combined acidic layers until it was strongly basic. The basic mixture was extracted with CH_2Cl_2 (5 × 150 mL), and the combined extracts were dried over Na_2SO_4 and concentrated to produce 0.181 g (66%) of a gummy tan solid. Purification by sublimation (90 °C, 2 mm) gave **1** as a waxy white solid; mp 224–227 °C (sealed tube) (lit.[4] mp 265–268 °C). Resublimation produced no significant change in melting point. NMR ($CDCl_3$) δ 1.5–2.2 (12 H, m), 2.45–2.75 (1 H, br s, exch), 2.90–3.25 (2 H, br s, NCH); M+ found, *m/e* 137.1208 (calcd for $C_9H_{15}N$, *m/e* 137.1206).

***N*-Methyl-2-azaadamantane-*anti*-4,8-diol (2b).** Treatment of 0.980 g (6.4 mmol) of **12** with CH_3NH_2 using the reaction conditions for **2a** produced 1.06 g (90%) of **2b** after recrystallization from acetonitrile: mp 198–201.5 °C; IR (Nujol) 3362 cm^{-1}; NMR (D_2O + DCl) δ (DSS) 4.30 (1 H, m, CHOH), 4.10 (1 H, m, CHOH), 3.43 (2 H, m, CHN), 3.02 (3 H, s, CH_3), 1.56–2.40 (8 H, m); M^+ found, *m/e* 183.1258 (calcd for $C_{10}H_{17}NO_2$, *m/e* 183.1260).

***N*-Ethyl-2-azaadamantane-*anti*-4,8-diol (2c).** Treatment of 0.50 g (3.29 mmol) of **12** with $EtNH_2$ using the reaction conditions for **2a** produced 0.446 g (69%) of **2c** after recrystallization from acetonitrile: mp 178–179 °C; IR (Nujol) 3338 cm^{-1}; NMR (D_2O) δ (DSS) 1.01 (3 H, t, CH_3), 1.5–2.6 (8 H, m), 2.75 (4 H, m, NCH), 3.95 (2 H, s, CHOH); M^+ found, *m/e* 197.1414 (calcd for $C_{11}H_{19}NO_2$, *m/e* 197.1417).

***N*-Isopropyl-2-azaadamantane-*anti*-4,8-diol (2d).** A solution of 1.00 g (6.58 mmol) of **12** and 1.94 (2.39 mmol) of isopropylamine in 14 mL MeOH was heated at 130 °C in a steel bomb for 24 h. After the solution was cooled, the solvent was evaporated and the residue recrystallized from acetonitrile to produce 0.869 g (63%) of **2d**: mp 169–172 °C; IR (Nujol) 3284 cm^{-1}; NMR (D_2O + DCl) δ (DSS) 1.38 (6 H, dd, CH_3) 1.6–2.6 (8 H, m), 3.55–4.35 (5 H, m, CHNH, CHOH); M^+ found, *m/e* 211.1567 (calcd for $C_{12}H_{21}NO_2$, *m/e* 211.1573).

***N*-Isoamyl-2-azaadamantane-*anti*-4,8-diol (2e).** Treatment of 1.00 g (6.58 mmol) of **12** with 2.87 g (32.9 mmol) of isoamylamine using the reaction conditions for **2d** produced 1.058 g (67%) of **2e** after recrystallization from acetonitrile: mp 113–116.5 °C; IR (Nujol) 3320 cm^{-1}; NMR (D_2O + DCl) δ (DSS) 0.92 (6 H, d, CH_3), 1.4–2.4 (11 H, m), 3.20–3.67 (4 H, m, CHN), 4.12 (1 H, m, CHOH), 4.28 (1 H, m, CHOH); M^+ found, *m/e* 239.1874 (calcd for $C_{14}H_{25}NO_2$, *m/e* 239.1886).

***N*-Benzyl-2-azaadamantane-*anti*-4,8-diol (2f).** Treatment of 1.00 g (6.58 mmol) of **12** with 3.52 g (33.0 mmol) freshly distilled benzylamine using the reaction conditions for **2d** produced 1.157 g (68%) of **2f** after recrystallization from benzene: mp 121–123.5 °C; IR (Nujol) 3440 cm^{-1}; NMR (D_2O + DCl) δ (DSS) 1.75–2.42 (8 H, m, ring CH_2, CH), 3.43, 3.49 (2 H, br d, CHN), 4.15 (1 H, m, C*H*OH), 4.54–4.70 (3 H, m, C*H*OH, CH_2Ph), 7.54 (5 H, s, Ph); M^+ found *m/e* 259.1566 (calcd for $C_{16}H_{21}NO_2$, *m/e* 259.1573).

***N*-Phenyl-2-azaadamantane-*anti*-4,8-diol (2g).** To a stirred solution of 0.400 g (2.63 mmmol) of **12** dissolved in 5 mL of trifluoroethanol under N_2 was added 0.270 g (2.89 mmol) of freshly distilled aniline. The mixture was brought to reflux for 2 days and then stirred at room temperature for 5 days. Column chromatography on silica gel eluting with CH_2Cl_2/acetone (85:15) produced 0.237 g (37%) of **2g**: mp 173–174 °C; IR (Nujol) 3320, 1595, and 1497 cm^{-1}; NMR (D_2O + DCl) δ (DSS) 1.98–2.11 (6 H, m, ring CH_2's), 2.49 and 2.54 (2 H, br d, ring CH's), 4.25 and 4.34 (4 H, br d, NCH and C*H*OH), 7.59–7.71 (5 H, m, Ph); M^+ found, *m/e* 245.1413 (calcd for $C_{15}H_{19}NO_2$, *m/e* 245.1417.

Acknowledgment. This work was supported in part by a grant from the National Cancer Institute (Grant CA25436). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. The authors thank Marvin Thompson for mass spectral determinations and Stephen Fesik for some of the NMR data.

Registry No. **1**, 768-41-2; **2a**, 78127-55-6; **2b**, 78127-56-7; **2c**, 78127-57-8; **2d**, 78127-58-9; **2e**, 78127-59-0; **2f**, 78127-60-3; **2g**, 78127-61-4; **3**, 16473-11-3; **4**, 13534-07-1; **11**, 13534-08-2; **12**, 78127-62-5; **14**·HCl, 78127-63-6; ammonia, 7664-41-7; methylamine, 74-89-5; ethylamine, 75-04-7; isopropylamine, 75-31-0; isoamylamine, 107-85-7; benzylamine, 100-46-9; aniline, 62-53-3.

