of the d_1 product is formed in an $S_N(AE)^{tele}$ reaction of the d_2 starting material, and the rest (22.4 – 11.7 = 10.7%) is formed in an $S_N(AE)^{ipso}$ reaction of d_1 starting material. So from 66.1% of d_1 product, 10.7% undergoes an $S_N(AE)^{ipso}$ reaction, and the rest (66.1 – 10.7 = 55.4%) undergoes an $S_N(AE)^{tele}$ reaction, or in other words k/k_D = 10.7/55.4 = 0.18. From k_H/k_D and k/k_D, k_H/k can be calculated. k_H/k is the ratio of the reaction rate of the $S_N(AE)^{tele}$ reaction in the undeuterated compound and the rate of the $S_N(AE)^{ipso}$ reaction.

Registry No. 6, 81044-13-5; **6** picrate, 81044-14-6; **7a**, 80935-78-0; **7b**, 81044-15-7; **8a**, 81044-16-8; **8b**, 81044-17-9; **11a**, 81044-18-0; **11b**, 81044-19-1; **11c**, 81063-98-1; **11d**, 81044-20-4; **15a**, 80935-81-5; **15b**, 81044-21-5; **15c**, 81044-22-6; **19a**, 51532-07-1; **19b**, 81044-23-7; **20a**, 81044-24-8; 2,6-naphthyridin-1(2*H*)-one, 80935-77-9; 2,6-dideuterio-1,5-naphthyridine *N*-oxide, 81044-25-9.

Synthesis of Novel Phosphorus Heterocycles: 1,3-Dihydro-2,1-Benzoxaphosphole 1-Oxides[1,2]

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Received September 9, 1981

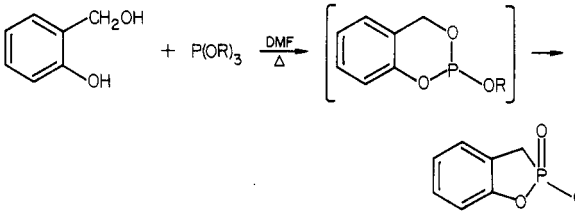
A class of novel phosphorus heterocycles, 1,3-dihydro-2,1-benzoxaphosphole 1-oxides, has been prepared by two different routes. One general approach involves the cyclization of ortho-substituted phenylphosphinic acid derivatives under either thermal or solvolytic conditions. The other route involves a novel metal–halogen exchange on the corresponding ortho-substituted aryl bromide with subsequent intramolecular transposition of the phosphorus moiety. The mechanisms for these various transformations are discussed in some detail.

Previous work in our laboratory has centered around the syntheses of phosphorus heterocycles I–III (Chart I).[3,4] Therefore, the synthesis of the oxygen analogue (IV) of heterocycle III was desired to complete this series of phosporus heterocycles. Westheimer and others have previously reported the synthesis of the monocyclic phosphorus ester V.[5]

The thrust of this paper is to describe our synthetic approaches to the 1,3-dihydro-2,1-benzoxaphosphole 1-oxide ring system IV. The spectral characteristics of this heterocycle, as well as its hydrolysis in weak base, are also discussed.

Results and Discussion

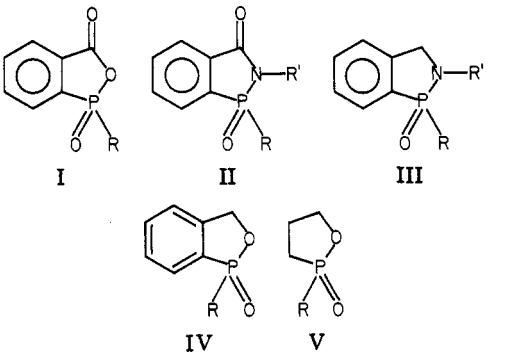
Phosphorus heterocycles IV are named 1,3-dihydro-2,1-benzoxaphosphole 1-oxides. They have not been reported but are isomeric to the so-called "phosphaindan",[6] obtained from the reaction of *o*-hydroxybenzyl alcohol with trialkyl phosphite as outlined in eq 1.



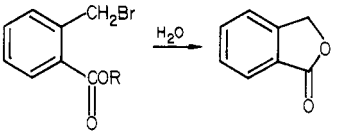
(1)

A similar synthetic approach to the 1,3-dihydro-2,1-benzoxaphosphole 1-oxide ring system was not possible, since the phosphorus moiety in IV is bonded directly to the aromatic ring. However, two general approaches for the synthesis of IV were considered. One route paralleled

Chart I



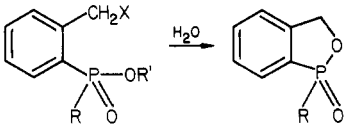
the reported synthesis of phthalide.[7] In particular, it is known that the solvolysis of *o*-carboxybenzyl bromide or its alkyl ester yielded phthalide[7] as shown in eq 2. By



(2)

R = H, alkyl

analogy, solvolysis of the corresponding phosphinate or phosphonate might provide the desired 1,3-dihydro-2,1-benzoxaphosphole 1-oxide as depicted in eq 3.



(3)

IV

Toward this end, either diethyl *o*-tolylphosphonate[8] (**1a**) or ethyl *o*-tolylmethylphosphinate[4] (**1b**) was brominated

(1) J. A. Miles, U.S. Patent 4 219 519, Aug 26, 1980.
(2) R. C. Grabiak, U.S. Patent 4 250 320, Feb 10, 1981.
(3) J. A. Miles and R. W. Street, *J. Org. Chem.*, *43*, 4668 (1978).
(4) R. C. Grabiak, J. A. Miles, and M. T. Beeny, *J. Org. Chem.*, *46*, 3486 (1981).
(5) A. Eberhard and F. H. Westheimer, *J. Am. Chem. Soc.*, **87**, 253 (1965); E. A. Dennis and F. H. Westheimer, *ibid.*, *88*, 3431, 3432 (1966); M. Grayson and C. E. Farley *Chem. Commun.*, 830 (1951).
(6) A. B. Ageeva and B. E. Ivanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1494 (1967).
(7) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, 84, 1179 (1962); *Org. Synth.*, **16**, 71–9 (1937).
(8) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968); P. Tavs, *Chem. Ber.*, **103**, 2428 (1970); P. Tavs and H. Weitkamp, *Tetrahedron*, **26**, 5529 (1970); **23**, 4677 (1967).
(9) R. S. Macomber and G. A. Krudy, *J. Org. Chem.*, **46**, 4038 (1981).

