Studies on Organophosphorus Compounds; Part XX. A Facile Synthesis of α-Amino-Substituted Benzylphosphonic and -phosphinic Acids by Use of Thiophosphoramide

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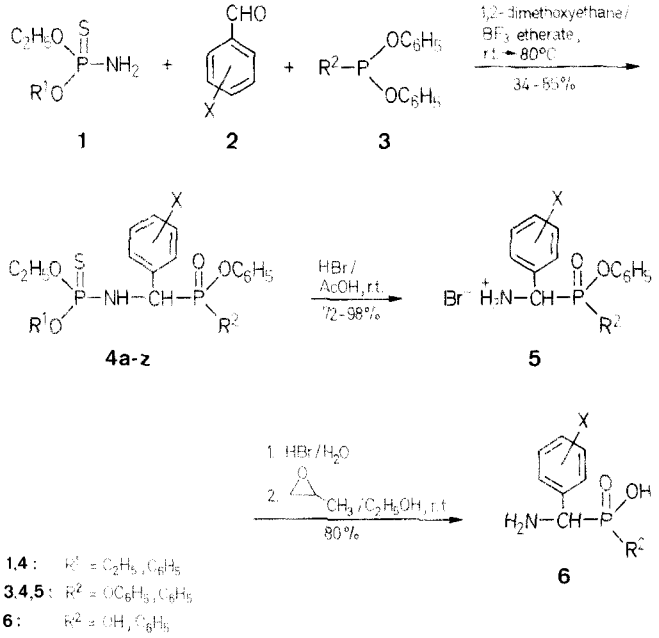
A facile method for the preparation of α-amino-substituted benzylphosphonic and -phosphinic acids is reported. It consists of the reaction of *O,O*-diethyl or *O*-ethyl *O*-phenyl phosphoroamidothioate (**1**) with a substituted benzylaldehyde (**2**) and a phosphorous or phosphonous ester (**3**) in the presence of a catalytic amount of boron trifluoride, followed by the selective cleavage of the protective groups of the resultant α-(thiophosphorylamino)-substituted benzylphosphonates or -phosphinates. The influence of variation in structure of the substrates on the yield of product is evaluated.

The discovery of the biological activity and chelating ability of aminoalkanephosphonic acids and peptide analogs derived therefrom has stimulated the investigation of the synthesis of these compounds. Some 1-aminoalkyl (or aralkyl)phosphonic acids (or: 1-aminoalkane- and 1-amino-1-arylalkanephosphinic acids) and their derivatives are available by various procedures[1-14]. One general method for the synthesis of these compounds involves the addition of a dialkyl phosphite to compounds having a C=N moiety, followed by hydrolysis and subsequent removal of the protective group of the amino or phosphonic acid functions. A systematic study is being carried on in this laboratory with the aim of developing a new and convenvient method for the synthesis of 1-aminoalkyl(aralykl)phosphonic acids based on the investigation of the influence of substrate structure on the yield of products[15-16].

We report here a facile synthetic method for the preparation of α-amino-substituted benzylphosphonic and -phosphinic acids (**6**). It consists of the reaction of *O,O*-diethyl or *O*-ethyl *O*-phenyl phosphoroamidothioate (**1**) with a substituted benzaldehyde (**2**) and a phosphorous or phosphonous ester (**3**) in the presence of a catalytic amount of boron trifluoride, followed by the successive cleavage of the thiophosphoryl and ester groups of the resultant α-(thiophosphorylamino)-substituted benzylphosphonate or -phosphinate (**4**). Our method is a modification of the reported three-component condensation of aldehydes with benzyl carbamate[9] or α,α-disubstituted benzylamines[6] and phosphorus(III) esters in which the NH_2 component is replaced by the phosphoroamidothioate **1**. The present new method affords higher yields in the condensation reaction and high purity of the resultant products in both steps of the sequence and it is simple to perform. The thiophosphoryl protecitve group in compounds **4** can be eliminated without cleavage of the ester group, thus providing an access to the hydrobromides of α-amino-substituted benzylphosphonates or -phosphinates (**5**) which are useful intermediates in phosphoruspeptide synthesis. The ester hydrobromides **5** can be converted into the free α-aminobenzylphosphonic or α-aminobenzylphosphinic acids **6** by the usual method of hydrolysis with hydrobromic acid followed by reaction with methyloxirane (propylene oxide).

