Tetrahedron Letters,Vol.23,No.25,pp 2529-2532,1982 0040-4039/82/252529-04$03.00/0
Printed in Great Britain

INFLUENCE OF THE CONSTRAINT OF BRIDGEHEAD STRUCTURE ON PHOSPHORUS REACTIVITY IN THE 1-PHOSPHABICYCLO[3.2.1]OCTANE SYSTEM

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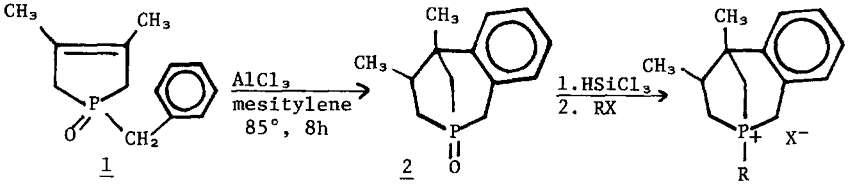
Summary: Nucleophiles attack the methiodide of the 3,4-benzo derivative of the title system to displace the P-methyl group in preference to the benzylic moiety. The trigonal bipyramidal intermediates (as well as a stable dioxyphosphorane) appear to undergo rapid isomerization.

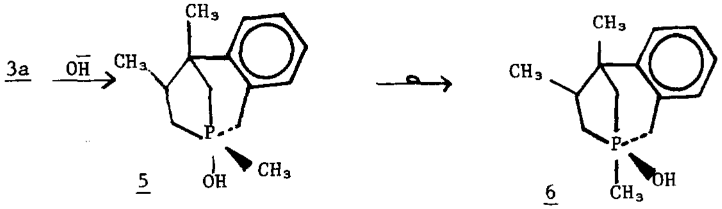
The placement of a phosphorus atom at the bridgehead position of a bicycloalkane framework should lead to a system of modified reactivity trends, especially when intermediates based on pentacovalent geometry are involved. Although a few such systems have been known for a number of years[1], no studies on the reactivity at phosphorus have been reported[2]. We recently described[3] a particularly simple synthesis of such a bicyclic compound, and its ready availability has allowed us to initiate such studies. The 1-phosphabicyclo[3.2.1]octane system of 2 is prepared in 90% yield[4] by the intramolecular Friedel-Crafts alkylation of the 1-benzylphospholane oxide derivative 1.

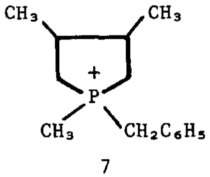


3a, $R=CH_3, X=I$
3b, $R=C_6H_5CH_2$, $X=Br$
3c, $R=OC_2H_5$, $X=I$
3d, $R=X=OC_2H_5$

The phosphonium salt 3a was also readily prepared[3], and since positive phosphorus forms pentacovalent intermediates in various reactions, our studies commenced with this species. Our efforts were instantly rewarded by the results obtained in the displacement with NaOH. While the usual conditions for this reaction (3N NaOH in aqueous ethanol at reflux, 20 hrs) were without effect on 3a, exposure to a 0.3N KOH solution based on dimethyl sulfoxide[5] (70 mole % in water) promoted decomposition at 25° with the evolution of methane (identified by gas chromatographic comparison with a known specimen). The reaction was complete in a few hours. The main (90%) product was phosphine oxide 2, identified by matching of NMR parameters; a minor product (4, 10%) had δ ^{31}P +60.1[6]. This surprising preference for the salt 3a to suffer displacement of a methyl rather than a benzylic group is without precedent[7], and is a striking example of the influence of the caged structure on the reactivity at phosphorus.

We interpret this result with the following generally accepted principles[8,9]. (1) ^-OH attacks phosphonium salts so as to assume an apical position in the resulting trigonal bipyramid (TBP), (2) the 5-membered ring component of the bicyclic system exerts its usual preference for an apical-equatorial disposition in the TBP, leaving the 7-membered component in its preferred diequatorial disposition, (3) the departing group must be located in an apical position. Structure 5 may then be written to express the preferred geometry of the initially formed TBP, recognizing that there will be distortions of the bond angles from the ideal values. The benzylic group cannot attain an apical position without forcing the 5-membered ring into the unfavored diequatorial disposition, and hence it cannot act as the preferred leaving group. However, isomerization of the TBP can result in a structure such as 6 where methyl has attained the apical position and hence departs.





