for **7** were determined by ^1H-^1H decoupling experiments at 360 MHz: $J_{3a,4e} = 4$, $J_{3a,4ax} = 11$, $J_{5,4e} = 4$, $J_{5,4ax} = 11$, $J_{5,5a} = 4$, $J_{5a,9a} = 9$ Hz.

(10) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.

0022-3263/81/1946-0367$01.00/0