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PHOSPHORUS HETEROCYCLE SYNTHESIS USING $RPX_2 \cdot AlX_3$ ADDITION TO 1,4-DIENES—1

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Abstract—A new synthetic sequence of phosphorus heterocycles was developed using $RPX_2 \cdot AlX_3$ complex addition to 1,4-dienes. For example, the reactions of $PhPX_2$ (X=Cl, Br), CH_3PCl_2 and PCl_3—$AlCl_3$ complexes with 1-allyl-cyclohex-1-ene to give two isomeric 2-phosphatricyclo [4.4.0.0^{4,6}] decanes (i.e. **2** and **4**) accompanied by a phosphorus acid chloride (**3**) are described. Several transformations of **2** into other ring systems, namely phosphadecaline and perhydrophosphindoline are mentioned.

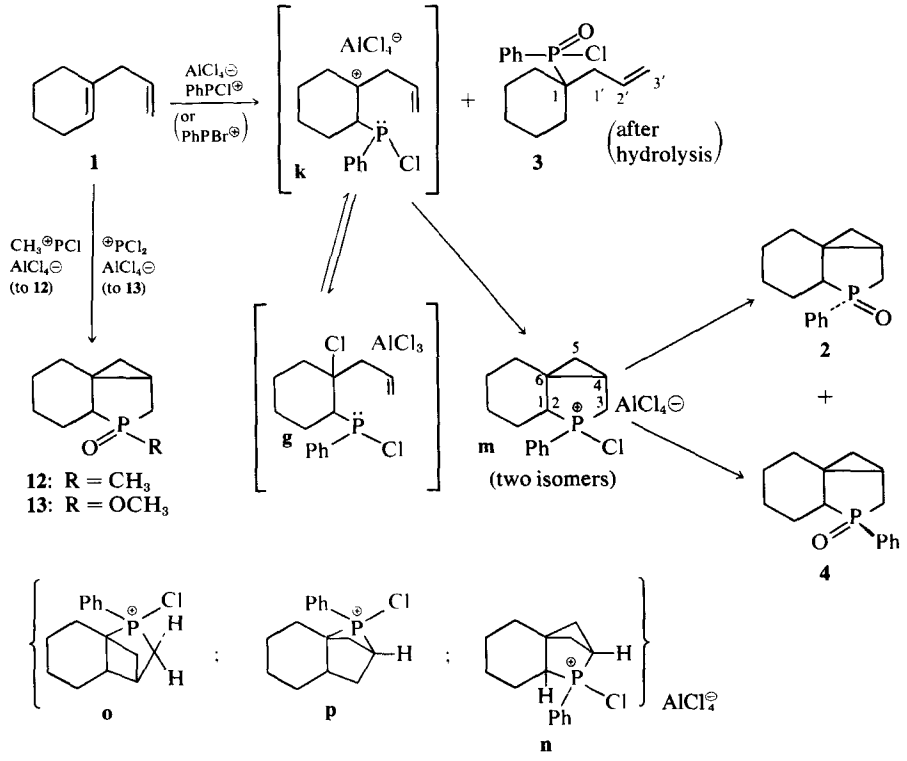
Olefins are known to react with $RPX_2 \cdot AlX_3$ complexes to give C-P bonds,[1] a reaction which has already been utilized by Jungermann, McBride[2] and others[3] in the preparation of phosphetanes using olefins such as 2,4,4-trimethyl-2-pentene as starting materials. Olefins in which a methyl group vicinal to the double bond is available, after the initial p^+ attack, for a 1,2-shift, thereby yield the more stable tertiary carbonium ion which can then undergo ring closure with the phosphorus to give the phosphetane.

It was interesting to check the possibility of preparing other phosphorus heterocycles by this type of reaction in which instead of methyl or hydrogen 1,2-shifts, a double bond should migrate. 1,4-dienes were chosen as substrates for this synthesis for which a priori several routes of cyclization could be described, each leading to different heterocycles (cf Scheme 1).

Various phosphorus heterocycles were indeed obtained by the use of different 1,4-dienes as substrates; the results of the reaction with 1-allyl-cyclohex-1-ene (**1**)[4] are reported herewith.