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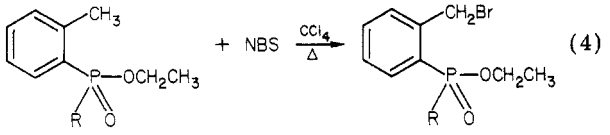
with *N*-bromosuccinimide[10] (NBS) to yield the corresponding benzyl bromide **2a** or **2b** in 70–75% yield (eq 4).



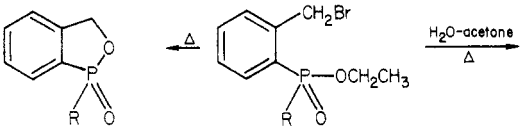
(4)

1a, R = OCH_2CH_3
b, R = CH_3
c, R = Ph

2a, R = OCH_2CH_3
b, R = CH_3

The bromination reaction was not clean, and the resulting product was always contaminated with 10–15% of unreacted starting material and 10–15% of an unidentified byproduct. Since efforts to purify bromides **2** were unsuccessful, the crude bromides **2** were used directly in the cyclization step.

Treatment of **2a** or **2b** in refluxing water–acetone under conditions similar to those of the solvolysis of *o*-carboxybenzyl bromide[7] gave no reaction (eq 5). However, simple



(5)

3a, R = OCH_2CH_3
b, R = CH_3

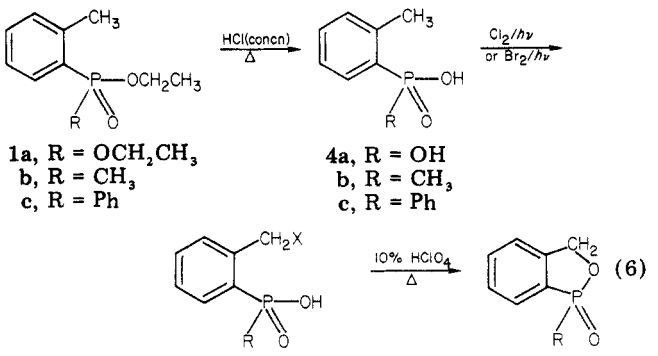
2a, R = OCH_2CH_3
b, R = CH_3

distillation of **2b** under reduced pressure afforded a clear oil, whose spectral properties were consistent with the desired cyclized **3b**. Thermolysis of **2b** in refluxing xylene or chlorobenzene also yielded the same product in approximately 75% yield.

On the other hand, crude **2a** was distilled at reduced pressure without cyclization to **3a**. The thermal cyclization of **2a** required refluxing in *o*-dichlorobenzene for at least 10 h to afford **3a**.

The progress of the reaction of either **2a** or **2b** was easily monitored by the disappearance of the appropriate CH_2Br signal at approximately 5.0 ppm in the NMR spectrum with concurrent appearance of the CH_2O multiplet of **3a** or **3b** centered around 5.35 ppm. In the case of **3b**, the disappearance of the ethyl ester protons in the NMR spectrum also indicated when the cyclization was complete.

Two slight variations of this thermal cyclization were also developed; these had some advantages with respect to yield and ease of isolation over the thermal method. In the first, hydrolysis of **1b** or **1c** in refluxing HCl gave the corresponding phosphinic acids **4b** or **4c** as white solids (eq 6). Photolytic chlorination or NBS bromination of



(6)

1a, R = OCH_2CH_3
b, R = CH_3
c, R = Ph

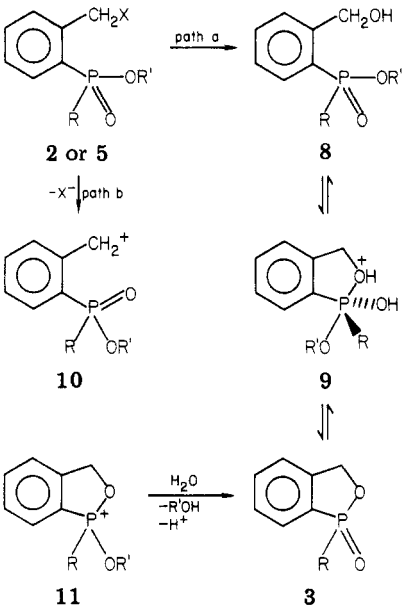
4a, R = OH
b, R = CH_3
c, R = Ph

5b, R = CH_3; X = Cl
c, R = Ph; X = Br

3b, R = CH_3
c, R = Ph

(10) H. J. Danken and L. L. McCoy, *J. Am. Chem. Soc.*, 81, 4863 (1959); W. J. Bailey and J. Bellow, *J. Org. Chem.*, 20, 693 (1955).

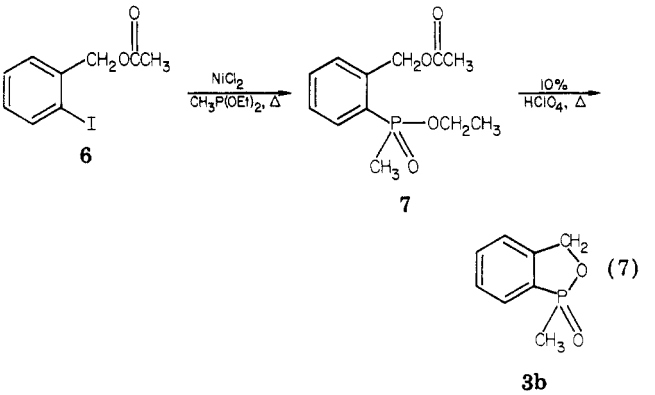
Scheme I



these acids afforded **5b** or **5c**, which were purified by recrystallization from the appropriate solvent. Although **1a** was easily hydrolyzed to **4a**, benzylic halogenation of **4a** was unsuccessful under the conditions reported herein.

Solvolysis of **5b** or **5c** in refluxing, dilute perchloric acid produced **3b** or **3c** in good yields (eq 6).