The yields of condensation products **4** depend on the nature of the groups R^1 and R^2 in reaction components **1** and **3**, respectively (see Table 1). Thus, *O,O*-diethyl phosphoroamidothioate (**1**, $R^1 = C_2H_5$) gives higher yields of products



4 than *O*-ethyl *O*-phenyl phosphoroamidothioate (**1**, $R^1 = C_6H_5$) and diphenyl phenylphosphonite (**3**, $R^2 = C_6H_5$) reacts more smoothly than triphenyl phosphite (**3**, $R^2 = OC_6H_5$). These facts can be rationalized by the difference in polarity between the P=S and P=O groups as well as by the inductive effect of a benzene ring in the molecule. Since the presence of boron trifluoride is essential in this reaction because of the weak nucleophilicity of phosphoroamidothioates **1**, the reaction may be assumed to proceed as follows: boron trifluoride coordinates with the carbonyl group and benzene ring of the benzaldehyde **2** to form a complex **7** whereby the electrophilicity of the carbonyl C-atom is enhanced, thus facilitating the nucleophilic attack by compounds **1** to give an intermediate **8** which undergoes condensation with a second molecule of **1** to afford intermediate **9** which in turn reacts with triphenyl phosphite (**3**, $R^2 = OC_6H_5$) or diphenyl phenylphosphonite (**3**, $R^2 = C_6H_5$) to give the condensation product **4**.

The formation of complex **7** has been shown by us[16]. The possible existence of intermediate **9** was evidenced by experimental data and by the fact that two equivalents of **1** with respect to the benzaldehyde **2** are required, otherwise the yield of **4** decreases by 50%.

Compounds **4** represent a series of hitherto unknown derivatives of α-amino-substituted benzylphosphonic and phosphinic acids, although most of their hydrolysis products (**6**) have been reported[2,4,5,7,8,10,16]. Compounds **4** can be recrystallized from polar solvent to give colorless crystals. The ^{31}P-NMR spectra show two doublets at $\delta = 13$ or 36 ppm and at $\delta = 68$ ppm, the first one being attributable to the P-atom of the diphenoxyphosphinyl or phenylphenoxy-

Table 1. Diphenyl α-(Diethoxy- or Ethoxyphenoxy-thiophosphinylamino)-benzylphosphonates (**4**, $R^2 = OC_6H_5$) and Phenyl α-(Ethoxyphenoxythiophosphinylamino)-benzylphenylphosphinates (**4**, $R^2 = C_6H_5$) Prepared

