

β -Benzotriazolylethyl Phosphates and Phosphonic Esters

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ABSTRACT

β -(1-Benzotriazolyl)ethyl dibutyl phosphate and the 2-benzotriazolyl analog were prepared from dibutyl phosphite and 1- and 2-(β -hydroxyethyl)benzotriazoles, respectively. Dialkyl β -(N-benzotriazolyl)ethylphosphonates were prepared from the corresponding dialkyl β -bromoethylphosphonates. In both types of compounds, elimination of benzotriazole occurs in base; interestingly, such elimination is significantly faster in each series for the 2-substituted benzotriazole than for the corresponding 1-isomer.

INTRODUCTION

Our previous work with 1-(α -heteroatomsubstituted methyl)benzotriazoles has shown that benzotriazole is a synthetically useful leaving group [1]. The successful use of N-(α -aminoalkyl)benzotriazoles in organic synthesis has stimulated us to investigate various N-(β -substituted-ethyl)benzotriazoles as potential synthons. We now report the synthesis of some derivatives of this type and some of their 1,2-elimination reactions.

RESULTS AND DISCUSSION

We prepared 1- (**1**) and 2-(2-hydroxyethyl)benzotriazole (**2**) from the sodium salt of benzo-

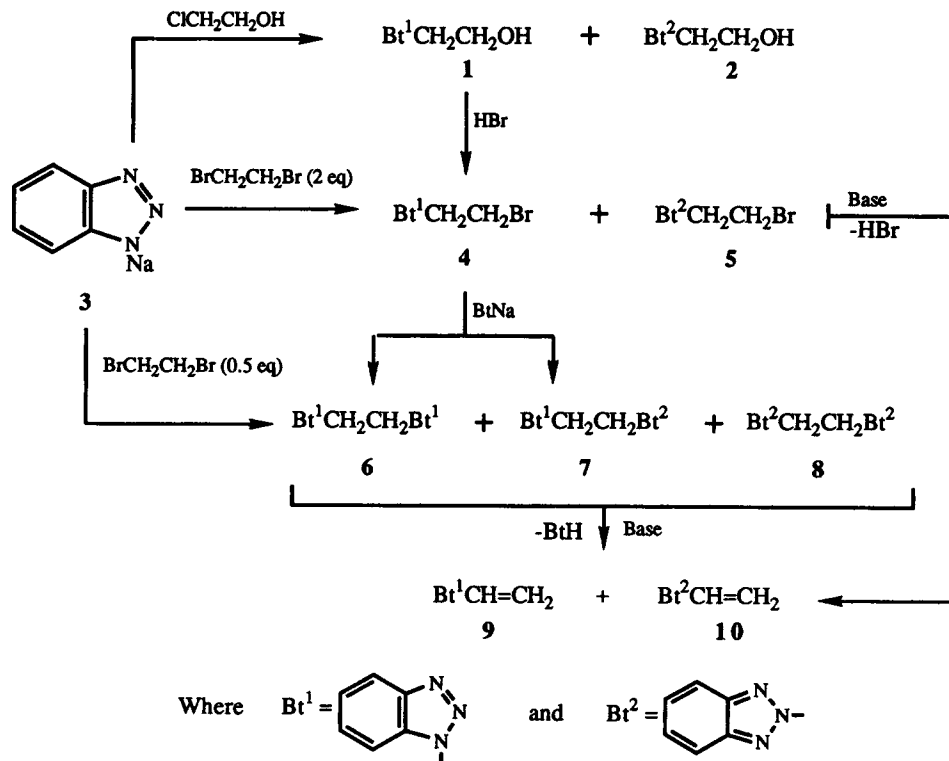
triazole (BtNa) (**3**) and 2-chloroethanol following the literature [2]. Compounds **1** and **2** were each converted into the corresponding 2-bromoethyl derivatives **4** (65%) and **5** (85%) [2]. Treatment of **4** with sodium benzotriazolate (**3**) gave a mixture of the 1,2-bis(benzotriazolyl)ethanes **6** and **7** (overall 87%) from which **6** was isolated (23%) (Scheme 1).