Synthesis of Novel Phosphorus Heterocycles: 2-Aryl-1-methyl-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-Oxides

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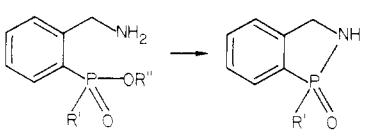
Received March 18, 1981

A class of novel phosphorus heterocycles, 2-aryl-1-methyl-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxides (**1**), has been prepared, beginning with the nickel-catalyzed Arbuzov reaction of diethyl methylphosphonite and *o*-iodotoluene and ending with an intramolecular alkylation of the suitably substituted phosphinanilide **18**. Overall yields for the five-step synthesis are generally in the 30–50% range. The crystalline 2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxides are stable, easily handled compounds with interesting chemical and spectral properties. In particular, the carbon-13 chemical shifts of the aromatic carbons in the benzazaphosphole nucleus were assigned according to the magnitude of the carbon–phosphorus coupling constants as well as by consideration of the mesomeric effects of the phosphorus substituent. Also, the phosphorus-31 chemical shifts of the monosubstituted *N*-aryl derivatives correlated with Hammet values (r = 0.9951), suggesting that π_{p-d} back-donation by the nitrogen lone pair was significant.

In the past decade there has been continuing interest in phosphorus heterocyclic chemistry, prompted to a large extent by developments in the concepts of pseudorotation[1] and pentacoordinate phosphorus chemistry.[2] Interest in our laboratories has focused on a variety of benzo-fused ring systems featuring the C–P–X–C linkage (X = O, N). Several syntheses of five- and six-membered C–N–P heterocycles **2**–**6** (Chart I) have appeared in the literature.[3-8]

Scheme I



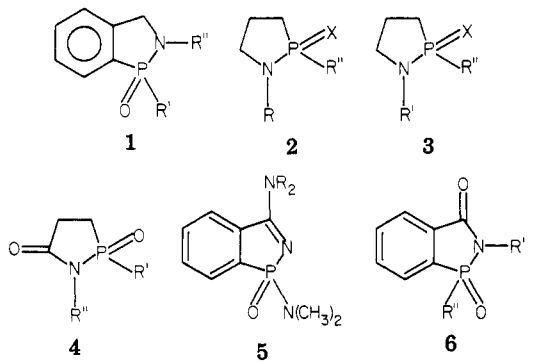
7 **1**

(1) *Organophosphorus Chem.*, 1–8 (1963–1979), and references therein.

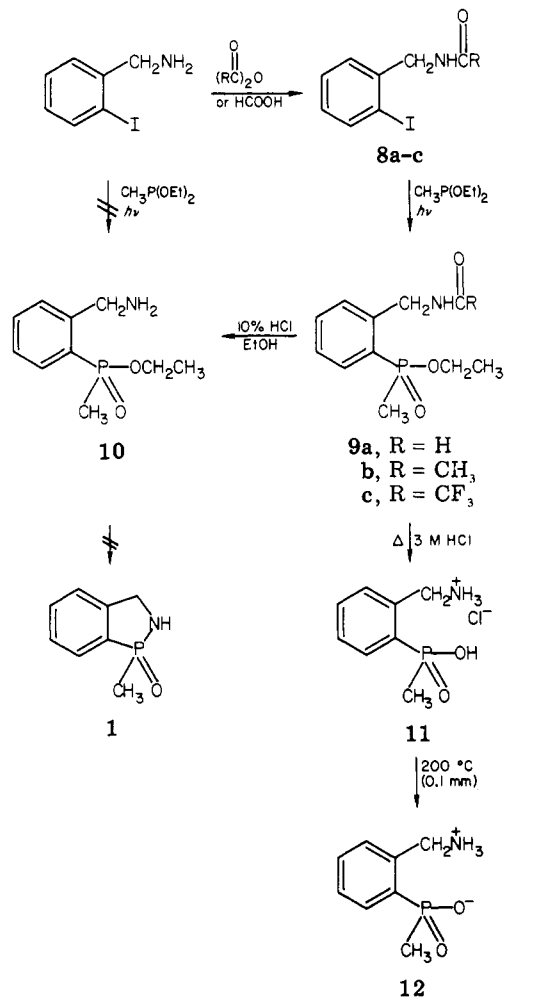
(2) For a comprehensive reference of current organophosphorus chemistry, see L. Maier and G. M. Kosalopoff, Eds., "Organic Phosphorus Compounds", Vol I–VII, Wiley Interscience, New York, 1976.

0022-3263/81/1946-3486$01.25/0

Chart I



Scheme II

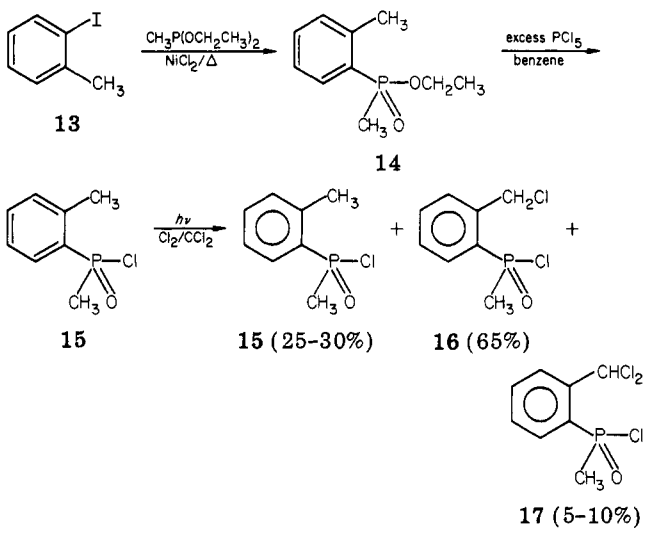


We report the synthesis of a new class of phosphorus heterocycles, 2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxides **1**.

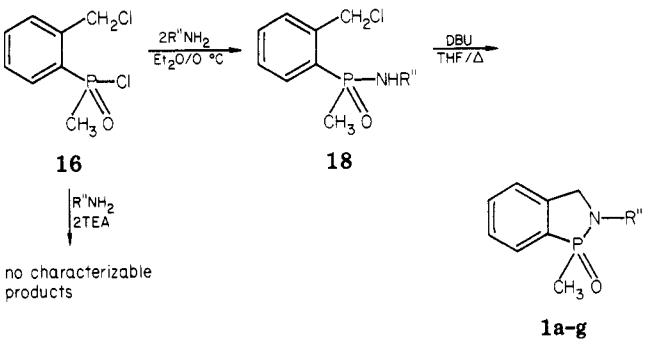
Results and Discussion

Our initial goal was the unsubstituted parent compound **1** (R′ = CH_3, R″ = H), which might be available via the intramolecular cyclization of **7** (Scheme I). Photolytic Arbuzov reaction[9] of *o*-iodobenzylamine in diethyl methylphosphonite (Scheme II) gave only tars. However, acylation of *o*-iodobenzylamine with formic acid, acetic anhydride, or trifluoroacetic anhydride gave amides **8a–c** which, when photolyzed under similar conditions, gave 70–80% yields of **9a–c**. Repeated attempts under a variety of conditions to remove selectively the acetyl or trifluoroacetyl groups in **9b** and **9c** were unsuccessful.[10] Mild heating of **9a**, however, in ethanolic 10% HCl gave pure **10** in 29% yield as a colorless oil. Unfortunately, efforts to scale up the conversion of **9a** to **10** beyond 2 g failed. Alternatively, **9a–c** were hydrolyzed completely in acidic solution to yield **11**. Thermolysis of **11** afforded the free amino acid **12** instead of the desired phosphorus heterocycle **1**, and this approach was eventually abandoned.