Addition of **1** to a preformed complex from phenylphosphonous dichloride and aluminium chloride in CH_2Cl_2 at 0° gave, after 5 hr, and following quenching in water, two main compounds which could be separated by chromatography: compound **2** m.p. 153–155°, $C_{15}H_{19}PO$, and compound **3**, an oil, $C_{15}H_{20}ClPO$; IR, ν_{max} 2950, 2900, 2840, 1220 (P=O), 910 (C=CH_2) 690 cm^{-1}, mass spectrum: *m/e* 282 (25%, M^+), 247 (2%, M—Cl), 241 (9%, M—CH_2CH=CH_2), 161, 163 (20% and 7%, $Ph\overset{+}{P}H(OH)Cl$), 160, 162 (17% and 6%, $Ph\overset{+}{P}(OH)Cl$), 125 (15%, $Ph\overset{+}{P}(OH)$), 122 (65%, M—PhP(OH)Cl), 81 (100%, 122—CH_2CH=CH_2) and 77 (60%, Ph), NMR ($CDCl_3$): δ 5·66–5·84 m and 6·46–6·87 m (—CH=CH_2), 3·22 m (J_{PH} = 27 Hz, two allylic protons). Compound **3** was thought to be the hydrolyzed addition product of $PhPCl_2$ to the trisubstituted double bond of **1**, obtained from the initial attack of $Ph\overset{\oplus}{P}Cl\ AlCl_4^{\ominus}$ at C-2 (to give **g**)† which is believed to be the first step in the synthesis of **2**. However, the NMR spectrum of **3** pointed to a linkage of the phosphorus to C-1, as the two C-1′, allylic protons were coupled with the P-atom to the extent of 27 Hz in accordance with a $^3J_{PH}$ coupling constant and excluding a $^4J_{PH}$ one (known to be 1-4 Hz)[5]. Furthermore, the mass spectrum pointed to a P(O)PhCl group which could be confirmed by the exchange of the chlorine atom by OMe, using NaOMe in MeOH (the NMR was identical with that of **3** except for an additional doublet at δ 3·64 J = 10·5 Hz); the mechanism for obtaining **3** is now being investigated. Compound **2** on the other hand did not contain chlorine or double bonds and according to the elemental analysis and mass spectra had to be a phosphatricyclic compound, one of four possible structures obtained from the intermediates **m–p** (Scheme 1). A priori, intermediates **m** and **n** should be preferred to **o** and **p** since they are obtained from a tertiary homoallylic carbonium ion, however, the distinction between the two is not clear cut. Although in the NMR spectrum of **2**, two protons which resonate at high field (δ 0·4–0·8) could be best attributed to a cyclopropanic ring supporting structure **m**, the presence of this moiety required further evidence as the influence of the phenyl and P=O groups' anisotropy on the various skeleton protons could only be estimated with diffi-

†Compound **g**, which was not isolated by itself, could in principle undergo ring closure by a second internal attack of a possible newly formed $R_2PX\ AlX_3$ complex. Although in this case such a product could not be isolated from the mixture, it was the main product obtained from other 1,4-dienic systems.



SCHEME 1.

culty. It was thus essential to determine the number of protons vicinal to the P-atom in order to distinguish between structures **m–p**. For this task, compound **2** was reduced by $HSiCl_3$[6] to **5** and, following addition of methyliodide, the corresponding phosphonium salt **6** was obtained. As expected, the protons vicinal to the P-atom were paramagnetically shifted, emerging from the methylenic envelope, and it turned out that three such protons existed, thereby cancelling out all other possible structures for **2** except the one including the cyclopropanic ring obtained from **m**.

An interesting similarity was found between the above reaction and the cycloaddition of CH_3PCl_2 to norbornadiene,[7] both resulting in similar products. However, although both dienes were 1,4-situated, compound **1** failed to react under the mild cycloaddition conditions, most probably because of the unfavored geometry causing less overlap between the two double bonds.

Performing the reaction on **1** with $PhPBr_2$ instead of $PhPCl_2$ and $AlCl_3$ (or $AlBr_3$) resulted in an additional compound (**4**), which accompanied compounds **2** and **3** and was isolated in the former case only in minute quantities. In this compound the presence of the cyclopropanic ring was obvious according to the NMR spectrum as the corresponding protons resonated at δ 0·1–0·3, a much higher field as compared to **2**; compound **4** therefore seems to be the P-epimer of **2**. The fact that **4** was obtained in higher yields using $PhPBr_2$ instead of $PhPCl_2$ can be best explained by the smaller difference in size between the phenyl and bromine groups as compared with the phenyl and chlorine which makes the bromine competitive to the phenyl in the intermediate.

