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THE SYNTHESIS OF THE 8-PHOSPHABICYCLO[3.2.1]OCTANIC SYSTEM

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Abstract—The 8-phosphabicyclo[3.2.1]octanic system was synthesized in two different ways: (a) a double Michael addition of aryl phosphine to 2,6-cycloheptadienone (b) a Diels–Alder cycloaddition of dichlorophenylphosphine to 3,5-cycloheptadienyl-1-acetate. The stereochemistry of the isomeric phosphines (I, II and IX) was determined by investigation of the NMR spectra of their derivatives (oxides, ketals, benzyl phosphonium salts and the uranyl nitrate complexes of the oxides and the ketals). The conformations of several compounds are discussed, as well as the hydrolysis mechanism of two benzyl phosphonium salts which gave a mixture of products.

A GREAT deal of work has been done, and is being done on the configurational and conformational problems of the tropanic system.[1] We were interested in the examination of the hitherto unknown 8-phosphabicyclo[3.2.1]octanic system, the phosphorus analog of the aza-compound. Our interest in such a system, which is geometrically different from the aza system, was focused on the configurational problems due to the P-atom, as opposed to the conformational problems in the case of the aza systems. The problems arising from the NMR spectra of such compounds were also of interest, as the phosphine oxide group, in this cases, has a definite position in relation to the other parts of the molecule, as will be shown later. Bridged phosphorus compounds are quite rare,[2–4] and most of the synthesis by which the known compounds were prepared, were specific for each particular case, and could not be applied, even in modified form, to other systems. In the preparation of the phosphabicyclo[3.2.1]octanic system, known synthesis for phosphorus heterocyclic compounds were used—synthesis which can be and are now being expanded for the preparation of other bicyclic systems.

One of the synthetic approaches was a double Michael addition of phenylphosphine to 2,6-cycloheptadienone,[6] and another, a Diels–Alder cycloaddition of dichlorophenylphosphine to 3,5-cycloheptadienyl-1-acetate.[5] (See Scheme 1). The latter method with its special problems will be discussed further in the text.

Addition of phenylphosphine to 2,6-cycloheptadien-1-one under a nitrogen atmosphere at 140° gave, after 12 hr, a viscous oil. Following crystallization from acetone, a crystalline adduct was obtained in ca. 40% yield. Apart from this adduct and traces of the reactants, some oligomeric substance was also obtained. According to a chromatoplate, the crystalline material was made up of two compounds. The predominating one (compound I) could be separated and purified from the minor component (II) by sublimation or crystallization. The NMR spectra of I, which turned out to be the expected 8-phenyl-8-phosphabicyclo[3.2.1]octan-3-one, is very complex.

Although the molecule possesses a plane of symmetry, due to spin spin nonequivalence, the spectrum is not first order. Further complexity of the spectrum results from long range coupling effects between the P atom, and protons situated as far as four bonds from it, and also because of the small chemical shift differences between the protons. However, after preparation[7] of the four-deutero compound d_4-I, the NMR signals could unequivocally be assigned to the various protons, as is shown in Table 1. The NMR spectrum of compound I clearly showed that a one-to-one adduct was obtained, as the intensity of resonance of the phenyl multiplet at δ 7·20–7·35, and the different alicyclic protons was in the ratio of 1:2. Even more significant was the mass spectrum of the compound in which similiarity to the fragmentation of the tropanic system was recognized. The base peak of the spectrum at *m/e* 108 is due to the $Ph—P^{\oplus}$ fragment. Second in intensity was the molecular peak at *m/e* 218 (72%), other peaks were observed due to the loss of CO, $CH_2{=}CH_2$ and $CH_2{=}C{=}O + H$ as was expected.

The above data, together with a correct elemental analysis and appropriate IR spectrum [ν_{max}^{KBr} 3030, 1590, 1500 (Ph); 1700 (C=O); 1445 (Ph—P)] confirms the proposed 8-phenyl-8-phosphabicyclo[3.2.1]octanic structure for compound I. The purity of phosphine I was ascertained from the NMR spectrum of its methiodide (III) and benzyl phosphonium salt (IV), which in each case, exhibited only one doublet; for the P—CH_3 in compound III at δ 2·91 (J = 15 c/s) and for the P—CH_2—Ph in compound (IV) at δ 4·65 (J = 14 c/s). The NMR spectra of these compounds (shown in Table 1) was more detailed than that of the parent phosphine, due to the anisotropy effect of the phosphonium cation.

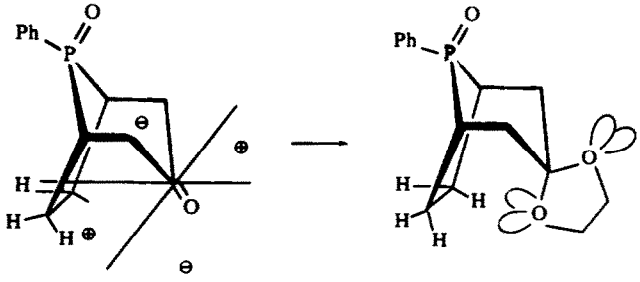
As compounds I and II were very sensitive to oxygen, the minor compound (II) could not be separated by chromatography. However, following the oxidation of the mixture with H_2O_2, and crystallization from MeCN, the two oxides V and VI which appeared in two different crystalline forms could be separated. It was found that the predominating phosphine oxide (V) is related to I, since it could be directly obtained by oxidation of pure I. The other oxide (VI) which was obtained in only ca. 10% was the oxidation product of II, which itself could not be purified before.

Since compound V (m.p. 235–237°) and compound VI (m.p. 247–248°) have the same elemental CHOP analysis, show the same molecular ion at *m/e* 234 and have quite similar IR spectra, except for the finger print region, they are assumed to be epimeric with respect to the P atom. The NMR spectra of the two isomers were, however, quite different (Table 1), while in compound VI all the alicyclic protons showed resonance lines in a narrow range (δ 1·80–2·90), in compound V they were spread over a much greater range (δ 1·60–3·60 ppm).