4	R^1	R^2	X	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	MS *m/e*
a	C_2H_5	OC_6H_5	H	85	129.5–130.5 (ethanol)	$C_{23}H_{27}NO_5P_2S$ (491.4)	491 (M^+)
b	C_2H_5	OC_6H_5	4-CH_3	58	129.8–130.6 (ethanol)	$C_{24}H_{29}NO_5P_2S$ (505.45)	505 (M^+)
c	C_2H_5	OC_6H_5	4-F	66	103.9–104.3 (aqueous ethanol)	$C_{23}H_{26}FNO_5P_2S$ (509.4)	510 ($M^+ + 1$)
d	C_2H_5	OC_6H_5	4-Cl	54	102.0–103.0 (aqueous ethanol)	$C_{23}H_{26}ClNO_5P_2S$ (525.9)	526 (M^+)
e	C_2H_5	OC_6H_5	2-Cl	59	158.0–159.7 (aqueous ethanol)	$C_{23}H_{26}ClNO_5P_2S$ (525.9)	525 (M^+)
f	C_2H_5	OC_6H_5	4-Br	63	107.4–108.4 (aqueous ethanol)	$C_{23}H_{26}BrNO_5P_2S$ (570.3)	570 (M^+)
g	C_2H_5	OC_6H_5	2-Br	48	167.9–168.9 (ethyl acetate)	$C_{23}H_{26}BrNO_5P_2S$ (570.3)	570 (M^+)
h	C_2H_5	OC_6H_5	3-Br	48	121.5–122.2 (aqueous ethanol)	$C_{23}H_{26}BrNO_5P_2S$ (570.3)	570 (M^+)
i	C_2H_5	OC_6H_5	4-NO_2	49	144.6–145.6 (ethanol)	$C_{23}H_{26}N_2O_7P_2S$ (536.4)	536 (M^+)
j	C_2H_5	OC_6H_5	3-NO_2	47	114.4–115.4 (ethanol)	$C_{23}H_{26}N_2O_7P_2S$ (536.4)	536 (M^+)
k	C_2H_5	OC_6H_5	4-OCH_3	78	110.2–110.5 (aqueous ethanol)	$C_{24}H_{29}NO_6P_2S$ (521.45)	522 ($M^+ + 1$)
l	C_2H_5	OC_6H_5	3-OCH_3	77	96.1–97.0 (aqueous ethanol)	$C_{24}H_{29}NO_6P_2S$ (521.45)	522 ($M^+ + 1$)
m	C_2H_5	OC_6H_5	4-$N(CH_3)_2$	34	125.8–126.8 (aqueous ethanol)	$C_{25}H_{32}N_2O_5P_2S$ (534.5)	534 (M^+)
n	C_2H_5	OC_6H_5	4-OH	81	131.4–132.4 (ethyl acetate)	$C_{23}H_{27}NO_6P_2S$ (507.4)	506 (M^+)
o	C_6H_5	OC_6H_5	H	53	96.2–97.0 (aqueous ethanol)	$C_{27}H_{27}NO_5P_2S$ (539.5)	540 ($M^+ + 1$)
p	C_6H_5	OC_6H_5	4-CH_3	62	117.0–117.8 (aqueous ethanol)	$C_{28}H_{29}NO_5P_2S$ (553.5)	554 ($M^+ + 1$)
q	C_6H_5	OC_6H_5	4-F	48	116.4–117.0 (aqueous ethanol)	$C_{27}H_{26}FNO_5P_2S$ (557.5)	557 (M^+)
r	C_6H_5	OC_6H_5	4-Cl	53	145.5–146.1 (aqueous ethanol)	$C_{27}H_{26}ClNO_5P_2S$ (573.9)	573 (M^+)
s	C_6H_5	OC_6H_5	4-Br	46	149.3–149.9 (ethanol)	$C_{27}H_{26}BrNO_5P_2S$ (618.35)	620 ($M^+ + 2$)
t	C_6H_5	OC_6H_5	3-NO_2	45	101.6–102.8 (ethanol)	$C_{27}H_{26}N_2O_7P_2S$ (584.5)	585 ($M^+ + 1$)
u	C_6H_5	C_6H_5	H	71	122.1–123.5 (aqueous ethanol)	$C_{27}H_{27}NO_4P_2S$ (523.5)	524 ($M^+ + 1$)
v	C_6H_5	C_6H_5	4-CH_3	73	98.6–99.8 (aqueous ethanol)	$C_{28}H_{29}NO_4P_2S$ (537.5)	538 ($M^+ + 1$)
w	C_6H_5	C_6H_5	4-F	67	106.3–106.5 (aqueous ethanol)	$C_{27}H_{26}FNO_4P_2S$ (541.5)	541 (M^+)
x	C_6H_5	C_6H_5	4-Cl	70	114.4–115.7 (aqueous ethanol)	$C_{27}H_{26}ClNO_4P_2S$ (557.9)	558 ($M^+ + 1$)
y	C_6H_5	C_6H_5	4-Br	50	115.9–116.5 (aqueous ethanol)	$C_{27}H_{26}BrNO_4P_2S$ (602.35)	604 ($M^+ + 2$)
z	C_6H_5	C_6H_5	3-NO_2	44	134.1–135.1 (ethanol)	$C_{27}H_{26}N_2O_6P_2S$ (568.5)	569 ($M^+ + 1$)

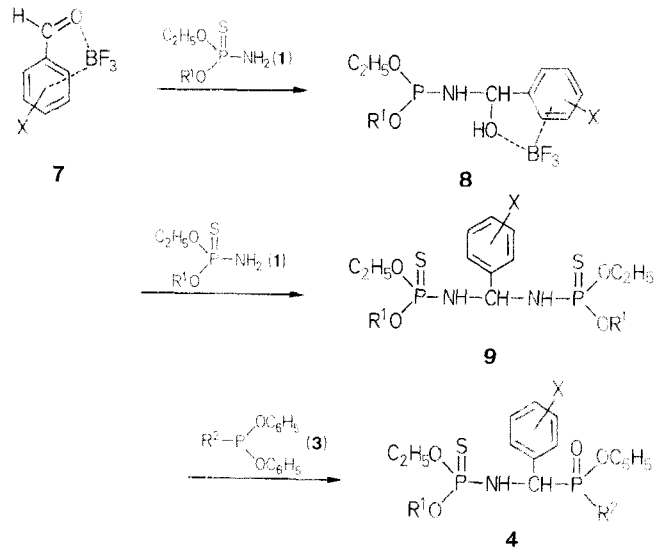
[a] The microanalyses showed the following maximum deviations from the calculated values: C ±0.46, H ±0.24, N ±0.26, P ±0.41, S (only for **4e,q,w**) ±0.36; exception: **3p** (C −0.62).

phosphinyl group, respectively, and the second one to the P-atom of the *N*-thiophosphoryl group. The appearance of these signals as doublets is due to P-P splitting, which is proven by the fact that both doublets have identical coupling constants. The ^{31}P-NMR chemical shifts of compound **4** correlate linearly with the Hammett σ constants of the substituents X. The effect of X on the chemical shifts of the P-atom in the diphenoxyphosphinyl or phenylphenoxyphosphinyl group is more marked than that on the more distant *N*-thiophosphoryl moiety. The correlation between the ^{31}P-NMR chemical shifts of the P-atom of the diphenoxyphosphinyl group of compounds **4** and the Hammett constant of X can be depicted by the following equation.

