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THE SYNTHESIS OF A PHOSPHADECALONE SYSTEM

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Abstract—The 2-phosphabicyclo[4.4.0]decan-5-onic system (2) was synthesized by a double Michael addition of phenylphosphine to propenylcyclohexenyl ketone (1). This dienone (1) can be prepared starting from either cyclohexanone by a known method, or from cyclohexene by its acylation with crotonic anhydride in the presence of $SnCl_4$. The NMR of the phosphine and several of its derivatives in comparison with the aza analog, as well as the Mass spectra fragmentation pattern, are discussed.

Being interested in the synthesis of phosphasteroids,[1] several approaches directed towards the preparation of phosphaheterocyclic systems by ring closure to a phosphorinane on an already existing mono or polycyclic ring system were undertaken.[2]

Herewith, we report the synthesis of the 2-phosphabicyclo[4.4.0]-decan-5-one system, starting from cyclohexene or cyclohexanone, by a double Michael addition of $PhPH_2$ to a a suitable dienonic intermediate, i.e., propenylcyclohexenylketone (**1**) a method which has already been utilized by us in the preparation of several other phosphabicyclic compounds.[3] Propenylcyclohexenylketone (**1**) was obtained by the acylation of cyclohexene with crotonic anhydride in the presence of $SnCl_4$ at − 20°; conditions similar to those used in the acylation of 1,3,3-tri-methyl-cyclohex-1-ene,[4] however, in contrast to the latter, double bond migration does not occur. Indeed, compound **1** was obtained together with 1-methyl-4,5,6,7-tetrahydroindan-3-one, which was found to be the exclusive product when crotonic acid instead of the anhydride was used, being a result of the acidic catalysed electrocyclyzation process.[5] Although the indanone could be removed by fractional distillation, its presence did not disturb the course of the addition reaction. Among other methods suitable for the dienone synthesis, starting from ketones in order to expand the scope of the reaction, was the one developed by Nazarov,[6] adding vinylacetylene to cyclohexanone followed by elimination and water addition to the triple bond, or in much lower yield the cyclohexenyl-lithium addition to acrolein or crotonaldehyde followed by MnO_2 oxidation;[7] our experience with the latter method, as mentioned by Nazarov, starting from cholestanone, was unsatisfactory.

Reacting **1** with phenylphosphine, monitored by IR spectrum, under nitrogen atmosphere at 120° for *ca* 1 h gave, after chromatography, the expected phosphadecalone **2**, (Scheme 1). Compound **2** turned out to be, according to the NMR spectrum (appearance of two double of doublets at δ 0·93 ($J_{\underline{P}CC\underline{H}_3}$ = 16·5 and $J_{C\underline{H}C\underline{H}_3}$ = 7 Hz) and δ 1·27 ($J_{\underline{P}CC\underline{H}_3}$ = 13 and $J_{C\underline{H}C\underline{H}_3}$ = 7 Hz)) an inseparable mixture of two isomers (**2a** and **2b**) in different amounts. However, upon oxidation with H_2O_2, the oxide of the main isomer (**3a**) could be crystallized out separately; m.p. 180° (CH_3CN) NMR: δ 1·07 dd ($J_{\underline{P}CC\underline{H}_3}$ = 15, $J_{C\underline{H}C\underline{H}_3}$ = 7 Hz; $C—C\underline{H}_3$), 2·6–3·4 m (C-4, C-6 three protons). For NMR as well as mass spectrum study, the trhee-deuterio compound d_3-**3a** was prepared, by boiling **3a**, which was found to be stable under basic conditions, with NaOD in MeOD; in the NMR spectrum of d_3-**3a** the multiplet of the protons adjacent to the carbonyl at δ 2·6–3·4 disappeared. The mass spectra of **2**,**3a** and d_3-**3a**, shown in Scheme 2, exhibited much similarity in the fragmentation pattern to that of 1-methyl-4-phosphorinanone studied by Toube,[8] thus further support the proposed structures. Additional derivatives of **2a**, namely the methiodide (**4**) and benzyl phosphonium salt (**5**) gave after crystallization as far as could be seen from the NMR spectrum only the derivatives of the main isomer (**2a**) (e.g., in the case of **4** δ 1·26 dd (3H, $J_{\underline{P}CC\underline{H}_3}$ = 18 and $J_{C\underline{H}C\underline{H}_3}$ = 7·2) and 2·72 d ($J_{\underline{P}—C\underline{H}_3}$ = 13 Hz)).