The identification of the various proton pairs in V was possible after the four-deuterio compound d_4-V, was prepared[8] by boiling V with NaOD in MeOD. The disappearance of the multiplets at δ 2·40–3·00, and δ 3·30–3·60, thus leaving only the C_1 and C_5 protons at δ 2·63, showed clearly that the former resonance lines must be assigned to the C_2 and C_4 protons. The C_1 and C_5 protons were also identified by the NMR spectra of the uranyl nitrate complex discussed below. The preparation of d_4-VI did not provide any important information additional to that which we had obtained from compound VI itself. In the NMR spectra of both phosphine oxides, the phenylic protons were divided into two groups, in the ratio of 2:3 as expected. As it is known that peroxide oxidation of phosphines is accompanied by

configurational retention,[9] it seems that the stereochemistry of the phenyl group attached to the P-atom, in compounds I and II must be the same as in the corresponding oxides V and VI. The stereochemistry of these compounds, as is shown in Scheme 1, is discussed below.

Ketalization of V and VI with ethylene glycol yielded the corresponding ketals VII and VIII as was expected. The ketals and their four-deuterio derivatives d_4-VII and d_4-VIII, which were prepared by ketalization of d_4-V and d_4-VI were synthesized mainly for stereochemical study. Substituting the carbonly function with the ketal group altered the magnetic anisotropy in the vicinity of the neighbouring protons. Thus, the C_2 and C_4 protons (appearing at δ 2·40–3.00 and δ 3·30–3·60 in V which were previously deshielded, moved toward higher field at δ 1·80–2·20 and δ 2·64–3·00, while the C_6 and C_7 protons which appeared to be shielded before, by the carbonly group, now suffered a relatively strong deshielding effect. This deshielding effect was especially strong on two C_6, C_7 protons adjacent to the ketal which moved

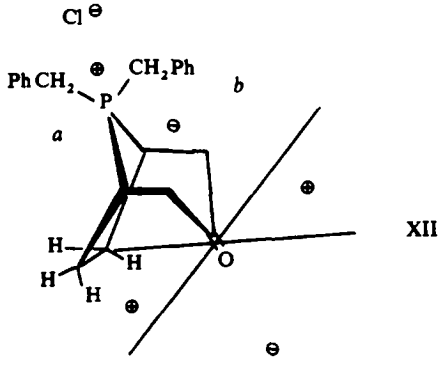


V VII

downfield by about 0·5 ppm, from δ 1·60–2.10 in V to δ 2·20–2·60 in VII. The identification of the protons was done by comparing the compounds with their deuterated derivatives. Comparing the NMR spectra of the second isomeric phosphine oxide (VI) and d_4-VI with their ketals VIII and d_4-VIII (Table 1) it can be shown that there is the same direction of chemical proton shift, as in the case of the first isomer, that is, a movement of the two C_6C_7 protons downfield and of the C_2C_4 protons upfield. The same shift direction in both isomers shows quite clearly that the conformation of the phosphorinanonic ring is the same in both ketones and also that the conformation of the phosphorinanic ring is the same in both ketals. In the case of the ketals, the chair conformation is the only one which fits the NMR data. This is understandable when one inspects the Dreiding models. A boat conformation would give rise to severe steric interactions between the ketal group and the P = O or phenyl on the P atom, a twist conformation is impossible because of the rigidity of the bicyclic system.

By reacting 2,6-cycloheptadien-1-one with Ph-CH_2PH_2, which is a stronger neucleophile than Ph-PH_2, under the same conditions as described before for the preparation of compounds I and II, it was found that the reaction was complete after only 2 hr. It yielded, apart from some oligomeric substance and traces of the reactants, two phosphines, as could be seen on a TLC plate. As crystallization and distillation were unsuccessful, the phosphines had to be purified by careful chromatography

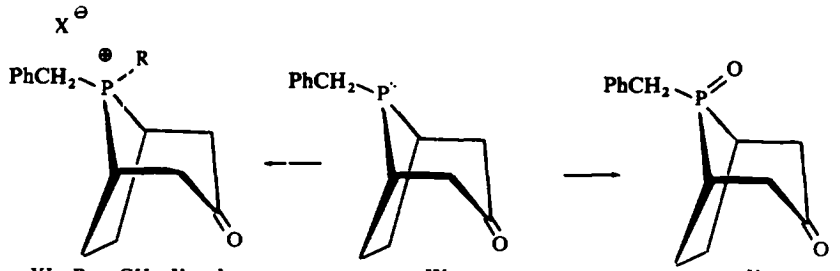
under nitrogen. This resulted in one major fraction from which the phosphine (IX), slightly contaminated with its oxide (X), was obtained; further eluation yielded the pure oxide X. The second isomeric phosphine, which appears in minor quantities, as well as its oxide, could, as yet, not be purified. The phosphine IX is the expected 8-benzyl-8-phosphabicyclo[3.2.1]octan-3-one. It gave a molecular peak at *m/e* 232 and the required CHOP elemental analysis. The NMR spectrum of the alicyclic protons of IX was, in this case, also very complex (due to the reasons mentioned above in the discussion of compound I), however, the integration ratio of about 5:2:10 between the phenyl, benzylic and alicyclic protons fitted the requirements of the compound. The appearance of only one doublet at δ 3·27d (J = 14 c/s) (2H) for the benzylic protons clearly showed the purity of this phosphine. Should another isomer have been present, a second doublet for the benzylic protons would have been observed, as one of the isomeric benzylic protons would then have entered the carbonyl's deshielding cone. The purity of compound IX was also shown by the preparation of its pure oxide X and methiodide XI (Table 1). Another salt which was prepared was the benzyl chloride phosphonium salt XII, the NMR of which showed clearly two benzylic groups to which the doublets at δ 4·07 (J = 14 c/s) (2H) and δ 4·78 (J = 14 c/s) (2H) were attributed. The difference of 0·7 ppm between the two benzylic group signals can be rationalized by examining the dreiding model of the salt (XII). Assuming that the phosphorinanonic ring is in the chair conformation, one of the benzylic groups (group b, Fig 1) is situated in the deshielding cone of the carbonyl



