LARGE-RING PHOSPHORUS HETEROCYCLES

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Abstract - Ozonolysis of 3-phospholene derivatives bearing cycloalkano
rings fused at the double bond provides a simple method for the preparation
of cyclic phosphorus compounds with 7-9 ring members. The resulting
diketones are useful precursors for a number of derivatives, as has been
demonstrated especially for the 9-membered (phosphonane) system. A second
double bond present in a 6-membered ring fused to the 3-phospholene is
attacked selectively by electrophiles; this has led to the synthesis of
5,6-dibromo- and 5,6-epoxy-3,8-diketophosphonanes. The double bond of a
phenanthrene fused at its 9,10-position to a 3-phospholene oxide (prepared
by oxidative photolysis of 1,3,4-triphenyl-3-phospholene oxide) also can be
cleaved by ozonolysis to produce dibenzo derivatives of 3,8-diketophospho-
nanes. This ring is non-planar and rigid, as evidenced by the presence of
two ^{13}C NMR signals for the carbonyl and for the α-carbons. The dibromo
diketophosphonane has similar ^{13}C NMR spectral features, but in the
absence of the bromines the ring equilibrates rapidly and gives a ^{13}C NMR
spectrum with single signals for the 2,9- and 3,8-carbons. The dibenzo
derivative was reduced to the diol; dehydration then gave the first
example of a phosphonin oxide (non-planar). Deoxygenation with trichloro-
silane-pyridine gave the phosphonin, of interest for future studies as a
potentially aromatic system.

INTRODUCTION

Phosphorus heterocycles with more than six members in the ring are still rare, and most of
the fundamental properties of these rings remain to be established. Especially to be asked
are questions about the conformational properties of the larger rings and the nature of
electron delocalization in unsaturated rings containing Hückel numbers (4n + 2) of π-
electrons. We have devised a new synthetic approach of considerable generality that pro-
vides β,β'-diketo derivatives of rings with seven or more members, and we have initiated our
studies on conformational and electronic effects with emphasis on the 9-membered ring
(phosphonane). Our results to date are summarized in this report.

## THE BASIC SYNTHETIC METHOD

Our approach to large rings was first announced in 1977 (1), and as seen in Scheme 1
consists of two fundamental operations: [1] the construction by the McCormack method of a
3-phospholene with a cycloalkane ring fused at the double bond, [2] oxidative cleavage of
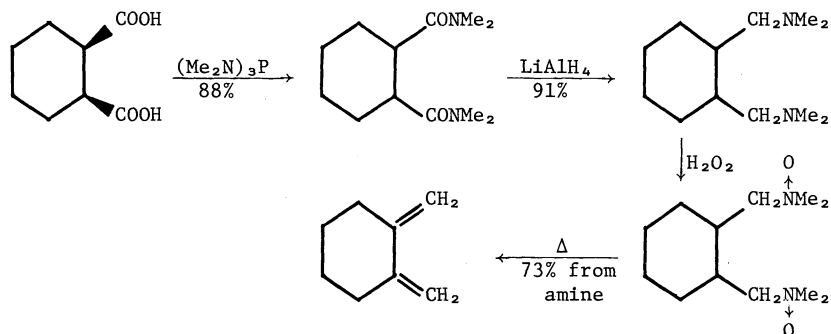the double bond with ozone.

Scheme 1
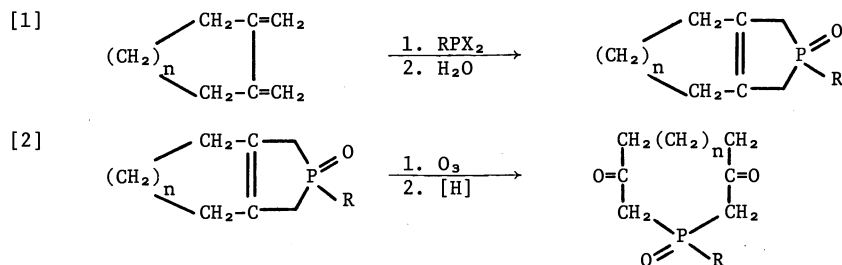
Our initial work produced the new heterocyclic compounds seen in Scheme 2, which depicts the
efficiency and generality of the process.

