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Synthesis of Phosphoric Esters of Bridgehead Alcohols

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Abstract—Dibenzylphosphates of 1-adamantanol and kemantane, 1-adamantyl phosphate, and a series of diphenyl phosphates of bridgehead alcohols have been prepared.

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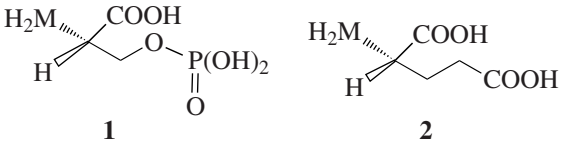
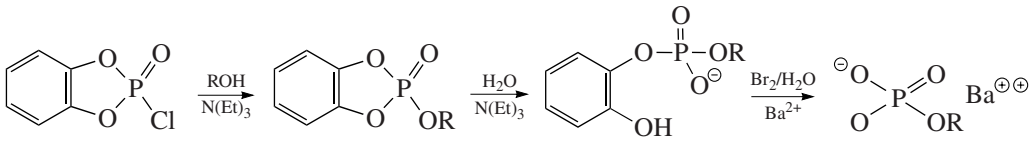
Bioisosteric replacement is a widespread method used in the design of chemical compounds with a definite physiological activity. In this method, a carboxylic group (–COOH) is often replaced by phosphonic analogue (–$PO(OH)_2$), while a methylene unit (–CH_2–) is replaced by an ether unit (–O–). The combination of these two variants provides for the use of a phosphate group (–O–$PO(OH)_2$) as bioisosteric for a –CH_2COOH fragment. For example, S-serine-O-phosphate (**1**) shows very high activity to certain subtypes of glutamic acid (**2**) receptors (figure) [1, 2]. An attempt to apply similar bioisosteric replacement for some derivatives of adamantylacetic acid has shown that there are very few studies on the synthesis of phosphate esters of substituted or unsubstituted adamantanols [3].[1] We found a method for the preparation of similar compounds using 2-chloro-1,3-dioxa-2-phosphorindane 2-oxide only ([3], Scheme 1, R = 1-adamantyl or 2-adamantyl).

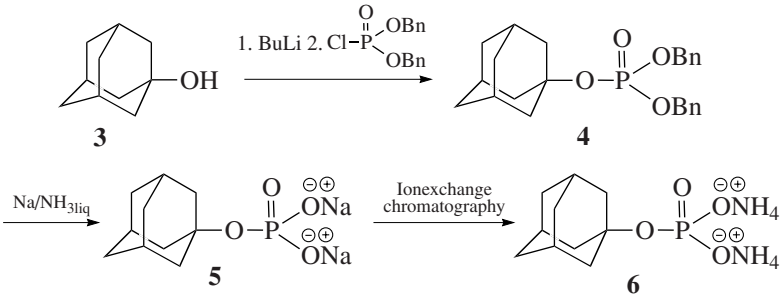


Examples of bioisosteres

In this work, we use other methods for the synthesis of phosphates of substituted and unsubstituted adamantanols. A convenient approach was applied to the synthesis of 1-adamantyl phosphate through 1-adamantyl dibenzyl phosphate (Scheme 2).



Scheme 1.