Although **4** was only obtained in small quantities, it was important for the stereochemistry study; we assume the β-direction (the same direction as the cyclopropanic ring towards the perhydrophosphindoline) for the P=O group in compound **2** and the α-direction for it in **4**, on the basis of the following reasons:

a. The C-5-protons in **2** resonate at δ 0·9–1·2 in comparison to 0·1–0·3 found for **4**, due to the paramagnetic shift of the β (P=O) group in the former.

b. The 3α-proton which can unequivocally be identified in **2** at δ 2·7 giving a double doublet (J = 15, and 4·5 Hz) after P-irradiation, in a heterodecoupling experiment, is shifted upfield in the P-cyclohexanic analog (**8**) derived from **2** (*vide infra*), due to cancelling of the phenyl paramagnetic shift which had a greater influence in **2**.

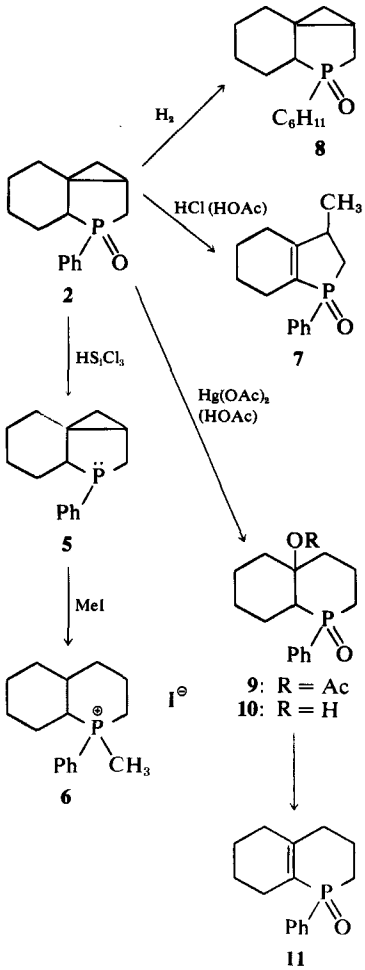
c. Complexation of **2** (and **12**) by $Eu(fod)_3$ causes the downfield shift of several protons among which

the 5β-proton showed a Δδ value of 3·9 ppm similar to 4·5 ppm found for 3β-H (for a substrate/Eu(fod)$_3$ ratio of *ca* 1).

In this complexed spectra a third broad signal was found to be shifted by the same order of magnitude (Δδ 4·5 ppm) as 3β-H and 5β-H, pointing at first glance to a *cis* (1β-H) ring junction of the perhydrophosphindoline system in which the 1β-proton is the corresponding one, but further consideration could not exclude the *trans* (1α-H) configuration in which the above broad signal could be attributed to the 10β-proton, thus leaving this problem open until further evidence will be available.

With the purpose of checking the possibilities of changing **2** into other phosphorus heterocycles, several reactions directed to open the cyclopropanic ring were performed on **2** (Scheme 2).

Acidic treatment (boiling conc. HCl) gave compound **7** in which, according to the NMR spectrum (δ 1·22d (J = 6 Hz); >CH—CH$_3$, and no other low field signals) the C_5—C_6 bond was cleaved to give a tetrasubstituted double bond and a secondary Me group. Opening of the 3-membered ring, on the other hand, by hydrogenation at room temperature and atmospheric pressure or even 60–100 psi failed, the only site which was reduced was the phenyl group (comp **8**). This tendency to undergo easy saturation was already found by us in several cases.[8]



SCHEME 2.

Among other conditions which were studied in order to open the cyclopropanic ring, $Hg(OAc)_2$[9] in acetic acid was found to be efficient in opening, this time, the C_4—C_6 bond to give the phosphadecalinic system **9**. The NMR of **9** showed clearly the disappearance of the cyclopropanic ring and the entering of a tertiary acetoxy group; hydrolysis of the acetate gave the alcohol **10** which then by elimination with $SOCl_2$ gave the unsaturated phosphine oxide **11** (Scheme 2). The above reactions clearly show the use of the synthesis for the preparation of several P-heterocycles. Similar to the synthesis of **2**, compounds **12** and **13** were obtained, starting with $PCl_3 \cdot AlCl_3$ or $CH_3PCl_2 \cdot AlCl_3$ respectively. The P=O orientation in these compounds seems to be as in **2**, according to the similar 5β-proton shift by Eu(fod)$_3$ in the NMR spectrum.

EXPERIMENTAL

M.ps were taken on a Unimelt Thomas & 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 either on a Varian HA-100 spectrometer or a JEOL JNM-C-60HL spectrometer on 5–10% solns. in $CDCl_3$ (unless otherwise indicated), containing TMS as an internal standard. Mass spectra were taken with a Hitachi-Perkin-Elmer RMU-6 instrument.