$\delta = -1.88\sigma + 12.53$

$r = 0.97$, $n = 12$, confidence level 99.9%

The ^{31}P-NMR chemical shifts of compounds **4** show a dependence on the position of the nuclear substituents X. In general, the signal of the *para*-substituted compound is shifted to lower field than that of the *meta*-substituted compound, whereas the *ortho*-substituted compoundshows

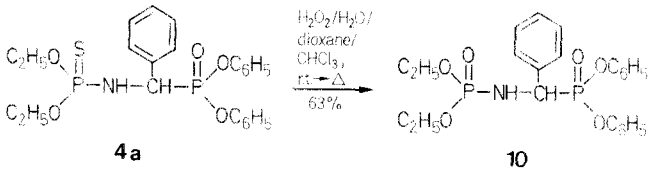


the least effect. Thus, ^{31}P-NMR spectrometry provides a means for distinguishing these isomers.

The *N*-thiophosphoryl group in **4** can be selectively removed with retention of the ester groups by treatment of **4** with a saturated solution of hydrogen bromide in acetic acid to give the hydrobromide **5** of the corresponding α-amino-substituted phosphonic or phosphinic ester in more than 90% yield. The thiophosphoryl group can therefore be considered as a useful NH_2-protecting group in this synthesis.

Our attempts to use optically active ethyl phenyl phosphoroamidothioate (**1**, $R^1 = C_6H_5$), $[\alpha]_D^{25}$: +4.60 (c = 2.0, chloroform), for the induced asymmetric synthesis of compounds **4** failed; the product **4o** thus obtained has the same optical rotation as compound **1** ($R^1 = C_6H_5$) and a racemic α-aminobenzylphosphonic acid resulted from hydrolysis of **4o** with hydrobromic acid.

Treatment of diphenyl α-(diethoxythiophosphinylamino)-benzylphosphonate (**4a**) with aqueous hydrogen peroxide results in S/O exchange to give the oxygen analog **10**.



Melting points were determined on a Mettler FP61 apparatus. Optical rotations were recorded on WZZ-1 apparatus. Mass spectra were measured with a Finnigan 4021 spectrometer. IR spectra were obtained with a Shimadzu 440 spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM-360 L spectrometer and ^{31}P-NMR spectra were recorded on a Varian XL-200 spectrometer.

Diphenyl α-(Diethoxy- or Ethoxyphenoxythiophosphinylamino)-benzylphosphonates (4, $R^2 = OC_6H_5$) and Phenyl α-(Ethoxy-phenoxythiophosphinylamino)-benzylphenylphosphinates (4, $R^2 = C_6H_5$); General Procedure:

To a stirred solution of *O,O*-diethyl phosphoroamidothioate[17] (**1**, $R^1 = C_2H_5$; 3.383 g, 0.020 mol) or *O*-ethyl *O*-phenyl phosphoroamidothioate[17] (**1**, $R^1 = C_6H_5$; 4.344 g, 0.020 mol) and the benzaldehyde **2** (0.01 mol) in dry 1,2-dimethoxyethane (50 ml), a solution of boron trifluoride etherate (1.3 ml) in 1,2-dimethoxyethane (10 ml) is slowly added at room temperature. Stirring is continued for 20 min at room temperature and for 15 min at 80 °C. Then, triphenyl phosphite (**3**, $R^2 = OC_6H_5$; 3.723 g, 0.012 mol) or phenyl diphenylphosphonite (**3**, $R^2 = C_6H_5$; 3.532 g, 0.012 mol) is added, the mixture is refluxed for 5 h, and concentrated under reduced pressure. The oily residue is dissolved in chloroform (150 ml). This solution is washed with water (3 × 60 ml), dried with magnesium sulfate, and evaporated. The remaining crude product **4** is purified by recrystallization (see Table 1).