In an alternative synthesis of **3b**, *o*-iodobenzyl acetate **6** was converted into **7** by a reaction described by Tavs[8] (eq 7). Solvolysis of **7** with perchloric acid yielded het-



(7)

6

7

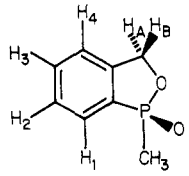
3b

erocycle **3b** in excellent yields. There are two possible mechanisms for the perchloric acid cyclization of these ortho-substituted phenylphosphinic acid derivatives. The first mechanism envisioned for this cyclization (Scheme I, path a) involved the hydrolysis of the benzylic halide (**2b**, **2c**, or **5b**, **5c**) to yield alcohol **8**. Alcohol **8** was then presumably cyclized under the acidic conditions to yield **3** via intermediate **9**.

The second mechanism (path b) involved the intramolecular reaction of the benzyl carbocation **10** with the phosphoryl oxygen to generate **11**. Hydrolysis of **11** (R′ = Et) under the acidic conditions might then yield the phosphorus heterocycle **3**, analogous to the hydrolysis of 2-methoxy-2-oxo-5,5-dimethyl-1,2-oxaphosphol-3-ene.[9] In addition, it should be noted that the hydrolysis of the phosphorus ester **2** to yield **5** could precede the cyclization step irrespective of path a or b.

Regardless of the mechanism, it is conceivable that alcohol **8** might be in equilibrium with **3**, under aqueous conditions. In the case of **3b**, this equilibrium reaction was tentatively demonstrated. For example, an aqueous so-

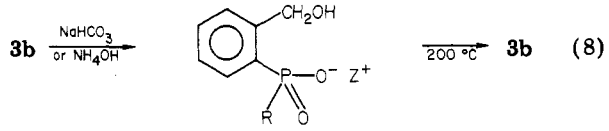
Table I



proton	chemical shift, δ	coupling constants, Hz
H_1	7.80	$J_{1,P} = 8.1, J_{1,2} = 8.0$
H_2	7.61	$J_{1,2} = 8.0, J_{2,3} = 7.1$
H_3	7.49	$J_{3,4} = 7.7, J_{2,3} = 7.1, J_{3,P} = 4.3$
H_4	7.36	$J_{3,4} = 7.7$
H_A	5.29	$J_{A,B} = -13.9, J_{A,P} = 10.9$
H_B	5.49	$J_{A,B} = -13.9, J_{B,P} = 3.6$
CH_3	1.83	$J_{H,P} = 14.8$

lution of **3b** was acidic to litmus paper and liberated CO_2 upon the addition of sodium bicarbonate. Furthermore, the hygroscopic nature of recrystallized **3b** provided some indirect evidence for this equilibrium reaction. In the 270-MHz proton NMR spectrum of a hygroscopic sample of **3b**, the presence of an impurity in **3b** was quite apparent (~13%). This impurity was tentatively identified as the ring-opened phosphinic acid on the basis of the following proton assignments: CH_3, 1.66 ppm (d, J_{HP} = 14.6 Hz); CH_2, 4.74 ppm (s); OH, 5.89 ppm (br s).

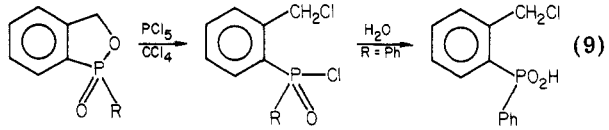
Attempts to prepare pure phosphinic acid (R = CH_3) were unsuccessful. However, two inorganic salts of **8** (R = CH_3) were easily isolated in pure form as illustrated in eq 8. Thermolysis of **12b** at 200 °C regenerated **3b** with the concurrent loss of ammonia and water.



(8)

12a, R = CH_3; Z = Na^+
b, R = CH_3; Z = NH_4^+

Additional proof for the benzoxaphosphole 1-oxide structure **3** was derived from the reaction of **3** with 1 equiv of phosphorus pentachloride at 0 °C to yield the ring-opened phosphinyl chloride **13** (eq 9) in essenitally quanti-



(9)

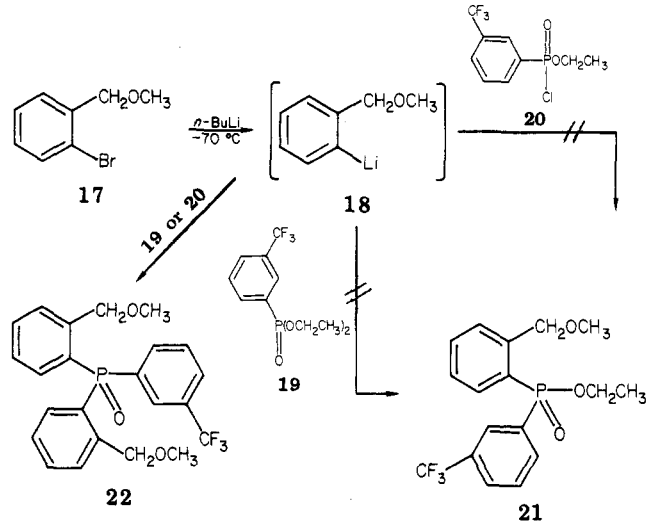
3

13b, R = CH_3
c, R = Ph

tative yields. The spectral and physical properties of **13b** were identical with those reported previously in an earlier paper.[4]

The proton NMR spectrum of **3b** was entirely consistent with the proposed structure. Table I lists the chemical shifts and coupling constants as determined by a combination of 60- and 270-MHz spectra.[11] Of the two diastereomeric methylene protons in **3b**, the proton syn to the phosphorus oxygen bond was assumed to be deshielded on the basis of literature precedent.[4,12,13]

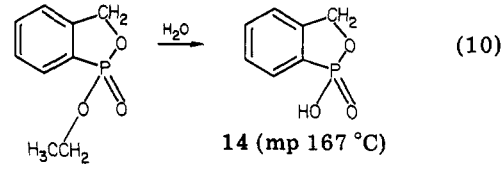
Scheme II



17 **18** **19** **20** **21** **22**

The carbon-13 spectrum of **3b** was measured, and the chemical shifts were assigned to the appropriate carbons. These spectral data were reported in a previous paper describing the related 2,1-benzazaphosphole 1-oxides (III).[4] In that paper,[4] the analysis of the carbon-13 NMR spectrum of **3b** served as a basis for carbon assignments in heterocycle III.