Scheme III



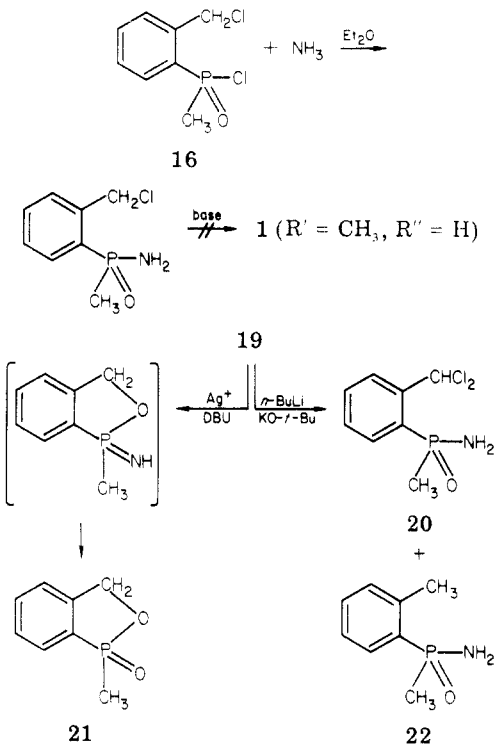
Scheme IV



A different synthetic route (Scheme III) was conceived which would permit preparation of N-substituted derivatives of **1** (R′ = CH_3). Reaction of *o*-iodotoluene (**13**) with diethyl methylphosphonite in the presence of a catalyst such as anhydrous $NiCl_2$[11] gave excellent yields of **14**. Treatment of crude **14** with a 20% molar excess of PCl_5 in benzene provided **15** (94% yield based on **13**). Chlorination of **15** gave **16** in a maximum yield of 65% based on NMR assay of the reaction mixture. Very careful monitoring of the reaction was essential, since chlorination beyond ~70% consumption of **15** gave rapidly increasing

(3) D. J. Collins, J. W. Heatherington, and J. M. Swans, *Aust. J. Chem.*, **27**, 1759 (1974).
(4) D. G. Hewitt and G. L. Newland, *Aust. J. Chem.*, **30**, 579 (1977).
(5) J. A. Miles and R. W. Street, *J. Org. Chem.*, **43**, 4668 (1978).
(6) L. Lopez and J. Barans, *J. Chem. Soc., Perkin Trans. 1* 1806 (1977).
(7) A. N. Pudovik, R. M. Kondrat'wa, and V. K. Khairullin, *J. Russ. Acad. Sci.*, **9**, 1939 (1969); **6**, 1375 (1968).
(8) J. Luher and A. Schmidpeter, *J. Chem. Soc., Chem. Commun.*, 887 (1976).
(9) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).
(10) Conditions studied included pyridine–water, ethanol–water containing a catalytic amount of HCl and 7% sodium carbonate in aqueous ethanol.
(11) P. Tavs, *Chem. Ber.*, **103**, 2428 (1970); P. Tavs and H. Weitkamp, *Tetrahedron*, **26**, 5529 (1970).

Scheme V



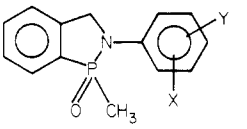
amounts of dichlorinated **17**. Small quantities of **17** were always present in the chlorinated reaction mixture, independent of length of chlorination, but **17** became the predominant or only product upon longer reaction times. Fractional distillation of the mixture of **15–17** gave nearly pure **16** in about 60% isolated yield, and recovered **15** was available for recycling.

Preparation of N-substituted derivatives of **1** ($R' = CH_3$) was attempted first by reaction of **16** with the corresponding amine in a single step (Scheme IV). Addition of various primary alkylamines or anilines to a solution of **16** in the presence of 2 equiv of triethylamine gave intractable gums which defied purification or characterization. However, when the sequence was performed stepwise, the route was successful with *N*-aryl substituents. An ether solution of **16** was added dropwise at 0 °C to 2 equiv of the corresponding aniline. Workup generally afforded white crystalline solids readily characterized as the phosphinanilides **18**. Ring closure to the 2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxide **1** was accomplished cleanly with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing anhydrous THF. DBU·HCl is very hygroscopic but also totally insoluble in anhydrous THF. Consistently high yields of **1** were obtained following simple column chromatography to remove small amounts of dichloroanilide resulting from contamination of **16** with **17**.

Attempts to prepare the N-unsubstituted derivative **1** ($R' = CH_3$ and $R'' = H$) by using this two-step sequence led to some unusual results. Reaction of **16** with anhydrous ammonia produced phosphinamide **19** in 62% yield. Treatment of **19** with DBU or silver tetrafluoroborate provided the O-alkylated product **20**, instead of the N-alkylated product, after aqueous workup. The structure of **20** was confirmed by comparison of its spectral properties with those of authentic material.[12] In the presence of either *n*-butyllithium or potassium *tert*-butoxide **19** apparently underwent a disproportionation reaction to give, in low yields, equal amounts of **21** and **22** as identified

(12) J. A. Miles, U.S. Patent 4 219 519, (1980).

Table I. Partial Proton and Phosphorus NMR Spectral Data[a]

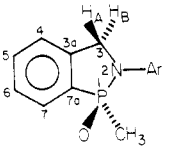


entry	Y	Y	proton NMR data CH_3P	proton NMR data misc	^{31}P chemical shift
a	H	H	1.92 (14)		41.3
b	4-CH_3O	H	1.83 (14)	3.77 (CH_3O)	40.8
c	3-Cl	4-Cl	1.87 (14)		42.3
d	3-CF_3	H	1.9 (14)		42.1
e	4-Br	H	1.87 (14)		41.8
f	2-CH_3	6-CH_3	1.75 (14)	2.23, 2.43 (2 CH_3)	41.0
g	4-C_6H_5O	H	1.83 (14)		
h	2-CH_3O	H	1.65 (14)	3.77 (CH_3O)	41.5

[a] The proton chemical shifts are reported in parts per million relative to tetramethylsilane, while the J_{HP} coupling constants in parentheses are reported in hertz. The phosphorus-31 chemical shifts are reported in parts per million downfield from 85% H_3PO_4, the external reference.

by NMR and mass spectral analysis (Scheme V). This observation is unexplained at this time.

