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New Quinoline-2, -3, and 4-yl-(amino) methylphosphonates: Synthesis and Study on the C–P Bond Cleavage in Quinoline-2 and -4 Derivatives under Acidic Conditions

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ABSTRACT: *Synthesis of new quinoline-(amino)methylphosphonic acids, their phosphonate esters, and phosphine oxides is presented. The desired new compounds were efficiently obtained by nucleophilic addition of phosphorous species to quinoline-derived Schiff bases. In addition, it was discovered that heating of quinolin-2 and quinolin-4-yl-(amino)-methylphosphonates with aqueous HCl leads to their decomposition resulting in a rupture of the C—P bond, rejecting of the phosphorus containing fragment, and formation of the corresponding secondary quinoline-2 and quinoline-4-alkylamines. Two alternative mechanistic pathways for this cleavage are postulated.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:617–624, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20704

INTRODUCTION

As phosphorus analogues of natural aminocarboxylic acids, the α-aminomethylphosphonic acids and their phosphonate esters exhibit a variety of intriguing biological properties and thus they have found diverse applications in many areas of modern medicine and agriculture [1]. On the contrary, small and simple heteroaromatics often have surprisingly complex biological properties and belong to one of the most important classes of compounds in medicinal chemistry [2]. Especially nitrogen-containing heterocycles, such as quinoline and quinoline derivatives, are well-known structural scaffolds in medicinal chemistry endowed with numerous important pharmacological activities, such as antituberculosis [3], antiproliferation [4], anti-inflammatory [5], anticancer [6], and antioxidant [7] activity. In addition, quinoline derivatives have found application in preparation of new nano- and mesostructures with enhanced electronic and photonic properties [8]. Considering the aforementioned aspects, the fusion of heteroaromatic fragment with phosphorus-containing moiety could result in valuable chemical and biological properties of such heteroaromatic phosphonates and their derivatives, therefore the development of new protocols leading to those compounds would be especially desirable [9].

Herein, as a part of our continuous interest in the preparation of heteroaromatic phosphonates [10], we wish to disclose the results of our recent study on the synthesis of new quinoline-(amino)methylphosphonic acids, their phosphonate esters, and phosphine oxides.

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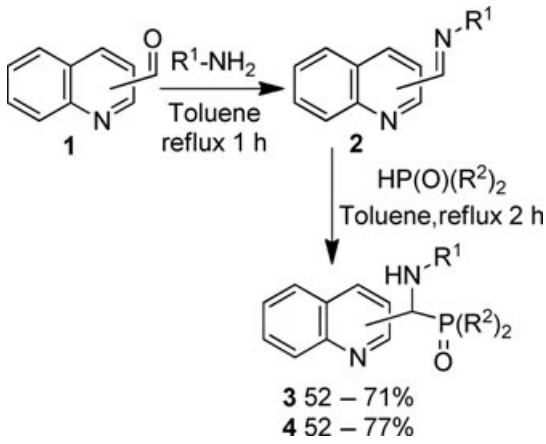


SCHEME 1

RESULTS AND DISCUSSION

Initially, we have prepared the quinoline-(amino)methylphosphonic diethyl esters **3** and diphenylphosphine oxides **4** by addition of diethyl phosphite or diphenylphosphine oxide, respectively, to quinoline-derived Schiff bases **2** (the protocol often referred to as the Pudovik reaction) [1,11]. The corresponding quinoline Schiff bases **2** were prepared in situ from quinoline carboxaldehydes **1** and secondary amines (benzyl- and *n*-butyl amine) (Scheme 1, Table 1).

Addition of diethyl phosphite or diphenylphosphine oxide to quinoline imines **2** proceeded well at reflux of toluene. After 2 h, the reaction was completed and the desired products, that is to say, quinoline α-aminoalkylphosphonic diethyl esters **3** and diphenylphosphine oxides **4** were isolated, with good overall yields, as nonhygroscopic white solids after simple crystallization (no chromatographic purification was required). In the case of diethyl esters **3,** these compounds were isolated and characterized as oxalate salts obtained by treatment of crude esters **3** with oxalic acid [$(COOH)_2 2H_2O$] in acetone. The structures of compounds **3** and **4** were unambiguously confirmed by standard spectroscopic techniques.