Of interest was the comparison of compound **2** with its aza analog **6** which has already been prepared by Nazorov[9] by adding aniline and formaldehyde to 1-acetylcyclohexene, and was synthesized by us in the same manner as **2** except for the use of aniline as the nucleophile.† Compound **6**‡ turned out to be a mixture of two isomers each one

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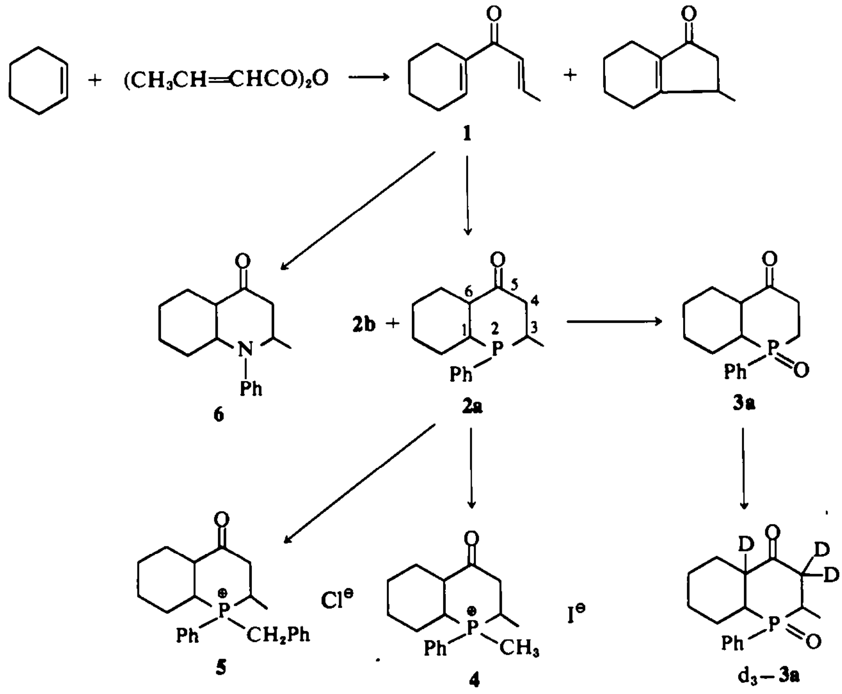
†Attempts to prepare compound **2** by reacting phenylphosphin instead of aniline with formaldehyde and 1-acetyl-cyclohexene in the presence of catalytic amounts of base, failed.

‡The mass fragmentation of **6** behaves very similarly to that of 1-methyl-4-piperidone[8]: *m/e* 243 (M^+, 100%); 201 ($M—CH_2{=}C{=}O$; 57%) 200(201—H, 95%); and 228 ($M—CH_3$, 70%).



SCHEME 1

exhibiting a separate ABX system (δ_{A_1} 2·57 dd ($J_{A_1B_1} = 17$, $J_{A_1X_1} = 7$), δ_{B_1} 2·81 dd $J_{B_1X_1} = 4{\cdot}5$), δ_{A_2} 2·59 dd ($J_{A_2B_2} = 16{\cdot}5$, $J_{A_2X_2} = 7{\cdot}5$), δ_{B_2} 2·83 dd ($J_{B_2X_2} =$ 4 Hz) and $\delta_{\;1}$, δ_{X_1}, δ_{X_2} 4·0 m) for the C-3, C-4 protons, thus showing an equatorial C-2-Me position in both cases, leaving the *cis*, *trans* isomerization to be the only distinguishing factor between them. Treatment of **6** with base in order to obtain the *trans* isomer exclusively, as was found in the case of N-Methyl-4-keto-decahydroquinoline[10] failed as **6** decomposed. We assume that the C-3-Me in the phospha compounds is equitorial as well. Furthermore, as no isomerizations occur on basic treatment of **3a** we prefer the *trans* configuration as in the aza compounds, and an equatorial phenyl in the main oxide **3a**; this assumption is in accordance with the paramagnetic shift of *ca* 0·5 ppm of the C-4, C-6 protons, α-to the carbonyl in **3a** as compared to **2a** due to the anisotropic paramagnetic effects of the P=O group in the former. The principle embodied in this synthetic sequence is now being further investigated in polycyclic compounds.