XII

FIG. 1

function, and this causes its appearance 0·7 ppm lower field than the other group (a). In the methiodid XI, the only benzylic group appears approximately in the same place as group (a) in XII at δ 4·05d (J = 14 c/s). As it is known that the salt formation of phosphines is accompanied by retention of configuration, the configuration of the benzyl group in the phosphine IX must be the same as in the salt XI, i.e., equatorial to the phosphorinanonic ring, and according to a similar argument, this should also be the configuration in oxide X. The above P-configuration determination in the salts, obtained from the benzyl phosphine system (IX), can also be used in the structural determination of the phenyl phosphine derivatives. It turned out that in both cases the main isomer was the one in which the aryl group was equatorial to the phosphorinanonic ring. This is the configuration in which, according to a Dreiding model, the aryl group is furthest away from the cycloheptanonic skeleton. In the

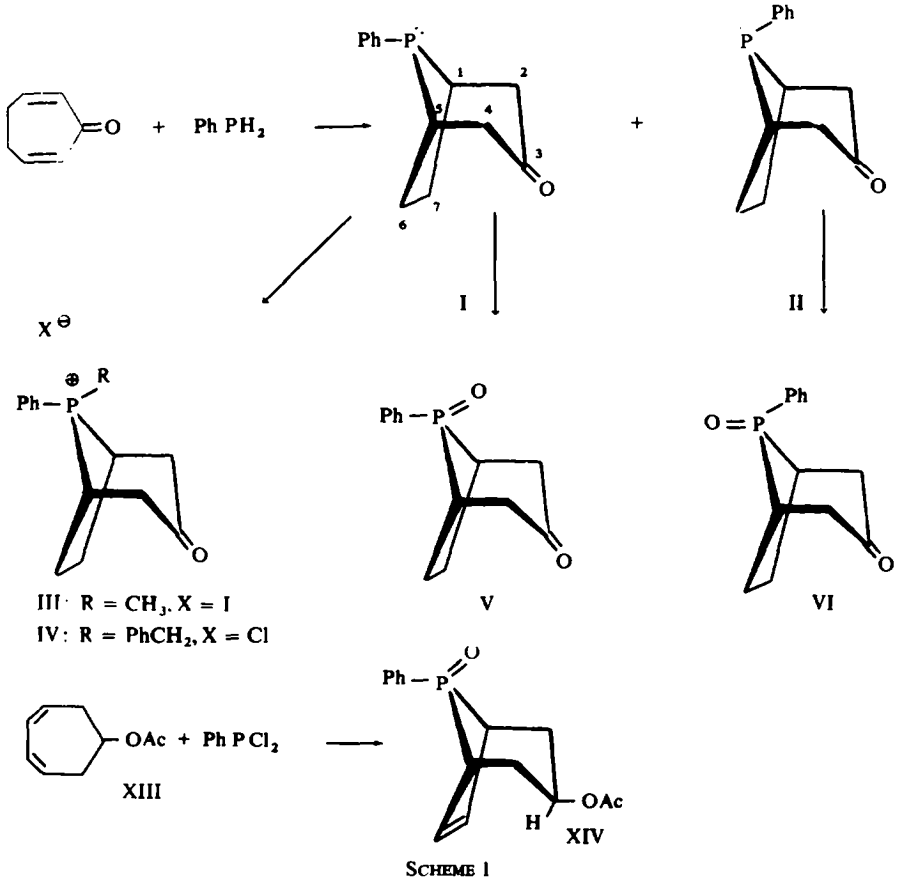


XI: R = CH_3, X = I
XII: R = $PhCH_2$, X = Cl

IX

X

NMR spectrum of the phenyl benzyl phosphonium salt IV, the benzylic protons resonate at δ 4·65d (J = 14 c/s) (2H) (in D_2O) and δ 4·99d (in d_6DMSO) which reasonably fits the value shown by the benzylic b-group of compound XII (Fig. 1); i.e., the phenyl in compound IV, is on the same side as the benzyl in compound IX. When the NMR spectrum of the mixture of the phenyl benzyl phosphonium salts derived from the phenyl phosphine mixture of I and II was recorded, two doublets at δ 4·21 (J = 14 c/s) and δ 4·65 (J = 14 c/s) were observed. This shows again that the phosphine II is indeed the P-epimer of I. The structural determination of compounds I and II also shows the structure of their closely related derivatives. (Scheme 1).



III: R = CH_3, X = I
IV: R = $PhCH_2$, X = Cl

V

VI

XIII

XIV

SCHEME 1

Looking for further evidence for the suggested stereochemistry, uranyl nitrate complexes of several phosphine oxides were prepared,[10] and their NMR spectra, in pyridine, were recorded and compared to the uncomplexed compounds. Burdett and Burger[10] have shown that protons located on atoms as far as two bonds removed from the phosphorus, as well as the ^{31}P resonance itself, in uranyl complexes of the type $UO_2(NO_3)_2(O{=}PR_3)_2$ are paramagnetically shifted. This shift may be accounted for, at least in part, by the anisotropy of the uranyl group. It was interesting to see whether or not this anisotropy effect would lead to a distinction between the C_2,C_4 and C_6,C_7 protons in the two isomeric phosphine oxides. The complexes of the uranyl nitrate are known to possess a fixed geometry, and such a geometry as is shown for the complex V, (Fig 2) would result in a stronger paramagnetic effect on the nearer

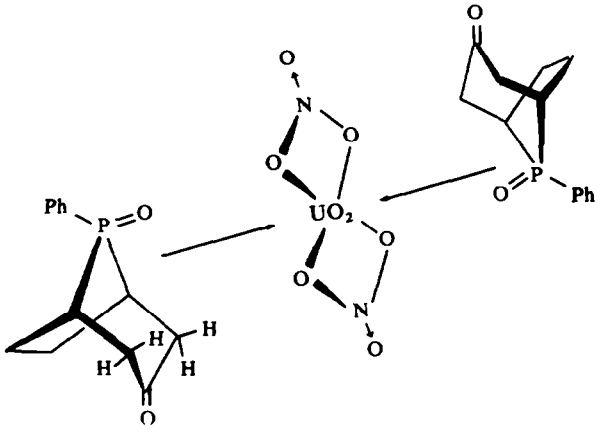


FIG. 2

C_2,C_4 protons as compared to the C_6,C_7 ones, and *vice versa* for compound VI. The same effect would also be seen in the ketals. Indeed, the results (Table 2) clearly showed a differentiation between the further and nearer proton pairs, apart from the much stronger paramagnetic shift of the C_1 and C_5 protons, which was of the same order of magnitude as reported.[10] These results, as shown in Table 2, support the proposed stereochemistry, which was concluded from the benzylic phosphonium salts discussed previously.