The reaction of 1,2-dibromoethane with an aqueous solution of BtNa (molar ratio 2:1) led to a mixture from which 1-(β -bromoethyl)benzotriazole **4** (25%) and the disubstituted compound **6** (5%) were separated by fractional crystallization. When the reaction was carried out in methanol, the isolated yield of **4** increased to 31%. The reaction of 1,2-dibromoethane with an aqueous solution of BtNa (**3**) (molar ratio 1:2) under reflux for 3 days gave a mixture of the isomeric 1,2-bis(benzotriazolyl)ethanes **6-8** (83%).

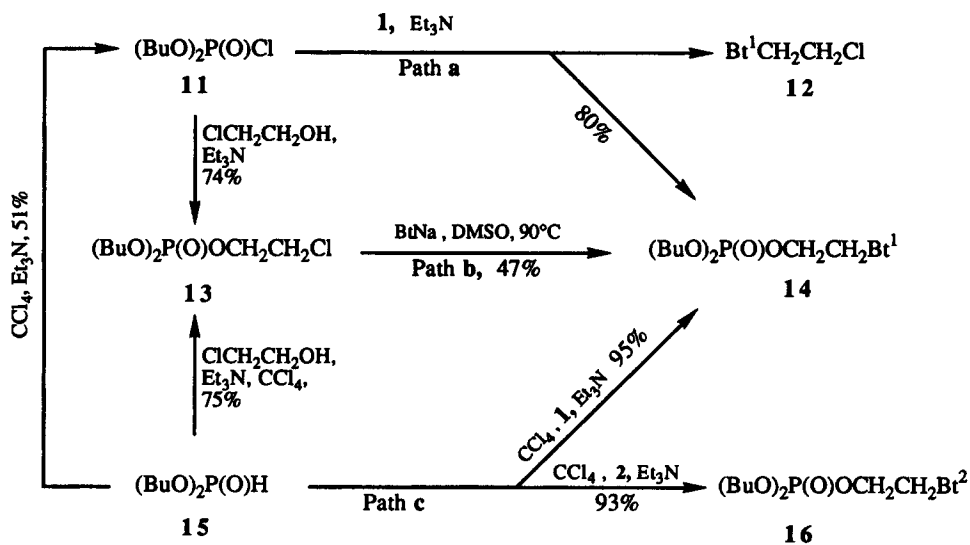
Benzotriazole, sodium methoxide, and 1,2-dibromoethane (in a molar ratio of 2:2:1) reacted in methanol to give the three expected products **6-8**, together with 1- (**9**) and 2-vinylbenzotriazole (**10**). The ¹H NMR spectrum of the reaction mixture allowed estimation of the ratio of **6:7:8:9:10** as 25:43:6:25:1. Obviously, **10** is obtained from **5** by elimination of hydrogen bromide or from **8** by elimination of benzotriazole.

The benzotriazolylethyl phosphate **14** was prepared by **path a** in Scheme 2. The dibutyl chlorophosphate (**11**) was obtained by the reaction of commercially available dibutyl phosphite (**15**) with carbon tetrachloride [3]. Heating a neat mixture of the chlorophosphate **11** with 1-(2-hydroxy-

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SCHEME 1



SCHEME 2

ethyl)benzotriazole (1) at 150°C for 1 hour led to a complex mixture, shown by ^1H and ^{13}C NMR spectroscopy to be the expected phosphate 14 (about 15%), 1-(2-chloroethyl)benzotriazole (25%), and unreacted 11. However, refluxing 1 and 11 in carbon tetrachloride gave only the phosphate 14 in 80% yield (Scheme 2). Phosphate 14 was characterized by its ^1H and ^{13}C NMR spectra.

Another route to phosphate 14 involved preliminary formation of the mixed orthophosphate

ester 13 using Steinberg's method [3] followed by treatment with either benzotriazole or BtNa. Dibutyl 2-chloroethylphosphate (13) was obtained by reaction of dibutyl chlorophosphate (11) with 2-chloroethanol (74%) and also by the reaction of 15 with carbon tetrachloride and 2-chloroethanol (75%). The reaction of phosphate 13 with BtNa failed in tetrahydrofuran and in dimethylformamide and gave little product in methanol; but, in dimethyl sulfoxide (path b), the desired phosphate

14 was obtained in 47% yield together with 2-butylbenzotriazole (about 13%). Advantageously, in a one-pot sequence, **1** was treated with dibutyl phosphite **15** in carbon tetrachloride to afford pure **14** (95%). Similarly, **2** yielded **16** (93%).

