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SYNTHESIS OF 1-PHOSPHAADAMANTANE

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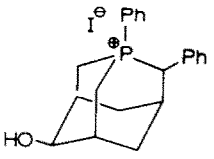
Abstract—The annelation reaction between 1,2,3,6-tetrahydro-1-phenyl-4-(1-pyrrolidinyl)phosphorin 1-oxide (**4**) and ethyl 2-bromomethyl-3-bromopropanoate (**5**) yielded a mixture of two stereoisomers of the 3-phosphabicyclo[3.3.1]nonane derivative **6**. The keto function of **6** was reductively removed to furnish **8** which with $LiAlH_4$ was reduced to **9**. Treatment of **9** with trichlorosilane gave the 1-phenylphosphoniaadamantane **11**. The phenyl group of **11** was cleaved with sodium to give the title compound **1**, or with NaOH to give the oxide **12** of **1**. With benzyl bromide, **1** was quaternized to **13**.

In a recent communication,[1] we discussed our interest in polycyclic phosphorus compounds which contain this element in a bridgehead position, in particular in phosphatriptycene[2] and the hitherto unknown 1-phosphadamantane (**1**). We also reported the synthesis of 6 - *exo* - hydroxy - 1,2 - diphenyl - 1 - phosphoniatricyclo[3.3.1.1^{3,7}]decane iodide (**2**), the first derivative of **1**.[1] Other heteroadamantanes are known;[3] in the present context, 1-azaadamantane (**3**)[4] and 1-phosphaadamantanes containing nitrogen or oxygen as additional heteroatoms[3,5] are of interest.



2

Although, with the synthesis of **2**, we had accomplished part of our goal, i.e. the construction of the 1-phosphaadamantane skeleton, our main objective, the conversion of **2** to the corresponding tertiary phosphine, was not achieved.[1] Reason was the benzylic nature of the P–C(2) bond; its high reactivity led to its preferential cleavage in all attempts to cleave the phosphorus–phenyl bond, thus leading to ring opened products. We therefore investigated a similar, but more direct approach to **1**.