Scheme 2

(1)

(2)

CH₃, 82%
C₆H₅, 78%
OH, 45%

(3), CH₃, 94%
(4), C₆H₅, 88%
(5), OH, 84%
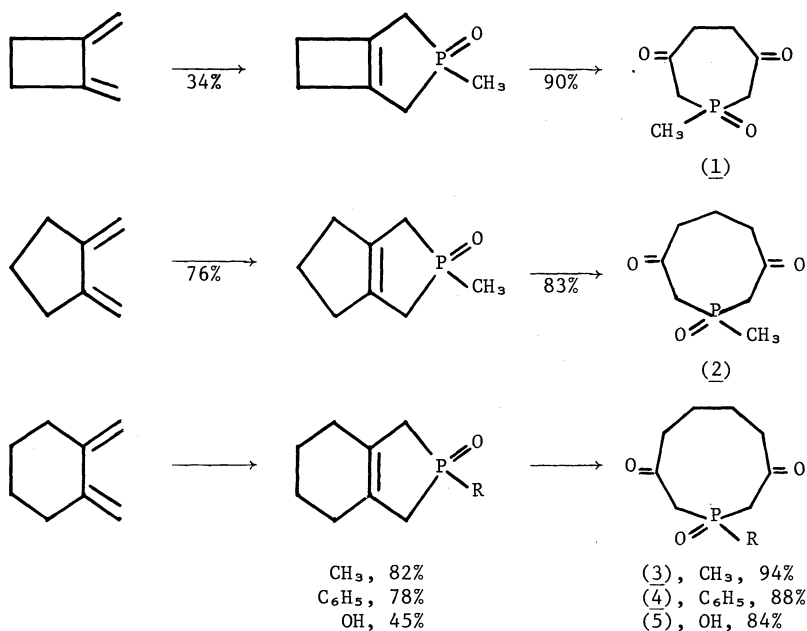
The dienes used in these syntheses were prepared by a standard route as exemplified in Scheme 3 with the cyclohexane derivative.

Scheme 3

Notable is the use of Burgada's method (2) employing a phosphorus reagent for the one-step conversion of a carboxylic acid to an amide. The starting dicarboxylic acids were either available commercially (for cyclohexane) or synthesized from readily available materials (for cyclopentane and cyclobutane).

The McCormack cycloadditions proceeded under conventional conditions with these dienes, the yields reported in Scheme 2 being achieved after periods of 15-20 days of standing at room temperature. The bicyclic products were easily crystallized solids, fully characterized by spectral methods.

The ozonolyses were conducted at -78°C in solvents of CH_3OH or CH_2Cl_2, as appropriate, by passage of ozone until a blue color developed. The ozonides were decomposed with trimethyl phosphite; the diketo products crystallized on concentration of the solutions.

Thus, while several steps are involved in our new synthetic approach, the process is not difficult and reasonable quantities of the heterocycles can be prepared for further studies. This is especially true of the 9-membered ring, where a starting quantity of 10 g. of cyclohexane-1,2-dicarboxylic acid produced 4.4 g. of diketophosphonane 3. This has figured in our decision to commence our investigations into the conformational properties of the large rings with this system. Also, the fully unsaturated system would be a heteroannulene, $(CH=CH)_n\overset{..}{P}R$, the first member (with n=4) above the phosphole system (n=2) that is conceivably capable of possessing cyclic delocalization. This phenomenon has been observed in certain derivatives of the corresponding nitrogen system (3) (azonine), but never before sought in

the phosphorus series. Monocyclic thionins are also unknown, although a dibenzo (non-aromatic) derivative is known (4). To be sure, representatives (6 and 7) of the phosphonin ring system have been reported in (5) and (6), respectively, but neither type is suitable for a study of this aspect of the phosphonin ring.