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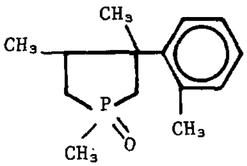
The P-benzyl salt 3b was cleaved readily under the usual conditions with refluxing aqueous NaOH, also forming oxide 2. The greater resistance of P-methyl to cleavage is in line with expectations[7]. It was also confirmed that P-benzyl cleavage takes precedence over P-methyl in the related monocyclic 7; refluxing in 3N NaOH gave only 1,3,4-trimethylphospholane oxide.

TBP isomerizations are generally accepted to proceed by the Berry pseudorotation mechanism[8], but in tied-back phosphoranes mechanical constraints are present that would raise the energy of this bond-bending process. Nevertheless, NMR studies[9] clearly indicate that isomerization is facile for some caged pentaoxyphosphoranes even at low temperatures, and the alternative of turnstile rotation was proposed as having special significance in these cases.

The identity of the minor component 4 has not yet been established. However, its rather downfield ^{31}P shift of +60.1 strongly suggests that it possesses a 5-membered ring; non-cyclic or larger-ring systems are found at considerably higher field[10]. A possible structure is shown as 8, which could originate from the higher energy TBP 9.



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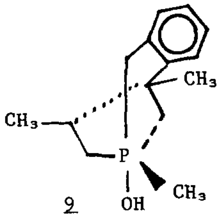

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Similar observations on the reactivity of 3a towards other reagents and conditions confirm the general tendency to retain the benzylic group at the expense of methyl:

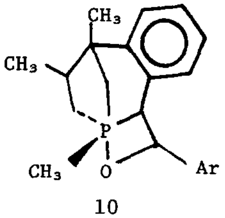
1. Alcoholic $NaOC_2H_5$. A heterogeneous mixture of 4 ml of 1.5M $NaOC_2H_5$ in ethanol and 0.04 g of salt 3a was stirred at 25° for 1 day. Methane was again evolved; the phosphorus compound remaining had δ ^{31}P +44.1 and is assigned structure 3c. It was hydrolyzed on addition of water to give oxide 2. The novelty of the reaction is revealed by considering the path taken by the phospholanium ion 7; under the same conditions, only benzyl is displaced and methyl remains on phosphorus.

2. Lithium Aluminum Hydride. A suspension of 0.058 g of salt 3a and 0.003 g of $LiAlH_4$ was stirred in a medium of 2 ml of CH_2Cl_2 and 0.5 ml of ether for 3 days at 25°. Chloroform extraction of the water-quenched, basified mixture provided a product that was mostly (89%) the starting salt 3a, but significantly there was an 11% contribution from oxide 2. This requires the elimination of the P-CH_3 group from the TBP resulting from hydride addition, the phosphine having been oxidized to 3a during work-up. When the same conditions were applied to monocyclic

salt 7 for 4 days, 70% was destroyed, exclusively with P-benzyl cleavage.

3. Wittig conditions. With a strong base, salt 3a is capable of losing a proton from any of the four different carbons attached to phosphorus to form an ylide, but a preference for anion formation at the benzylic group might be expected. When an ylide was prepared (0.2 g of 3a and 0.2 g of NaH in 6 ml of diglyme at 25°, providing a light yellow solution after 5 hr) and quenched with p-chlorobenzaldehyde and then water, it was found that the carbon of the ylide was primarily derived from the methyl group. Thus, the ^{31}P NMR spectrum taken on the chloroform extractables showed that the major product was oxide 2 (56% of the total integrated area, which provides an approximate product analysis). Other peaks were found at δ +37.7 (11%, salt 3a), +39.7 (6.5%), +42.3 (5.6%), and +59.6 (11.4%). Although it was not isolated, p-chlorostyrene was identified in the reaction product from its ^{1}H NMR spectrum.