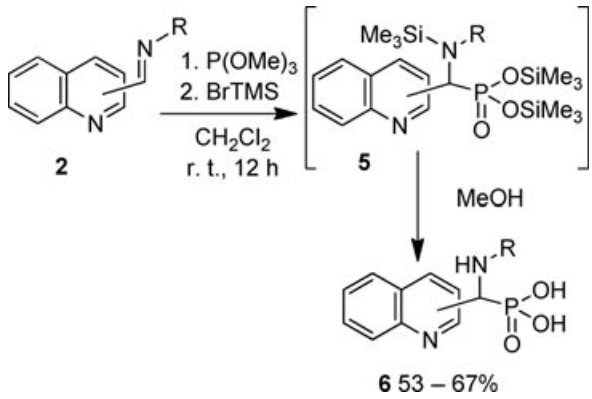
Subsequently, we turned our attention toward the synthesis of quinoline-(amino) methylphosphonic acids **6**. Our interest toward the preparation of these compounds brought us to investigate first the acidic hydrolysis of the quinoline-derived aminophosphonic acid esters **3**, the classical approach used in the synthesis of aminophosphonic acids [1,11]. In spite of many attempts, however, this method did not work in our case and resulted only in decomposition of the starting quinoline-derived esters **3**. Our difficulty with the aforementioned protocol led us to think about milder reaction conditions that would not require the use of strong acid. As a consequence, we examined the application of silylated phosphoesters, and to our satisfaction the desired quinoline-(amino)methylphosphonic acids **6**, were efficiently prepared by addition of this reagent to the appropriate imines **2**. The silylated phosphoesters were prepared in situ from trimethyl phosphite and bromotrimethylsilane (BrTMS) (Scheme 2, Table 2) [10b,e].

The presence of a bulky trimethylsilyl group in the formed phosphonate ester increases the power of such a nucleophile due to formation of a stable, three-coordinated phosphorus moiety with a free electron pair at phosphorus. Also, lack of the possibility of tautomerization in the formed a three-coordinated, silylated phosphorus ester into less nucleophilic a four-coordinated phosphonate-like ester, additionally secure a nucleophilic character of the applied reagent. Therefore, nucleophilic addition of the silylated phosphorus ester to imines

TABLE 1 Synthesized Quinoline–Derived Aminoalkylphosphonates **3** and **4**

Quinoline	*Schiff Base*	R^1	R^2	*Product (%)*[a]
Quinoline-3	**2a**	nBu	OEt	**3a** (71)[b]
Quinoline-3	**2b**	Bn	OEt	**3b** (55)[b]
Quinoline-4	**2c**	nBu	OEt	**3c** (52)[b]
Quinoline-4	**2d**	Bn	OEt	**3d** (62)[b]
Quinoline-4	**2e**	nBu	Ph	**4a** (77)
Quinoline-4	**2f**	Bn	Ph	**4b** (65)
Quinoline-2	**2g**	nBu	Ph	**4c** (57)
Quinoline-2	**2h**	Bn	Ph	**4d** (52)

[a]Yield of isolated product after crystallization.
[b]Product isolated as oxalate salt.



SCHEME 2

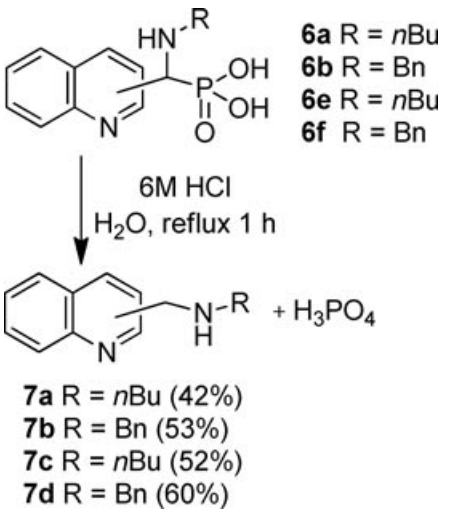
TABLE 2 Synthesized Quinoline α-Aminoalkylphosphonic Acids **6**

Quinoline	*Schiff Base*	R^1	*Product* (%)[a]
Quinoline-2	**2e**	*n*Bu	**6a** (57)
Quinoline-2	**2f**	Bn	**6b** (56)
Quinoline-3	**2a**	*n*Bu	**6c** (55)
Quinoline-3	**2b**	Bn	**6d** (53)
Quinoline-4	**2c**	*n*Bu	**6e** (56)
Quinoline-4	**2d**	Bn	**6f** (67)

[a]Yield of isolated product after crystallization.

2 proceeded easily at room temperature for 12 h. Formed silylated phosphonic intermediates **5** were then treated, in situ, with methanol, as a desilylating agent, to produce the desired quinoline-(amino)methylphosphonic acids **6** in good yields (53%–67%) (Scheme 2, Table 2). All compounds were isolated as crystalline solids after simple recrystallization from MeOH. Again no chromatographic purification was required in the presented case.