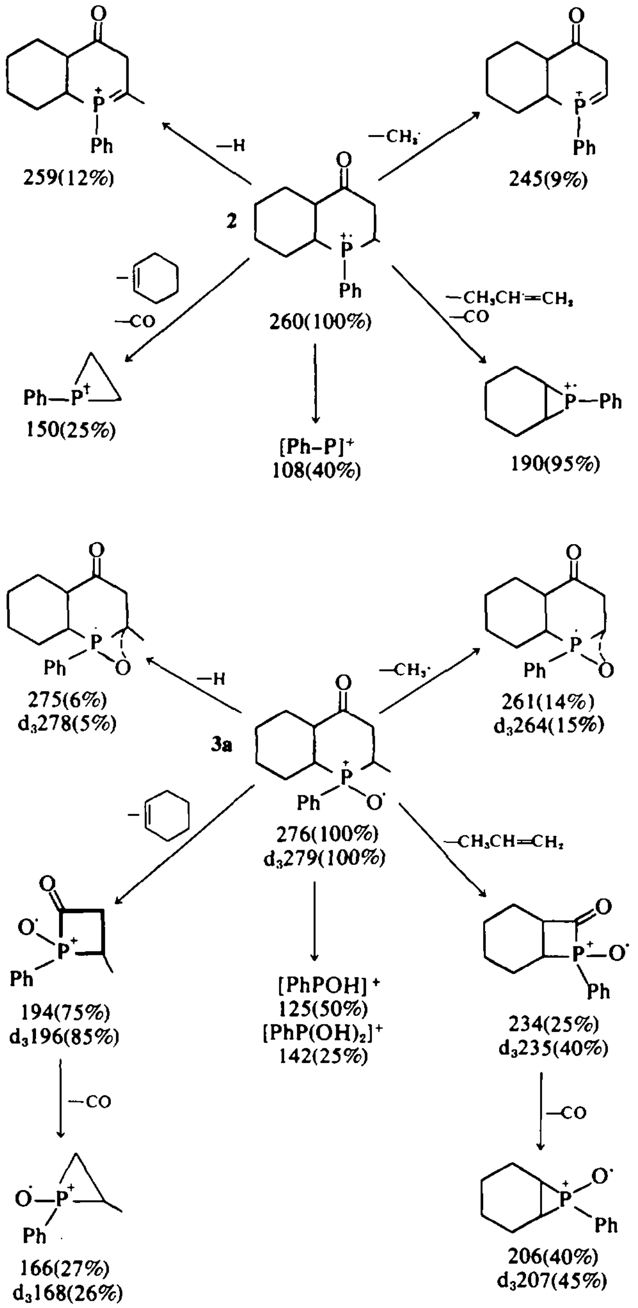
EXPERIMENTAL

M.ps were taken on a Unimelt Thomas and Hoover's Capillary m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord model 337 spectrophotometer NMR spectra were taken on a Varian HA-100 or Jeol JMN-C-60 HL spectrometers using 5–10% solutions in $CDCl_3$, with TMS as an internal standard. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 instrument.

1-*Propenylcyclohex*-1′-*enylketone* (**1**). To a soln of crotonic anhydride (6·2 g) dissolved in dry CH_2Cl_2(50 ml), $SnCl_4$ (20 g) were slowly added with stirring at − 20°, followed by a soln of cyclohexene (3·2 g) in dry CH_2Cl_2 (10 ml). The solution was stirred at − 20° for an additional h, then poured on ice water (30 g). The organic layer was separated, washed 3 times with 10% Na_2CO_3, water then dried (Na_2SO_4) and the solvent evaporated. Compound **1** was obtained pure after fractional distillation at 72°–74°/0·4 mm (lit. 64°–65°/0·3 mm), $\nu_{max}^{CHCl_3}$ 2910, 1680, 1655, 1625, 1605, 1455, 960 cm^{-1}. NMR ($CDCl_3$) δ 1·65 m (4H), 1·86 dd (J = 5 and 2 Hz, 3H), 2·2 m (4H), 5·5–7·1 m (3H).

2-*Phenyl*-3-*methyl*-2-*phosphabicyclo* [4.4.0] *decan*-5-*one* (**2**). A mixture of **1** (4 g) and phenylphosphine (3·7 g) was heated for 1 h under N_2 at 115–120° on an oil bath. When the reaction was over, depending on the IR spectrum of the mixture (i.e. disappearing of the band at 1660 cm^{-1} and appearance of the CO band at 1700 cm^{-1}) the soln was cooled to room temp and then purified by chromatography under N_2 on a silica gel column (Merck 7734). Elution with light petroleum ether; $CHCl_3$ (1; 1) yielded **2** (3 g) as a white crystalline compound, ν_{max}^{KBr} 3060, 1700, 1430, 1320, 1200, 1095, 1000, 890 cm^{-1}, NMR ($CDCl_3$) δ 0·93 dd (J = 16·5, J = 7 Hz), 1·27 dd (J = 13, J = 7 Hz); 1·2–2·2 m (8H); 2–3·3 m (5H) and 7·5–7·8 m (5H). (Found: *m/e* 260, $C_{16}H_{21}OP$ requires: 260).