Reaction of phenylphosphonous dichloride (or dibromiae) with 1-allylcyclohex-1-ene[4]. (**1**). To a stirred soln of $AlCl_3$ (1·0 g) and $PhPCl_2$ (1·36 g) in dry CH_2Cl_2 (20 ml) a soln of **1** (0·9 g) in CH_2Cl_2 (10 ml) was slowly added at 0°. The mixture was stirred under N_2 at room temp for 5 hr, then ice water was slowly added, the two phases separated, and the aqueous soln extracted several times with CH_2Cl_2. The combined CH_2Cl_2 soln was washed with small portions of 5% $NaHCO_3$ aq, then water, dried (Na_2SO_4) and evaporated yielding a viscous oil (1·54 g) which was then chromatographed on silicagel column; elution with EtOAc gave **2** (0·5 g), whereas **3** (0·8 g) and **4** (0·05 g) needed 5% MeOH-EtOAc to be eluted. 2-phenyl-2-oxo-2-phosphatricyclo [4.4.0.0^{4,6}] decane (**2**); m.p. 153°–155° (CH_2Cl_2-cyclohexane), ν_{max}^{KBr} 2950, 1440, 1180, 1130, 1100, 1020, 820, 740, 690 cm^{-1}. NMR ($CDCl_3$), after P-irradiation at 24.286.820 Hz, δ 0·4–0·6 m (C-4-H), 1·0–1·9 m (10 H, C_5, C_7—C_{10} protons), 2·2 d (C—3β—H, $J_{H_{3\alpha}H_{3\beta}}$ = 15 Hz, $J_{H_4H_{3\beta}}$ = 0 Hz), 2·7 dd (C—3α—H, $J_{H_4H_{3\alpha}}$ = 4·5 Hz), 2·1 dd (C—1—H, J = 12 and 4·5 Hz (estimated)), 7·4–7·9 m (Ph, 5H). Mass spectrum *m/e*: 246 (100%, M^+), 231 (7%, $[M—CH_3]^+$), 218 (11%, $[M—Et]^+$), 205 (15%, $[M—C_3H_5]^+$), 125 (17%, PhP(OH)), 121 (20%), 93 (25%), 91 (21%), 81 (37%) and 79 (50%). (Found: C, 72·97; H, 7·77; P, 12·56; $C_{15}H_{19}PO$ requires: C, 73·15; H, 7·77 and P, 12·57%).

Compound **3**, an oil ν_{max}^{neat} 2950, 2900, 2840, 1450, 1430,

1220, 1100, 915, 690 cm^{-1}; NMR ($CDCl_3$) δ 1·6 brs (10 H), 3·22 m (2H, J_{PH} = 27 Hz), 5·66–6·84 m (2H) and 6·46–6·87 m (1H, —CH=CH$_2$), 7·6 m (3H) and 7·8 m (2H, Ph). (Found: *m/e* 282 (15%); $C_{15}H_{20}$ ClPO requires: M^+ *m/e* 282).

Compound **4**, m.p. 94°–95° (CH_2Cl_2-cyclohexane). Very hygroscopic crystals, $C_{15}H_{19}PO$, ν_{max}^{neat} 2910, 2850, 1450, 1200, 1170, 1140, 1125, 1100, 1000, 900, 870, 810 cm^{-1}, mass spectrum *m/e*: 246 (80%, M^+), 231 (14%, $[M—CH_3]^+$), 231 (14%, $[M—CH_3]^+$), 218 (14%, $[M—Et]^+$), 217 (14%), 204 (11%, $[M—C_3H_6]^+$), 153 (11%), 149 (14%), 140 (17%), 125 (35%, PhPOH), 121 (25%); NMR ($CDCl_3$) δ 0·1–0·3 m (two cyclopropanic protons), 0·8–2·2 m (9H, C_7—C_{10} + one cyclopropanic proton), 2·3–2·8 m (3H, C—3—H and C—1—H), 7·3–7·9 m (5H, Ph). Performing the reaction with $PhPBr_2$ yielded compounds **2** and **4** in ratio of ~2:4 respectively.