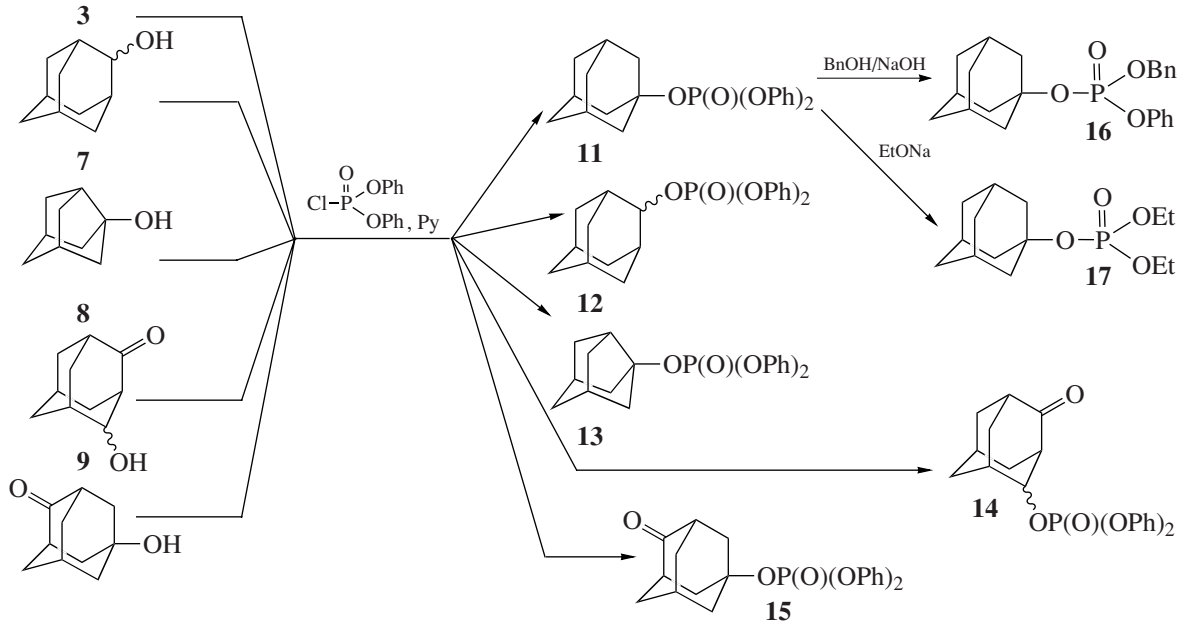


Scheme 2.

At the first stage, 1-adamantanol (**3**) was treated with a solution of BuLi in THF and reacted with dibenzyl chlorophosphate [5] to give 1-adamantyl dibenzyl phosphate **4** in 50% yield. ^{31}P NMR spectrum (one signal at $\delta = -5.5$ ppm) and ^1H NMR spectrum confirmed unambiguously the structure of compound **4** (see Experimental).

Benzyl groups were removed by treatment with sodium in liquid ammonia [6]. The resulting disodium

[1] A similar problem was discussed in the report [4]; however, that work dealt with dithiophosphate derivatives.



Scheme 3.

salt of 1-adamantyl phosphate (**5**) was immediately converted into ammonium salt (**6**) by ion-exchange chromatography. The ^{31}P NMR spectrum of compound **6** showed one signal at $\delta = -3.40$ ppm, while ^{1}H NMR spectrum displayed a wide singlet centered at 4.87 ppm (8 H) from the protons of two ammonium ions. No signals of aromatic protons were detected.

The synthesis of 1-adamantyl phosphates according to Scheme 2 was found to be rather convenient to prepare compound **6** in 47% yield (from compound **3**). However, the first stage of this scheme proved to be unacceptable for substituted adamantanols containing a carbonyl group when carbonyl should be retained in the course of the reaction. Therefore, we tried to prepare corresponding dibenzyl phosphates from diphenyl phosphates using transesterification reaction. The diphenyl phosphates were prepared with the use of procedures [5, 7] by the reaction of different bridgehead alcohols (**3**, **7**–**10**) with diphenyl chlorophosphate in pyridine (Scheme 3).

The diphenyl phosphates of bridgehead alcohols (**11**–**15**) were obtained in high yields (about 90%), and their structure was confirmed by ^{31}P NMR spectroscopy (one signal), ^{1}H NMR and IR spectroscopy (absorption bands of P=O at 1285–1295 cm^{-1} and C–O–P at 1195–1200 cm^{-1}). Carbonyl-containing alcohol **9** prepared by procedure [8] as a mixture of *endo*- and *exo*- isomers in the ratio 4 : 1 was converted into corresponding diphenyl phosphate **14** also as a mixture of isomers with the same ratio (from ^{1}H NMR spectrum, the signal from proton at C^{4}: 5.12 and 4.78 ppm).

Further, we attempted to replace both phenyl groups by benzyl ones using compound **11** as an example. However, the reaction of 1-adamantyl diphenyl phosphate with sodium benzylate (generated in situ from benzyl alcohol and sodium hydride) [6] led only to 1-adamantyl benzyl phenyl phosphate **16** in low yield (10%).[2] The structure of compound **16** was proved on the basis of elemental analysis and ^{1}H NMR spectra (a signal of C$\underline{H_2}$Ph group at 5.12 ppm with the intensity corresponding to two protons). This result implies that transesterification is not suitable for the synthesis of dibenzyl phosphates of substituted and unsubstituted adamantanols.