2-*Phenyl*-2-*oxo*-3-*methyl*-2-*phosphabicylo* [4.4.0] *decan*-3-*one decan*-3-*one* (**3a**) & (**3b**). Compound **2** (1 g) was dissolved in chloroform (20 ml) and 30% H_2O_2 (1 g) was added. The heterogeneous mixture was stirred vigorously for 12 h, diluted with more chloroform and washed several times with a 5% $FeSO_4$ soln until a negative KI test



SCHEME 2

was obtained, then washed again with water and dried over Na_2SO_4. Evaporation left a crystalline residue (0·8 g) which after filtrating through a silica gel column was crystallized from acetonitrile to give pure isomer **3a** (0·6 g) m.p. 178°–180°, ν_{max}^{KBr} 1705, 1435, 1175, 1110, 915, 745, 720, 690, 555, 525 cm^{-1}. (Found: C, 69·37; H, 7·57; P, 11·03; $C_{16}H_{21}O_2P$ requires: C, 69·47; H, 7·61; P, 11·23%) NMR ($CDCl_3$) δ 1·07 dd (J = 15; J = 7 Hz: 3H), 1·7 m (8H), 2·2–2·6 m (2H), 2·7–3·5 m (3H), 7·5–7·9 m (5H). Compound **3b** could not be obtained in a pure state.

4, 4, 6-d_3-2-*phenyl*-2-*oxo*-3-*methyl*-2-*phosphabicyclo* [4.4.0]*decan*-3-*one* (d_3-**3a**). Compound **3a** (100 mg dissolved in a solution prepared from CH_3OD (4 ml), Na (100 mg) and D_2O (3 ml), was heated under N_2 for 1 h, then cooled and evaporated under reduced press. The residue was dissolved in $CHCl_3$ and washed with a small portion of D_2O, then dried (Na_2SO_4) and evaporated to yield the crystalline oxide d_3-**3a** (80 mg) m.p. 177–181° (CH_3CN);

ν_{max}^{KBr} 3040, 2900, 2200, 2100, 1700, 1435, 1175, 1100, 1020, 740, 715, 690, 650, 550, 510 cm^{-1}. (Found: *m/e* 279 $C_{16}H_{18}D_3O_2P$ requires: 279).

2-*Phenyl*-2,3-*dimethyl*-2-*phosphoniumbicyclo* [4.4.0] *decan*-5-*one iodide* (4). Compound 2 (0·5 g) was dissolved in acetone (5 ml) and MeI (0·55 g) was added. The phosphonium salt precipitated out immediately as a white ppt. The salt was crystallized from acetone. 0·6 g, m.p. 215°–216°, ν_{max}^{KBr} 2900, 1710, 1435, 1310, 1110, 920, 885, 760, 740, 710, 690, 470 cm^{-1}. (Found: C, 50·61; H, 5·79; P, 7·68; I. 31·70; $C_{17}H_{24}POI$ requires: C, 50·74; H, 5·97; P, 7·71; I, 31·59%). NMR ($CDCl_3$) δ 1·26 dd (J = 18 and 7 Hz); 1·4–2·0 m; 2·72 d. (J = 13 Hz, P–CH_3), 3·0–4·1 m (5H), 7·75 m (3H) and 8·20 m (2H, Ph),

2-Benzyl-2-phenyl-3-methyl-2-phosphoniubicyclo [4.4.0] *decan-5-one chloride* (**5**). Compound **2** (200 mg) was dissolved in acetonitrile (5 ml), and feshly distilled benzyl chloride (400 mg) was added. The mixture was refluxed under N_2 for 2 h. After cooling, a white solid was obtained. The salt was crystallized from acetonitrile m.p. 262°–263°, ν_{max}^{KBr} 1720, 1590, 1440, 1110, 995, 850, 780, 740, 730, 705, 690, 490 cm^{-1}, NMR (D_2O) δ 1·08 dd (J = 17 and 6·5 Hz, CH_3), 1·4–2·2 m, 2·5–3·6 m, 4·5 m (CH_2Ph) 7·4 brs (5H), 7·9 m (3H) and 8·15 m (2H, Ph).

2-*Phenyl*-3-*methyl*-2-*azabicyclo* [4.4.0] *decan*-5-*one* (**6**). A mixture of **1** (2·8 g) and aniline (2·8 g) was dissolved in dioxane; water (2; 1) (30 ml), and was heated to reflux overnight. After cooling the solvent was removed under reduced pressure and the oily residue chromatographed through a silica gel column to give after elution with light petroleum; $CHCl_3$ (1; 1) an oily product (2 g), ν_{max}^{neat} 2910, 1705, 1600, 1495, 1450, 1310, 1145, 1105, 985 cm^{-1}. (Found *m/e* 273(100%) as required) NMR ($CDCl_3$) δ 1·21 d (J = 6·5 Hz), 1·7 m, 2·3–3·1 m, 3·7–4·2 m, 6·5–7·2 m.

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