Table 2. Diphenyl α-Aminobenzylphosphonate Hydrobromides (**5**, $R^2 = OC_6H_5$) and Phenyl α-Aminobenzylphenylphosphinate Hydrobromides (**5**, $R^2 = C_6H_5$) Prepared

5	R^2	X	Yield [%]	m.p. [°C]	Molecular Formula[a]
a	OC_6H_5	H	90.5	194.0–194.8	$C_{19}H_{19}BrNO_3P$ (420.2)
b	OC_6H_5	4-CH_3	90	181.4–182.0	$C_{20}H_{21}BrHO_3P$ (434.25)
c	OC_6H_5	4-F	91	185.5–186.9	$C_{19}H_{18}BrFNO_3P$ (438.2)
d	OC_6H_5	4-Cl	91	179.7–180.6	$C_{19}H_{18}BrClNO_3P$ (454.7)
e	OC_6H_5	2-Cl	98	180.5–181.3	$C_{19}H_{18}BrClNO_3P$ (454.7)
f	OC_6H_5	4-Br	94	187.2–188.7	$C_{19}H_{18}Pr_2NO_3P$ (499.1)
g	OC_6H_5	2-Br	72	187.4–187.9	$C_{19}H_{18}Br_2NO_3P$ (499.1)
h	OC_6H_5	3-Br	90	184.3–185.4	$C_{19}H_{18}Br_2NO_3P$ (499.1)
i	OC_6H_5	3-NO	94	174.0–175.0	$C_{19}H_{18}BrN_2O_5P$ (465.2)
k	OC_6H_5	4-OCH_3	90	154.2–155.7	$C_{20}H_{21}BrNO_4P$ (450.25)
l	OC_6H_5	3-OCH_3	89	156.9–157.9	$C_{20}H_{21}BrNO_4P$ (450.25)
u	C_6H_5	H	86	210.4–211.4	$C_{19}H_{19}BrNO_2P$ (404.2)
v	C_6H_5	4-CH_3	84	202.9–203.1	$C_{20}H_{21}BrNO_2P$ (418.25)
x	C_6H_5	4-Cl	93	210.2–210.4	$C_{19}H_{18}BrClNO_2P$ (438.7)
z	C_6H_5	3-NO_2	91.5	200.1–200.4	$C_{19}H_{18}BrN_2O_4P$ (449.2)

[a] The microanalyses showed the following maximum deviations from the calculated values: C ±0.38, M ±0.17, N ±0.18, P ±0.48; exceptions: **5a** (P −0.55), **5f** (C −0.53, P −0.54), **5i** (P −0.62), **5k** (C −0.54), **5v** (C −0.56), **5z** (N −0.48).

Diphenyl α-Aminobenzylphosphonate Hydrobromides (5, $R^2 = OC_6H_5$) and Phenyl α-Aminobenzylphenylphosphinates (5, $R^2 = C_6H_5$); General Procedure:

The respective compound **4** (1 mmol) is dissolved in a saturated solution of hydrogen bromide in acetic acid (15 ml). After 30 min at room temperature, the mixture is evaporated under reduced pressure. The remaining oily hydrobromide **5** crystallizes upon addition of anhydrous ether; it is recrystallized from ethanol or ether.

Diphenyl α-(Diethoxyphosphinylamino)-benzylphosphonate (10):

Aqueous hydrogen peroxide (33%; 20 ml) is added slowly to a stirred solution of compound **4a** (0.491 g, 1 mmol) in dioxane (10 ml) + chloroform (10 ml) at room temperature. After the addition is complete, the solution is refluxed for 2 h. Additional aqueous hydrogen peroxide (33%; 10 ml) is then added at 50 °C and the mixture is stirred at 100 °C for 4 h, then concentrated under reduced pressure. The oily residue is dissolved in chloroform (100 ml). This solution is washed with water (2 × 80 ml), dried with magnesium sulfate, and evaporated. The residue is dissolved in ethyl acetate (20 ml), and this solution kept in the refrigerator overnight. Product **10** is isolated by suction, and recrystallized from ethyl acetate; yield: 0.299 g (63%); m.p. 173–174 °C; (Ref.[16], m.p. 172.9–174 °C).