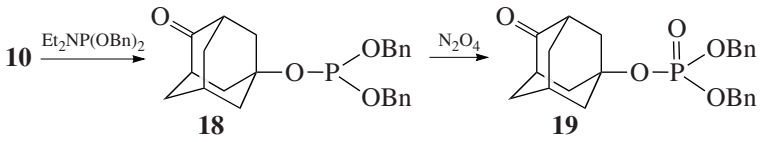
To obtain dibenzyl phosphates based on carbonyl-containing adamantanols, we applied another approach [9, 10] using kemantane (**10**) as an example (Scheme 4). At the first stage, $Et_2NP(OBn)_2$ prepared from hexaethylphosphoric triamide by the reaction

$$P(NEt_2)_3 + 2BnOH = Et_2NP(OBn)_2 + 2NHEt_2$$

was reacted with kemantane to produce compound **18**. If the process is carried out after slight evacuation, most kemantane is sublimed avoiding the reaction. To prevent the sublimation, the reactants were kept at 110–120°C and vacuum heating was used only at the end of the reaction, unreacted kemantane (10–15%) being sublimed.

4-Oxo-1-adamantyl dibenzyl phosphite **18** was oxidized without isolation and purification at about 20°C. We studied three oxidizing systems that are used to convert phosphites into phosphates [7], namely: (1) hydrogen peroxide–urea complex, (2) iodosobenzene, and (3) nitrogen(IV) oxides; the latter yielded 4-oxo-1-ada-

[2] The replacement of phenyl groups by ethyl ones in compound **11** proceeds easily to give 1-adamantyl diethyl phosphate **17** in 46% yield. Its analogue, 2-adamantyl diethyl phosphate, is readily generated from **12** in 52% yield.



Scheme 4.

mantyl dibenzyl phosphate **19** in the highest yield (24%). The structure of compound **19** was confirmed by ^{31}P NMR data (a sole signal at δ = 5.4 ppm) and ^{1}H NMR spectra (signals from ten protons of phenyl groups at δ = 7.36 ppm and four protons of C$\underline{H_2}$Ph groups at δ = 5.0 ppm). 4-Oxo-1-adamantyl dibenzyl phosphate **19** can be further converted according to Scheme 2 (second stage) to the corresponding kemantane phosphate.

Thus, in this work we have elaborated convenient methods for preparing phosphate esters of bridgehead alcohols, carbonyl-containing being included. Ten novel compounds were obtained and fully characterized.

EXPERIMENTAL

^{1}H and ^{31}P NMR spectra were recorded on a Bruker AMX-400 spectrometer operating at 400 MHz using TMS as an internal reference. IR spectra were recorded on an UR-20 and Specord 75 IR spectrometers (as Nujol mulls). The course of the reaction was monitored by thin layer chromatography (TLC) using Silufol UV-254 plates. Chromatographic separation was carried out on columns packed with Lancaster silica gel (60–200 μm).

1-Adamantyl dibenzyl phosphate (4). A solution of butyllithium (2.4 mL) in hexane was added to a solution of 0.836 g of 1-adamantanol (**3**) in 20 mL of anhydrous THF at –78°C, the mixture was stirred for 15 min, and a solution of dibenzyl chlorophosphate in anhydrous THF was added at –65 to –70°C. The reaction mixture was stirred until room temperature was reached, 20 mL of water was added, and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was separated, washed with water, and dried with sodium sulfate. The solution was concentrated, and the residue was purified by chromatography using benzene–ethyl acetate mixture (3 : 1) as an eluent to give 1 g (50%) of compound **4** as a yellowish oil. ^{31}P NMR ($CDCl_3$, δ, ppm): –5.5. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.30–7.40 (m, 10H), 5.0–5.1 (m, 4H), 2.18 (br s, 3H), 2.09 (br s, 6H), 1.63 (br s, 6H).

1-Adamantyl diammonium phosphate (6). Sodium metal (0.23 g) was dissolved in 15–20 mL of ammonia that was condensed under dry argon at –78°C, and a solution of 0.421 g of compound **4** in anhydrous THF was dropped. The reaction mixture was stirred for 30–40 min and quenched with methanol. The mixture was warmed to room temperature, then the solvent was removed. The resultant sodium salt **5** was purified by ion-exchange chromatography using distilled water as an eluent (a column with calculated amount of ion-exchange resin as a K^+ form was washed prior to use with 2 L of 1 N NH_4Cl solution and 1.5 L of distilled water) to obtain 0.25 g (93%) of compound **6**. ^{31}P NMR (DMSO-d^6, δ, ppm):[3] –3.40. ^{1}H NMR (DMSO-d^6, δ, ppm): 4.70–5.1 (br s, 8H, $2NH_4$), 2.08 (br s, 3H, bridgehead), 1.97 (br s, 4H, bridgehead),1.59 (br s, 8H, bridgehead).