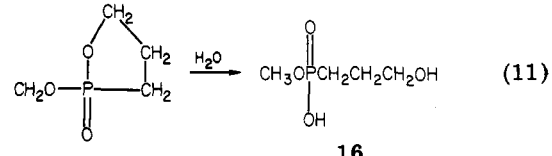
An interesting observation was made during the isolation and purification of **3a**. When a sample of **3a** was stirred in water for 1 h or merely exposed to air for several days at ambient temperature, **3a** was hydrolyzed to yield **14** (eq 10).



(10)

3a (mp 60 °C) **14** (mp 167 °C)

Dennis and Westheimer[5] had previously studied the transition-state geometry of the hydrolysis of the cyclic phostonate **15** and concluded that pseudorotation was inhibited by the five-membered ring. Consequently, hydrolysis of **15** yielded the ring-opened half ester **16** (eq 11).



(11)

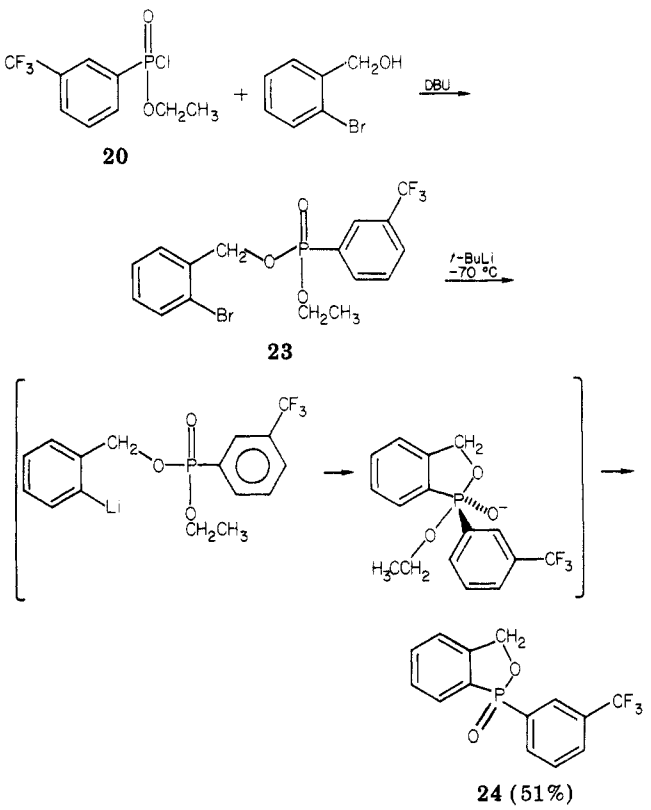
15 **16**

In the case of **3a**, pseudorotation might also be sterically constrained by the fused five-membered ring analogous to **15**. Therefore, the hydrolysis of the exocyclic ester in **3a** presumably involved cleavage of the ethyl–oxygen bond analogous to that reported in the related monocyclic system.[9] The mechanism of this hydrolysis probably resembled an S_N2-type reaction.

Although the solvolytic cyclization route offered a fairly straightforward entry into the benzoxaphosphole 1-oxide ring system, other directive metalation studies underway in this laboratory prompted us to examine an alternative approach, in which the C–P bond was formed in the final step of the sequence. This novel route potentially offered greater flexibility in the introduction of other substituents into the parent ring system.

(11) We are indebted to W. H. Urry of the University of Chicago for his help in measuring the 270-MHz spectra of this compound and assisting in its interpretation.
(12) B. E. Manganoff and R. O. Hutchins, *J. Org. Chem.*, **42**, 1022 (1977).
(13) K. C. Chen, S. E. Ealick, D. Van der Helm, J. Barycki, and K. D. Berlin, *J. Org. Chem.*, **42**, 1170 (1977).

Scheme III



Metal–halogen exchange with *n*-butyllithium at −70 °C on **17** was readily accomplished to give **18** (Scheme II). Treatment of **18** at low temperature with either **19** or **20** gave no evidence of the desired **21**. Instead, the only isolated product was phosphine oxide **22**.

In another approach, metal–halogen exchange with 2 equiv of *tert*-butyllithium on the mixed phosphonate diester **23** gave benzoxaphosphole 1-oxide **24** in approximately 51% yield (Scheme III). This intramolecular phosphonylation was somewhat analogous to that reported by Hellwinkel.[14] The scope of this novel cyclization has not been defined, but it represents a one-step route to the 2,1-benzoxaphosphole 1-oxide ring system from readily available starting materials.[15]

Experimental Section

General Methods. All melting points are uncorrected. NMR spectra were obtained on a Varian T-60, T-60A, or EM-360 or a JEOL FX-100 spectrometer by using $CDCl_3$ solutions (unless otherwise specified) with Me_4Si as an internal standard. Mass spectra were obtained on Varian CH7 or 311A instruments. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, or Industrial Testing Laboratories, St. Louis, MO.

Diethyl (α-Bromo-*o*-tolyl)phosphonate (2a). A mixture of diethyl *o*-tolylphosphonate[16] (**1a**; 22.8 g, 0.10 mol), *N*-bromosuccinimide (17.8 g, 0.10 mol), benzoyl peroxide (0.10 g), and 150 mL of CCl_4 was refluxed for 10 min on the steam bath. After this time, succinimide floated to the surface. The mixture was filtered and concentrated under reduced pressure. NMR analysis indicated it to be 67% **2a**, 15% starting material, and 18% unknown byproduct. This was distilled to give 18 g of a clear oil: bp 122–125 °C (0.30 mm); 80% pure by NMR ($CDCl_3$) δ 4.9 (s, 2, CH_2Br). The material was used as obtained.