α-Aminobenzylphosphonic Acid (6a):

A solution of compound **4o** ($[\alpha]_D^{25}$: +4.59° (c = 2.1, chloroform); 0.41 g, 0.083 mol) in acetic acid (10 ml) is heated at 80 °C, 40%

Table 3. Spectral Data of Compounds **4** and **5**

Compound	IR (KCl) ν [cm^{-1}]	^{1}H-NMR (CCl_4) δ [ppm]	^{31}P-NMR ($CDCl_3$/85% H_3PO_{4ext}) δ [ppm]
4a	1210 (P=O); 1030 (P–O–C_2H_5); 950 (P–O–Ar)	7.40 (m, 16H, 3C_6H_5, NH); 5.41 (m, 1H, CH); 3.92 (m, 4H, 2O–CH_2–CH_3); 1.10 (m, 6H, 2O–CH_2–CH_3)	13.023, 12.473, 67.875, 68.320
4b	1200 (P=O); 1020 (P–O–C_2H_5); 950 (P–O–Ar)	7.30 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.21 (m, 1H, CH); 3.82 (m, 4H, 2O–CH_2–CH_3); 2.41 (s, 3H, CH_3); 1.10 (t, 6H, 2O–CH_2–CH_3)	13.184, 12.638, 68.987, 68.438
4c	1200 (P=O); 1020 (P–O–C_2H_5);	7.04 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.41 (m, 1H, CH); 3.60 (m, 4H, 2O–CH_2–CH_3); 0.93 (m, 6H, 2O–CH_2–CH_3)	12.274, 12.215, 69.470, 68.912
4d	1200 (P=O); 1030 (P–O–C_2H_5);	7.31 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.40 (m, 1H, CH); 3.81 (m, 4H, 2O–CH_2–CH_3); 1.10 (t, 6H, 2O–CH_2–CH_3)	12.340, 11.784, 69.423, 68.862
4e	1200 (P=O); 1020 (P–O–C_2H_5);	7.02 (m, 15H, 2C_6H_5, C_6H_5, C_6H_4, NH); 5.60 (m, 1H, CH); 3.71 (m, 4H, 2O–CH_2–CH_3); 1.01 (m, 6H, 2O–CH_2–CH_3)	12.100, 11.563, 68.252, 67.710
4f	1210 (P=O); 1040 (P–O–C_2H_5); 940 (P–O–Ar)	7.20 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.31 (m, 1H, CH); 3.72 (m, 4H, 2O–CH_2–CH_3); 1.00 (t, 6H, 2O–CH_2–CH_3)	12.194, 11.640, 69.326, 68.769
4g	1200 (P=O); 1020 (P–O–C_2H_5); 950 (P–O–Ar)	7.05 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.71 (m, 1H, CH); 3.72 (m, 4H, 2O–CH_2–CH_3); 1.00 (m, 6H, 3O–CH_2–CH_3)	12.100, 11.563, 68.252, 67.710
4h	1200 (P=O); 1030 (P–O–C_2H_5); 930 (P–O–Ar)	7.30 (m, 15H, 2C_6H_4, NH); 5.32 (m, 1H, CH); 3.81 (m, 4H, 2O–CH_2–CH_3); 1.10 (m, 6H, 2O–CH_2–CH_3)	12.132, 11.583, 69.058, 68.504
4i	1200 (P=O); 11030 (P–O–C_2H_5); 940 (P–O–Ar)	7.10 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.72 (m, 1H, CH); 3.72 (m, 4H, 2O–CH_2–CH_3); 0.94 (t, 6H, 3O–CH_2–CH_3)	11.340, 10.792, 69.863, 68.863
4j	1200 (P=O); 1020 (P–O–C_2H_5);	7.21 (m, 15H, 2C_6H_5, C_6H_5, C_6H_4, NH); 5.31 (m, 1H, CH); 3.70 (m, 4H, 2O–CH_2–CH_3); 0.93 (t, 6H, 2O–CH_2–CH_3)	11.229, 10.644, 69.046, 69.015