Later on, intrigued by the unusual decomposition of quinoline-derived esters **3** under acidic conditions, we decided to study this phenomenon closely and we also discovered that the quinoline-(amino)methylphosphonic acids **6** undergo decomposition in a similar fashion when submitted to strong acid. After heating of phosphonic acids **6a,b** and **6e,f**, derivatives of quinoline-2 and -4, for 1 h at reflux in the presence of aqueous 6 M HCl, evaporation of the solvent, neutralization of the crude reaction mixture with Na_2CO_3, and extraction with CH_2Cl_2 the secondary amines **7a–d** were isolated and their structures were unambiguously confirmed



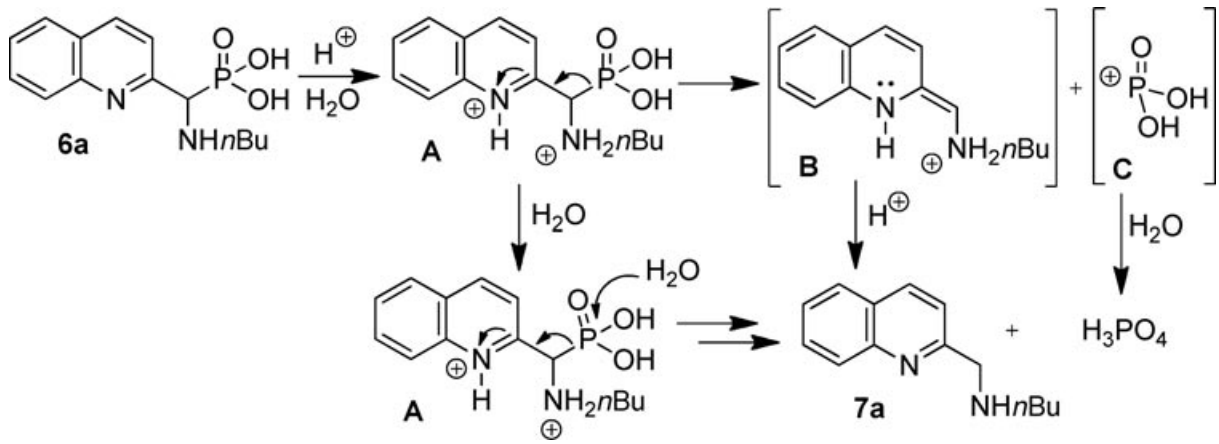
SCHEME 3

by NMR spectroscopy (Scheme 3). The remaining aqueous layer was concentrated, dissolved in D_2O, and ^{31}P NMR spectra was recorded showing a sharp singlet at $\delta_P \sim 1.12$ ppm corresponding to the phosphoric acid (for comparison: ^{31}P NMR spectrum of pure phosphoric acid in D_2O exhibits a singlet at 0.98 ppm).

In light of the obtained results, it is safe to say that the decomposition of quinoline α-aminoalkylphosphonic diethyl esters **3** and phosphonic acids **6** is a result of C—P bond cleavage by strong acids. In fact, the C—P bond cleavage is a known process recognized to play a very important role in biological tasks exhibited by organophosphorus compounds and is present in living organisms and catalyzed by enzymes [12]. Taking into account the obtained data, literature reports [12,13a–c] and previous experience of our group [10a,13d–h], two alternative mechanistic pathways of the cleavage of the quinoline-(amino)methylphosphonic acid **6a**, as a model substrate, under acidic conditions can be postulated (Scheme 4).

In both mechanisms (shown in Scheme 4), a driving force that triggers the cleavage of the C—P bond is the presence of a positive charge on protonated nitrogen in the quinoline-derived aminophosphonate of type **A**. The first proposed mechanistic pathway is dissociative-type $S_N1(P)$ mechanism [13d,e,f] that relies on the rupture of the C—P bond in the protonated aminophosphonic acid **A** and the subsequent formation of two intermediate products: an enamine-like moiety **B** and a metaphosphate-like moiety **C**. The enamine-like intermediate **B** transforms into the amine **7a** by incorporation of a proton. In turn, the intermediate **C** is actually the "protonated" metaphosphate (a phosphinylium [14], or phosphacylium cation [15]) and is closely associated with the well-known monomeric metaphosphate ($HOPO_2$) [16,17]. The metaphosphates, as transient species, are postulated as the putative intermediates in biological phosphoryl-transfer reactions [17] and also in many fragmentations of organophosphorus compounds [16,17]. The **C** as reactive intermediate can therefore react with a nucleophilic solvent (water) to form in this case phosphoric acid, as the final product.

The second postulated mechanism is associative-type $S_N2(P)$ mechanism that involves a direct nucleophilic attack of water molecule at phosphorus in the protonated aminophosphonate **A** prior to the cleavage of the C—P bond (Scheme 4). Further reorganizations lead to the formation of the final products, i.e., the secondary amine **7a** and phosphoric acid. On the other hand, on the basis of our last findings, the occurrence of the