The intermediate in the Wittig reaction is an oxaphosphetane[11] with TBP structure at phosphorus, and its decomposition is subject to the usual requirement that the group departing be located apically[8]. Structure 10 would then be the preferred intermediate if the benzylic group provided the anionic center. However, the constraints of the cage hinder the isomerization of 10 to a form with the benzylic carbon apical. With methyl as the anionic center, isomerization of the initially formed TBP (11) can provide 12 which can decompose to the products observed. The minor phosphorus products (not identified) may arise from cleavage of other C-P bonds in higher energy TBP forms. Thus, the product with δ ^{31}P +59.6 is suggested to have a 5-membered ring as would result from cleavage of the benzylic group.



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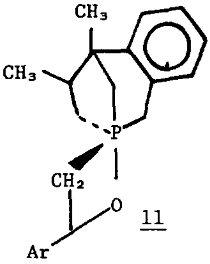

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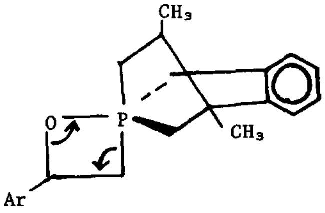

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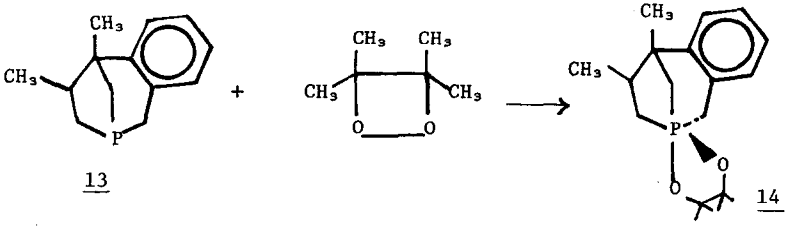
Polyoxyphosphoranes frequently have stable TBP and can be observed by NMR, or even isolated. Dioxyphosphorane 14 was formed by adding 0.0918 g of 3,3,4,4-tetramethyl-1,2-dioxetane in 0.5 ml of benzene-d_6 to phosphine 13 (0.0625 g in 0.5 ml of benzene-d_6) in a 5-mm NMR tube. The reaction was exothermic, and within 5 min the ^{31}P NMR signal for phosphine 12 (-43.1) had been replaced by a major new signal at -29.1, in the region expected[12] for cyclic dioxyphosphoranes and therefore assigned to 14. A small amount of oxide 2 was also formed[13].



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Compound 14 (in C_6D_6) was observed over a period of 6 weeks at 25° and found to be stable. This is in considerable contrast to the instability observed for the related product (δ -14.3) from 1-benzylphospholane; its decomposition was complete in 6 hours. The ^{13}C NMR spectrum of 14 was of poor quality but possessed a feature supporting the concept of rapid isomerization of the TBP; only one signal was obtained for the carbons attached to oxygen in the dioxaphospholane moiety (δ 76.2, $^2J_{PC}$ = 2.2 Hz on both 15 MHz and 22.5 MHz instruments.) In a non-isomerizing TBP, these carbons are chemically non-equivalent and might have been expected to give different signals. That they did not may be attributed to a rapid equilibration between TBP forms (a coincidence of two different signals is also a possibility). The presence of coupling from ^{31}P rules out an explanation based on rapid equilibration through a dipolar form with four-coordinate P, since this would prevent ^{31}P coupling[14]. Attempts to isolate 14 for further characterization and low-temperature NMR experiments in another solvent have not yet been successful. When diethyl peroxide was reacted with 13, no signal was observed in the dioxyphosphorane region, but a new signal developed at +45.1. This shift (cf. to 3c, +44.1), and the fact that water converted the species to oxide 2, allows assignment of structure 3d. The ^1H NMR spectrum supported 3d by possessing an ethoxy group showing no coupling to ^{31}P ($-OCH_2-$, q, δ 4.41). Similarly, the ^{13}C NMR spectrum showed no coupling to these carbons ($-OCH_2$, s, δ 63.0). This is a consequence of the well-known exchange in such positive species[12,13], which is frequently observed in phosphine-peroxide reactions.

References and Notes

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(Received in USA 11 February 1982)