4k	1200 (P=O); 1030 (P–O–C_2H_5); 950 (P–O–Ar)	7.11 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.24 (m, 1H, CH); 3.72 (m, 4H, 2O–CH_2–CH_3); 3.70 (s, 3H, OCH_3); 1.00 (t, 6H, 2O–CH_2–CH_3)	13.216, 12.657, 68.998, 68.441
4l	1200 (P=O); 1030 (P–O–C_2H_5); 940 (P–O–Ar)	7.02 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.01 (m, 1H, CH); 3.72 (m, 4H, 2O–CH_2–CH_3); 3.54 (s, 3H, OCH_3); 1.02 (m, 6H, 3O–CH_2–CH_3)	12.989, 12.442, 68.822, 68.281
4m	1200 (P=O); 1020 (P–O–C_2H_5); 940 (P–O–Ar)	7.02 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.72 (m, 1H, CH); 3.71 (m, 4H, 2O–CH_2–CH_3); 2.71 [s, 6H, $N(CH_3)_2$]; 1.02 (m, 6H, 2O–CH_2–CH_3)	13.622, 13.067, 68.873, 68.316
4n	1200 (P=O); 1030 (P–O–C_2H_5); 950 (P–O–Ar)	7.21 (m, 15H, 2C_6H_5, C_6H_4, NH); 5.50 (m, 1H, CH); 3.82 (m, 4H, 2O–CH_2–CH_3); 1.93 (s, 1H, OH); 1.10 (m, 6H, 2O–CH_2–CH_3)	13.611, 13.062, 68.916, 68.365
4o	1210 (P=O); 1030 (P–O–C_2H_5); 940 (P–O–Ar)	7.00 (m, 21H, 4C_6H_5, NH); 5.20 (m, 1H, CH); 3.90 (m, 2H, O–CH_2–CH_3); 1.00 (m, 3H, O–CH_2–CH_3)	15.05, 67.91
4p	1210 (P=O); 1030 (P–O–C_2H_5); 950 (P–O–Ar)	7.20 (x, 20H, 3C_6H_5, C_6H_4, NH); 5.30 (m, 1H, CH); 4.00 (m, 2H, O–CH_2–CH_3); 2.50 (s, 3H, CH_3); 1.20 (m, 3H, O–CH_2–CH_3)	
4q	1210 (P=O); 1040 (P–O–C_2H_5); 960 (P–O–Ar)	7.00 (m, 20H, 3C_6H_5, C_6H_4, NH); 5.30 (m, 1H, CH); 3.85 (m, 2H, O–CH_2–CH_3); 1.00 (m, 3H, O–CH_2–CH_3)	
4r	1205 (P=O); 1030 (P–O–C_2H_5); 950 (P–O–Ar)	7.30 (m, 20H, 3C_6H_5, C_6H_4, NH); 5.50 (m, 1H, CH); 4.10 (m, 2H, O–CH_2–CH_3); 1.30 (m, 3H, O–CH_2–CH_3)	
4s	1205 (P=O); 1030 (P–O–C_2H_5); 945 (P–O–Ar)	7.20 (m, 20H, 3C_6H_5, C_6H_4, NH); 5.50 (m, 1H, CH); 4.00 (m, 2H, O–CH_2–CH_3); 1.20 (m, 3H, O–CH_2–CH_3)	
4t	1210 (P=O); 1030 (P–O–C_2H_5); 950 (P–O–Ar)	7.20 (m, 20H, 3C_6H_5, C_6H_4, NH); 4.10 (m, 2H, O–CH_2–CH_3); 1.20 (m, 3H, O–CH_2–CH_3)	
4u	1201 (P=O); 1030 (P–O–C_2H_5); 940 (P–O–Ar)	7.10 (m, 21H, 4C_6H_5, NH); 5.30 (m, 1H, CH); 3.90 (m, 2H, O–CH_2–CH_3); 1.10 (m, 3H, O–CH_2–CH_3)	36.50, 68.00
4v	1210 (P=O); 1025 (P–O–C_2H_5); 930 (P–O–Ar)	7.25 (m, 20H, 3C_6H_5, C_6H_4, NH); 5.50 (m, 1H, CH); 4.00 (m, 2H, O–CH_2–CH_3); 2.50 (s, 3H, CH_3); 1.25 (m, 3H, O–CH_2–CH_3)	
4w	1220 (P=O); 1025 (P–O–C_2H_5); 930 (P–O–Ar)	7.00 (x, 20H, 3C_6H_5, C_6H_4, NH); 5.30 (m, 1H, CH); 3.80 (m, 2H, O–CH_2–CH_3); 0.90 (m, 3H, O–CH_2–CH_3)	