(6)   (7)
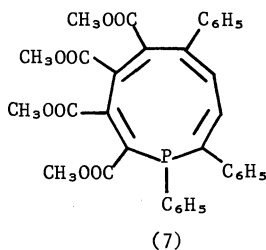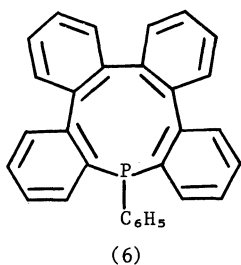
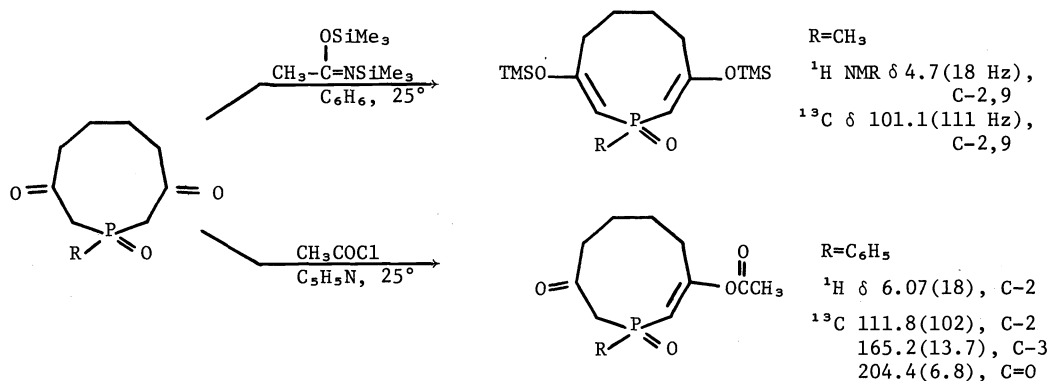### SPECTRAL AND CHEMICAL PROPERTIES OF DIKETOPHOSPHONANES

Data from spectral studies of three diketophosphonanes are summarized in Table 1, and provide convincing proof of the correctness of the structure assignments. ^{1}H NMR spectra have also been prepared, but are not resolved into an interpretable display at 100 MHz, except that the α-CH$_2$ signals are pulled out from the others and are generally found at $\underline{\delta}$ 3-4 as a complex multiplet.

TABLE 1. Spectral data for diketophosphonanes

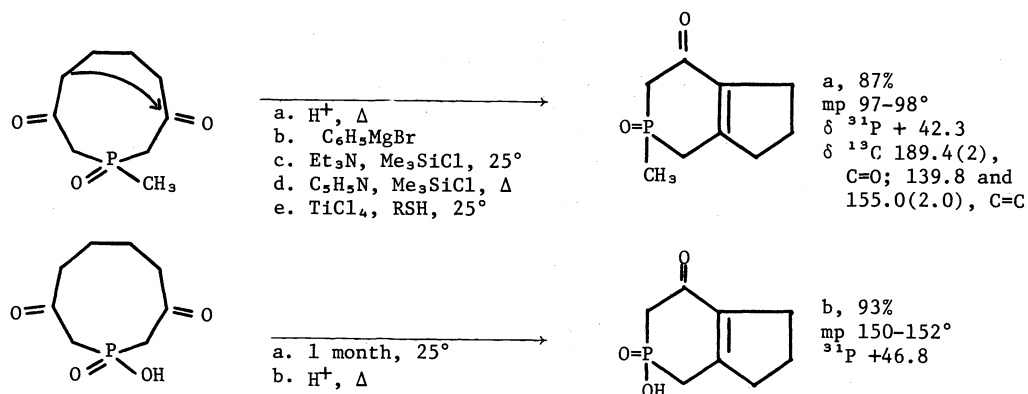| Phosphonane	$\nu_{C=O}$, cm^{-1}	δ ^{31}P(CDCl$_3$)	δ ^{13}C (J_{CP})			
			C_α	C_β	C_γ	C_δ
3	1700	+32.0	46.1(54.7)	206.0(4.9)	44.5	23.4
4	1680	+25.4	47.6(54.7)	206.1(4.9)	44.4	23.6
5	1690	+26.5	47.4(77.2)	205.8(2.9)	42.5	23.0

The carbonyls have normal chemical reactivity and form bis-2,4-dinitrophenylhydrazones (P-CH$_3$, m.p. 181°). A monosemicarbazone (m.p. 242°) forms from the P-CH$_3$ ketone with semi-carbazide. With NaBH$_4$, both carbonyls are reduced, and a diol is formed. The product is a mixture (by ^{31}P NMR) of all of the three diastereoisomers that accompany the presence of the chiral centers, but the mixture has not yet been separated. Enol character is high in the diketones, though not detectable by direct spectroscopy; H-D exchange occurs rapidly in D$_2$O solution without a catalyst, and the 2,2,9,9-tetradeutero derivative is formed. Enolic forms can be trapped with silylating agents or on acetylation, as shown in Scheme 4. These products are very sensitive to hydrolysis, and have not been obtained in pure form.