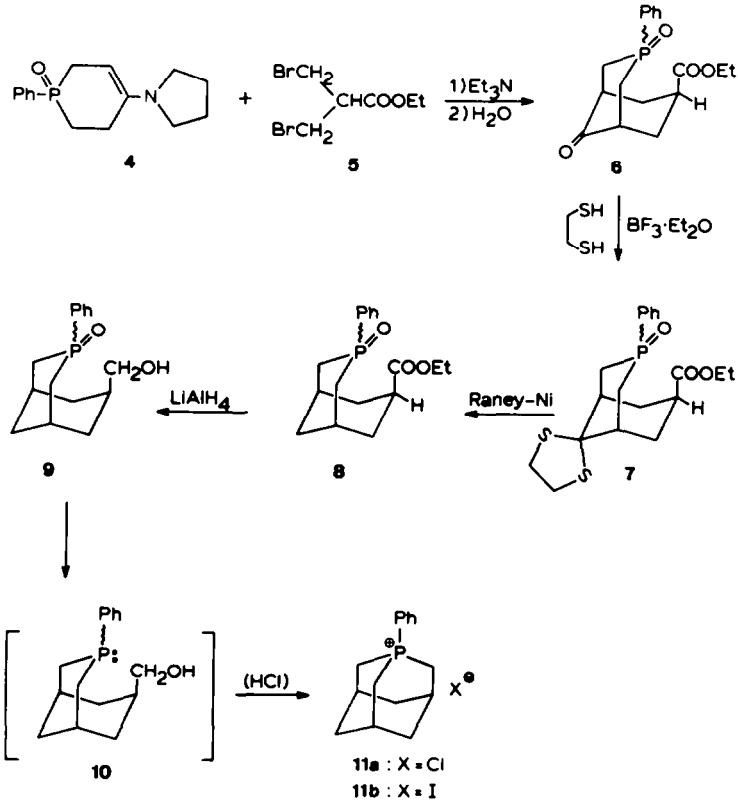
RESULTS AND DISCUSSION

As with **2**, the construction of the phosphaadamantane skeleton followed the strategy developed by Speckamp *et al.*[4c,d] for azaadamantane (Scheme 1). The annelation reaction between the enamine **4**[7] and the dibromide **5**[8] gave the phosphabicyclononane **6** in 52% yield as a mixture of two stereoisomers, according to the ^1H and ^{31}P NMR spectrum. The stereochemistry of **6** is not known; however, from earlier work on the nitrogen analogues[7d] and on the analogous intermediates in the synthesis of **2**,[1] it is highly probable that the ester group occupies the *endo*-position; consequently, the two isomers must differ in the configuration at phosphorus. As separation was not easily possible at this or later stages, the subsequent reactions were carried out with the mixtures of the two stereoisomers.

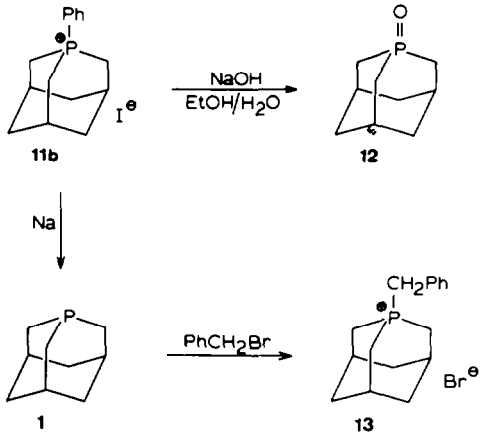
The removal of the keto function in **6** by conversion to the dithioketal **7**, followed by reduction with Raney-nickel to **8**, was achieved in 59% overall yield. The reduction of **8** to **9** with lithium aluminum hydride occurred almost quantitatively. The intermediate products **7**, **8** and **9** were characterized by their NMR and mass spectra and used without further purification. In analogy to the synthesis of **2**, we next envisaged the reduction of **9** with trichlorosilane to **10** which than would be cyclized to **11a** by the action of methanolic HCl. However, when actually performing the reaction, it appeared that the second step occurred spontaneously, probably under the influence of traces of HCl which might be formed as a by-product in the reduction. After addition of potassium iodide and crystallization from ethanol/water, **11b** was isolated in 34% yield; this yield is much higher than that leading to **2**.[1] The elemental analysis and the field desorption mass spectrum of **11b** (m/z = 231, rel. intensity 100%, 11^+, the phosphonium ion part of **11b**) were in agreement with the assigned structure, as was the ^1H NMR spectrum (see Experimental); characteristic is the ^{13}C NMR spectrum which—in contrast to those of all precursors—reflects the C_{3v} symmetry of the skeleton of **11b** by its very simple appearance, i.e. 3 signals in the aliphatic region; the solvent-dependent ^{31}P NMR signal was found at δ = 4.8 ppm ($CDCl_3/CF_3COOD$) or δ = 9.1 ppm (CD_3OD/D_2O).

As expected, and in contrast to **2**, the removal of the phenyl substituent from **11b** posed no problems. Boiling **11b** with NaOH in ethanol/water gave the tertiary phosphine oxide **12** in quantitative yield; the spectral data were in full agreement with the assigned structure (see Experimental; δ (^{31}P) = 34.8 ppm) (Scheme 2).

Treatment with sodium in refluxing toluene gave **1** in 64% yield as a white solid. Again, the NMR spectra are very simple: three broad signals in the ^1H NMR spectrum (δ = 1.87, 1.89, 1.95 ppm, assignment not yet possible), three signals in the ^{13}C NMR spectrum (δ = 21.2 {$\underline{C}H$}, 22.5 {P–$\underline{C}H_2$}, 31.8 ppm {CH–$\underline{C}H_2$–CH}, with the expected proton and phosphorus couplings, see Experimental). We wish to point out that the phosphorus chemical shift of **1**

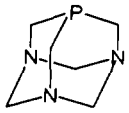


Scheme 1.



Scheme 2.