SCHEME 4

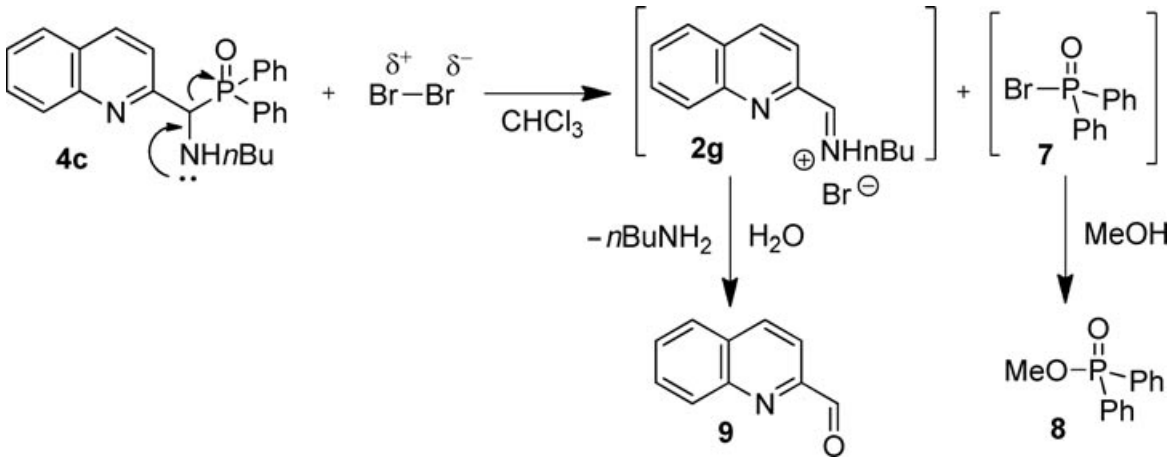
second postulated mechanism [13a,b] seems to be questionable [13h].

We found lately that cleavage of the heterocyclic aminophosphonates, considered here can also occur in aprotic solvents (such as chloroform, dichloromethane), by use of electrophilic reagents (i.e., elemental bromine Br_2, nitronium tetrafluoroborate $NO_2^+BF_4^-$ and others) (Scheme 5) [13h]. Heating of aminophosphine oxide **4c** (1 mmol) in $CHCl_3$ for 3 h in the presence of Br_2 (3 mmol), after evaporation of the solvent, leads to the mixture composed of bromide **7** and imine **2g**. Subsequent treatment with MeOH (5 h at room temperature) and extraction of acidified solution with CH_2Cl_2 allows isolation of ester **8** (80%) [13f] and aldehyde **9** (product of decomposition of the imine **2g**).

Similar mechanistic pathway of C—P bond cleavage can be postulated for quinoline-4-(amino)methylphosphonic acid **6e,f**, which also decomposes under acidic conditions with formation of corresponding secondary amines **7c**,**d** and phosphoric acid (Scheme 3). Also the proposed mechanism would explain the decomposition of quinoline-2 and -4 α-aminoalkylphosphonic diethyl esters **3**.

In addition, examining both proposed mechanisms (Scheme 4), it is clear, that the corresponding quinoline-3 derivatives should not have decomposed under acidic conditions due to the lack of the possibility of formation of an enamine-like structure **B** (Scheme 4). This fact was confirmed experimentally. Heating of the acid **6c**, as a model substrate, for 3 h with 6 M HCl, does not lead to decomposition products and the intact starting material is recovered. I addition, heating of diethyl esters **3a** with 6 M HCl for 1 h leads to the formation of the corresponding stable phosphonic acid **6c** and the cleavage of the C—P bond does not take place.

In conclusion, as a continuation of our earlier work on the synthesis of quinoline aminophosphonates [13d], we have presented here an efficient



SCHEME 5

protocol for the synthesis of a new group of quinoline-2, -3, and -4 (amino)methylphosphonic acids, their phosphonate esters, and phosphine oxides via nucleophilic addition of appropriate phosphorus species to quinoline-derived Schiff bases. The desired new quinoline-derived phosphonates were obtained in good yields as crystalline, nonhygroscopic solids after simple crystallization, no chromatographic purification was required. In addition, we observed that quinoline-2 and -4 (amino)methylphosphonic acids and their diethyl esters decompose under acidic conditions with formation of corresponding secondary amines and phosphoric acid, as a result of C—P bond cleavage. Two possible mechanistic pathways were postulated to explain this phenomenon. The corresponding quinoline-2 and -4 aminodiphenylphosphine oxides **4** also decomposed under acidic conditions in the same manner. In addition, we found that cleavage of the heterocyclic aminophosphonates considered here can occur in aprotic solvent by use of electrophilic reagent, and this fact makes the occurrence of the second postulated mechanism, the associative-type $S_N2(P)$, questionable. Further investigations are currently underway in our laboratory to understand better the nature of the cleavage of C—P bond in heterocyclic phosphonates so that these results will be a subject of a separate communication.

EXPERIMENTAL

^{1}H (300 MHz), ^{13}C (75 MHz), and ^{31}P (120 MHz) NMR spectra were recorded on a Bruker Avance TM DRX (300 MHz; Bruker BioSpin GmbH, Rheinstetten, Germany) spectrometer. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane (Me_4Si, δ .0) for ^{1}H NMR, $CDCl_3$ (δ 7.0) for ^{13}C NMR, and external 85% phosphoric acid (δ 0.0) for ^{31}P NMR. Coupling constants (J) are reported in hertz. Infrared (IR) spectra were taken as neat, and the only most representative frequencies (in cm^{-1}) are reported. High-resolution mmass spectrometry (HRMS) analyses were performed on LCT Premier XE Waters apparatus, on mode ESI+ (time of flight mass spectrometry ES+). Reported melting points are uncorrected. All reagents were used as received from the commercial supplier. All solvents for extractions and reactions were of technical grade and were dried before use by using standard techniques.