Scheme 4

R=CH$_3$
^{1}H NMR δ 4.7(18 Hz),
                    C-2,9
^{13}C δ 101.1(111 Hz),
                    C-2,9

R=C$_6$H$_5$
^{1}H δ 6.07(18), C-2
^{13}C 111.8(102), C-2
            165.2(13.7), C-3
   204.4(6.8), C=O

It is a characteristic of 1,3-diketones of the cyclononane system for transannular aldol condensation to occur, and we have found that the diketophosphonanes also exhibit this property. As noted in Scheme 5, the reaction occurs under a variety of conditions, but is best performed for preparative purposes by simply heating the diketone with p-toluene-sulfonic acid in benzene.

Scheme 5

a. H⁺, Δ
b. C₆H₅MgBr
c. Et₃N, Me₃SiCl, 25°
d. C₅H₅N, Me₃SiCl, Δ
e. TiCl₄, RSH, 25°

a, 87%
mp 97-98°
δ ³¹P + 42.3
δ ¹³C 189.4(2),
  C=O; 139.8 and
  155.0(2.0), C=C

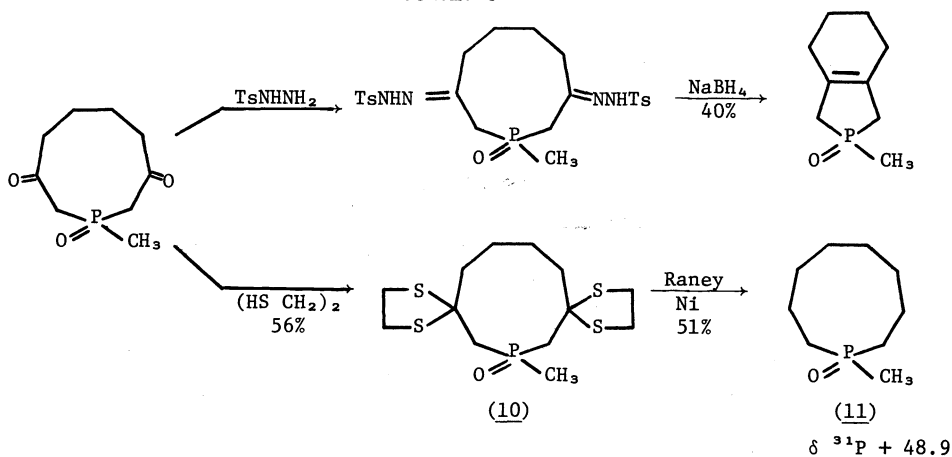a. 1 month, 25°
b. H⁺, Δ

b, 93%
mp 150-152°
³¹P +46.8

Most of the conditions stated in Scheme 5 were employed with other synthetic objectives in mind; methods c and d were aimed at silylation of the enol, and e was an attempt to form the bis-thioether. Even attempted Grignard addition (b) resulted in the condensation. Apparently there is some tendency for β,γ-enol form 9 to exist to some extent along with the more prominent α,β form 8.

(8)   (9)
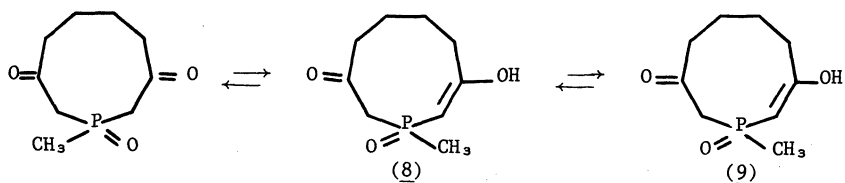
The tendency for the aldol condensation to occur is so great that the phosphinic acid 5 in the solid state is largely converted to the bicyclic product in about one month. These bicyclic aldol products represent a new ring system; they may have synthetic value of their own, which we are now exploring.

Another application for the diketones is service as the precursor of the parent phosphonane ring (11). As seen in Scheme 6, this is accomplished by conversion to the bis-ethylene-thioketal 10, and then desulfurization with Raney nickel. This represents the first synthesis of a C-unsubstituted phosphonane. Another conventional route for C=O to CH₂ conversion, involving NaBH₄ reduction of the p-tosylhydrazone, failed completely to provide the parent; instead another type of transannular reaction occurred and the original 3-phos-pholene oxide was formed. 1-Methylphosphonane oxide has been reduced to the phosphine, δ ³¹P -33.8(CDCl₃) and this in turn to the methiodide, m.p. 265-267°, δ ³¹P +31.9 (CDCl₃).