2-Phenyl-2-methyl-2-phosphonium-tricyclo [4.4.0.0^{4,6}] *decane iodide* (**6**). To a stirred soln of **2** (100 mg) in dry benzene (10 ml) an excess of $HSiCl_3$ (1·5 ml) was added in one portion. The mixture was stirred under N_2 at r.t. for 1/2 hr and then refluxed for 2 hr. After cooling, N_2-purged water (5 ml) were added, causing the precipitation of a white solid. The mixture was filtered under N_2, yielding a turbide benzene soln. The white solid was washed twice with 10 ml portions benzene. The combined benzenic soln was washed with 5% $NaHCO_3$ aq, then water, dried (Na_2SO_4) and evaporated yielding a viscous oil. This oil was immediately dissolved in acetone (3 ml) and MeI (0·5 ml) added. The phosphonium salt precipitated out immediately as a white ppt m.p. 192°–193° (acetone), ν_{max}^{KBr} 2900, 2860, 2830, 1450, 1440, 1230, 1150, 1105, 1095, 1035, 1020, 960, 900, 820, 750 cm^{-1}.

NMR($CDCl_3$), after P-irradiation at 24.286.470 Hz, δ 0·7–0·9 m (two cyclopropanic protons), 1·1–1·2 m (one cycloproponic proton), 1·3–2·2 m (8H), 3·15 d (C-3β-H, $J_{H_{3\alpha}H_{3\beta}}$ = 15 Hz), 3·4–3·9 m (C-3α-H and C-1-H), 2·60 d ($J_{P\text{-}CH_3}$ = 14 Hz), 7·6–8·4 m (5H, Ph). (Found: C, 51·60; H, 6·00; $C_{16}H_{22}$ IP requires: C, 51·55 and H, 5·96%).

Acidic opening of compound **2** *to* **7**. A soln of **2** (500 mg) in conc HCl (30 ml) was refluxed for 5 hr. After cooling the aqueous soln was extracted with $CHCl_3$ the organic soln was washed with 5%-$NaHCO_3$-aq, then water, dried (Na_2SO_4) and evaporated yielding an oil (400 mg). Upon chromatography on a silica gel column **7** (300 mg) eluted with 5%-MeOH-EtOAc was obtained. $C_{15}H_{19}PO$, an oil, ν_{max}^{neat} 2990, 2900, 2850, 1620, 1450, 1440, 1150, 1120, 1050 cm^{-1}; NMR ($CDCl_3$) δ 1·22 d (C-CH_3, J = 6 Hz), 1·4–2·9 m (all other protons) and 7·7–8·3 m (5H, Ph); mass spectrum *m/e*: 246 (100%, M^+), 245 (47%), 231 (55%, $[M—CH_3]^+$), 218 (8%, [m—Et]$^+$), 125 (14%, PhPOH), 121 (8%) 107 (10%), 105 (7%), 93 (10%) and 91 (20%).

Hydrogenation of compound **2** *to* **8**. Compound **2** (250 mg) in EtOH (20 ml) was hydrogenated over 10%-PtO_2 on charcoal at atm press or 100 PSI at r.t., for 48 hr. The product obtained following evaporation of the solvent was crystallized from CH_2Cl_2-cyclohexane; $C_{15}H_{25}PO$, m.p. 201°, ν_{max}^{KBr} 2900, 2850, 1450, 1190, 1130, 910, 850, 820, 775, 745 cm^{-1}. Mass spectrum *m/e*: 252 (50%, M^+), 237 (5%, $[M—CH_3]^+$, 224 (5%, [M-Et]$^+$), 211 (9%, $[M—C_3H_5]^+$), 210 (7%, $[M—C_3H_6]^+$), 171 (24%, $[M—C_6H_9]^+$) 170 (100%, $[M—C_6H_{10}]^+$). NMR ($CDCl_3$) δ 0·3–0·6 m (1H, cyclopropanic), 0·8–2·3 m (all other protons).

Opening of the cyclopropanic ring in **2** *to give* **9**. A soln of **2** (500 mg) and $Hg(OAc)_2$ (1 g) in glacial AcOH (25 ml) was heated on an oil bath at 75° for 72 hr. After cooling ice-water (50 ml) was added, and the aqueous soln extracted several times with $CHCl_3$. The combined organic soln was washed with 5%-$NaHCO_3$ aq, then water dried (Na_2SO_4) and evaporated to give the product (400 mg) which was cleaned by chromatography on a silica gel column, eluted with 5%-MeOH-EtOAc. $C_{17}H_{23}PO_3$; m.p. 213°–214° (CH_2Cl_2-cyclohexane), ν_{max}^{KBr} 2920, 2850, 1710, 1230, 1150, 1110, 940, 830, 730, 690 cm^{-1}; mass spectrum *m/e*: 306 (100%, M^+), 263 (31%, M-$COCH_3$), 246 (72%, M-HOAc), 245 (80%, 246-H), 244 (23%), 231 (14%, M-HOAc-CH_3); NMR ($CDCl_3$) δ 1·0–1·9 m (7H), 2·28 s ($OCOCH_3$), 2·14 m (1H) 2·4–3·0 m (5H), 3·2–4·0 m (2Hα to P=O) and 7·4–8·0 m (5H, Ph).