Synthesis of Quinolin-3 and -4-yl-(amino) methylphosphonate Diethyl Esters **3a–d**

Neat secondary aromatic or aliphatic amine (5.0 mmol) was introduced at room temperature to a solution of appropriate quinolinecarboxaldehyde (5.0 mmol) in toluene (30 mL), and the reaction was stirred at reflux for 1 h. After that time, anhydrous Na_2SO_4 was added and the mixture was stirred for additional 0.5 h. After removal of the drying agent, the reaction was concentrated under reduced pressure affording crude imines **2** that were used directly in the next step. The imines (5.0 mmol) were dissolved in dry toluene (30 mL), and diethyl phosphite (0.65 mL, 5.0 mmol) was added. The mixture was heated to reflux for 2 h and then was concentrated under reduced pressure, affording crude esters **3** as thick oils. The esters **3** were characterized as oxalate salts. The oxalates were obtained in the following way: The crude ester (1.0 equiv) was dissolved in acetone (5 mL), and oxalic acid $(COOH)_2 2H_2O$ (2.0 equiv.) in acetone (5 mL) was added and the mixture was refrigerated. The separated precipitate was filtered, washed with cold acetone (10 mL), and dried on air.

Quinolin-3-yl-methyl(N-butylamino)phosphonate Diethyl Ester (**3a**): Oxalate; white solid; yield 71%; mp 128–134°C. ^{1}H NMR (D_2O): $\delta = 9.01$ (s, 1H, Qu-2), 8.92 (s, 1H, Qu-4), 8.10–7.74 (m, 4H, Qu-6, Qu-7, Qu-8, Qu-9), 5.25 (d, 1H, CH-P $J = 18.71$ Hz), 4.13–3.97 (m, 4H, OCH_2CH_3), 3.00–2.92 (m, 2H, CH_2CH_3), 1.48–1.40 (m, 4H, CH_2CH_2), 1.19–1.10 (m, 3H, CH_3), 0.74–0.63 (m, 6H, CH_3). ^{31}P NMR (D_2O): $\delta = 15.63$ (s).

Quinolin-3-yl-methyl(N-benzylamino)phosphonate Diethyl Ester (**3b**): Oxalate; white solid; yield 55%; mp 96–100°C. ^{1}H NMR (D_2O): $\delta = 8.95$ (s, 1H, Qu-4), 8.91 (s, 1H, Qu-2), 8.14–7.83 (m, 4H, Qu-6, Qu-7, Qu-8, Qu-9), 7.30–7.14 (m, 5H, Ph), 5.11 (d, 1H, CH-P $J = 19.50$ Hz), 4.20 (s, 2H, CH_2Ph), 4.18–3.96 (m, 4H, OCH_2CH_3), 1.20–0.98 (m, 6H, CH_3). ^{31}P NMR (D_2O): $\delta = 16.30$ (s).

Quinolin-4-yl-methyl(N-butylamino)phosphonate Diethyl Ester (**3c**) [13d]: Oxalate; white solid; yield 52%; mp 104–108°C. ^{1}H NMR (D_2O): $\delta = 9.71$ (d, 1H, Qu-2 $J = 5.48$ Hz), 8.99–8.52 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 5.20 (d, 1H, CH-P $J = 19.01$ Hz), 4.17–4.00 (m, 4H, OCH_2CH_3), 3.05–2.94 (m, 2H, CH_2CH_3), 1.48–1.42 (m, 4H, CH_2CH_2), 1.21–1.12 (m, 3H, CH_3), 0.84–0.73 (m, 6H, CH_3).^{31}P NMR (D_2O): $\delta = 15.01$ (s).

Quinolin-4-yl-methyl(N-benzylamino)phosphonate Diethyl Ester (**3d**): Oxalate; white solid; yield 62%; mp 126–130°C. ^{1}H NMR (D_2O): $\delta = 9.68$ (d, 1H, Qu-2 $J = 5.39$ Hz), 8.92–8.55 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 7.27–7.10 (m, 5H, Ph), 5.17 (d, 1H, CH-P $J = 18.20$ Hz), 4.10 (s, 2H, CH_2Ph), 4.95–4.35 (m, 4H, OCH_2CH_3), 1.77–1.60 (m, 6H, CH_3). ^{13}C NMR (D_2O): $\delta = 165.9$ $(COOH)_2$, 151.4, 143.8, 138.6, 135.3, 134.6, 130.4, 130.0, 129.4,

129.1, 129.0, 128.7, 128.6, 128.2, 127.3, 127.2, 124.4, 122.2, 120.9, 120.8, 65.36 (OCH_2), 51.24 (CHP) (d, $J_{CP} = 13.72$ Hz), 43.0, 15.45 (CH_3). ^{31}P NMR (D_2O): $\delta = 19.84$ (s). IR (neat): 3422 (NH), 1169 (P=O), 1044 (P-O) cm^{-1}. HRMS Calcd for $C_{21}H_{26}N_2O_3P$ $(M + H)^+$ 385.1603. Found 385.1705.