Compounds **14** and **16** are unstable in basic conditions, as shown by the appearance of NMR signals indicating the formation of 1- and 2-vinylbenzotriazoles **9** and **10** in the presence of sodium hydroxide. The Bt² isomer **16** was more prone to elimination; the reaction with sodium hydroxide occurred rapidly at room temperature to afford **10** (87%). The reaction was exothermic and was complete within 40 minutes. The Bt¹ isomer **14** underwent elimination much more slowly (ca. 10 hours) to afford 1-vinylbenzotriazole (**9**) (95%).

The mass spectral fragmentation patterns of **14** and **16** were quite distinct. For **16**, the M⁺ ion (m/z 335.1739) has an intensity of 26.3% and base peak at m/z = 145, which corresponds to 2-vinylbenzotriazole (**10**). On the other hand, the molecular ion for **14** has an intensity of 36.3%, and the peak corresponding to 1-vinylbenzotriazole (**9**) has an intensity of 65.2%. The base peak in this case is at m/z = 117, which corresponds to loss of nitrogen from 1-vinylbenzotriazole. For **10**, the corresponding peak at m/z = 117 has an intensity of only 3.9%. Obviously, 2-vinylbenzotriazole (**10**) cannot lose nitrogen as readily as its 1-isomer. Under electron impact conditions, it seems that Bt² isomers are also more prone to undergo 1,2-elimination reactions.

Attempted preparation of **20** by the Arbuzov reaction [4] with triethyl phosphite (**18**) and 1-(2-bromoethyl)benzotriazole (**4**) at 160°C for 4 hours gave a mixture of diethyl phosphite (**17**) (30%), 1-vinylbenzotriazole (**9**), and unreacted starting materials (Scheme 3). Milder reaction conditions (reflux in tetrahydrofuran) gave back starting materials.

Kosolapoff [5] has studied the isomerizations of trialkyl phosphites with alkyl halides and dihalides to form phosphonates. Thus, reaction of triethyl phosphite (**18**) with 1,2-dibromoethane (1:4 molar ratio; reflux 3 hours), followed by distilla-

tion of the ethyl bromide formed, afforded the 2-bromoethylphosphonate **19** in 68% yield. Reaction of this with the sodium salt of benzotriazole afforded the expected phosphonate **20** in 53% yield. Similarly, reaction of trioctyl phosphite **21** with ethylene bromide afforded **22** (70%), which, upon treatment with BtNa, afforded the dioctyl phosphonate **23** (60%).

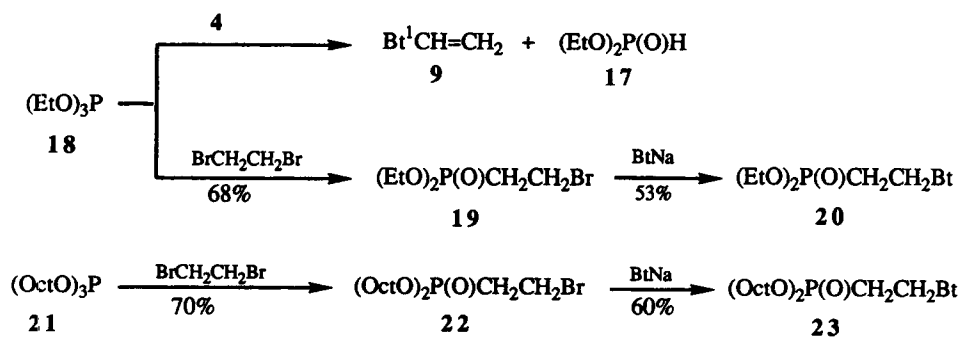
CONCLUSIONS

In comparison to N-(α -substituted-methyl) benzotriazoles [1], N-(β -substituted-ethyl)-benzotriazole derivatives are more difficult to prepare: the β -substituted-ethyl derivatives do not undergo the benzotriazol-1-yl to benzotriazol-2-yl isomerization, but they undergo elimination in basic conditions. Thus, the reaction of **4** or **5** with sodium hydroxide afforded the vinyl benzotriazole, as did **4** with triethyl phosphite. Similarly, the phosphates **14** and **16** also afforded 1- and 2-vinylbenzotriazole, respectively, when treated with sodium hydroxide. Apparently, Bt² is a better electron-withdrawing group, and, if the 1,2-elimination is of the E1cb type, it could be a better group for the stabilization of the intermediate carbanion.