Scheme 6

TsNHNH₂   TsNHN=   =NNHTs   NaBH₄
                                           40%

(HS CH₂)₂   Raney
  56%   Ni
                               51%

(10)   (11)

δ ³¹P + 48.9

The basic method of creating diketophosphonanes can be extended by employing triene 12 in the McCormack reaction, and then performing addition reactions at the cyclohexene double bond before applying the ozonolysis procedure. The triene is easily prepared by the general sequence already outlined in Scheme 3. The McCormack reaction proceeds readily; the products, which can be characterized as partially reduced isophosphindoles, are formed in high yield. They are useful also for another purpose; they may be aromatized to iso-phosphindolines by refluxing in benzene with dichlorodicyanobenzoquinone (DDQ), as we have reported elsewhere (7). The utility of the phospholene oxide (13) formed from triene 12 in phosphonane synthesis rests upon the considerable difference in the reactivity of the two double bonds. The double bond in the 3-phospholene ring is relatively unreactive to electrophilic addition, making possible the regiospecific attack of, e.g., Br_2 at the cyclohexene double bond (Scheme 7). The product is then ozonized under the general conditions to form the 5,6-dibromo-3,8-diketophosphonanes (P-CH$_3$, 81%; P-C$_6$H$_5$, 76% P-OH, 45%). These products, all crystalline solids, show some tendency to lose HBr on standing.

Scheme 7

(12)   (13)

Br$_2$
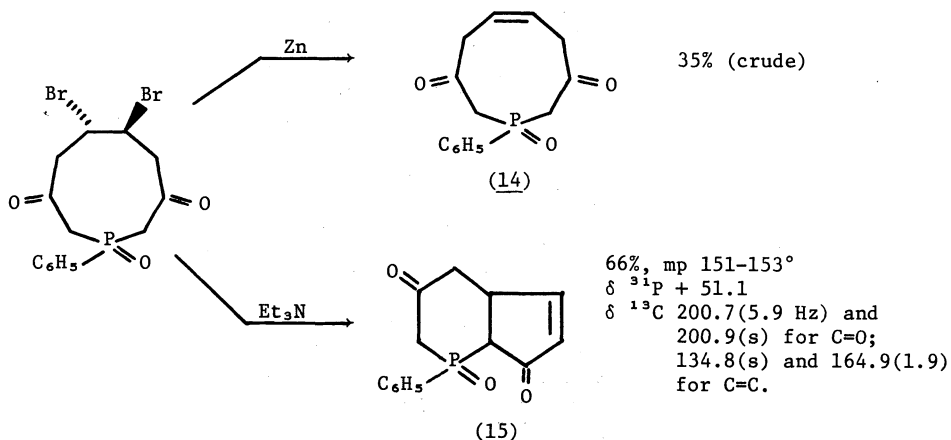CH$_2$Cl$_2$
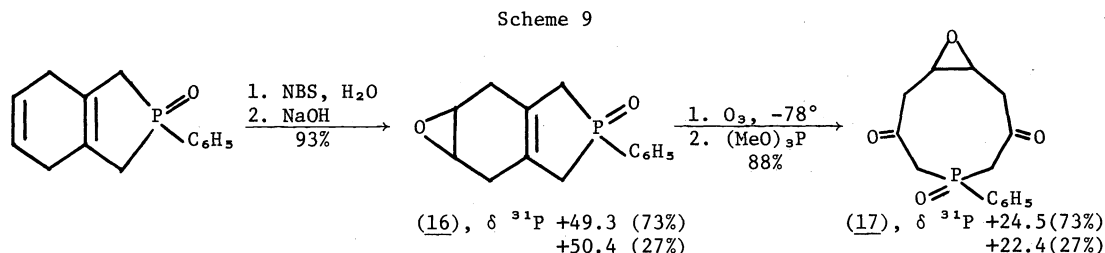-78°