Preparation of Quinolin-4 and -2-yl-(amino) methyldiphenylphosphine Oxides **4a–d**

Protocol described above for the preparation of esters **3a–d** was followed. Here, diethyl phosphite was replaced by diphenylphosphine oxide. Crude diphenylphosphine oxides **4** were purified by crystallization from a mixture of toluene and hexane (1:1).

Quinolin-4-yl-methyl(N-butylamino)diphenylphosphine Oxide (**4a**): White solid; yield 77%; mp 140–144°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.83$ (d, 1H, Qu-2 $J = 4.55$ Hz), 7.89–7.26 (m, 15H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9 and Phs), 5.38 (d, 1H, CH-P $J = 11.67$ Hz), 2.52–2.45 (m, 2H, CH_2), 1.35–1.15 (m, 2H, CH_2), 0.85–0.76 (m, 2H, CH_2), 0.59–0.54 (m, 3H, CH_3).^{31}P NMR ($CDCl_3$): $\delta = 31.18$ (s).

Quinolin-4-yl-methyl(N-benzylamino)diphenylphosphine Oxide (**4b**): White solid; yield 65%; mp 150–156°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.87$ (d, 1H, Qu-2 $J = 4.79$ Hz), 7.82–7.05 (m, 20H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9 and Phs), 5.25 (d, 1H, CH-P $J = 12.20$ Hz), 3.60 (dd, 2H, CH_2Ph $J = 13.23$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 149.0$, 148.9, 142.3, 138.4, 132.1, 131.9, 131.8, 131.5, 131.2, 131.1, 130.0, 129.0, 128.9, 128.5, 128.3, 128.0, 127.9, 127.4, 126.2, 122.7, 120.5, 55.0 (d, $J_{CP} = 78.07$ Hz), 51.3. ^{31}P NMR ($CDCl_3$): $\delta = 31.96$ (s). IR (neat): 3286 (NH), 1185 (P = O), 1067 (P-O) cm^{-1}. HRMS Calcd for $C_{29}H_{26}N_2OP$ $(M + H)^+$ 449.1704. Found 449.1715.

Quinolin-2-yl-methyl(N-butylamino)diphenylphosphine Oxide (**4c**): White solid; yield 57%; mp 92–94°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.17$ (d, 1H, Qu-4 $J = 4.45$ Hz), 7.88–7.33 (m, 15H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9, and Phs), 5.12 (d, 1H, CH-P $J = 12.69$ Hz), 2.49–2.39 (m, 2H, CH_2), 1.30–1.25 (m, 2H, CH_2), 1.14–1.07 (m, 2H, CH_2), 0.72–0.67 (m, 3H, CH_3).^{31}P NMR ($CDCl_3$): $\delta = 29.30$ (s).

Quinolin-2-yl-methyl(N-benzylamino)diphenylphosphine Oxide (**4d**): White solid; yield 52%; mp 98–104°C. ^{1}H NMR (DMSO-d_6): $\delta = 8.20$ (d, 1H, Qu-4 $J = 8.49$ Hz), 7.82–7.05 (m, 20H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9, and Phs), 5.10 (dd, 1H, CH-P $J = 11.31$ Hz), 3.72–3.46 (m, 2H, CH_2Ph). ^{13}C NMR ($CDCl_3$): $\delta = 156.51$, 149.5, 147.5, 136.1, 132.3, 132.2, 132.0, 131.9, 131.8, 131.7, 129.3, 129.0, 128.5, 128.3, 128.2, 128.0, 127.6, 127.1, 126.3, 126.2, 121.9, 64.2 (d, $J_{C\text{-}P} = 78.37$ Hz), 52.7 (d, $^3J_{C\text{-}P} = 13.65$ Hz). ^{31}P NMR (DMSO-d_6): $\delta = 30.14$ (s). IR (neat): 3296 (NH), 1191 (P=O), 1069 (P-O) cm^{-1}. HRMS Calcd for $C_{29}H_{26}N_2OP$ $(M + H)^+$ 449.1704. Found 449.1896.

Synthesis of Quinolin-2, -3 and -4-yl-(amino) methylphosphonic Acids **6a-f**

To a solution of crude imine **2** (prepared as described above, 2.5 mmol) in CH_2Cl_2 (25 mL), trimethyl phosphite (0.32 g, 2.5 mmol) was added, followed by bromotrimethylsilane (1.6 g, 10 mmol). The mixture was stirred for 24 h at room temperature and evaporated under reduced pressure. The resulted oil was treated with methanol (5 mL) and refrigerated for several hours. The products, quinolin-2, -3, and -4-yl-(amino)methylphosphonic acids **6a–f**, separated as white solids and were collected by filtration, washed with diethyl ether (15 mL), and dried in air.