EXPERIMENTAL

Melting points were determined on a bristoline hot-stage microscope and are uncorrected. The ¹H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT mode) spectrometer with Me₄Si as internal standard. The ¹³C NMR spectra were recorded at 75 MHz on the same instrument using the solvent peak (CDCl₃, δ 77.0) as reference. High resolution mass spectrometry was carried out on a Finnigan Mat 95 instrument. Flash chromatography was run on an EM Science silica gel 60 (230–400 mesh).

The following compounds were prepared by known literature procedures: 1-(2-hydroxyethyl)benzotriazole (**1**), mp 90–91°C (Ref. [2], mp 90–91°C); 2-(2-hydroxyethyl)-benzotriazole (**2**), mp 69–71°C (Ref. [2], mp 70–71°C); 1,2-bis(benzotriazol-



SCHEME 3

1,1-yl)ethane (**6**), mp 159–162°C (Ref. [2], mp 161–162°C); 1,2-bis(benzotriazol-1,2-yl)ethane (**7**), mp 135–137°C (Ref. [2], mp 136–137°C); dibutyl chlorophosphate (**11**), bp 89–95°C/1–2 mm (Ref. [3], bp 110–1113°C/6 mm); diethyl 2-bromoethylphosphonate (**19**), bp 92°C/2 mm (Ref. [6], bp 86–87°C/2 mm).

1-(2-Bromoethyl)benzotriazole (**4**)

Method A. 1,2-Dibromoethane (15.0 g, 0.008 mol) was added to a solution of benzotriazole (4.77 g, 0.04 mol) in aqueous NaOH (2 N; 22 mL, 0.04 mol) and the reaction mixture heated at 80–85°C for 2 hours, cooled, extracted with Et₂O (3 × 20 mL), and dried (MgSO₄). The filtrate was kept at 0°C for 2 days and the solid obtained collected and dissolved in methanol. Upon cooling, the colorless crystals of 1,2-bis(benzotriazol-1-yl)ethane (**6**) (0.3 g, 5%) were filtered off. The methanol was removed under reduced pressure and the residue recrystallized from Et₂O to afford **4** as colorless flakes (2.25 g, 25%), mp 118–121°C (Ref. [2], mp 119–120°C).

Method B. Sodium methoxide (2.16 g, 0.04 mol) was added to a solution of benzotriazole (4.77 g, 0.04 mol) in MeOH (400 mL). After 30 minutes, 1,2-dibromoethane (15.0 g, 0.04 mol) was added and the reaction mixture stirred at ambient temperature for 24 hours. The solution was concentrated to 100 mL and the mixture cooled overnight. The solid thus obtained was filtered off and recrystallized from Et₂O to afford **4** as colorless flakes (2.8 g, 31%), mp 119–121°C (Ref. [2], mp 119–120°C).

1,2-Bisbenzotriazolylethane (**6–8**)

Method A. Benzotriazole (38.2 g, 0.32 mol) was dissolved in aqueous NaOH (2 N; 170 mL, 0.35 mol) and 1,2-dibromoethane (30 g, 0.16 mol) added slowly. The mixture was heated under reflux for 3 days to afford a pale yellow oil which separated out. Et₂O (150 mL) was added to the mixture and the oil slowly solidified. The solid was filtered off and the filtrate washed with Et₂O (3 × 25 mL), and the ether was removed to yield more solid (total yield: 35.1 g, 83%), which was mainly a mixture of the Bt¹Bt¹ (**6**) and the Bt¹Bt² (**7**) isomers (as evidenced by NMR spectroscopy).

Method B. A mixture of 1,2-dibromoethane (15 g, 0.08 mol), benzotriazole (19.1 g, 0.16 mol), and NaOMe (8.64 g, 0.16 mol) in MeOH (100 mL) was heated under reflux for 48 hours. H₂O (200 mL) was added, and the white solid obtained was collected and dried. Recrystallization from ethanol afforded a mixture of the three isomers **6–8** (in a ratio of 36:64:3 by NMR) as colorless needles (6.3 g, 30%).