Ethyl Methyl(α-bromo-*o*-tolyl)phosphinate (2b). A mixture of ethyl methyl-*o*-tolylphosphinate[8] (**1b**; 19.8 g, 0.10 mol) *N*-bromosuccinimide (17.8 g, 0.10 mol), benzoyl peroxide (0.10 g), and 150 mL of CCl_4 was refluxed for 1 h on the steam bath. Succinimide was filtered off and the dark red solution concentrated to give a dark oil. NMR analysis indicated approximately 75% **2b**, 10% starting material, and 15% unknown byproduct: NMR ($CDCl_3$) δ 4.8, 5.25 (AB doublets, 2, J = 11 Hz, CH_2Br). The oil was used as obtained.

1-Ethoxy-1,3-dihydro-2,1-benzoxaphosphole 1-Oxide (3a). A mixture of diethyl α-bromo-*o*-tolylphosphonate (2.28 g 0.0072 mol) in 25 mL of 1,2-dichlorobenzene was refluxed for 10 h. The resulting mixture was distilled under reduced pressure. After removal of the *o*-dichlorobenzene at 25–50 °C (1.0 mm), the high-boiling fraction distilling at 100–140 °C (0.30 mm) was collected. This light yellow oil was crystallized from benzene-petroleum ether to give 1.06 g (75%) of **3a** as colorless crystals: mp 60 °C; NMR ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz), 3.8–4.4 (quintet, 2, J_{HH} = 7 Hz, J_{HP} = 7 Hz), 5.3 (d, 2, J = 8 Hz), 7.4–8.2 (m, 4).

Anal. Calcd for $C_9H_{11}O_3P$: C, 54.6; H, 5.55. Found: C, 54.81; H, 5.61.

1-Methyl-1,3-dihydro-2,1-benzoxaphosphole 1-Oxide (3b). Crude (~75% pure) ethyl methyl(α-bromo-*o*-tolyl)phosphinate (**2b**, 10 g) was distilled under reduced pressure. A clear oil was collected between 80 and 130 °C at 0.10 mm. The oil was slurried with ether and cooled to give a colorless solid. It was collected and recrystallized from ether to afford 3.0 g (70%) of colorless, hygroscopic crystals: mp 70–72 °C; NMR (see Table I, text); mass spectrum, *m/e* (relative intensity) 168 (20), 153 (40), 105 (14), 58 (53), 47 (13), 43 (58), 42 (100).

Anal. Calcd for $C_8H_9O_2P$: C, 57.14; H, 5.36. Found: C, 57.02; H, 5.39.

Alternatively a mixture of methyl(α-cloro-*o*-tolyl)phosphinic acid (**5b**; 12.25 g, 0.05 mol) and 50 mL of 10% $HClO_4$ was heated at 100 °C for 0.5 h with vigorous stirring. The reaction mixture was cooled to room temperature and then extracted with CH_2Cl_2. The extracts were dried over anhydrous potassium carbonate, filtered through Celite, and concentrated to yield a tan oil. The oil was Kugelrohr distilled [150 °C (0.10 mm)] to give a colorless oil. Crystallization from anhydrous ether gave colorless crystals of **3b** (5.5 g, 66%; mp 70–72 °C) identical in all respects to **3b** prepared by the previously described method.

In a third method, a suspension of **7** (80 g, 0.31 mol) in 200 mL of 10% $HClO_4$ was heated at reflux until homogeneous (~0.5 h). After cooling, the solution was extracted continuously for 48 h. The extracts were dried over $MgSO_4$ and concentrated to leave 83.9 g of a colorless liquid. Bulb-to-bulb distillation at 150 °C (1.5 mm) gave **3b** (42.75 g, 82%) as a viscous light yellow oil which was worked up and crystallized as described previously.

1-Phenyl-1,3-dihydro-2,1-benzoxaphosphole 1-Oxide (3c). A mixture of (α-bromo-*o*-tolyl)phenylphosphinic acid (**5c**; 3.95 g, 0.013 mol) and 10 mL of 10% $HClO_4$ was heated to 100 °C for 4.5 h with stirring. The mixture was cooled and extracted with methylene chloride. The extracts were dried over sodium sulfate, concentrated, and Kugelrohr distilled [180 °C (0.60 mm)]. The colorless oil was crystallized from ether to give **3c** (2.2 g, 76%) as white crystals: mp 99–101 °C; NMR ($CDCl_3$) δ 5.2–5.8 (m, 2), 7.3–8.3 (m, 9); mass spectrum, *m/e* (relative intensity) 230 (89), 201 (67), 183 (35), 165 (65), 153 (30), 137 (45), 105 (39), 89 (60), 77 (78), 63 (51), 47 (100).

Anal. Calcd for $C_{13}H_{11}O_2P$: C, 67.83; H, 4.82. Found: C, 67.63; H, 4.80.

Methyl(α-chloro-*o*-tolyl)phosphinic Acid (5b). A mechanically stirred solution of methyl *o*-tolylphoshinic acid[18] (**4b**; 34.0 g, 0.20 mol) in 400 mL of ethanol-free chloroform was irradiated from below with a 275-W GE sunlamp such as to maintain gentle reflux. Chlorine gas was bubbled through the solution while the reaction was monitored by NMR aliquots. After 70–75% conversion (as measured be the CH_2Cl signal at ~5.0 ppm), the reaction was stopped and chloroform removed. The viscous oil

(14) D. Hellwinkel, G. Hofmann, and I. Lammeszahl, *Tetrahedron Lett.*, 3241 (1977).

(15) Other metalation routes were considered. A new approach to the benzazaphosphole 1-oxide III via directive metalation was successful and will be the subject of a full paper now in preparation.

(16) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).

(17) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1980, p 86.

(18) Phosphinic acid **4b** was prepared by refluxing a solution of **1b** in 12 M HCl for 12 h, followed by CH_2Cl_2 extraction of the homogeneous solution. The extracts were dried over $MgSO_4$ to leave **4b** after vacuum concentration.

remaining was diluted with 50 mL of concentrated H_2SO_4 and stirred for 1 h. Crushed ice (200 g) was added carefully and sitrring continued until precipitation occurred. Suction filtration gave a tan solid which was air-dried. Two recrystallizations from CCl_4 gave **5b** as white needles: mp 138–139 °C; NMR ($CDCl_3$) δ 1.7 (d, J = 14 Hz, 3 H), 5.05 (s, 2 H), 7.3–8.2 (m, 4 H), 11.7 (s, 1 H); mass spectrum , m/e (relative intensity) 206 (40), 204 (100), 170 (27), 169 (56), 168 (16), 160 (50), 153 (53), 151 (36), 149 (29).