Proton NMR. In the proton NMR spectra of **1a–h** the



1a-h

methylene ring protons appeared as a degenerate AB portion of a ABP system[13] around 4.5–5.0 ppm. The spin–spin interaction of these methylene protons with phosphorus probably occurs through nitrogen, since the ring-opened precursors **18** exhibited no phosphorus coupling to the methylene protons. For example, the methylene protons in **18a** ($R'' = C_6H_5$) appeared as an AB quartet with $\nu_A = 5.4$ ppm, $\nu_B = 5.13$ ppm, and $J_{AB} = -11$ Hz.

On the other hand, the methylene protons in the 270-MHz proton NMR spectrum[14] of **1a** appeared as a phosphorus-coupled AB octet with $J_{AP} = 6.4$ Hz, $J_{BP} = 3.2$ Hz, and $J_{AB} = -14.2$ Hz. The chemical shifts of H_A and H_B, 4.80 and 4.74 ppm, respectively, were calculated by assuming an AB spin system. The proton syn to the P–O bond was assigned as H_A due to the deshielding effect of the P–O bond, analogous to that reported in the literature.[15]

Other pertinent proton NMR data are listed in Table I. The magnetic nonequivalence of the two *o*-methyl groups in **1f** was presumably a result of restricted rotation about the *N*-phenyl axis.

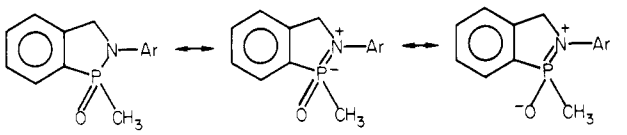
Phosphorus-31 NMR. The phosphorus chemical shifts obtained from the completely decoupled spectra of the

(13) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969; see examples 82–97 on pp 299–303.

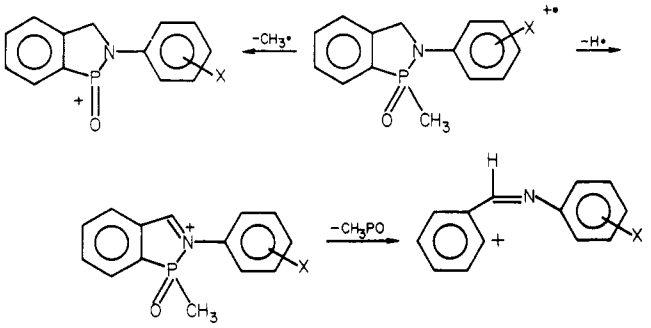
(14) We are indebted to Professor W. H. Urry of the University of Chicago for measuring these spectra for us.

(15) (a) B. E. Maryanoff and R. O. Hutchins, *J. Org. Chem.*, **42**, 1022 (1977); (b) K. C. Chen, S. E. Ealick, D. Van der Helm, J. Barycki, and K. D. Berlin, *J. Org. Chem.*, **42**, 1170 (1977).

Scheme VI



Scheme VII

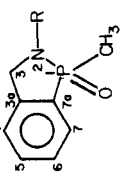


various derivatives of **1** are tabulated in Table I. These phosphorus-31 chemical shifts are dependent upon the nature and position of the substituent in the *N*-aryl ring. A Hammett treatment of these phosphorus-31 chemical shifts afforded an excellent correlation (r = 0.9951). In general, correlation of phosphorus-31 chemical shifts with substituent effects has been complicated by ionic and covalent bonding effects.[16-18] However, perturbation of the empty d orbitals of phosphorus are known to influence the magnetic environment around phosphorus and thus its chemical shift.[16] Therefore, back donation by the lone pair on nitrogen in **1** might account for the shielding of the phosphorus-31 signal by electron donating groups in the N-aryl ring as depicted in Scheme VI.

Carbon-13 NMR. Partial peak assignments of the carbon-13 NMR spectra of **1a–h** are shown in Table II. In every case, carbon 7a was masked by the other aromatic carbons and was not identified. Also, the *N*-aryl carbons were not assigned, since they were not intrinsic to the heterocyclic ring system. The low-field doublet of weak intensity was assigned to the quaternary carbon 3a. The high-intensity singlet was assigned to ring carbon 5 because phosphorus coupling to the para carbon in aromatic rings is usually small.[19-21] Of the three remaining aromatic carbons (C-4, C-6, and C-7), the doublet with the largest J_{CP} coupling constant was assigned as carbon 7, while the other two carbons were arbitrarily assigned as shown in Table II.

The doublet corresponding to the *P*-methyl carbon was easily discerned in the carbon-13 NMR spectra of **1**. The large J_{CP} coupling constant for this *P*-methyl carbon was dependent upon the steric bulk of the nitrogen substituent. For example, the sterically congested analogues **1f** and **1h** exhibited larger J_{CP} values for the *P*-methyl carbon than the other *N*-aryl derivatives. Also, the J_{CP} values for the C-3 methylene carbon were larger in **1f** and **1h** relative to the other analogues. These larger coupling constants

Table II. Carbon-13 NMR Spectral Data[a]

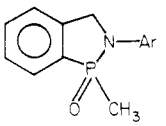


compd	R	chemical shift							
		CH_3P	C-3	C-3a	C-4	C-5	C-6	C-7	misc
1a	C_6H_5	16.8 (91.2)	51.6 (13.2)	*b*	128.4 (11.8)	132.5 (0)	124.0 (8.8)	127.8 (13.2)	
1b	*p*-$CH_3OC_6H_4$	16.0 (92.7)	52.5 (13.1)	140.6 (16.2)	128.4 (11.8)	132.2 (0)	123.8 (8.9)	127.6 (13.3)	55.5 (CH_3)
1c	3,4-$Cl_2C_6H_3$	16.7 (91.2)	51.8 (12.8)	139.5 (16.2)	*c*	*c*	*c*	*c*	
1d	*m*-$CF_3C_6H_4$	16.3 (91.1)	51.8 (13.2)	139.7 (16.1)	128.7 (13.2)	*c*	124.2 (8.9)	127.8 (15.7)	
1e	*p*-BrC_6H_4	16.7 (92.6)	51.8 (13.3)	*b*	128.6 (12.8)	132.6 (0)	124.0 (8.8)	127.8 (14.7)	
1f	2,6-$(CH_3)_2C_6H_3$	15.7 (97.1)	51.1 (14.7)	141.8 (16.2)	*c*	*c*	*c*	*c*	18.2 (CH_3), 19.1 (CH_3)
1g	*p*-$C_6H_5OC_6H_4$	*b*	52.3 (13.3)	*b*	128.6 (11.7)	132.6 (0)	124.0 (8.8)	*b*	
1h	*o*-$CH_3OC_6H_4$	15.6 (97.6)	53.7 (14.8)	141.7 (17.7)	127.1 (11.3)	131.0 (0)	123.2 (8.8)	127.0 (14.2)	54.7 (CH_3)
20[12]		16.2 (100)	72.2 (0)	143.8 (19)	129 (11.8)	132.9 (3)	122.6 (11.8)	127.6 (13.3)	

[a] All spectra were recorded in $CDCl_3$ with Me_4Si as the internal standard. Chemical shifts are given in parts per million, while the values in parentheses are J_{CP} in hertz. [b] Data reduction missed one of the two peaks, and therefore its exact position was not determined, although the doublet was quite evident. [c] These carbons were superimposed with the other aromatic carbon signals.