Dibutyl 2-Chloroethylphosphate (**13**)

Method A. Triethylamine (2.22 g, 22 mmol) was added to a solution of dibutyl chlorophosphate (**11**) (4.58 g, 20 mmol) and 2-chloroethanol (1.61 g, 20 mmol) in CCl₄ (30 mL) and refluxed for 3 hours. After cooling, the precipitate was filtered off and the solvent removed under reduced pressure to give crude **13**. Distillation afforded pure **13** as a colorless oil (4.0 g, 74%), bp 112–115°C/1 mm. Anal. found: M⁺, *m/z*, 273.1014; C₁₀H₂₂ClO₄P requires M⁺, *m/z*, 273.1022. Results by ¹H NMR, δ 4.26 (m, 2H), 4.06 (q, *J* = 6.8 Hz, 4H), 3.71 (t, *J* = 5.6 Hz, 2H), 1.68 (m, 4H), 1.42 (m, 4H), and 0.94 (t, *J* = 7.5 Hz, 6H); by ¹³C NMR, δ (67.74, 67.65, *J*_{P-C} = 6.75 Hz), (66.71, 66.64, *J*_{P-C} = 5.25 Hz), (42.43, 42.33, *J*_{P-C} = 7.5 Hz), (32.14, 32.05, *J*_{P-C} = 6.75 Hz), 18.5, and 13.4.

Method B. A mixture of dibutyl phosphite (**15**) (19.4 g, 0.1 mmol), CCl₄ (30.8 g, 0.2 mol), 2-chloroethanol (8.8 g, 0.11 mol), and triethylamine (10.2 g, 0.11 mol) was refluxed for 6 hours. The precipitate was filtered off, CCl₄ (200 mL) was added to the filtrate, and the solution was washed with H₂O (2 × 50 mL) and dried (MgSO₄). The solvent was removed under reduced pressure and the crude oil distilled to afford **13** as a colorless oil (20.5 g, 75%), bp 112–115°C/1 mm, identical (TLC, ¹H NMR, ¹³C NMR) to that prepared above.

2-(Benzotriazol-1-yl)ethyl Dibutyl Phosphate (**14**)

A solution of triethylamine (2.22 g, 22 mmol), **1** (3.28 g, 20 mmol), and dibutyl phosphite (**15**) (3.88 g, 20 mmol) in CCl₄ (6.16 g, 40 mmol) was refluxed for 6 hours. The precipitate was filtered off and the solvent removed under reduced pressure to give **14** as a yellow oil (6.75 g, 95%). Anal. found: M⁺, *m/z*, 355.1711; C₁₆H₂₆N₃O₄P requires M⁺, *m/z*, 355.1739. Results by ¹H NMR, δ 8.1–8.05 (m, 1H), 7.7–7.4 (m, 3H), 4.94 (t, *J* = 5.0 Hz, 2H), 4.54 (m, 2H), 3.83 (m, 4H), 1.51 (m, 4H), 1.28 (m, 4H), and 0.87 (t, *J* = 7.3 Hz, 6H); by ¹³C NMR, δ 145.8, 133.5, 127.4, 123.9, 119.8, 109.6, (67.68, 67.60, *J*_{P-C} = 6.3 Hz), (65.42, 65.35, *J*_{P-C} = 5.25 Hz), (48.12, 48.03, *J*_{P-C} = 6.75 Hz), (31.97, 31.88, *J*_{P-C} = 6.75 Hz), 18.4, and 13.3.

2-(Benzotriazol-2-yl)ethyl Dibutyl Phosphate (**16**)

Prepared as above from **1**. Phosphate **16** was obtained as a yellow oil (6.6 g, 93%). Anal. found: M⁺, *m/z*, 355.1739; C₁₆H₂₆N₃O₄P requires M⁺, *m/z*, 355.1739. Results by ¹H NMR, δ 7.9–7.85 (m, 2H), 7.4–7.35 (m, 2H), 4.99 (m, 2H), 4.75–4.65 (m, 2H), 3.90 (dq, *J* = 1.5, 6.3 Hz, 2H), 1.54 (quintet, *J* = 8.2 Hz, 4H), 1.35–1.2 (m, 4H), and 0.86 (t, *J* = 7.3 Hz, 6H); by ¹³C NMR, δ 144.4, 126.4, 117.9 (67.65, 67.57,

$J_{P-C} = 6.0$ Hz), (64.79, 64.72, $J_{P-C} = 5.25$ Hz), (56.21, 56.11, $J_{P-C} = 7.5$ Hz), (32.01, 31.92, $J_{P-C} = 6.75$ Hz), 18.4, and 13.4.