($\delta = -59.0$ ppm) is unexpectedly low as compared to that of its close structural analogue 1,3,5-triaza-7-phosphaadamantane (**14**) ($\delta = -101.6$ ppm).[5a] However, it compares favourably with chemical shift values for normal tertiary phosphines; an empirical approach based on increments[9] predicts $\delta = -45.5$ ppm. The slight upfield shift for **1** compared to the predicted value may, with appropriate caution, be taken as evidence for very slight residual strain in the molecule. A detailed analysis of the spectral and structural properties of **1** will be the topic of a future publication.



14

Compound **1** was further characterized by conversion to the benzyl-phosphonium salt **13** by reaction with benzyl bromide in benzene at room temperature (yield 24%). Other aspects of the chemistry of **1** are presently being investigated.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were recorded on a Varian MAT CH-5 mass spectrometer with electron impact at 70 eV or on a Varian MAT 711 by the field desorption method. NMR spectra were recorded on a Bruker WH 90 or WM 250 spectrometer. ^{1}H Chemical shifts are given in δ (ppm) from internal TMS; ^{13}C chemical shifts are given in δ (ppm) from TMS with the solvent peaks as internal standard; ^{31}P chemical shifts are given in δ (ppm) from external 85% H_3PO_4. Positive shifts are downfield in all cases. The IR spectra were recorded on a Perkin–Elmer 580B spectrophotometer; frequencies are given in cm^{-1}. Elemental analyses were performed at the Microanalytical Department of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands. All solvents were distilled under argon and were oxygen free.

1 - *Phosphatricyclo*[3.3.1.1^{3,7}]*decane* (1 - *phosphaadamantane*, **1**)

Sodium (0.3 g, 13 mmol) was suspended in boiling toluene (40 mL). After cooling to room temperature **11b** (161 mg,

0.45 mmol) was added and the mixture was heated under reflux for 4 h. Filtration and evaporation of the filtrate gave **1** (26.5 mg) as a white solid. To the sodium and residual **11b** toluene (40 mL) was added and boiling was repeated for 4 h. Filtration and evaporation gave another 11.5 mg. In the same way, a third fraction could be obtained of 6.5 mg (total yield 44.5 mg, 64%). ^{1}H NMR (C_6D_6) δ 1.87, 1.89, 1.95 (3s, assignment not yet possible). ^{31}P NMR (C_6D_6) δ −59.0. ^{13}C NMR (C_6D_6) δ 21.2 (d, $^1J_{CH}$ = 138, CH), 22.5 (dt, $^1J_{PC}$ = 12, J_{CH} = 140, P–CH_2), 31.8 (t, J_{CH} = 124, $CHCH_2CH$). *m/z* (rel. intensity) 154 (100) $[M]^+$, 76 (13). HRMS Calc ($C_9H_{15}P^+$): 154.0911. (Found: 154.0920.)

7 - *Ethoxycarbonyl* - 3 - *phosphabicyclo*[3.3.1]*nonan* - 9 - *one* 3 - *oxides* (**6**)

Compound **4**[7] (6.20 g, 23.8 mmol) was dissolved in MeCN (10 mL) together with Et_3N (6.34 g, 63 mmol) and **6**[8] (6.51 g, 23.8 mmol) in MeCN (10 mL) was added dropwise at −30°. After standing at room temperature for 2 h the solution was evaporated. The brownish–white solid residue was dissolved in water (20 mL) and after stirring at room temperature for 14 h the solution was extracted twice with $CHCl_3$ (30 mL). The combined organic layers were dried with $CaCl_2$ and evaporated. A dark brown oil (8.2 g) remained; it was subjected to column chromatography on kieselgel. Elution with $CHCl_3$ (300 mL) gave a mixture of two stereoisomers of **6** (3.95; 52% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.17, 1.26 (2 tr, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 2.28–3.21 (m, 11H), 4.08, 4.18 (2q, $^3J_{HH}$ = 7, 2H, OCH_2), 7.31–7.78 (m, 5H, Ph). ^{31}P NMR ($CDCl_3$) δ 27.4, 25.7. IR (CCl_4): 3430, 2980, 2940, 1725 (νC=O), 1435, 1203 (νP=O), 1179 (νP=O).