Anal. Calcd for $C_8H_{10}ClO_2P$: C, 46.97; H, 4.93; Cl, 17.33. Found: C, 46.83; H, 4.91; Cl, 17.52.

Phenyl-*o*-tolylphosphinic Acid (4c). The Tavs[8] reaction of *o*-iodotoluene and dimethyl phenylphosphonite[19] was utilized to prepare dimethyl phenyl *o*-tolylphosphinate in 50–70% yields: NMR ($CDCl_3$) δ 2.45 (s, 3 H), 3.8 (d, J = 11 Hz, 3 H), 7.0–8.0 (m, 9 H). This ester was heated at reflux in 47% HBr overnight and then poured into ice–water. The off-white solid which precipitated was collected and recrystallized from ethanol to give white prisms: 71%; mp 175–177 °C; NMR ($CDCl_3$) δ 2.3 (s, 3 H), 7.0–8.0 (m, 9), 13.1 (s, 1 H).

Anal. Calcd for $C_{13}H_{13}O_2P$: C, 67.24; H, 5.60. Found: C, 67.10; H, 5.66.

(α-Bromo-*o*-tolyl)phenylphosphinic Acid (5c). A suspension of *o*-tolylphenylphosphinic acid (15 g, 0.065 mol) in carbon tetrachloride (75 mL) was heated to reflux with a 275-W GE sunlamp and treated dropwise with a solution of 1 equiv of bromine in 25 mL of CCl_4. after the addition was complete, an additional 0.10 equiv of Br_2/CCl_4 was added. The solution was cooled and washed once with dilute sodium thiosulfate. The CCl_4 was removed under reduced pressure, and the solid remaining was recrystallized from ethanol to give 15 g of faintly pink crystals, mp 147–148 °C.

Anal. Calcd for $C_{13}H_{12}BrO_2P$: C, 50.16; H, 3.86; Br, 25.72. Found: C, 50.11; H, 3.79; Br, 25.99.

Ethyl Methyl[*o*-(acetoxymethyl)phenyl]phosphinate (7). A magnetically stirred solution of *o*-iodobenzyl alcohol (100 g, 0.42 mol) in 250 mL of acetic anhydride was heated at reflux for 2 h. Excess acetic anhydride was removed under reduced pressure. The colorless oil remaining (113.8 g, 97%) was identified as *o*-iodobenzyl acetate (**6**) by its NMR spectrum ($CDCl_3$): δ 2.05 (s, 3 H), 5.05 (s, 2 H), 7.0 (m, 1 H), 7.3 (d, J = 3 Hz, 2 H), 7.8 (d, J = 6 Hz, 2 H). It was used without further purification.

Under a static nitrogen atmosphere a mechanically stirred mixture of **6** (113 g, 0.41 mol) and anhydrous $NiCl_2$[20] (2.7 g, 0.021 mol) was heated to 170 °C. Diethyl methylphosphonite (61.2 g, 0.45 mol) was added dropwise at such a rate as to maintain gentle distillation of ethyl iodide, which was collected in a dry ice cooled receiver. After the addition was complete, the dark mixture was heated for 0.5 h more at 165–175 °C and then cooled to ambient temperature. The mixture was partitioned between CH_2Cl_2 and 5% HCl. The CH_2Cl_2 layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Bulb-to-bulb distillation [140 °C (0.25 mm)] afforded 85.2 g of **7** (81%) as a colorless oil: NMR ($CDCl_3$) δ 1.32 (t, J = 6 Hz, 3 H), 1.75 (d, J = 14 Hz, 3 H), 2.1 (s, 3 H), 4.05 (sextet, 2 H), 5.55 (AB pattern, J_{AB} = 12 Hz, 2 H), 7.2–8.1 (m 4 H); mass spectrum, m/e (relative intensity) 214 (26), 168 (85), 154 (25). mass spectrum, m/e (relative intensity 214 (26), 168 (85), 154 (25).

Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.25; H, 6.69. Found: C, 55.36; H, 6.67.

This oil was contaminated with small amounts of *o*-iodobenzyl acetate as determined by proton NMR and elemental analyses.

Methyl[*o*-(hydroxymethyl)phenyl]phosphinic Acid Sodium Salt (12a). A magnetically stirred mixture of **3b** (2 g, 0.0119 mol) and sodium bicaronate (1 g, 0.119 mol) in 10 mL of H_2O was heated at reflux for 2 h and then concentrated under reduced pressure. recrystallization of the residue from methanol–acetone yielded white plates, identified as the monohydrate of **12a**: 2.3 g (93% yield); mp 124–126 °C; NMR (Me_2SO–d_6) δ 1.12 (d, J = 14 Hz, 3 H), 4.7 (s, 2 H), 7.2–7.6 (m, 4 H), 7.9 (br s, 1 H).

Anal. Calcd for $C_8H_{10}O_3PNa{\cdot}H_2O$: C, 42.49; H, 5.35. Found: C, 42.49; H, 5.36.

Methyl[*o*-(hydroxymethyl)phenyl]phosphinic Acid Ammonium Salt (12b). A magnetically stirred mixture of **3b** (1 g, 0.0595 mol) in 10 mL of concentrated ammonium hydroxide was heated at reflux overnight and then concentrated in vacuo. recrystallization from methanol–acetone mixtures yielded **12b** as white, feathery needles: 1.1 g (91% yield); mp 146–149 °C; NMR (Me_2SO–d_6) δ 1.15 (d, J = 14 Hz, 3 H), 4.72 (s, 2 H), 5.2–7.0 (br s, 5 H), 7.2–8.0 (m, 4 H).

Anal. Calcd for $C_8H_{14}NO_3P$: C, 47.29; H, 6.95; N, 6.89. Found: C, 47.33; H, 6.96; N, 6.84.