1. O$_3$, -78°
2. (MeO)$_3$P
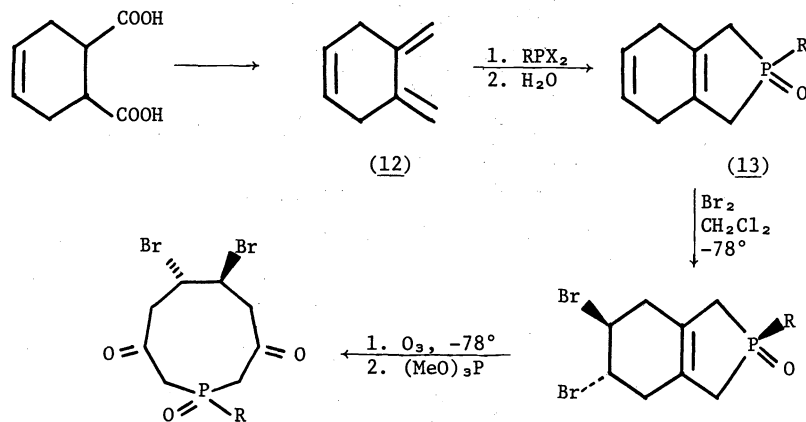
From diene:

CH$_3$, 81%
C$_6$H$_5$, 76%
OH, 45%

The dibromo-diketones are useful as precursors of other novel compounds (Scheme 8). Thus, a double bond may be introduced into the diketophosphonane system by debromination with zinc to give 14. An attempt to perform double dehydrohalogenation with triethylamine gave instead yet another form of transannular reaction, this time an internal alkylation which bridged the ring to create a bicyclic structure (15). This new system also can become of value as a synthetic intermediate.
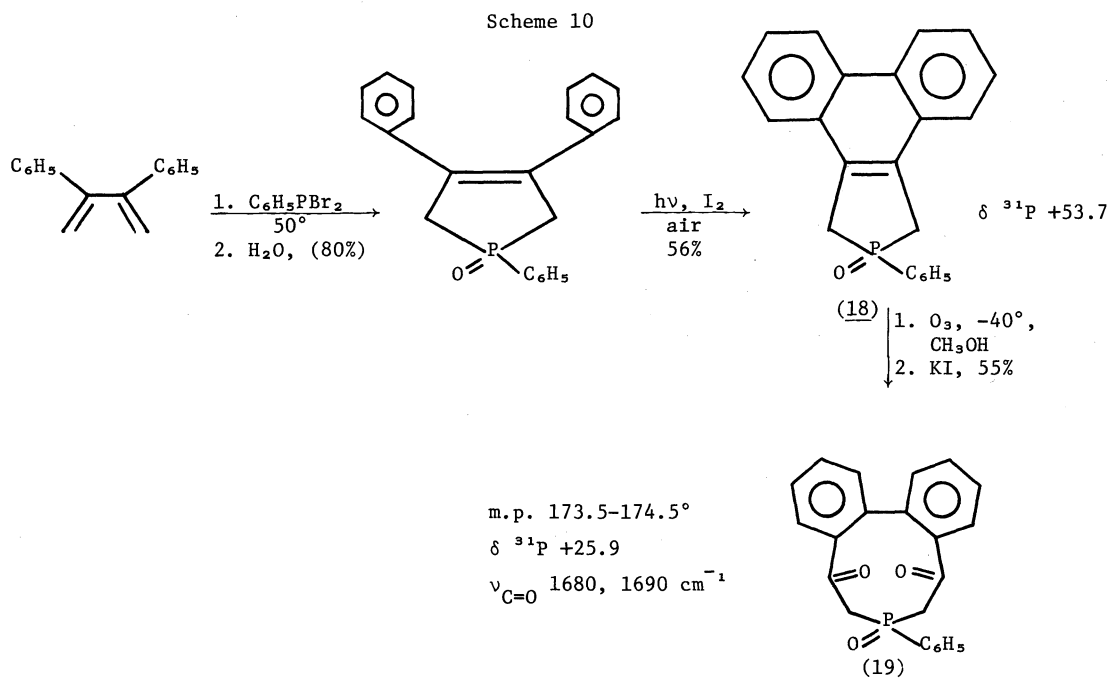
Scheme 8

Zn

35% (crude)

(14)

Et$_3$N

66%, mp 151-153°
δ ^{31}P + 51.1
δ ^{13}C 200.7(5.9 Hz) and
   200.9(s) for C=O;
   134.8(s) and 164.9(1.9)
   for C=C.

(15)

The cyclohexene double bond in <u>13</u> can also be epoxidized indirectly, by first forming the bromohydrin and then dehydrohalogenating it with base (Scheme 9). Two diastereoisomers are formed in the bromohydrin synthesis and thus the epoxide is also an isomer mixture, as is easily seen by ^{31}P NMR analysis. The ozonolysis proceeds smoothly to give the epoxyphosphonane <u>17</u> (Scheme 9).