The most impressive result, which also showed the paramagnetic spacial effect of the uranyl complex in this series of recorded spectra, was the differentiation between the ketalic protons in the ketal VII, caused by the uranyl complex. The multiplet at δ 3·90 assigned to the ketalic protons of VII was divided into two groups in complexed VII, one remaining approximately in the same region as in the uncomplexed comp. VII at δ 3·87, while the other was diamagnetically shifted to δ 3·75. This, once more, can only be rationalized by the assumption that the complex is situated on the same side as the ketal function. Such a distribution was also seen in the isomeric uncomplexed ketal VIII where two katalic protons were diamagnetically shifted by the phenyl group (δ 3·66 and δ 3·93).

Once the stereochemistry of the phosphine I, and phosphine oxides V and VI was assigned by the NMR spectrum of the benzyl phosphonium salts (IV, XI and XII) and the uranyl complexes, the correlation between the chemical shifts of the various protons attached to the bicyclic skeleton and the stereochemistry could be checked. Such correlations are made with difficulty in bicyclic systems, where it is not always easy to predict into which region of magnetic anisotropy the various protons enter. This is especially true for the compounds under discussion, where, besides the carbonyl and phenyl groups (whose anisotropy is known), the P = O group is also present Very little is known about the anisotropy distribution caused by this group, and the attendant difficulties, were also encountered in the NMR spectrum of 9-phenyl-9-phosphabicyclo[4.2.1]nonane derivatives previously reported.[2]

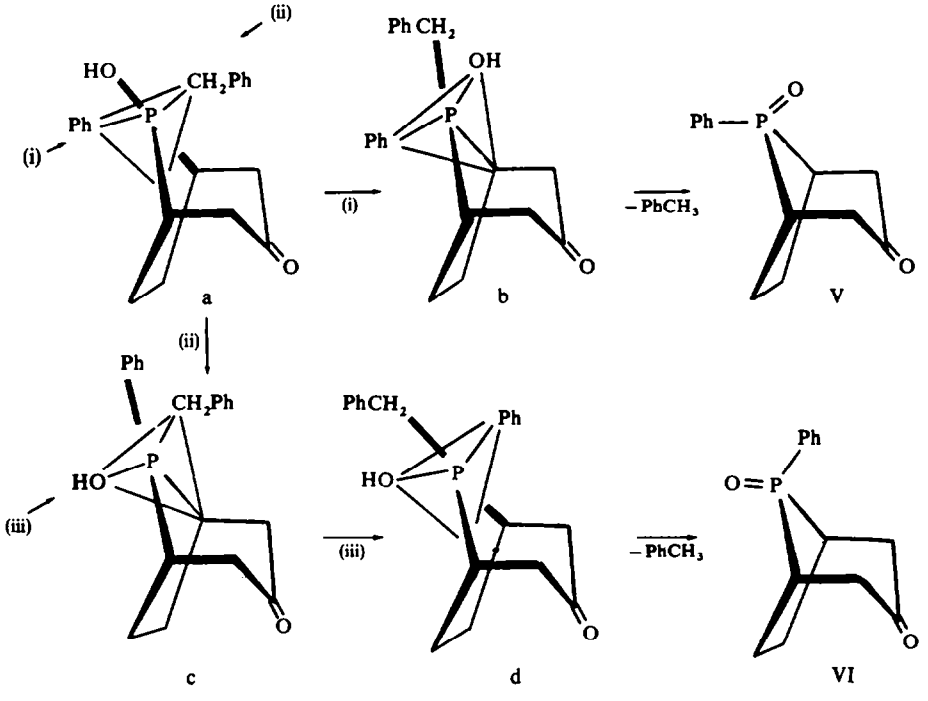
In the NMR spectrum of compound I, it was interesting to note that each of the C_6 and C_7 protons resonate in the same place. This shows that one pair enters the shielding cone of the carbonyl group, and therefore resonates in the same place as the pair diamagnetically influenced by the phenyl group. At lower field (δ 2·52–2·66 and δ 2·72–3·00), the deshielded protons C_2,C_4 adjacent to the carbonyl, appear as expected. Comparing the NMR spectrum of compound V, with the above compound I, the most significant change was the downfield shift of about 0·7 ppm, of two of the C_2,C_4 protons, obviously resulting from the additional anisotropy of the P=O group. This pair is most likely the C_2,C_4 axial protons; the second C_2,C_4 pair—the equatorial ones, remained almost unchanged, as is also the case for the C_6,C_7 protons, which are further away from the P=O group. The NMR spectrum of compound VI is much more complicated as all the protons resonate in a narrower range δ 1·80–2·90. Nevertheless, this observed contraction fits the assigned stereochemistry, as in this compound, when compared to its isomer V, the anisotropy effects of the phenyl and P=O, on the alicyclic protons nearer the latter groups, are in opposite directions. The C_6,C_7 protons nearer to the P=O are, in this instance deshielded, and consequently the signals shift downfield, while the previously paramagnetically shifted C_2,C_4 axial protons are now diamagnetically effected by the phenyl, and move upfield, so that all the protons are now in the same narrow range.

The basic hydrolysis of two of the phosphonium salts, gave a mixture of products and are of some interest. When compound XI or IV was treated with alkali, a mixture of oxides was obtained in every case; although in different ratios. Compound IV yielded mainly (ca. 90%) oxide V, which, in the light of previous arguments, may well be the more stable one, while XI gave rise to a mixture of isomers in the ratio of about 3:1.