Quinolin-2-yl-methyl(N-butylamino)phosphonic Acid (**6a**): White solid; yield 57%; mp 194–196°C. ^{1}H NMR (D_2O): $\delta = 8.90$ (d, 1H, Qu-4 $J = 8.46$ Hz), 8.09–7.22 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 4.12 (d, 1H, CH-P $J = 16.69$ Hz), 2.70–2.56 (m, 2H, CH_2), 1.35–1.29 (m, 2H, CH_2), 0.96–0.89 (m, 2H, CH_2), 0.49–0.44 (m, 3H, CH_3).^{31}P NMR (D_2O): $\delta = 3.90$ (s).

Quinolin-2-yl-methyl(N-benzylamino)phosphonic Acid (**6b**): White solid; yield 56%; mp 182–186°C. ^{1}H NMR (D_2O): $\delta = 8.32$ (d, 1H, Qu-4 $J = 8.52$ Hz), 7.43–7.26 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 6.90–6.60 (m, 5H, Ph), 4.08 (d, 1H, CH-P $J = 13.04$ Hz), 3.82 (t, 2H, CH_2Ph $J = 5.99$ Hz). ^{31}P NMR (D_2O): $\delta = 3.55$ (s).

Quinolin-3-yl-methyl(N-butylamino)phosphonic Acid (**6c**): White solid; yield 55%; mp 190–196°C. ^{1}H NMR (D_2O): $\delta = 8.92$ (s, 1H, Qu-2 $J = 4.96$ Hz), 7.96–7.60 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-9), 4.57 (d, 1H, CH-P $J = 16.22$ Hz), 2.82–2.66 (m, 2H, CH_2), 1.37–1.33 (m, 2H, CH_2), 0.96–0.89 (m, 2H, CH_2), 0.49–0.44 (m, 3H, CH_3). ^{31}P NMR (D_2O): $\delta = 7.56$ (s). IR (neat): 3389 (NH), 1176 (P = O) cm^{-1}. HRMS Calcd for $C_{14}H_{20}N_2O_3P(M + H)^+$ 295.1133. Found 295.1245.

Quinolin-3-yl-methyl(N-benzylamino)phosphonic Acid (**6d**): White solid; yield 53%; mp 168–172°C. ^{1}H NMR (D_2O): $\delta = 9.13$ (s, 1H, Qu-2), 9.06 (s, 1H, Qu-4), 8.27–7.23 (m, 19H, Qu-6, Qu-7, Qu-8, Qu-9, and Phs), 4.19 (d, 1H, CH-P $J = 17.04$ Hz), 4.43 (dd, 2H, CH_2Ph $J = 13.11$ Hz). ^{31}P NMR (D_2O): $\delta = 7.55$ (s). IR (neat): 3388 (NH), 1159 (P = O) cm^{-1}. HRMS Calcd for $C_{17}H_{18}N_2O_3P$ $(M + H)^+$ 329.0977. Found 329.1074.

Quinolin-4-yl-methyl(N-butylamino)phosphonic Acid (**6e**): White solid; yield 56%; mp 140–142°C. ^{1}H NMR (D_2O): $\delta = 9.44$ (d, 1H, Qu-2 $J = 5.91$ Hz),

8.79–8.29 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 5.92 (d, 1H, CH-P $J = 17.25$ Hz), 3.52–3.43 (m, 2H, CH_2), 2.15–1.97 (m, 2H, CH_2), 1.85–1.55 (m, 2H, CH_2), 1.09 (t, 3H, CH_3 $J = 7.36$ Hz). ^{13}C NMR (D_2O): $\delta = 150.1$ 143.0, 137.1, 135.2, 130.6, 126.9, 124.3, 120.9, 119.1, 55.5 (d, $J_{C\text{-}P} = 124.72$ Hz), 48.0 (d, $^3J_{C\text{-}P} = 3.52$ Hz), 27.0, 18.7, 12.2. ^{31}P NMR (D_2O): $\delta = 5.83$ (s). IR (neat): 3412 (NH), 1085 (P=O) cm^{-1}. HRMS Calcd for $C_{14}H_{20}N_2O_3P$ $(M + H)^+$ 295.1133. Found 295.1211.

Quinolin-4-yl-methyl(N-benzylamino)phosphonic Acid (**6f**): White solid; yield 67%; mp 152–154°C. ^{1}H NMR (D_2O): $\delta = 8.43$ (d, 1H, Qu-2 $J = 3.01$ Hz), 7.71–7.35 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 6.62–6.42 (m, 5H, Phs), 4.92 (d, 1H, CH-P $J = 18.24$ Hz), 3.79 (s, 2H, CH_2Ph). ^{31}P NMR (D_2O): $\delta = 5.80$ (s).