<div align="center">Scheme 9</div>

(<u>16</u>), δ ^{31}P +49.3 (73%)
            +50.4 (27%)

(<u>17</u>), δ ^{31}P +24.5(73%)
            +22.4(27%)

Yet another type of diketophosphonane has been prepared by the ozonolysis route, this time a dibenzo derivative (<u>19</u>, Scheme 10). For this purpose, the 9,10-double bond of a phenanthrene serves as the site of attack for generation of the cyclic diketone by ozonolysis, a technique recently applied to a cyclopentanophenanthrene (8). No previous example of a phospholene oxide fused to the 9,10-position of phenanthrene has been reported, but we have devised a simple route to such compounds. We employ a well-known oxidative photochemical technique for joining the two benzene rings of a stilbene moiety at their <u>ortho</u> positions, as applied to the readily formed 1,3,4-triphenylphospholene oxide. The ozonolysis must be performed with more care than usual, since a prolonged reaction period appears to lead to side reactions that reduce the product purity.

<div align="center">Scheme 10</div>

δ ^{31}P +53.7

(<u>18</u>)

1. O$_3$, -40°,
   CH$_3$OH
2. KI, 55%

m.p. 173.5-174.5°

δ ^{31}P +25.9

ν$_{C=O}$ 1680, 1690 cm^{-1}

(<u>19</u>)

CONFORMATIONAL ASPECTS

The dibenzodiketophosphonane <u>19</u> has a unique ^{13}C NMR spectrum that will serve to introduce the topic of the conformation of the phosphonane system. The spectrum of an analytically pure sample, giving a single sharp ^{31}P NMR signal, has <u>two</u> ^{13}C signals in the carbonyl region (in CDCl$_3$, 194.7, $^2J_{PC}$ = 3.9 Hz and 194.6(s)), as well as <u>two</u> signals for α-CH$_2$ (47.8, $^1J_{PC}$ = 53.7 Hz and 46.4, $^1J_{PC}$ = 57.6). It is obvious that the ring has adopted a conformation that lacks symmetry and does not undergo ready equilibration with an equivalent form. A molecular model immediately shows the cause of the asymmetry; it is physically impossible for the two carbonyls to lie in the same plane in the center of the ring. The ring therefore must be puckered with the carbonyl oxygens in an <u>anti</u> relation. This twisting also allows the biphenyl moiety to approach the preferred orthogonal relation of the two benzene rings. One C=O is then <u>syn</u> to oxygen on P, the other is <u>syn</u> to P-phenyl,

and therefore they become non-equivalent and give different ^{13}C signals. The constraint
imposed by the unsaturation centers makes it extremely difficult for any form of ring
inversion to occur. That the carbonyls are differently located relative to P=O is
revealed by their possessing different $^2J_{PC}$ values; the dihedral angles (ϕ) relating the
carbonyl carbon to oxygen on P can be quite different in some conformations; models
suggest as extremes the values of $\phi \sim 0°$ and $\phi \sim 80°$. Angle ϕ is known in other systems
to have some influence on $^2J_{PC}$ of phosphine oxides (9). However, a striking change in the
spectrum occurs in DMSO solution; all coupling parameters are modified, and both carbonyls
show coupling, 196.2 (2.9 Hz) and 196.7 (3.9 Hz). Apparently a conformation with different
ϕ values is stabilized by this solvent. In future work, other solvents will be tested
and barriers to ring inversion will be measured.

When the monocyclic diketo phosphonane 3 is examined by ^{13}C NMR, only one set of signals
for the α-, β-, γ- and δ-carbons is seen, as recorded in Table 1. However, an X-ray
analysis of this crystalline solid (10), in work to be described elsewhere, revealed that
the conformation adopted by the solid is not symmetrical. The shape adopted is quite
similar to one of the low-energy forms (the twist-chair-chair) predicted by Hendrickson
(11) for cyclononane, with the P atom not lying on the C_2 axis. This shape has in fact not
been found experimentally before, the twist-chair-boat and twist-boat-chair being the ones
encountered to date. Apparently, the barrier to ring inversion in solution is less than
that of the dibenzo case, and there is rapid equilibration between two equivalent confor-
mations. Low-temperature NMR studies could define the energy barrier for this process.