For $C_{10}H_{23}N_2O_4P$ anal. calcd. (%): C, 45.09; H, 8.70; N, 5.26.

Found (%): C, 45.15; H, 8.51; N, 5.14.

1-Adamantyl diphenyl phosphate (11). Diphenyl chlorophosphate (0.003 mol) was dropped to a solution of 0.002 mol of 1-adamantanol (**3**) in 6 mL of dry pyridine at 80–90°C, and the mixture was stirred for 3 h. The reaction mixture was cooled and diluted with methylene chloride. The precipitate of pyridinium hydrochloride was filtered off, the filtrate was washed with 1 N HCl (3 × 10 mL), water (3 × 10 mL), and a saturated solution of $NaHCO_3$ (3 × 10 mL) and dried with sodium sulfate. The solution was concentrated, and the residue was purified by passing through a small layer of silica gel using benzene as an eluent to give 0.3 g (98%) of compound **11**. IR (ν, cm^{-1}): 1286 (P=O), 1205 (P–O–C). ^{31}P NMR ($CDCl_3$, δ, ppm): –16.7. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.15–7.36 (m, 10H, arom.), 2.22–1.62 (m, 15H, bridgehead).

For $C_{22}H_{25}O_4P$ anal. calcd. (%): C, 68.74; H, 6.56.

Found (%): C, 68.96; H, 6.57.

2-Adamantyl diphenyl phosphate (12) was obtained, as compound **11**, from alcohol **7**. Yield 97%. IR (ν, cm^{-1}): 1290 (P=O), 1203 (P–O–C). ^{31}P NMR ($CDCl_3$, δ, ppm): –12.4. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.17–7.37 (m, 10H, arom.), 4.82 (br s, 1H, H–C–O, $W_{1/2}$ = 11.9 Hz), 4.60 (w s, 1H), 2.12–1.52 (m, 14H, bridgehead).

For $C_{22}H_{25}O_4P$ anal. calcd. (%): C, 68.74; H, 6.56.

Found (%): C, 68.58; H, 6.49.

3-*nor*-Adamantyl diphenyl phosphate (13) was obtained, as compound **11**, from alcohol **8**. Yield 97%. IR (ν, cm^{-1}): 1290 (P=O), 1200 (P–O–C). ^{31}P NMR ($CDCl_3$, δ, ppm): –15.34. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.07–7.25 (m, 10H, arom.), 2.49 (t, 1H), 2.12–2.26 (m, 4H), 1.90–2.07 (m, 4H), 1.37–1.53 (m, 4H).

[3] DMSO-d^6 was distilled under dry argon over calcium hydride, and the main fraction was collected into a receiver with freshly calcined molecular sieves (4 Å)

For $C_{21}H_{23}O_4P$ anal. calcd. (%): C, 68.10; H, 6.26.

Found (%): C, 68.30; H, 6.21.

4-Oxo-2-adamantyl diphenyl phosphate (14) was obtained, as compound **11**, from alcohol **9**. Yield 89%. IR (ν, cm^{-1}): 1285 (P=O), 1195 (P–O–C). ^{31}P NMR ($CDCl_3$, δ, ppm): –12.68. ^1H NMR ($CDCl_3$, δ, ppm): 7.19–7.37 (m, 10H, arom.), 5.12 and 4.78 (br s, 1H, H–C–O isomeric), 2.83 (s, 1H), 2.55 (s, 1H), 2.27 (br s, 2H), 1.57–2.40 (m, 9H).

For $C_{21}H_{23}O_5P$ anal. calcd. (%): C, 66.33; H, 5.82.

Found (%): C, 66.36; H, 5.75.

4-Oxo-1-adamantyl diphenyl phosphate (15) was obtained, as compound **11**, from kemantane (**10**). Yield 87%. IR (ν, cm^{-1}): 1295 (P=O), 1200 (P–O–C). ^{31}P NMR ($CDCl_3$, δ, ppm): –16.62. ^1H NMR ($CDCl_3$, δ, ppm): 7.20–7.25 (m, 10H, arom.), 2.67 (s, 2H, H-3, H-5), 2.39–2.41 (m, 7H), 1.70–2.05 (m, 4H).