Cleavage of Quinolin-2 and -4-yl-(amino) methylphosphonic Acids under Acidic Conditions and Isolation of the Products

A sample of corresponding quinolin-2 or -4-yl-(amino)methylphosphonic acids **6a,b** or **6e,f** (1.0 mmol) was dissolved in HCl (25 mL of 6 M aqueous solution) and heated at reflux for 1 h. After that time, the resulting reaction mixture was cooled down to room temperature and CH_2Cl_2 was added (25 mL). The resulting solution was alkalized with solid Na_2CO_3, and the layers were separated. The aqueous layer was additionally washed with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure, affording the amines **7a–d** as yellow oils. The amines **7a–d** were characterized as oxalate salts. The oxalates were obtained in the following manner: The crude amine (1.0 equiv.) was dissolved in acetone (5.0 mL), and oxalic acid $(COOH)_2 2H_2O$ (2.0 equiv.) in acetone (5.0 mL) was added and the mixture was refrigerated. The separated precipitate was filtered, washed with cold acetone (10 mL), and dried on air.

N-(Quinolin-2-ylmethyl)-N-butylamine (**7a**): Oxalate; white solid; yield 42%; mp 166–170°C. ^{1}H NMR (D_2O): $\delta = 8.70$ (d, 1H, Qu-4 $J = 8.58$ Hz), 7.94–7.57 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 4.51 (s, 2H, CH_2), 2.93–2.88 (m, 2H, CH_2), 1.42–1.32 (m, 2H, CH_2), 1.06–0.98 (m, 2H, CH_2), 0.55–0.50 (m, 3H, CH_3). ^{13}C NMR (D_2O): $\delta = 159.7$ $(COOH)_2$, 148.2, 146.2, 138.5, 135.7, 130.2, 128.5, 128.3, 121.4, 119.6, 48.1 ($QuCH_2$), 46.3 (NCH_2), 26.7, 18.3, 12.0. IR (neat): 3420 (N-H) cm^{-1}. HRMS Calcd for $C_{14}H_{19}N_2$ $(M + H)^+$ 215.1470. Found 215.1500.

N-(Quinolin-2-ylmethyl)-N-benzylamine (**7b**) [18]: Oxalate; white solid; yield 53%; mp 185–186°C. ^{1}H NMR (D_2O): $\delta = 8.73$ (d, 1H, Qu-4 $J = 8.60$ Hz), 7.88–7.55 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 7.07–6.95 (m, 5H, Phs), 4.51 (s, 2H, CH_2), 4.09 (m, 2H, CH_2). ^{13}C NMR (D_2O): $\delta = 160.7$ $(COOH)_2$, 148.3, 147.0, 137.9, 136.0, 130.6, 129.9, 129.7, 129.3, 129.1, 128.9, 128.6, 121.8 120.1, 51.8 ($QuCH_2$), 46.8 (CH_2Ph). IR (neat): 3422 (N-H) cm^{-1}. HRMS Calcd for $C_{17}H_{17}N_2$ $(M + H)^+$ 249.1313. Found 249.1368.

N-(Quinolin-4-ylmethyl)-N-butylamine (**7c**): Oxalate [13d]; white solid; yield 52%; mp 182°C–183°C. ^{1}H NMR (D_2O): $\delta = 8.66$ (d, 1H, Qu-2 $J = 4.48$ Hz), 8.08–7.54 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 4.62 (s, 2H, CH_2), 2.73–2.70 (m, 2H, CH_2), 1.55–1.37 (m, 2H, CH_2), 1.16–1.08 (m, 2H, CH_2), 0.98–0.90 (m, 3H, CH_3). ^{13}C NMR (D_2O): $\delta = 159.8$ $(COOH)_2$, 148.7, 143.3, 136.5, 134.9, 130.5, 126.1, 123.6, 120.6, 120.1, 48.1 ($QuCH_2$), 46.2 (CH_2), 26.8, 18.5, 12.1.

N-(Quinolin-4-ylmethyl)-N-benzylamine (**7d**): Oxalate; white solid; yield 60%; mp 182–184°C (dec.). ^{1}H NMR (D_2O): $\delta = 8.73$ (d, 1H, Qu-2 $J = 5.01$ Hz), 8.00–7.65 (m, 5H, Qu-6, Qu-7, Qu-8, Qu-3, Qu-9), 7.17–7.05 (m, 5H, Phs), 4.55 (s, 2H, CH_2), 4.19 (m, 2H, CH_2). ^{13}C NMR (D_2O): $\delta = 160.7$ $(COOH)_2$, 148.8, 143.6, 136.7, 135.1, 130.7, 129.9, 129.4, 128.9, 126.3, 123.8, 120.9, 120.8, 120.7, 51.6 ($QuCH_2$), 45.6 (CH_2Ph).

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