McEwens basic hydrolysis mechanism,[11] which was proposed for acyclic phosphonium salts, and explains configuration inversion, demands linearity between the hydroxide and the departing benzyl ion. Such a diapical situation is impossible in compounds IV and XI for two reasons. (1) The bicyclic ring skeleton in the salts, prevents facial approach to the phosphorus cation from the direction of this bicyclic skeleton, and (2) the ring strain which would arise in such a case, due to the CPC ring angle deformation, would be very large.[12]

The mechanism we would like to suggest for this hydrolysis, consists of an apical introduction of the nucleophile, a pseudo-rotation and an apical departure of the leaving group.[13] In the P^V intermediate, the C_1—P—C_5 angle cannot become 120°, therefore, one of the C_1—P or C_5—P bonds has to be apical, thus defining the mode

of pseudo-rotation and the direction of the OH group in the intermediate (a) (Scheme 2). From these considerations, the only possible P^V starting intermediates are (a) or its mirror image. Pseudo-rotation about the Ph—P bond as pivot in intermediate (a) will result in the formation of (b) in which the benzyl group is apical and in the proper leaving position to yield the oxide V with retention of the configuration. On the other hand, if two consequent pseudo-rotations occur, the first about the $PhCH_2$—P bond as pivot yielding intermediate (c) and the second about HO—P bond as pivot, compound (d) with an apical benzyl will be obtained. Consequent loss of the benzyl group will then lead to oxide VI with inverted configuration. In the hydrolysis mixture which contains the two isomeric oxides, the one obtained by one pseudo-rotation is highly predominant (90% in the case of XI and 70% in the case of IV). The obtaining of a higher yield of the inverted compound in the hydrolysis of XI could be attributed to either steric factors or to a difference in the pseudorotation about the Ph—P as compared to the CH_3—P bond, i.e., sp^2 towards sp^3 hybridization correspondingly.

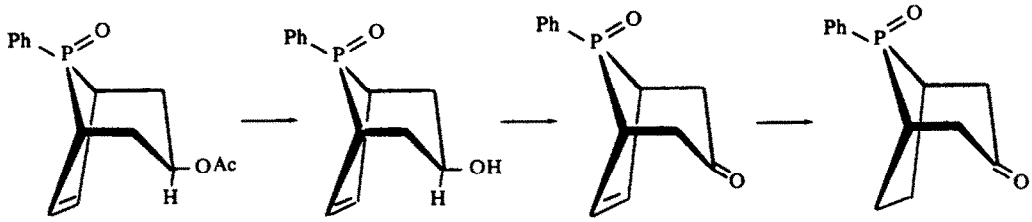


SCHEME 2

(i) The direction of one pseudo-rotation.
(ii) and (iii) The directions of the two alternating pseudo-rotations.

After proving that the 8-phospha[3.2.1]octanic system could be synthesized, it was of interest to see whether it could also be prepared from a 1,3-cycloheptadienic system by a Diels–Alder reaction. Such reactions between alkadienes and different trivalent phosphorous compounds are well known.[5] The only cyclo alkadienes which were submitted to such a reaction, and did not undergo this reaction, were cyclooctadiene,

which is known to be unreactive in normal Diels–Alder reactions, and cyclopentadiene. One explanation for the lack of reactivity of the latter compound may be the high degree of strain which would be created in the resultant product. The situation in regards to cyclohepta-1,3-diene is also not ideal, although this diene is known to undergo normal D.A. reactions with dienophiles like N-phenylmaleimide.[14] From a consideration of mechanism, such a reaction, which should be disrotatory, as has been shown lately[15] in the reaction of dichlorophenylphosphine with various dienes, could give rise to the desired products. The factors which disturb the reaction are two; one is the non planar dienic system found in the most stable conformation of cycloheptadiene, which has to be connected with only one P atom, instead of with two atoms, as is the case in most dienophiles; and the second factor is the strain of the phospha[3.2.1]ring system. This is quite high as can be seen from Dreiding models. Indeed it was found that the reaction was very slow and only a few per cent of product was obtained after several months of reaction between dichlorophenylphosphine and 1,3-cycloheptadienyl-1-acetate (XIII), (Scheme 1). Changing the conditions did not improve the yeild as by-products appeared. Fortunately, almost all of the resultant adduct was one diastereomer, out of the four possible ones. The NMR spectrum of this compound showed the various groups of protons in the molecule clearly identifiable as shown in Table 1. The required elemental analysis, mass spectrum [M$^{\oplus}$ 276] and IR spectrum (ν_{max}^{KBr} 3040, 1590, 1500 (Ø); 1440 (Ø—P); 3000, 1630 (C=C); 1735, 1240 (OAc); 1180 (P=O) cm^{-1}) showed that the compound was the expected 8-phenyl-8-phosphabicyclo[3.2.1]octa-6-en-1-acetate-(XIV). The configuration on the P atom was the same as in the more stable phenyl phosphinic compound *I*. This could be shown by the following correlation:



XIV XV XVI V

Hydrolysis of the acetate XIV to XV followed by oxidation to compound XVI and hydrogenation of the double bond gave a compound which was identical in all respects to the previously known phosphine oxide V. This also establishes the stereochemistry of the phosphorous atom of XIV. The acetate group on C_3 is most likely equatorial, as could be seen from the pattern of the C_3 proton in the NMR spectrum. This proton gave a heptet-like multiplet between δ 4·63 and δ 4·99, which was broader than the signal obtained for the same proton in the isomeric compound, where it was like a complicated triplet at δ 4·12–4·32. The details of the preparation of this isomer and other related compounds will be published later.

EXPERIMENTAL

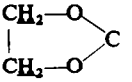
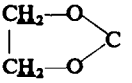
M.ps were taken on a Unimelt Thomas & Hoover's Capillary m.p. appratus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Infracord model 337 spectrophotometer equipped with a NaCl prism, UV spectra were recorded on a Perkin–Elmer 137 UV spectrophotometer. NMR spectra were taken

on a Varian HA-100 spectrometer for 5–10%, soln in $CDCl_3$ containing TMS as an internal standard. Mass spectra were taken with a Hitachi Perkin–Elmer RMU 6 instrument, the samples being introduced directly into the ion source through a vacuum-lock, electron energy 70 ev.

8-Phenyl-8-phosphabicyclo[3.2.1]*octan-3-one* (I). A mixture of cyclohepta-2,6-dien-1-one (13·5 g) and phenylphosphine (14 gr) was heated for 12 hr under N_2 at 140–150° on an oil bath. When the reaction was over, depending on the IR spectrum of the reaction mixture (i.e. disappearance of the band at 1650 cm^{-1} and appearance of the carbonyl band at 1700 cm^{-1}) the soln was cooled to room temp and the unreacted reactants were removed under high vacuum. The residue containing compounds I and II was crystallized and compound I crystallized out, m.p. 144–146° (acetone; 47%). Compound I was also obtained by sublimation of the above residue at 150°/0·4 mm λ_{max} 247 mμ (4·25); ν_{max}^{KBr} 3030, 1700, 1590, 1445 cm^{-1}. (Found: C, 71·24; H, 6·80; P, 13·64. $C_{13}H_{15}OP$ requires: C, 71·55; H, 6·93; P, 13·87%).