1-Hydroxy-1,3-dihydro-2,1-benzoxaphosphole 1-Oxide (14). A mixture of **3a** (4.0 g, 0.02 mol) in 15 mL of H_2O was heated on a steam bath for 1 h. The reaction mixture was taken to dryness under vacuum and the residue recrystallized from acetone to give **14** (3.4 g, 100%) as colorless crystals: mp 167 °C; NMR (Me_2SO–d_6) δ 5.1 (d, 2, J = 8 Hz), 7.2–7.8 (m, 4), 11.2 (s, 1).

Anal. Calcd for $C_7H_7O_3P$: C, 49.40; H, 4.12. Found: C, 49.26; H, 4.10.

[*o*-(Chloromethyl)phenyl]methylphosphinyl Chloride (13b). A stirred solution of **3b** (42.75 g, 0.254 mol) in 250 mL of CCl_4 was treated portionwise with solid PCl_5 (54.2 g, 0.26 mol) at 0 °C. The mixture was then stirred overnight at ambient temperatures under a static N_2 atmosphere. After concentration with a rotary evaporator and bulb-to-bulb distillation at 100 °C (0.7 torr), **13b** was isolated as a pale yellow oil, 50.45 g (89%). The spectral properties of **13b** were described in an earlier paper.[4]

[*o*-(Chloromethyl)phenyl]phenylphosphinic Acid. A magnetically stirred solution of **3c** (0.75 g, 3.26 mol) in 8 mL of CCl_4 was treated with PCl_5 (0.75 g, 3.6 mmol). After being stirred 1 h at ambient temperatures, the mixture was homogeneous and was then concentrated in vacuo. Bulb-to-bulb distillation at 180 °C and 0.1 torr yielded [*o*-(chloromethyl)phenyl]phenylphosphinyl chloride (**13c**) as a colorless oil, 0.9 g (100%). Mass spectroscopy showed the correct molecular ion, whose intensity was quite weak. NMR ($CDCl_3$) δ 5.15 (phosphorus coupled AB pattern, J_{AB} = –13 Hz, J_{HP} = 0.5 Hz), 7.2–8.2 (m, 9 H).

This acid chloride was stirred at ambient temperatures in 10% aqueous THF for 0.5 h. Concentration in vacuo yielded a viscous oil which was crystallized from CCl_4 to yield the corresponding acid as white needles: 0.7 g (81%); mp 147–148 °C. An analytical sample was prepared by recrystallization from acetone: mp 152–153 °C. NMR (acetone–d_6) δ 4.85 (s, 2 H), 7.1–8.1 (m, 9 H), 12.4 (s, 1 H).

Anal. Calcd for $C_{13}H_{12}ClO_2P$: C, 58.55; H, 4.54; Cl, 13.29. Found: C, 58.30; H, 4.60; Cl, 13.21.

Diethyl [3-(Trifluoromethyl)phenyl]phosphonate (19). This procedure is representative of the preparation of diethyl arylphosphonates by this method, a modification of that reported by Bott and co-workers.[21]

The Grignard reagent of *m*-(trifluoromethyl)phenyl bromide was prepared according to that described by Simons and Ramler[22] by starting with 12.5 g (.515 mol) of magnesium and 112.5 g (.5 mol) of *m*-bromobenzotrifluoride in 280 mL of anhydrous ether. The dark green Grignard solution was transferred to a 500-mL constant-addition funnel under N_2 pressure by using a double-ended needle.

The Grignard reagent was then added dropwise to a stirred solution of freshly distilled diethyl chlorophosphate (172.55 g, 1 mol) in 500 mL of anhydrous ether at –76 °C. After the addition (1.5 h) the mixture was stirred at ambient temperatures for 1.5 h and then poured into 300 mL of 5% HCl. The ether layer was washed with H_2O (3 × 500 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an orange oil. Fractional distillation yielded the desired ester as a colorless oil (131.15 g, 93%) at 100–115 °C (0.6–0.9 torr). The NMR spectrum was consistent with the structural assignment.

Anal. Calcd for $C_{11}H_{14}F_3O_3P$: C, 46.82; H, 5.00. Found: C, 46.84; H, 4.99.

Ethyl [3-(Trifluoromethyl)phenyl]phosphonochloridate (20). Under a $CaSO_4$ drying tube, a magnetically stirred solution of diethyl [3-(trifluoromethyl)phenyl]phosphonate (28.2 g, 0.1 mol) in 100 mL of CCl_4 was treated portionwise with solid PCl_5

(19) G. Kamai, *Zh. Obshch. Khim.*, 18, 443 (1948).

(20) The hydrate of $NiCl_2$ was heated in an open dish with a Bunsen burner and then held at 200 °C under high vacuum for 48 h. A light yellow, hygroscopic powder remained.

(21) R. W. Bott, B. F. Dowden, and C. Eahorn, *J. Organomet. Chem.*, 4, 291 (1965).

(22) J. H. Simons and E. D. Ramler, *J. Am. Chem. Soc.*, 65, 389 (1943).

(24.9 g, 0.12 mol) at 0 °C. After the mixture was stirred overnight at ambient temperature, the volatiles were removed in vacuo. Bulb-to-bulb distillation at 100 °C (0.2 mm) yielded a colorless oil: 26.55 g (98%); NMR ($CDCl_3/Me_4Si$) δ 1.5 (t, J = 7 Hz, 6 H), 4–4.7 (m, 4 H), 7.5–8.3 (m, 4 H); ^{31}P NMR ($CDCl_3$/85% H_3PO_4) δ 25.05.

[*m*-(Trifluoromethyl)phenyl]bis[*o*-(methoxymethyl)-phenyl]phosphine Oxide (22). Under a static N_2 atmosphere, a stirred solution of *o*-(methoxymethyl)phenyl bromide (5 g, 25 mmol) in 50 mL of ether was cooled in a dry ice–acetone bath. *n*-BuLi in hexane (15.6 mL, 25 mol, 1.6 M) was added dropwise. After the mixture was stirred for 0.5 h at −72 °C, a solution of **20** (6.8 g, 25 mmol) in 25 mL of ethyl ether was added rapidly in one portion. The temperature rose to −30 °C, and the yellow mixture was stirred for 1 h at −72 °C. After equilibrating to ambient temperature, the yellow mixture was poured into H_2O containing some EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield a yellow oil. Bulb-to-bulb distillation at 120 °C (0.2 mm) removed the low-boiling impurities as determined by GLC analysis. At 160 °C (0.1 mm) a colorless oil (4.35 g) was collected. Crystallization from methylcyclohexane yielded **22** as a white powder: 1.5 g (14%); Mp 90–92 °C; NMR ($CDCl_3/Me_4Si$) δ 3.17 (s, 6 H, 4.78 (s, 4 H), 6.8–8.1 (m, 12 H); mass spectrum, m/e (relative intensity) 434 (8), 419 (28), 403 (18), 387 (100).