(16) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R Van Wazer, "^{31}P Nuclear Magnetic Resonance", Wiley, 1967 pp 76–177.
(17) S. O. Grim and A. W. Yankowsky, *Phosphorus Sulfur*, **3**, 191 (1977).
(18) R. C. Grabiak, J. A. Miles, and G. M. Schwenzer, *Phosphorus Sulfur*, **9**, 197 (1980).
(19) T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Org. Chem.*, **40**, 3437 (1975).
(20) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley, 1972, p 27.
(21) G. A. Gray, *J. Am. Chem. Soc.*, **95**, 7736 (1973), and references cited therein.

Table III. Electron-Impact Mass Spectral Data[a]



compd	Ar	m/e M+	(M − 1)+	(M − 15)+	(M − 63)+	Ar	misc
1a	C_6H_5	243 (100)	242 (32)	228 (90)	180 (34)	77 (33)	
1d	m-$CF_3C_6H_4$	311 (35)	310 (12)	296 (64)	248 (24)	145 (22)	69 (100)
1e	p-BrC_6H_4	321 (100), 323 (91)	320 (30), 322 (43)	306 (76), 308 (70)	258 (10), 260 (12)	155 (8), 157 (8)	
1g	p-$C_6H_5OC_6H_4$	335 (100)	334 (18)	320 (30)	272 (5)		

[a] The numbers in parentheses correspond to the relative intensity with respect to the base peak.

probably reflect small structural changes to relieve steric strain in the fused 5-membered ring.

Mass Spectrometry. The major fragments obtained from the electron-impact mass spectra of the 2-aryl-1-methyl-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxides (1) are shown in Table III. In general, these spectra showed very little fragmentation, and the molecular ions were the parent ions in every case except one. The fragmentation pattern might be summarized as shown in Scheme VII.

Experimental Section

All proton NMR spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. The carbon-13 NMR spectra of these same solutions were measured on a JEOL FX-100 Fourier transform NMR spectrometer at 25 MHz with $CDCl_3$ as the internal deuterium lock. The FID was obtained from a pulse width of 5 μs (40° flip angle), a spectral width of 6024 Hz, and a pulse repetition of 0.8 by using 8K data points. The phosphorus-13 NMR spectra were also measured on a JEOL FX-100 Fourier transform NMR spectrometer at 40 MHz with $CDCl_3$ as an internal deuterium lock and 85% H_3PO_4 as an external standard. The FID was accumulated with a pulse width of 5 μs (40° flip angle), a spectral width of 10 000 Hz, a pulse repetition of 1 s and 16K data points. The mass spectra were measured on a Varian 311A mass spectrometer at 90 eV by using the direct probe method. All melting points are uncorrected. Elemental analyses were performed by Atlantic Microlabs or Industrial Testing Laboratories.

***N*-(*o*-Iodobenzyl)formamide (8a).** A solution of *o*-iodobenzylamine (77.5 g, 0.33 mol) in 400 mL of toluene and 50 mL of 90% formic acid was heated at reflux for 3.5 h with continuous water separation via a Dean–Stark trap. Upon cooling of the reaction mixture, the product precipitated and was collected, giving 61.8 g (72%) of white crystals: mp 107–109 °C; NMR ($CDCl_3$) δ 4.5 (d, 2, J = 8 Hz), 6.6 (br s, 1), 6.9–8.1 (m, 4), 8.4 (s, 1).

***N*-(*o*-Iodobenzyl)acetamide (8b).** Aqueous 10% NaOH was added to a solution of *o*-iodobenzylamine (10 g, 0.043 mol) in 50 mL of 5% HCl until the solution just began to cloud. Acetic anhydride (12 mL, threefold excess) was added in one portion followed by addition of a solution of sodium acetate (4.1 g) in 50 mL of H_2O. The product precipitated immediately from ethanol–water to give 7.1 g (66%) of colorless solid, mp 128–130 °C (lit.[22] mp 134–135 °C).

***N*-(*o*-Iodobenzyl)trifluoroacetamide (8c).** To 5 mL of trifluoroacetic anhydride was added in one portion *o*-iodobenzylamine (2.3 g, 0.01 mol). After 1–2 min at room temperature a strong exotherm occurred. The solution was concentrated under reduced pressure, giving an oil which crystallized upon being allowed to stand. The crude product was recrystallized from ligroin–ether to give 1.5 g (46%) of cream-colored crystals: mp 74–76 °C; NMR ($CDCl_3$) δ 4.6 (d, 2, J = 6 Hz), 7.0–8.1 (m, 5); mass spectrum, m/e 313.

Ethyl (α-Formamido-2-tolyl)methylphosphinate (9a). A suspension of 50 g (0.19 mol) of **8a** in 90 mL (3 equiv) of diethyl methylphosphonite[23] was irradiated[9] for 11 h. The resulting solution was concentrated under reduced pressure, and volatile material [below 50 °C (0.1 mm)] was distilled off under high vacuum. The pot residue was purified by column chromatography on silica gel by using 2–7% ethanol–benzene to give 24.0 g (55%) of 90% pure material contaminated with 10% **8a**. The sample was used as obtained: NMR ($CDCl_3$) δ 1.4 (t, 3, J = 8 Hz), 1.7 (d, 3, J = 15 Hz), 3.7–4.4 (m, 2), 4.4–5.1 (m, 2), 7.3–8.0 (m, 5), 8.3 (s, 1).

Ethyl [α-(Trifluoroacetamido)-2-tolyl]methylphosphinate (9c). A solution of 1.4 g (0.0042 mol) of **8c** in 5 mL of diethyl methylphosphonite was irradiated for 2 h. The solution was concentrated and low boilers [<60 °C (0.1 mm)] were removed. The crude product remaining (~90% pure) was used without further purification: NMR ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz), 1.7 (d, 3, J = 15 Hz), 3.6–4.3 (m, 2), 4.6 (t, 2, J = 7 Hz), 7.1–7.7 (m, 4), 9.0 (br s, 1); mass spectrum, m/e 329 (parent).