2,2,4,4-d₄-8-Phenyl-8-phosphabicyclo[3.2.1]*octan-3-one* (d_4-I). To a soln of I (100 mg) in dioxan (6 ml) under N_2, a mixture of DCl and D_3PO_4 (2 ml) (previously made by hydrolysis of PCl_5 (300 mg) with D_2O

TABLE 1

Comp.	H_1; H_5	H_2H_4; H_2H_4·	H_6H_7; H_6·H_7·	Aromatic protons	Other protons	Solvent
I	2·72–3·00(2H)	2·52–2·66(2H)* 2·72–3·00(2H)*	1·80†(4H)	7·30†(5H)	—	*a*
III	4·04†(2H)	3·20–3·70(4H)*	2·20–2·78(4H)	8·04–8·50(5H)	2·91d(J = 15)P—CH_3	*b*
IV	3·95†(2H)	3·10–3·80(4H)	2·20–2·70(4H)	7·28†(2H) 7·56†(3H) 7·84†(5H)	4·65d(J = 14)Ph—CH_2 4·99d(J = 19)Ph—CH_2	*b* *c*
V	2·40–3·00(2H)	2·40–3·00(2H)* 3·30–3·60(2H)*	1·60–2·10(2H)	7·42–7·62(3H) 7·65–7·88(2H)	—	*a*
VI	2·62–2·90(2H)	2·62–2·90(4H)*	2·62–2·90(2H) 1·80–2·40(2H)	7·50–7·70(3H) 7·73–7·96(2H)	—	*a*
VII	2·20–2·60(2H)	1·80–2·20(2H)* 2·64–3·00(2H)*	1·36–1·60(2H) 2·20–2·60(2H)	7·40–7·60(3H) 7·60–7·80(2H)	3·90(4H) 	*a*
VIII	2·26–2·80(2H)	1·94⁺(2H)* 2·15⁺(2H)*	2·26–2·80(4H)	7·44–7·64(3H) 7·64–7·90(2H)	3·66(2H) 3·93(2H) 	*a*
IX	1·70–2·80(2H)	1·70–2·80(4H)	1·70–2·80(4H)	7·36⁺(5H)	3·27d(J = 14)Ph—CH_2	*a*
X	2·00–2·70(2H)	2·00–2·70(4H)	2·00–2·70(4H)	7·16–7·40(5H)	3·28d(J = 14)Ph—CH_2	*a*
XI	1·90–3·20(2H)	1·90–3·20(4H)	1·90–3·20(4H)	7·56⁺(5H)	2·31d(J = 15)P—CH_3 4·05d(J = 14)Ph—CH_2 4·23d(J = 14)Ph—CH_2	*c* *c* *b*
XII	3·00–3·70(2H)	3·00–3·70(4H)	2·30–2·80(4H)	7·30–7·96(10H)	3·99d(J = 14)Ph—CH_2 4·50d(J = 14)Ph—CH_2 4·07d and 4·78d	*b* *c*
XIV	2·88⁺(2H)	2·08–2·50(4H)	6·13 m (2H)	7·25–7·50(3H) 7·50–7·80(2H)	2·03 s ($OCOCH_3$) 4·81 m C—3—H	*a* *b*
XV	2·87⁺(2H)	1·68–2·60(4H)	6·08 m (2H)	7·35–7·45(3H) 7·54–7·80(2H)	3·62 m C—3—H	*a*
XVI	2·86–3·18(2H)	3·20–3·44(2H) 2·20–2·86(2H)	6·27 m (2H)	7·40–7·60(3H) 7·60–7·88(2H)	—	*a*

Solvents: *a* $CDCl_3$ *b* D_2O *c* d_6-DMSO.

* Disappears in the deuterio compound.

† A narrow multiplet.

(2 ml)) was added. The mixture was stirred overnight, after which the solvent was removed under high vacuum. After repetition of the above procedure, compound d_4-I was obtained. (Found: M^+222; $C_{13}H_{11}D_4OP$ requires: MW 222); ν_{max}^{KBr} 3030, 2200, 2100, 1700, 1590, 1445 cm^{-1}.

8-Phenyl-8-methyl-8-phosphonium-bicyclo[3.2.1]*octan-3-one iodide* III. Compound I (2·2 g) was dissolved in acetone (50 ml) and MeI (1·7 g) was added, with stirring. The phosphonium salt precipitated out immediately as a white ppt. The salt was crystallized from water yielding 3·35 g (93%) m.p. 239–240° ν_{max}^{KBr} 3040, 1700, 1580, 1450 cm^{-1}; λ_{max} 252 (2·56), 260 (2·77), 266 (2·93), 272 (2·87) mμ. (Found: C, 46·62; H, 5·09; I, 35·09. $C_{14}H_{18}OP$ I. requires: C, 46·69; H, 5·04; P, 8·40; I, 35·24%).

8-Phenyl-8-benzyl-8-phosphonium-bicyclo[3.2.1]*octan-3-one chloride* IV. Compound I (2·2 g) was dissolved in freshly distilled acetonitrile (50 ml), and freshly distilled benzyl chloride (1·9 g) was added. The mixture was refluxed under N_2 overnight. After cooling and concentrating the volume of the acetonitrile to about half the original volume, a white solid was obtained. The salt was crystallized from EtOH–EtOAc m.p. 267–269°; ν_{max}^{KBr} 3050, 3020, 1705, 1580, 1565 cm^{-1}; λ_{max} 260 (3·09), 267 (3·20), 274 (3·08) mμ. (Found: C, 69·57; H, 6·47; P, 9·72; Cl, 10·58; $C_{20}H_{22}OPCl$. Requires: C, 69·66; H, 6·43; P, 9·22; Cl, 10·20%).