Hydrolysis of compound **9** *to* **10**. Compound **9** (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 $CHCl_3$, washed with water, dried and the solvent removed. $C_{15}H_{21}PO_2$, m.p. 264°–265° (CH_2Cl_2-cyclohexane), ν_{max}^{KBr} 3260, 2900, 2850, 2800, 1460, 1450, 1245, 1220, 1140, 1100, 1050, 960, 920, 835, 740, 690, 610 cm^{-1}. Mass spectrum *m/e*: 264 (20%, M^+), 263 (100%, M-H, 262 (9%, M-H_2), 225 (10%), 221 (12%), 165 (28%), 141 (20%), 125 (43%, PhPOH).

Elimination of compound **10** *to* **11**. To a soln of **10** (300 mg) in dry pyridine (10 ml), a soln of $SOCl_2$ (0·5 ml) in pyridine (3 ml) was added slowly at 0°. After the usual workup, **11** was obtained as a very hygroscopic oil, $C_{15}H_{19}PO$; ν_{max}^{neat} 3050, 2950, 2860, 1610, 1450, 1205, 1170, 1150, 1105, 1060, 1020, 905, 800 cm^{-1}. Mass spectrum *m/e*: 246 (50%, M^+), 244 (24%, M-H_2), 231 (6%, M—CH_3), 218 (7%, M–Et), 217 (9%, 218-H), 125 (19%, PhPOH), 121 (17%), 93 (23%), 91 (36%), 85 (100%, C_6H_{13}); NMR ($CDCl_3$) NMR ($CDCl_3$) δ 0·8–2·9 m (13H), 3·5 m (1H) and 7·3–8·0 (5H, Ph).

2-Methyl-2-oxo-2-phosphatricyclo [4.4.0.0^{4,6}] *decane* (**12**). Compound **12** was obtained from **1** by following the procedure as described for the prep of **3** and **4** using CH_3PCl_2 (instead of $PhPCl_2$). $C_{10}H_{17}PO$, m.p. 153° (CH_2Cl_2-cyclo-hexane), ν_{max}^{KBr} 2900, 2850, 1450, 1190, 1130, 910, 870, 850, 820, 775, 740 cm^{-1}. Mass spectrum *m/e*: 184 (100%, M^+), 169 (12%, M—CH_3), 156 (16%, M—Et), 155 (22%, 156-H, 143 (20%, M—C_3H_5), 142 (25%, M—C_3H_6), 93 (26%), 91 (20%), 81 (47%) and 79 (50%); NMR ($CDCl_3$) δ 0·3–0·7 m (one cyclopropanic protone), 0·8–2·3 m (13H), 1·46 d (J = 15 Hz, P—CH_3).

2-Methoxy-2-oxo-2-phosphatricyclo [4.4.0.0^{4,6}] *octane* **13**. Compound **13** was obtained from **1** by following a procedure as described for the prep of **3** using PCl_3 or PBr_3 (instead of $PhPCl_2$) followed by quenching of the reaction with MeOH in the presence of NEt_3 (10 ml). $C_{10}H_{17}PO_2$, an oil, ν_{max}^{neat} 2900, 2850, 1450, 1400, 1240, 1200, 1130, 970, 890, 830, 810, 780, 770, 730 cm^{-1}. Mass spectrum *m/e*: 200 (53%, M^+), 185 (17%, M—CH_3), 172 (19%, M—Et), 171 (9%, 172—H), 159 (7%, M—C_3H_5), 158 (5%, M—C_3H_6), 122 (14%, M—P(O)OCH_3), 107 (21%), 94 (17%), 93 (25%), 91 (20%), 85 (70%, C_6H_{13}), 83 (100%, C_6H_{11}); NMR ($CDCl_3$) δ 0·2–0·5 m (one cyclopropanic proton), 0·6–0·9 m (two cyclopropanic protons) 1·0–2·3 m (11H), 3·65 d (J_{POCH_3} = 10 Hz, POCH_3).

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