Ethyl (α-Amino-2-tolyl)methylphosphinate (10). A solution of 3.2 g (0.013 mol) of **9a** in a mixture of 5 mL of 10% HCl and 50 mL of ethanol was heated on a steam bath for 1.5 h. The solution was allowed to stand overnight at room temperature and then concentrated under reduced pressure. The residue was treated with aqueous sodium bicarbonate, and this mixture was thoroughly extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and concentrated to give 0.8 g (29%) of a colorless oil: NMR ($CDCl_3$) δ 1.3 (t, 3, J = 6 Hz), 1.7 (d, 3, J = 15 Hz), 1.8 (br s, 2), 3.7–4.4 (m, 2), 7.2–8.0 (m, 4); mass spectrum m/e 197 (parent). No other purification was performed, and the sample was used directly for cyclization studies.

(α-Amino-2-tolyl)methylphosphonic Acid Hydrochloride (11). A suspension of **8b** (26.5 g, 0.097 mol) in 60 mL (0.36 mol) of diethyl methylphosphonite was irradiated for 5 h. The resulting solution was concentrated under reduced pressure, and low boilers [<150 °C, (0.1 mm)] were removed. The residue (19.4 g, 79%) consisted of 90% **9b** and 10% **8b**. A solution of this material in 100 mL of ethanol and 80 mL of 12 M HCl was heated overnight on a steam bath. Concentration of the solution gave an oil which was dissolved in ethanol. Addition of ether induced the formation of white crystals: 9.7 g (58%); mp 192–197 °C; NMR (D_2O) δ 1.5 (d, 3, J = 16 Hz), 4.1 (s, 2), 7.1–7.8 (m, 4).

Anal. Calcd for $C_8H_{13}ClNO_2P$: C, 43.36; H, 5.91; Cl, 16.00. Found: C, 43.35; H, 5.96; Cl, 15.91.

(α-Amino-2-tolyl)methylphosphinic Acid (12). A sample of 11 (6.3 g, 0.029 mol) was heated to 200 °C under vacuum (0.1 mm) for 2.25 h. The residue (4.6 g, 96%) was boiled in ethanol to give white crystals: mp 285–295 °C; NMR (trifluoroacetic acid) δ 1.9 (d, 3, J = 15 Hz), 4.2–4.7 (m, 2), 7.0–8.1 (m, 5); mass spectrum, m/e 185.

Anal. Calcd for $C_8H_{12}NO_2P$: C, 51.89; H, 6.53; N, 7.56. Found: C, 51.93; H, 6.54; N, 7.59.

Methyl(2-tolyl)phosphinyl Chloride (15). A mixture of 218 g (1.0 mol) of *o*-iodotoluene and 6.5 g (0.05 mol) of anhydrous nickel chloride[11] (from $NiCl_2 \cdot 6H_2O$ by drying under vacuum at

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200 °C overnight) was stirred vigorously under an inert atmosphere at 160 °C as diethyl methylphosphonite (180 g, 1.3 mol) was added dropwise. Ethyl iodide distilled rapidly from the reaction mixture and was collected. Addition was maintained at such a rate to maintain a pot temperature of ~170 °C over 1.5 h. The dark solution was heated for an additional 1 h and then poured into ice–water after cooling. Extraction of the aqueous mixture with CH_2Cl_2 followed by water washing and drying over $MgSO_4$ gave, after solvent removal, 185 g (95%) of a colorless oil, **14**. The oil was combined with 500 mL of benzene and treated with PCl_5 (209 g, 1 mol) in portions. The solution was refluxed for 1 h, concentrated, and distilled (bulb to bulb) to give 175 g of a colorless oil [bp 100 °C (0.10 mm)] which was used as obtained: NMR ($CDCl_3$) δ 2.2 (d, 3, J = 14 Hz), 2.7 (d, 3, J = 1.5 Hz), 7.2–8.0 (m, 4).

(α-Chloro-2-tolyl)methylphosphinyl Chloride (16). A solution of 175 g of methyl(*o*-tolyl)phosphinyl chloride in 1 L of CCl_4 was brought to reflux (with vigorous stirring) with a 275-W GE sunlamp mounted below the flask. Chlorine gas was bubbled into the solution, and the course of the reaction was monitored every 5–7 min by NMR. After 0.5 h the reaction had reached 65–70% completion, as measured by the disappearance of the methyl resonance at δ 2.7 and the appearance of the chloromethyl resonance centered at δ 5.3. Small amounts (~5%) of the dichloromethyl product (**17**) were present as measured by the resonance at δ 8.2. Irradiation was halted and the solution concentrated. The oil remaining was fractionally distilled through a 1-ft Vigreaux column to remove unreacted **15**. This oil was again subjected to photolytic chlorination, isolated, and distilled. This process, after three recycles, provided 170 g of **16** [bp 110–120 °C (0.10 mm)] contaminated with <5% of **17** which codistilled and could not be separated: NMR ($CDCl_3$) δ 2.4 (d, 3, J = 14 Hz), 5.1 and 5.5 (dd, CH_2, J = 12 Hz, J_{HP} = 2 Hz), 7.3–8.2 (m, 4).

Anal. Calcd for $C_8H_9Cl_2OP$: C, 43.08; H, 4.07; Cl, 31.79. Found: C, 42.92; H, 4.11; Cl, 31.97.

General Procedure for Preparation of Phosphinanilides 18a–g. A solution of **16** (0.10 mol) in 100 mL of dry ether was added dropwise to a solution of the requisite aniline (0.21 mol) in 100 mL of dry ether at 0 °C under an inert atmosphere. After being stirred 1 h more, the mixture was suction filtered. The filter cake was washed with ether and slurried in 200 mL of ice-cold 1% HCl for 5 min. After suction filtration, the filter cake was washed with liberal amounts of cold water and dried over P_2O_5 under vacuum. The phosphinanilides were recrystallized or used directly.

***N*-Phenyl-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18a)** was prepared repeatedly according to the general procedure in 83–92% yields as colorless plates: mp 140–142 °C ($CHCl_3$–ether); NMR ($CDCl_3$) δ 1.8 (d, 3, J = 15 Hz), 5.0 and 5.4 (gem AB, J = 11 Hz), 6.7–8.2 (m, 10).

Anal. Calcd for $C_{14}H_{15}ClNOP$: C, 60.12; H, 5.41; Cl, 12.68; N, 5.01. Found: C, 59.91; H, 5.43; Cl, 12.55; N, 4.95.

***N*-(4-Methoxyphenyl)-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18b)** was prepared according to the general procedure in 85% yield as a white powder: mp 129–130 °C (THF–ligroin); NMR ($CDCl_3$) δ 1.8 (d, 3, J = 14 Hz), 3.6 (s, 3), 4.95 and 5.45 (gem AB, 2, J = 10 Hz), 6.5–8.0 (m, 9); mass spectrum, m/e (relative (intensity) 309 (99), 310 (22), 311 (38), 274 (49), 258 (100), 153 (24).