7 - *Ethoxycarbonyl* - 3 - *phosphabicyclo*[3.3.1]*nonan* - 9 - *one ethylenedithioacetal* 3 - *oxides* (**7**)

Compound **6** (1.6 g, 5 mmol) was dissolved in $CHCl_3$ (10 mL). 1,2-Ethanedithiol (3 mL) was added and the mixture was cooled to 0°. $BF_3{\cdot}OEt_2$ (1.7 mL) was added dropwise and the mixture was stirred for 1 h at 0°. After standing at room temperature for 16 h, the mixture was poured into dilute NaOH/$CHCl_3$. The organic layer was dried with $CaCl_2$ and evaporated. A white oil of two stereoisomers of **7** (1.9 g, 96%) remained. Attempted crystallization from ethyl acetate, ethanol and chloroform failed. ^{1}H NMR ($CDCl_3$) δ 0.81, 1.22 (2 t, $^3J_{HH}$ = 7, 3H, CH_2CH_3), 1.53–3.17 (m, 11H), 3.17–3.51 (m, 4H, S–CH_2CH_2–S), 3.75; 4.15 (2q, $^3J_{HH}$ = 7, 2H, CH_2–CH_3), 7.93–8.06 (m, 5H, Ph). ^{31}P NMR ($CDCl_3$) δ 26.7, 28.9. *m/z* (rel. intensity) 396 (41) $[M]^+$, 368 (12) $[M–C_2H_4]^+$, 47 (100). HRMS Calc ($C_{19}H_{25}O_3S_2P^+$): 396.0981. (Found: 396.0994.)

7 - *Ethoxycarbonyl* - 3 - *phosphabicyclo*[3.3.1]*nonane* 3 - *oxides* (**8**)

Compound **7** (4.05 g, 10.2 mmol) was dissolved in ethanol (150 mL), a suspension of Raney-nickel (15 g) in methanol was added and the solution was heated under reflux for 17 h; after 8, 11 and 14 h, fresh Raney nickel (7.5 g) was added. The solution was then filtered and evaporated. The residue was dissolved in chloroform, washed with dilute NaOH and dried with $CaCl_2$. After evaporation, a white foam of stereoisomers of **8** remained (1.90 g, 61% rel. to **7**). ^{1}H NMR ($CDCl_3$) δ 1.18, 1.22 (2t, $^3J_{HH}$ = 7, 3H, CH_2CH_3), 1.73–3.04 (m, 13H), 4.11 (q, $^3J_{HH}$ = 7, 2H, OCH_2), 7.29–7.60 (m, 3H, *o*, *p*-Ph), 7.60–8.02 (m, 2H, *m*-Ph). ^{31}P NMR ($CDCl_3$) δ 31.9, 33.0. *m/z* (relative intensity) 306 (30) $[M]^+$, 261 (15) $[M - OEt]^+$, 233 (36) $[M - COOEt]^+$, 194 (43), 166 (29), 154 (100), 140 (50), 125 (96) $[HP(O)Ph]^+$.

7 - *Hydroxymethyl* - 3 - *phosphabicyclo*[3.3.1]*nonane* 3 - *oxides* (**9**)

Compound **8** (1.75 g, 5.7 mmol) was dissolved in THF (100 mL) and $LiAlH_4$ (324.9 mg, 50% excess) was added. The mixture was stirred for 4 h. Then the excess $LiAlH_4$ was destroyed by ethyl acetate followed by dilute hydrochloric acid. The aqueous layer was separated and extracted with $CHCl_3$; the organic layer was evaporated to dryness, the residue dissolved in $CHCl_3$, washed with water, combined with the $CHCl_3$ extract and dried with $CaCl_2$. After evaporation, a light yellow foam of **9** (1.49 g, 99%) remained. ^{1}H NMR ($CDCl_3$) δ 1.58–3.00 (m, 12H), 3.67 (bs, $w_{1/2}$ = 8, –CH_2–OH, 2H), 5.38 (bs, 1H, OH), 7.18–7.49 (m, 3H, *o*, *p*-Ph), 7.60–8.02 (m, 2H, *m*-Ph). ^{31}P NMR ($CDCl_3$) δ 34.4, 35.8.