8-Phenyl-8-oxo-8-phosphabicyclo[3.2.1]*octan-3-ones* V *and* VI. The mixture of I and II (4·5 g) was dissolved in chloroform (60 ml) and 30% H_2O_2 (2·5 g) was added, dropwise, to the cooled soln. The heterogenous mixture was stirred vigorously for 2 hrs diluted with more chloroform and washed several times with a 5% $FeSO_4$ soln until a negative KI test was obtained, then washed again with water and dried over $MgSO_4$. Evaporation left a crystalline residue (4·6 g) which, after crystallization from acetonitrile, gave two different crystalline compounds: Compound V m.p. 235–237° (3·5 g); ν_{max}^{KBr} 3040, 1700, 1590, 1450, 1175, 810, 780, 750, 730, 690, 525, 495, 470 cm^{-1}; λ_{max} 253 (2·67), 259 (2·94), 265 (3·11), 271 (3·05) mμ. (Found: C, 66·66; H, 6·50; P, 13·13. $C_{13}H_{15}O_2P$, requires: C, 66·63; H, 6·46; P, 12·92%) and compound VI m.p. 247–278° (0·4 g); ν_{max}^{KBr} 3050, 3030, 1700, 1590, 1440, 1180, 800, 760, 730, 700, 550, 500 cm^{-1}; λ_{max} 254 (2·55), 260 (2·78), 266 (2·96), 273 (2·90) mμ. (Found: C, 66·52; H, 6·46; P, 13·29. $C_{13}H_{15}O_2P$, requires: C, 66·63; H, 6·46; P, 12·92%).

TABLE 2

Comp. / Protons	$\Delta\delta$ (c/s) C_1, C_5*	C_2, C_4	C_6, C_7	Ethylene-ketal
V	-40 ± 5	*a.* −7 *b.* −14	−7	—
VI	-37 ± 5	−4	*a.* −3 *b.* −10	—
VII	-54 ± 5	*a.* −3 *b.* −11	*a.* −5 *b.* 0	*a.* +3 *b.* +15
VIII	-47 ± 5	−1	*a.* −3 *b.* −11	0

a One pair of the protons.

b The second pair of the protons, most likely the pair which is geometrically nearer to the uranyl group.

* The ±5 c/s results from the uncertainty in the location of the C_1 and C_5 protons in the uncomplexed compounds.

2,2,4,4-d_4-*8-phenyl-8-oxo-8-phosphabicyclo*[3.2.1]*octan-3-ones*-d_4-V *and* d_4-VI. Compound V (100 mg), dissolved in a soln prepared from MeOD (8 ml), Na (100 mg) and D_2O (2 ml), was heated under N_2 for 1 hr, was cooled and evaporated under reduced press. The residue was dissolved in chloroform and washed with a small portion of D_2O. The chloroform soln was dried ($MgSO_4$) and evaporated to yield the crystalline oxide d_4-V (85 mg); ν_{max}^{KBr} 3040, 2200, 2100, 1700, 1590, 1445, 1175 cm^{-1}. (Found: $M^{\oplus}$222, $C_{13}H_{11}D_4O_2P$, requires: 222).

Compound d_4-VI was obtained by the same procedure as described for the preparation of compound d_4-V; ν_{max}^{KBr} 3050, 3030, 2200, 2100, 1700, 1590, 1445, 1180 cm^{-1}. (Found: $M^{\oplus}$222, $C_{13}H_{11}D_4O_2P$, requires: 222).

8-Phenyl-8-oxo-8-phosphabicyclo[3.2.1]*octan-3-ethylene ketals* VII *and* VIII. Compound V (100 mg) dissolved in benzene (25 ml) together with ethylene glycol (40 mg) was refluxed ozeotropically for 5 hr in

the presence of a catalytic amount of *p*-TsOH. The cooled soln was washed with 10% Na_2CO_3 aq, water, dried and evaporated to yield VII (100 mg) m.p. 180° (MeCN); ν_{max}^{KBr} 3040, 1590, 1445, 1175, 1110 cm^{-1}; λ_{max} 252 (2·56), 259 (2·84), 264 (3·06), 271 (3·00) mμ. (Found: C, 64·47; H, 6·91; P, 10·74. $C_{15}H_{19}O_3P$, requires: C, 64·74; H, 6·88; P, 10·88%).

Compound VIII was obtained by the same procedure, m.p. 192° (MeCN) ν_{max}^{KBr} 3050, 3030, 1590, 1450, 1180; 1110 cm^{-1}. (Found: C, 64·55; H, 6·90; P, 10·68, $C_{15}H_{19}O_3P$, requires: C, 64·74; H, 6·88; P, 10·88%).

2,2,4,4-d_4-*Ketals* d_4-VII *and* d_4-VIII. Compounds d_4-VII and d_4-VIII were obtained from d_4-V and d_4-VI respectively by the same procedure as described for VII.

Compound d_4-VII m.p. 180° (MeCN) (Found: M⊕282. $C_{15}H_{15}D_4O_3P$, requires: M⊕282).

Compound d_4-VIII m.p. 192° (MeCN) (Found: M⊕282. $C_{15}H_{15}D_4O_3P$, requires: M⊕282).

8-*Benzyl*-8-*phosphabicyclo*[3.2.1]*octan*-3-*one* (IX). A mixture of 2,6-cycloheptadienone (4·8 g) together with benzyl phosphine (5·4 g) was heated for 2 hr under N_2 at 150°, on an oil bath. Following high vacuum distillation of the unreacted reactants, the residue was separated by chromatography under N_2 on a silica gel column (Merck 7734). Elution with chloroform yielded IX (1·5 g) m.p. 150° (benzene–hexane); ν_{max}^{KBr} 3030, 1700, 1590 cm^{-1}. (Found: M⊕232. C, 72·63; H, 7·45; P, 13·32. $C_{14}H_{17}OP$, requires: M⊕232; C, 72·40; H, 7·38; P, 13·06%).

Further elution with $CHCl_3$–MeOH (95:5) yielded the corresponding oxide X m.p. 155° (benzene); ν_{max}^{KBr} 3040, 1700, 1590, 1180 cm^{-1}; λ_{max}^{KBr} 254 (2·04), 260 (2·07), 266 (2·00), 269 (1·89) mμ. (Found: C, 67·58; H, 6·91; P, 10·61, $C_{14}H_{17}O_2P$, requires: C, 67·73; H, 6·90; P, 11·20%).