Anal. Calcd for $C_{15}H_{17}ClNO_2P$: C, 58.28; H, 5.51; N, 4.53. Found: C, 58.21; H, 5.56; N, 4.48.

***N*-(3,4-Dichlorophenyl)-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18c)** was prepared according to the general procedure in 99% yield as a colorless powder: mp 148–149 °C (THF–ligroin); NMR ($CDCl_3$) δ 1.9 (d, 3, J = 14 Hz), 5.1 and 5.5 (gem AB, 2, J = 12 Hz), 6.9–8.0 (m, 7), 8.4 (d, NH, J = 12 Hz); mass spectrum, m/e (relative intensity) 347 (100), 349 (96), 351 (32), 311 (58), 296 (40), 151 (68), 137 (60).

Anal. Calcd for $C_{14}H_{13}Cl_3NOP$: C, 48.14; H, 3.74; N, 4.04; Cl, 30.7. Found: C, 48.18; H, 3.79; N, 4.00; Cl, 30.52.

***N*-[3-(Trifluoromethyl)phenyl]-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18d).** Prepared according to the general procedure with some modification. The product was soluble in the ether filtrate. The filtrate was washed with ice-cold 1% HCl and then washed with ice-cold water. The ether solution was dried (Na_2SO_4) and concentrated to leave a colorless oil which would not crystallize. Attempts to crystallize the oil from a solvent resulted in substantial decomposition. It was, therefore, used as obtained: NMR ($CDCl_3$) δ 1.9 (d, 3, J = 14 Hz), 5.15 (gem AB, 2, J = 11 Hz), 6.8–8.3 (m, 10).

***N*-(4-Bromophenyl)-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18e)** was prepared according to the general procedure in 78% yield as a colorless powder: mp 149–151 °C (THF–petroleum ether); NMR ($CDCl_3$) δ 1.8 (d, 3, J = 14 Hz), 5.2 (gem AB, 2, J = 12 Hz), 6.9–8.3 (m, 9); mass spectrum, MS m/e (relative intensity) 357 (80), 359 (100), 361 (31), 322 (40), 151 (53), 137 (52).

Anal. Calcd for $C_{14}H_{14}BrClNOP$: C, 47.10; H, 3.92; N, 3.92. Found: C, 47.28; H, 4.01; N, 3.86.

***N*-(4-Phenoxyphenyl)-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18g)** was prepared according to the general procedure in 75% yield as a glass (90% pure by NMR) and was used as obtained: NMR ($CDCl_3$) δ 1.8 (d, 3, J = 14 Hz), 5.05 (gem AB, 2, J = 10 Hz).

***N*-(2-Methoxyphenyl)-*P*-(α-chloro-2-tolyl)-*P*-methylphosphinamide (18h)** was prepared according to the general procedure in 52% yield as a white powder which was used as obtained: NMR ($CDCl_3$) δ 1.95 (d, 3, J = 14 Hz), 3.9 (s, 3), 5.22 (gem AB, 2, J = 10 Hz), 5.8 (d, NH, J = 10 Hz), 6.6–8.0 (m, 8).

General Procedure for Preparation of 2-Aryl-1-methyl-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-Oxides (1a–g). Under a static nitrogen atmosphere, a magnetically stirred solution of **18a–g** (0.1 mol) and DBU (0.1 mol) in 100 mL of anhydrous THF was heated at reflux for 4 h. After being stirred overnight at ambient temperature, the suspension was suction filtered and the filter cake washed with ethyl acetate. The combined filtrates were concentrated in vacuo and taken up in 200 mL of methylene chloride. This solution was washed successively with 1% HCl (100 mL) and water (100 mL). It was dried over $MgSO_4$ and concentrated under reduced pressure to leave crude **1a–h**. This material was recrystallized or purified further by silica gel column chromatography with ethyl acetate elution.

1-Methyl-2-phenyl-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-Oxide (19) was prepared via the general method described above in essentially quantitative yield as a colorless glass. The glass was swirled at atmospheric presure with methylcyclohexane on a rotary evaporator to induce solidification. A white solid was collected: mp 93–96 °C; NMR ($CDCl_3$) δ 1.9 (d, 3, J = 14 Hz), 4.8 (d, 2, J = 4 Hz), 7.0–8.2 (m, 9).

Anal. Calcd for $C_{14}H_{14}NOP$: C, 69.13; H, 5.80; N, 5.76. Found: C, 68.95; H, 5.84; N, 5.72.

The filtrate was concentrated and the remaining glass was chromatographed on silica gel with ethyl acetate elution. The first material isolated from the column consisted of nearly pure *N*-phenyl-*P*-[(α,α-dichloro-2-tolyl)phenyl]-*P*-methylphosphinamide in 3% yield. Recrystallization ($CHCl_3$–ligroin) gave a white solid: mp 156–157 °C; NMR ($CDCl_3$) δ 1.7 (d, 3, J = 14 Hz), 6.6–8.2 (m, 10), 8.6 (s, 1); mass spectrum, m/e (relative intensity) 315 (28), 313 (42), 277 (26), 242 (100), 180 (39).

Anal. Calcd for $C_{14}H_{14}Cl_2NOP$: C, 53.53; H, 4.49; Cl, 22.57; N, 4.46. Found: C, 53.31; H, 4.56; Cl, 22.40; N, 4.39.

Further elution with ethyl acetate gave additional **1a**, mp 93–96 °C. The yield of **1a** was essentially quantitative, based on 97% pure **18a**.

1-Methyl-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxide (1b) was prepared according to the general procedure as a beige solid which was recrystallized from ethyl acetate to give a colorless solid: mp 148–149 °C; 82% yield; NMR ($CDCl_3$) δ 1.8 (d, 3, J = 14 Hz), 3.9 (s, 3), 4.8 (unsymmetrical d, 2, J = 5 Hz), 6.9–8.1 (m, 8).

Anal. Calcd for $C_{15}H_{16}NO_2P$: C, 65.93; H, 5.90; N, 5.13. Found: C, 65.66; H, 5.98; N, 5.08.

1-Methyl-2-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxide (1c) was prepared according to the general procedure and purified via silica gel chromatography to give a white solid: mp 153–155 °C; 84% yield; NMR ($CDCl_3$) δ 1.8 (d, 3, J = 15 Hz), 4.8 (d, 2, J = 5 Hz), 7.2–8.1 (m, 7).

Anal. Calcd for $C_{14}H_{12}Cl_2NOP$: C, 53.87; H, 3.88; Cl, 22.72; N, 4.49. Found: C, 53.78; H, 3.89; Cl, 22.65; N, 4.51.