1 - *Phenyl* - 1 - *phosphoniatricyclo*[3.3.1.1^{3,7}]*decane iodide* (**11b**)

Compound **9** (1.6 g, 6.1 mmol) was suspended in a 1:1 mixture of toluene and *o*-xylene (30 mL) and cooled in an ice bath. Then $HSiCl_3$ (5 mL, 50 mmol) was added slowly under stirring. A slight gas evolution was observed. After 15 min the mixture was slowly warmed to 100° and heated for 1 h. Then, after standing at room temperature for 16 h, the solvent and excess $HSiCl_3$ were distilled off. Impure **11a** (1.6 g) remained as a white solid. ^{1}H NMR ($CDCl_3$; **11a** did not dissolve completely in $CDCl_3$; solution in methanol-d_4, methanol-d_4/CF_3COOD and DMSO-d_6 also failed; the spectrum could not be fully assigned due to substantial amounts of impurities) δ 1.75–3.44 (m, 15H, aliphatic H), 7.44–7.80 (m, 3H, *o*, *p*-Ph), 7.96–8.33 (m, 2H, *m*-Ph). ^{31}P NMR ($CDCl_3$) δ 5.3. The residue was extracted with boiling water (20 mL) and filtered. A solution of KI was added dropwise until precipitate was not formed any longer. The solution was heated to 80° and ethanol was added until the precipitate had completely dissolved. After cooling, colourless crystals of **11b** (734 mg, 34% based on **9**) were obtained which could be crystallised from ethanol/water, m.p. >390°. ^{1}H NMR ($CDCl_3$/CF_3COOD) δ 2.09 (bs s, $w_{1/2}$ = 8, 6H, CH-CH_2–CH), 2.69 (dd, $^2J_{PH}$ = 18, $^3J_{HH}$ = 3, 6H, P–CH_2), 2.89 (bd, $^2J_{PH}$ = 26, 3H, CH), 7.56–8.00 (m, 5H, Ph); (methanol-d_4/D_2O (10%); 250 MHz) δ 2.09 (bs, $w_{1/2}$ = 7.5, 6H, CH–CH_2–CH), 2.82 (dd, $^2J_{PH}$ = 14, $^3J_{HH}$ = 4, P–CH_2), 2.82 (bd, $^3J_{PH}$ = 29, CH); combined integration 9H; 7.69–7.79 (m, 2H, Ph), 7.80–7.96 (m, 3H, Ph). ^{31}P NMR ($CDCl_3$/CF_3COOD) δ 4.8; (methanol-d_4/D_2O (10%)) δ 9.1. ^{13}C NMR (D_2O/acetonitrile (1:1)) δ 23.8 (dt, $^1J_{PC}$ = 45.2, $^1J_{CH}$ = *ca* 140, P–CH_2), 27.8 (dd, $^2J_{PC}$ = 7, $^1J_{CH}$ = *ca* 140, CH), 32.9 (dt, $^3J_{PC}$ = 5, J_{CH} = 126, $CHCH_2CH$), 129.5 (dd, $^2J_{PC}$ = 7, J_{CH} = 165, *o*-C), 130.3 (dd, $^3J_{PC}$ = 10, J_{CH} = 158, *m*-C), 134.5 (s, J_{CH} = 171, *p*-C); (quaternary carbon not observed; possibly obscured by CH_3CN δ = 118 (bs)). Found: C, 49.90; H, 5.49; P, 8.40; I, 34.8. $C_{15}H_{20}IP$ (M = 358.18) requires: C, 50.30; H, 5.63; P, 8.65; I, 35.43%. *m/z* (FD) (%) 231 (100) $\mathbf{11}^+$.