Anal. Calcd for $C_{23}H_{22}F_3O_3P$: C, 63.59; H, 5.10. Found: C, 63.52; H, 5.05.

2-Bromobenzyl Ethyl [3-(Trifluoromethyl)phenyl]-phosphonate (23). Under a $CaSO_4$ drying tube, a magnetically stirred mixture of *o*-bromobenzyl alcohol (10 g, 53.5 mol) and DBU (8.5 g, 53.5 mmol) in 150 mL of anhydrous ether was treated drop wise with a solution of **20** (4.55 g, 0.0535 mol) in 100 mL of ether at 0.°C. The white suspension was stirred for 1 h at ambient temperature and then suction filtered. The ether filtrate was washed with H_2O and then with 5% HCl, dried over $MgSO_4$, and concentrated in vacuo to yield a yellow oil, 20.7 g. Bulb-to-bulb distillation at 110 °C (0.1 mm) removed starting alcohol. At 140 °C (0.05 mm), a pale yellow oil was collected: 15.5 g (68.5%); NMR (CCl_4/Me_4Si) δ 1.3 (t, J = 8 Hz, 3 H), 4.1 (pair of overlapping quintets, 2 H), 5.1 (AB, J = 13 Hz, 2 H), 7–8.2 (m, 8 H); ^{31}P NMR (CCl_4/85% H_3PO_4) δ 16.1; mass spectrum, m/e (relative intensity) 343 (85), 315 (100), 281 (32).

Anal. Calcd for $C_{16}H_{15}BrF_3O_3P$: C, 45.41; H, 3.57. Found: C, 44.65; H, 3.65.

^{31}P NMR indicated that diethyl [3-(trifluoromethyl)phenyl]-phosphonate was an impurity in **23**.

1-[2-(Trifluoromethyl)phenyl]-1,3-dihydro-2,1-benz-oxaphosphole 1-Oxide (24). Under a static N_2 atmosphere, a magnetically stirred solution of **23** (2.4 g, 0.00567 mol) in 50 mL of anhydrous THF was cooled in a dry ice–acetone bath and then treated dropwise with 6.1 mL (0.0116 mol) of 1.9 M *tert*-butyl-lithium in pentane (Alfa) such that the temperature never rose above −65 °C. The purple mixture was stirred at −72 °C for 1 h and then allowed to equilibrate to ambient temperature over a 45-min period. After the mixture was quenched with AcOH (1 mL), the solvents were removed in vacuo. The yellow residue was partitioned between CH_2Cl_2 and H_2O. The dried ($MgSO_4$) CH_2Cl_2 layer was concentrated in vacuo to yield a yellow glass, 1.7 g. Bulb-to-bulb distillation at 130 °C (0.2 mm) yielded a colorless oil which crystallized upon trituration with petroleum ether: 0.85 g (51%); mp 109–110 °C; ^{31}P NMR ($CDCl_3$/85% H_3PO_4) δ 47.4; ^{13}C NMR ($CDCl_3/Me_4Si$) δ 72.9 (CH_2); mass spectrum, m/e (relative intensity) 298 (70), 280 (10), 269 (26), 77 (100).

Anal. Calcd for $C_{14}H_{10}F_3O_2P$: C, 56.39; H, 3.38. Found: C, 56.41; H, 3.46.

Registry No. 1a, 15286-11-0; **1b**, 61820-30-2; **1c**, 80953-47-5; **2a**, 75777-37-6; **2b**, 80953-48-6; **3a**, 75777-31-0; **3b**, 75777-30-9; **3c**, 75777-29-6; **4b**, 61820-24-4; **4c**, 18593-18-5; **4c** methylester, 80953-49-7; **5b**, 80953-50-0; **5c**, 75777-35-4; **6**, 80953-51-1; **7**, 80953-52-2; **12a**, 80953-53-3; **12b**, 80953-54-4; **13b**, 78089-65-3; **13c**, 80953-55-5; **13c** acid, 80953-56-6; **14**, 75777-32-1; **17**, 52711-30-5; **19**, 54057-97-5; **20**, 80953-57-7; **22**, 80953-58-8; **23**, 77505-35-2; **24**, 75777-28-5; diethyl methylphosphonite, 15715-41-0; *m*-bromobenzotrifluoride, 401-78-5; diethyl chlorophosphate, 814-49-3.

Novel Syntheses of 5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic Acids[1,2]

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A fundamentally new approach to the synthesis of the title compounds was devised in which the crucial step was the intramolecular displacement of methanesulfinate ion or bromide ion by the sodium enolates of properly disposed substituted malonate esters such as **13a–13c** and **20**. As integral parts of the above process, a new four-carbon alkylation of the pyrrole nitrogen atom, a novel synthesis of 2-(methylthio)pyrroles, and the use of the dimethylsulfonium moiety as a meta directing group in the pyrrole system were developed.

5-Aroyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acids (**1**) are antiinflammatory and analgesic agents of considerable potency,[3] and linear, multistep syntheses of this class of compounds have been reported.[3,4] In this publication we describe new, short syntheses of these agents which embrace concepts not heretofore utilized for synthetic purposes in the pyrrole area.

One of the successful synthetic strategies, of several considered, was based on two important literature precedents. Firstly, the reaction of 1-(2-hydroxyethyl)-2-nitro-5-acetylpyrrole (**2**) with strong bases effects cyclization to the pyrrolo[2,1-*b*]oxazole derivative **3** by displacement of nitrile ion.[5] Secondly, spiro activated cyclopropanes, such as **4**, are transformed, with singular ease,

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