1-Methyl-2-[3-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxide (1d) was prepared according to

the general procedure as a yellow oil, which, after chromatography, was slurried with ether to afford a white solid: mp 163–164 °C; 50% yield.

Anal. Calcd for $C_{15}H_{13}F_3NOP$: C, 57.88; H, 4.21; N, 4.50. Found: C, 57.77; H, 4.19; N, 4.47.

1-Methyl-2-(4-bromophenyl)-2,3-dihydro-1*H*-benzazaphosphole 1-oxide (1e) was prepared according to the general procedure in essentially quantitative yield as white crystals (CCl_4–ether–ligroin): mp 135–136 °C; mass spectrum, *m/e* (relative intensity) 321 (100), 323 (91), 306 (76), 308 (70), 180 (40), 121 (42).

Anal. Calcd for $C_{14}H_{13}BrNOP$: C, 52.21; H, 4.04; N, 4.35. Found: C, 52.10; H, 4.08; N, 4.32.

1-Methyl-2-(4-phenoxyphenyl)-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxide (1g) was prepared according to the general procedure as a white, crystalline solid: 40% yield; mp 176–177 °C; mass spectrum, *m/e* (relative intensity) 355 (100), 320 (30).

1-Methyl-2-(2-methoxyphenyl)-2,3-dihydro-1*H*-2,1-benzazaphosphole 1-oxide (1h) was prepared according to the general procedure in 75% yield as an uncrystallizable yellow glass: mass spectrum, *m/e* (relative intensity) 273 (32), 258 (24), 113 (28), 108 (22), 84 (100), 86 (69).

***P*-(α-Chloro-2-tolyl)-*P*-methylphosphinamide (19).** A four-necked, round-bottom flask equipped with an addition funnel, a gas inlet, a mechanical stirrer, and a cold finger condenser was dried with a hot gun under a N_2 atmosphere. Ammonia (~25 mL) was condensed at the cold finger, and 100 mL of precooled anhyd ether was added. The phosphinyl chloride (**16**) was added dropwise over a period of 15 min under a N_2 atmosphere. After the mixture was stirred an additional 0.5 h, the cold finger was removed, and the system was swept with N_2. Sunction filtration yielded a white solid which was extracted with ethyl acetate in a Soxhlet extractor. The ethyl acetate solution was cooled in an ice bath to yield white plates in several crops: 6.2 g (62% yield); mp 137–138 °C; NMR (Me_2SO-d_6) δ 1.55 (d, 14, 3, *J* = 14 Hz), 4.7 (br s, 2), 5.2 (AB pattern, 2, *J* = 11 Hz), 7.4–8.1 (m, 4); mass spectrum, *m/e* (relative intensity) 205 (17), 203 (45), 152 (42), 151 (100), 143 (11).

Anal. Calcd for $C_8H_{11}ClNOP$: C, 47.19; H, 5.45; Cl, 17.41; N, 6.88. Found: C, 46.95; H, 5.54; Cl, 17.29; N, 6.81.

Registry No. **1a**, 78089-50-6; **1b**, 78089-51-7; **1c**, 78089-52-8; **1d**, 78089-53-9; **1e**, 78089-54-0; **1f**, 78089-55-1; **1g**, 78089-56-2; **1h**, 78089-57-3; **8a**, 78089-58-4; **8b**, 78108-43-7; **8c**, 78108-44-8; **9a**, 78089-59-5; **9b**, 78089-60-8; **9c**, 78089-61-9; **10**, 78089-62-0; **11**, 78108-45-9; **12**, 78089-63-1; **13**, 615-37-2; **14**, 61820-30-2; **15**, 78089-64-2; **16**, 78089-65-3; **17**, 78089-66-4; **18a**, 78089-67-5; **18b**, 78089-68-6; **18c**, 78089-69-7; **18d**, 78089-70-0; **18e**, 78089-71-1; **18f**, 78089-72-2; **18g**, 78108-46-0; **18h**, 78108-47-1; **19**, 78089-73-3; formic acid, 64-18-6; acetic anhydride, 108-24-7; trifluoroacetic anhydride, 407-25-0; diethyl methylphosphonite, 15715-41-0; *o*-iodobenzylamine, 39959-51-8; benzenamine, 62-53-3; 4-methoxybenzenamine, 104-94-9; 3,4-dichlorobenzenamine, 95-76-1; 3-(trifluoromethyl)benzenamine, 98-16-8; 4-bromobenzenamine, 106-40-1; 4-phenoxybenzenamine, 139-59-3; 2-methoxybenzenamine, 90-04-0; 2,6-dimethylbenzenamine, 87-62-7; *N*-phenyl-*p*-(α,α-dichloro-2-tolyl)-*p*-methylphosphinamide, 78089-74-4.

Novel Efficient Total Synthesis of Antiviral Antibiotic Distamycin A

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In connection with an attempt to design a flexible synthesis of analogues of distamycin A (**14**) for a structure–activity study, by starting from 4-[[(*tert*-butyloxy)carbonyl]amino]-1-methylpyrrole-2-carboxylic acid (**3**) and the corresponding formyl derivative (**9**), the distamycin A precursor **12** was prepared. The versatility of **12** is demonstrated by direct attachment, after activation, of preformed β-aminopropionamidine dihydrobromide to give **14** in fair yield. We conclude that N- and/or ring-substituted derivatives of **3** and **9** may lead to the corresponding analogues of **12** and thus serve as useful precursors, to which the amino amidine or derivatives thereof can be attached. After hydrogenation of the corresponding nitro compound, **3** and **9** were prepared with (*tert*-butyloxy)carbonyl fluoride and formic anhydride, respectively. Amide bond formations were accomplished with carbodiimides, occasionally via intermediary active esters (**8**, **13**).

Distamycin A (**14**) is an antibiotic with pronounced antiviral and oncolytic properties. It probably exerts its action by binding to A-T rich regions in DNA. Some aspects of the chemistry and biology of this compound have been reviewed recently.[1-4] The substance was isolated by extracting the fermentation broth of *Streptomyces distallicus*, which also contained other antibiotics of similar structure.[1,5,6] The structure of **14** was established from spectroscopic studies of the parent compound and some of its degradation products and proved by synthesis.[5,7] Since there are relatively few antiviral drugs with favorable therapeutic indices available today, distamycin A and selected analogues have received considerable attention, and this has brought about the development of improved modifications of the original synthesis.[8,9] Although several derivatives of **14** have been prepared and screened for their biological activities, the structural modifications have been largely restricted to the N-terminal acyl group and, preferentially, the C-terminal amidine moiety.[1,10,11] A few derivatives containing *N*-propylpyrrole residues have, however, been synthesized and examined with respect to DNA-binding properties.[12-15]

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