For $C_{21}H_{23}O_5P$ anal. calcd. (%): C, 66.33; H, 5.82.

Found (%): C, 66.06; H, 5.70.

1-Adamantyl benzyl phenyl phosphate (16). Sodium hydride (1.44 g) was added to a solution of 3.84 g of compound **11** and 3.4 mL of benzyl alcohol in 30 mL of anhydrous THF under an atmosphere of dry argon at 0°C, and the mixture was stirred for 5 h. The reaction mixture was poured into water and extracted with methylene chloride (3 × 15 mL); the organic layers were combined, washed with water (3 × 30 mL), and dried with sodium sulfate. The solvent was removed, and the residue was chromatographed using benzene–ethyl acetate mixture (3 : 1) as eluent to give 0.4 g (10%) of compound **16**. ^{31}P NMR ($CDCl_3$, δ, ppm): –4.8. ^1H NMR ($CDCl_3$, δ, ppm): 7.30–7.40 (m, 10H), 5.12 (s, 2H), 2.18 (br s, 3H), 2.09 (br s, 6H), 1.63 (br s, 6H).

1-Adamantyl diethyl phosphate (17). A solution of sodium metal (0.3 g) in 3 mL of absolute EtOH was added to a solution of 1.155 g of compound **11** in 5 mL of absolute EtOH. The mixture was stirred for 8 h, poured onto ice, and extracted with methylene chloride (3 × 5 mL); the organic solution was washed with water (5 × 5 mL). The organic layer was separated and dried with sodium sulfate. The solvent was removed, and the residue was chromatographed with benzene–ethyl acetate mixture (3 : 1) as eluent to give 0.4 g (46%) of compound **17** as yellowish oil. ^{31}P NMR ($CDCl_3$, δ, ppm): –5.49. ^1H NMR ($CDCl_3$, δ, ppm): 3.94–4.01 (br s, 4H), 2.01 (s, 3H), 1.98 (s, 6H), 1.56 (s, 6H), 1.23–1.27 (m, 6H).

For $C_{14}H_{25}O_4P$ anal. calcd. (%): C, 58.32; H, 8.74.

Found (%): C, 58.74; H, 8.35.

2-Adamantyl diethyl phosphate was obtained in a similar manner from compound **12**. Yield 52%. ^{31}P NMR ($CDCl_3$, δ, ppm): –5.42. ^1H NMR ($CDCl_3$, δ, ppm): 4.56 (s, 1H), 4.08–4.16 (m, 4H), 2.11 (s, 3H), 1.73–1.88 (m, 6H), 1.54–1.57 (m, 6H), 1.33–1.37 (t, 6H, J = 8 Hz).

For $C_{14}H_{25}O_4P$ anal. calcd. (%): C, 58.32; H, 8.74.

Found (%): C, 58.53; H, 8.36.

4-Oxo-1-adamantyl dibenzyl phosphate (19). A mixture of 2.49 g of kemantane and 4.75 g of dibenzyl $Et_2NP(OBn)_2$ was heated at 110–120°C under dry argon for 3 h; diethylamine was distilled off under atmospheric pressure. The residue was heated at the same temperature in vacuum (100 mmHg). The reaction mixture was cooled to room temperature and dissolved in 15 mL of anhydrous CH_2Cl_2. A solution of nitrogen(IV) oxide in CH_2Cl_2 was dropped to the resultant solution of 4-oxo-1-adamantyl dibenzyl phosphite (**18**) at –20°C until the reaction mixture became bright blue. Excess nitrogen oxide was removed by purging the reaction mixture with dry argon for 1 h with stirring. The resultant solution was washed with a saturated solution of $NaHCO_3$ (3 × 30 mL), water (3 × 30 mL), and dried with sodium sulfate. The solvent was removed, and the residue was chromatographed to obtain 1.5 g (24%) of compound **19** as a yellowish oil. ^{31}P NMR ($CDCl_3$, δ, ppm): –5.40. ^1H NMR ($CDCl_3$, δ, ppm): 7.36 (s, 10H), 5.02–5.05 (t, 4H), 2.63 (s, 2H), 2.30 (br s, 7H), 1.93–1.96 (m, 4H).

For $C_{14}H_{24}O_4P$ anal. calcd. (%): C, 67.47; H, 6.50.

Found (%): C, 67.6; H, 6.38.

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