1-Vinylbenzotriazole (9)

NaOH (4 g, 0.1 mol) was added to a solution of **14** (3.1 g, 9 mmol) in DMF (6 mL) and the mixture stirred at ambient temperature for 10 hours. The solution was diluted with water (100 mL) and the organic material extracted with Et₂O (3 × 25 mL), washed with water (50 mL), and dried (MgSO₄). The solvent was removed under reduced pressure and the residue recrystallized from pet. ether (bp 60–80°C) to give **9** as colorless needles (1.2 g, 95%), mp 27–29°C (Ref. [2], mp 29–30°C).

2-Vinylbenzotriazole (10)

Prepared as above from **16** with a reaction time of 2 hours. After distillation, the product **10** was obtained (87%), bp 65–70°C/1.5–2 mm (Ref. [2], bp 84–85°C/3 mm).

Diethyl 2-Bromoethylphosphonate (22)

Commercially available trioctyl phosphite (TCI, mixture of isomers) (4.2 g, 10 mmol) and 1,2-dibromoethane (7.5 g, 40 mmol) were heated under reflux for 3 hours and the excess dibromoethane distilled off under reduced pressure (6–7 mm Hg). The residue was purified by distillation to give pure **22** as a colorless oil (3.0 g, 70%), bp 165–175°C/1–1.5 mm. Anal. found: M + 1, m/z , 413.1820; C₁₈H₃₉BrO₃P requires M + 1, m/z , 413.1820. Results by ¹H NMR, δ 4.06 (m, 4H), 3.51 (m, 2H), 2.5–2.3 (m, 2H), and 1.8–0.7 (m, 30H); by ¹³C NMR, δ (64.5, 64.47, $J_{P-C} = 6.75$ Hz), 40–10 (PCH₂CH₂Br signals and other octyl group signals).

Diethyl 2-(Benzotriazolyl)ethylphosphonate (20)

A solution of benzotriazole (1.19 g, 10 mmol) and NaOH (0.4 g, 10 mmol) in water (15 mL) was added

to diethyl 2-bromoethylphosphonate (**19**) (2.45 g, 10 mmol) and stirred at 90°C for 6 hours. The solution was then washed with Et₂O (2 × 80 mL), the organic fraction washed with water (2 × 30 mL) and dried (MgSO₄). The solvent was removed under reduced pressure and the residue purified by column chromatography to yield a mixture of the Bt¹ and Bt² isomers **20** as a yellow oil which was not separated (1.5 g, 53%). Anal. found: M⁺, m/z , 283.1091; C₁₂H₁₈N₃O₃P requires M⁺, m/z , 283.1085. Results by ¹H NMR, δ 8.1–7.3 (m, 4H), 5.05–4.85 (m, 2H), 4.2–4.0 (m, 4H), 2.75–2.5 (m, 2H), and 1.35–1.2 (m, 6H); by ¹³C NMR, Bt¹ isomer: δ 145.3, 132.3, 126.9, 123.5, 119.3, 108.9, (61.59, 61.51, $J_{P-C} = 6$ Hz), 41.7, (27.01, 25.14, $J_{P-C} = 140.25$ Hz), and (15.79, 15.71, $J_{P-C} = 6$ Hz); Bt² isomer: δ 143.8, 126.0, 117.4 (61.59, 61.51, $J_{P-C} = 6$ Hz), 50.2, (27.28, 25.41, $J_{P-C} = 140.25$ Hz), and (15.85, 15.79, $J_{P-C} = 4.5$ Hz).

Dioctyl 2-(Benzotriazolyl)ethylphosphonate (23)

Prepared as above from **22**. The mixture of the Bt¹ and Bt² isomers **23** was obtained as a yellow oil (2.7 g, 60%) which was not separated. Anal. found: M⁺, m/z 451.2971; C₂₄H₄₂N₃O₃P requires M⁺, m/z , 451.2964. Results by ¹H NMR, δ 8.1–7.3 (m, 4H), 5.06–4.86 (m, 2H), 4.15–3.9 (m, 4H), 2.75–2.4 (m, 2H), 1.8–0.7 (m, 30H); by ¹³C NMR, δ 145.8, 144.3, 132.8, 127.4, 126.4, 123.9, 120.0, 117.9, 109.2, 64.9, 64.4, 50.7, 46.4, 42.1; PCH₂CH₂Bt and other octyl groups peak between 38 and 12 ppm.

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