That an appreciable barrier to ring inversion can develop in a monocyclic compound is seen
in the case of 1-phenyl-5,6-dibromo-3,8-diketophosphonane oxide. Its ^{13}C NMR spectrum is
similar to that of the dibenzo compound, in showing doubling of some of the ring carbons
(C-2,9 at 48.4 ($^1J_{PC}$ = 54.7 Hz) and 47.4 (49.8); C-3,8 at 201.3 (3.4) and 199.8 (6.8)).
The solid-state conformation was also determined (10); the twist-chair-chair structure was
again found, with the bromines occupying pseudo-equatorial positions. The presence of these
substituents is clearly responsible for raising the energy barrier for the ring intercon-
version, which requires passage of the ring through forms with substantial non-bonded
interactions. Heavily-substituted cyclononanes are also known to possess barriers of a
size that lead to single conformations in solution at room temperature (12). An attempt to
determine $\Delta G^{\ddagger}$ for the phosphonane by high-temperature NMR failed because of the instability
of the compound.

CONSTRUCTION OF PHOSPHONIN DERIVATIVES

Several of the derivatives of the monocyclic phosphonanes were prepared with a long-range
goal in mind of conversion to the fully unsaturated phosphonin ring. While this goal has
not yet been achieved, it has been possible to utilize the dibenzo derivative 19 for this
purpose, as shown in Scheme 11. The first step involves the reduction of the two carbonyls,

Scheme 11
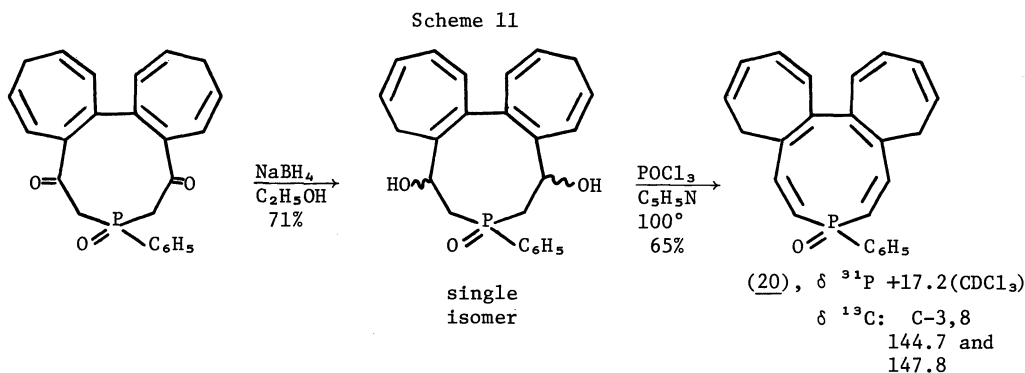
and this was accomplished smoothly with NaBH$_4$. The reaction is stereospecific; only one of
three possible diastereoisomeric forms is obtained, as indicated by the ^{31}P NMR spectrum
consisting of a single sharp peak (δ +29.9). The dehydration of the diol also occurs
smoothly, and thereby is formed the first known member of the phosphonin oxide system,
20, a crystalline solid. The ring appears to be non-planar on the basis of the presence of
two different signals tentatively assigned for the carbons β- to phosphorus (the α-carbons
are not clearly distinguishable from the aromatic carbons).

The critical step of deoxygenation of the phosphonin oxide was effected in 93% yield with
the trichlorosilane-pyridine complex on refluxing in benzene and thus we have completed the
first rational synthesis of a phosphonin (Scheme 12). The phosphine forms a crystalline
methiodide with the correct elemental analysis. Characterization of the phosphonin is

incomplete at this writing; the product appears to be a stable solid, however, and the stage is now set for detailed exploration for the possible presence of cyclic delocalization.

Scheme 12
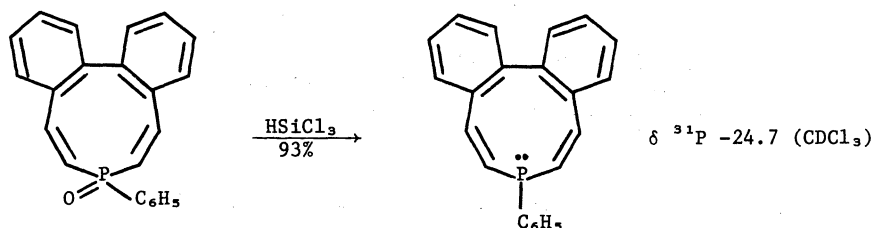
$\delta\ ^{31}P\ -24.7\ (CDCl_3)$

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