1 - *Phosphatricyclo*[3.3.1.1^{3,7}]*decane oxide* (**12**)

Compound **11b** (50 mg, 0.14 mmol) was dissolved in boiling ethanol (35 mL) and sodium hydroxide (0.3 g, 7.5 mmol) dissolved in water (1 mL) was added. Boiling was continued for 1 h. After partial evaporation and cooling to room temperature a white precipitate appeared which was filtered off. The filtrate was evaporated and the residue extracted with chloroform (30 mL), the extract was filtered and the filtrate evaporated. The residue was dissolved in pentane (50 mL) and filtered through kieselgel (no elute), chloroform (50 mL, 0.5 mg), and finally methanol (50 mL, 24 mg, **12**, 100% based on **1**). Attempts to crystallize **12** from methanol/chloroform or chloroform failed. ^{1}H NMR (methanol-d_4) δ 1.78 (bs, $w_{1/2}$ = 7, 6H, $CHCH_2CH$), 2.13 (dd, $^2J_{PH}$ = 16, $^3J_{HH}$ = 4, 6H, P–CH_2), 2.59 (bd, $^3J_{PH}$ = 30, 3H, CH). ^{31}P NMR (methanol-d_4) δ 34.8. ^{13}C NMR (methanol-d_4) δ 5.5 (dd, $^2J_{PC}$ = 6, J_{CH} = 129, CH), 7.5 (dt, $^1J_{PC}$ = 58, J_{CH} = 130 ± 2, PCH_2) 8.3 (dt, $^3J_{PC}$ = 5, $^1J_{CH}$ = 132, $CHCH_2CH$) IR($CDCl_3$) 2920 (s), 1440 (m), 1400 (w), 1334 (w), 1242 (s, νP=O), 1150 (s), 1090 (m), 1042 (m), 960 (s), 855 (s). *m/z* (rel. intensity) 170 (83) $[M]^+$, 169 (40), 71 (40),

57 (38), 44 (76), 42 (100). HRMS Calc ($C_9H_{15}OP^+$): 170.0860. (Found: 170.0860.)

1 - *Benzyl* - 1 - *phosphoniatricyclo*[3.3.1.1^{3,7}]*decane bromide* (**13**)

Compound **1** (20 mg, 0.13 mmol) was dissolved in benzene-d_6 (0.5 mL) and benzyl bromide (35 mg, 0.20 mmol) was added. A white precipitate was formed. After shaking for 2 h filtration gave crystalline **13** (10 mg, 24%). After one crystallization from chloroform the m.p. was 335–338°. ^{1}H NMR ($CDCl_3$) δ 1.87 (bs, $w_{1/2}$ = 8, 6H, $CHC\underline{H}_2CH$), 2.60 (bd, $^3J_{PH}$ = 26, 3H, C$\underline{H}$) 2.74 (dd, $^2J_{PH}$ = 13, 6H, P–$C\underline{H}_2$), 4.43 (d, $^2J_{PH}$ = 17, 2H, benzylic H), 7.15–7.51 (m, 5H, Ph). ^{31}P NMR ($CDCl_3$) δ 12.0.^{13}C NMR ($CDCl_3$) δ 23.4 (dt, $^1J_{PC}$ = 43, $^1J_{CH}$ = 139, P–$\underline{C}H_2$), 28.0 (dd, $^2J_{PC}$ = 6.9, $^1J_{CH}$ = 138, $\underline{C}H$); 29.2 (d, $^1J_{PC}$ = 40.2, benzylic C) 34.1 (dt, $^3J_{PC}$ = 4.8, $^1J_{CH}$ = 129, CH–$\underline{C}H_2$–CH), 127.1 (d, $^2J_{PC}$ = 9.8, quaternary C), 128.1 (s, *p*-$\underline{C}$, $^1J_{CH}$ obscured by noise), 129.2 (dd, $^4J_{PC}$ = 3.2, $^1J_{CH}$ = 162, *m*-$\underline{C}$), 130.1 (dd, $^3J_{PC}$ = 5.3, $^1J_{CH}$ = 161, *o*-$\underline{C}$). *m/z* (rel. intensity 245) (100) $[M-Br]^+$, 244 (77) $[M-HBr]^+$, 154 (76) $[M-PhCH_2Br]^+$, 91 (60), 44 (79). HRMS. Calc. ($C_{16}H_{22}P^+$) 245.1459. (Found: 245.1470.) Found: C, 58.27; H, 6.71; Br, 23.62. $C_{16}H_{22}BrP$ (M = 325.22), requires: C, 59.09; H, 6.82; Br, 24.57.

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