8-*Benzyl*-8-*oxo*-8-*phosphabicyclo*[3.2.1]*octan*-3-*one*-X. Compound IX was oxidized under the same conditions as described for I and II yielding X which was identical in all respects with the compound obtained before by air oxidation.

8-*Benzyl*-8-*methyl*-8-*phosphonium*-*bicyclo*[3.2.1]*octan*-3-*one iodide* XI. Compound IX (550 mg) dissolved in acetone (5 ml) was treated with MeI (400 mg). Following the same work-up as described for the methiodide III, methiodide XII was obtained, m.p. 285° (H_2O); ν_{max}^{KBr} 3030, 3020, 1705, 1590 cm^{-1}; λ_{max}^{KBr} 253 (2·43), 259 (2·39), 266 (2·28), 269 (2·05) mμ. (Found: C, 48·08; H, 5·40; I, 34·14, $C_{15}H_{20}OPI$, requires: C, 48·15; H, 5·39; P, 8·09; I, 33·91%).

8-*Dibenzyl*-8-*phosphium*-*bicyclo*[3.2.1]*octan*-3-*one chloride* XII. Compound XIII was obtained from IX, by following the same procedure as described for the preparation of IV, yielding crystals, m.p. 208° (EtOH–EtOAc); ν_{max}^{KBr} 3040, 3020, 1705, 1600, 1580 cm^{-1}; λ_{max} 250 (2·56), 254 (2·70), 260 (2·86) 266 (2·76), 270 (2·56) mμ. (Found: C, 70·25; H, 6·80; P, 9·73; Cl, 10·65; $C_{21}H_{24}OPCl$, requires: C, 70·29; H, 6·74; P, 9·44; Cl, 9·98%).

Hydrolysis of compound IV. To a soln of IV (80 mg) in water (2 ml) a 2% NaOH aq (2 ml) was added dropwise, toluene was immediately detected. After 2 hr of stirring, the soln was neutralized by the addition of a 5% NCl aq and was extracted with chloroform. The chloroform was washed with water, dried and evaporated. The white solid thus obtained was crystallized from acetonitrile yielding a mixture of V and VI in the ratio of ca. 9:1 respectively.

Hydrolysis of compound XII. Hydrolysis of XII (100 mg) under the same conditions described for the hydrolysis of IV, gave an oily mixture of the two possible epimeric 8-methyl-8-oxo-8-phosphabicyclo-[3.2.1]octan-3-ones in ratio of ca. 3:1 according to the NMR spectrum data.

3,5-*Cycloheptadiene*-1-*acetate* XIII. 3,5-cycloheptadien-1-ol (2 g) dissolved in pyridine (10 ml) was heated on a steam bath for 1 hr with Ac_2O (4 ml). The cooled mixture was poured into crushed ice, which was then extracted several times with 100 ml portions of ether, the ether was washed with 10% HCl aq water, 5% $NaHCO_3$ aq and then with water again, dried and evaporated. The residue was distilled yielding XIII, b.p. 78–79°/7 mm (2·2 g); ν_{max}^{neat} 3000, 1740, 1100, 1600 cm^{-1}; NMR spectrum: δ 2·02 s ($OCOCH_3$) (3H); 2·56 t (J = 2) (allylic protons) (4H); 5·04–5·20 m (C-1-H) (1H); 5·60–6·10 m (olefinic protons) (4H).

3-*Acetoxy*-8-*phenyl*-8-*oxo*-8-*phosphabicyclo*[3.2.1]*octa*-6-*ene* XIV. 3,5-cycloheptadeiene-1-acetate (1·52 g) was mixed with dichlorophenylphosphine (1·63 ml) and a trace of copper stearate in an ampule and sealed under N_2. After 2 months, the mixture was poured into crushed ice, then extracted with several portions of 100 ml ether. The ether was washed with 5% $NaHCO_3$ aq, water, then dried and evaporated. The residue, after high vacuum evaporation at 100°, was chromatographed on a silica gel column (Merch 7734). Elution with chloroform gave XIV, m.p. 172–173° (EtOAc); λ_{max} 206 (4·17); 220 (4·08); 255 (2·67); 260 (2·84); 266 (2·96); 272 (2·89) mμ; ν_{max}^{KBr} 3040, 3000, 1735, 1630, 1590, 1440, 1240, 1180 cm^{-1}. (Found: C, 64·97; H, 6·20; P, 12·45. $C_{15}H_{17}O_3P$, requires: C, 65·21; H, 6·20; P, 13·11%).

3-*Hydroxy*-8-*phenyl*-8-*oxo*-8-*phosphabicyclo*[3.2.1-*octan*-6-*ene* XV. Compound XIV (100 mg) was left overnight in the presence of methanolic KOH (1%; 10 ml). The soln was neutralized by the dropwise

addition of 5% HCl aq and most of the solvent was removed under reduced press. The residue was diluted with ether, washed with water, dried and the solvent removed. The product was crystallized from EtOAc, m.p. 254°; ν_{max}^{KBr} 3350, 1425, 1330, 1250, 1190, 1160, 1020, 1065, 1040, 1005, 995 cm^{-1}. (Found: C, 66·72; H, 6·53; P, 12·03; $C_{13}H_{15}O_2P$, requires: C, 66·63; H, 6·46; P, 12·92%).

8-Phenyl-8-oxo-8-phosphabicyclo[3.2.1]*-octan-6-en-3-one* XVI. To a cooled, stirred soln of XV (50 mg) in acetone (10 ml) Jones reagent was added. After 1 hr (at 0–5°) the excess of reagent was destroyed by adding a few drops of MeOH and the solvent was removed under reduced press. The residue was diluted with ether, washed with water, dried and the solvent was removed. Crystallization from EtOAc yielded XVI, m.p. 207–208° ν_{max}^{KBr} 1700, 1430, 1250, 1190, 1165, 1120, 990 cm^{-1}. (Found: C, 67·40; H, 5·38; P, 12·91. $C_{13}H_{13}O_2P$, requires: C, 67·24; H, 5·64; P, 13·34%).

Hydrogenation of compound XVI *to* V. Compound XVI (10 mg) in abs EtOH (10 ml) was hydrogenated over 10% PtO_2 on charcoal at atm press and room temp for 15 hr. The product obtained following the work-up was identical in all respects with V.

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