Table 3. (continued)

Compound	IR (KCl) ν [cm^{-1}]	^{1}H-NMR (CCl_4) δ [ppm]	^{31}P-NMR ($CDCl_3$/85% H_3PO_{4ext}) δ [ppm]
4x	1220 (P=O); 1030 (P–O–C_2H_5); 935 (P–O–Ar)	7.20 (m, 20H, $3C_6\underline{H}_5$, $C_6\underline{H}_4$, N$\underline{H}$); 5.50 (m, 1H, C$\underline{H}$); 4.00 (m, 2H, O–C$\underline{H}_2$–CH_3); 1.20 (m, 3H, O–CH_2–C$\underline{H}_3$)	
4y	1220 (P=O); 1025 (P–O–C_2H_5); 930 (P–O–Ar)	7.20 (m, 20H, $3C_6\underline{H}_5$, $C_6\underline{H}_4$, N$\underline{H}$); 5.50 (m, 1H, C$\underline{H}$); 4.00 (m, 2H, O–C$\underline{H}_2$–CH_3); 1.15 (m, 3H, O–CH_2–C$\underline{H}_3$)	
4z	1200 (P=O); 1030 (P–O–C_2H_5); 930 (P–O–Ar)	6.80 (m, 20H, $3C_6\underline{H}_5$, $C_6\underline{H}_4$, N$\underline{H}$); 5.20 (m, 1H, C$\underline{H}$); 3.50 (m, 2H, O–C$\underline{H}_2$–CH_3); 0.70 (m, 3H, O–CH_2–C$\underline{H}_3$)	
5a	1190 (P=O); 960 (P–O–Ar)	7.70 (br., 3H, N$\underline{H}_3^+$); 6.75 (m, 15H, $3C_6\underline{H}_5$); 5.02 (m, 1H, C$\underline{H}$)	
5b	1200 (P=O); 930 (P–O–Ar)	7.71 (br., 3H, N$\underline{H}_3^+$); 6.72 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.00 (m, 1H, C$\underline{H}$); 1.85 (s, 3H, C$\underline{H}_3$)	
5c	1200 (P=O); 960 (P–O–Ar)	7.70 (br., 3H, N$\underline{H}_3^+$); 6.71 (x, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.00 (m, 1H, C$\underline{H}$)	
5d	1210 (P=O); 960 (P–O–Ar)	7.70 (br., 3H, N$\underline{H}_3^+$); 6.91 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.01 (m, 1H, C$\underline{H}$)	
5e	1210 (P=O); 950 (P–O–Ar)	8.00 (br., 3H, N$\underline{H}_3^+$); 6.81 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.10 (m, 1H, C$\underline{H}$)	
5f	1200 (P=O); 950 (P–O–Ar)	7.75 (br., 3H, N$\underline{H}_3^+$); 6.80 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.01 (m, 1H, C$\underline{H}$)	
5g	1220 (P=O); 960 (P–O–Ar)	8.10 (br., 3H, N$\underline{H}_3^+$); 6.91 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 4.91 (m, 1H, C$\underline{H}$)	
5h	1220 (P=O); 950 (P–O–Ar)	7.80 (br., 3H, N$\underline{H}_3^+$); 6.61 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.01 (m, 1H, C$\underline{H}$)	
5i	1220 (P=O); 950 (P–O–Ar)	8.00 (br., 3H, N$\underline{H}_3^+$); 6.71 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.10 (m, 1H, C$\underline{H}$)	
5k	1210 (P=O); 960 (P–O–Ar)	7.74 (br., 3H, N$\underline{H}_3^+$); 6.60 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.00 (m, 1H, C$\underline{H}$); 3.41 (s, 3H, OC$\underline{H}_3$)	
5l	1220 (P=O); 970 (P–O–Ar)	7.72 (br., 3H, N$\underline{H}_3^+$); 6.71 (m, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 5.00 (m, 1H, C$\underline{H}$); 3.42 (s, 3H, OC$\underline{H}_3$)	
5u	1240 (P=O); 930 (P–O–Ar)	7.65 (br., 3H, N$\underline{H}_3^+$); 6.80 (d, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 4.90 (m, 1H, C$\underline{H}$)	
5v	1240 (P=O); 930 (P–O–Ar)	7.70 (br., 3H, N$\underline{H}_3^+$); 6.80 (d, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 4.85 (m, 1H, C$\underline{H}$)	
5x	1240 (P=O); 930 (P–O–Ar)	7.68 (br., 3H, N$\underline{H}_3^+$); 6.80 (d, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 4.91 (m, 1H, C$\underline{H}$)	
5z	1240 (P=O); 930 (P–O–Ar)	7.72 (br., 3H, N$\underline{H}_3^+$); 6.80 (d, 14H, $2C_6\underline{H}_5$, $C_6\underline{H}_4$); 4.89 (m, 1H, C$\underline{H}$)	

hydrobromic acid (10 ml) is added, and the mixture is refluxed at 120 °C for 5 h. It is then concentrated under reduced pressure and the residue is dissolved in ethanol (10 ml). To this solution, propylene oxide is added dropwise until pH 6 is attained. The precipitated solid is isolated by suction, and recrystallized from aqueous ethanol; yield: 0.13 g (80%); m.p. 279–281 °C (reported: m.p. 281–282 °C[7], 280 °C[11], 271–273 °C[2], 272 °C[4], 272–273 °C[1]). The product shows no optical rotation.

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