In the presence of formaldehyde.

$$\underset{1}{RhCl(CO)(Ph_3P)_2} \underset{HCHO}{\overset{-CO}{\rightleftharpoons}} \underset{3}{RhCl(Ph_3P)_2} \xrightarrow[\text{catalytic cycle}]{H_2,\ CH_2=CHCN} RhCl(Ph_3P)_2 + CH_3CH_2CN \quad (6)$$

It is yet to be investigated whether the hydrogenation with **1** also proceeds *via* the hydride route (cf. eq. 1) initiated by the formation of the oxidative addition of H_2 to give $RhClH_2(CO)(Ph_3P)_2$.

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(9) The rate hydrogenation with **1** is much slower than that with **2**. For example, the hydrogenation of acrylonitrile with **2** proceeds fairly rapidly even at 25°C under atmospheric pressure of hydrogen.
(10) The solid was isolated by the same manner described in ref. 1.
(11) IR of **1** shows a strong ν_{CO} at 1995 cm^{-1} (KBr).
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(14) The concentration of **3** would be negligible in the reactor, and the hydrogenation would not occur if the system produces free CO, which we have intended to avoid.

Syntheses of Phosphonamides Containing Aminobenzylphosphonic Acid and Aminopenicillanic Acid

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This paper reports new phosphonamide derivatives which contain diethyl aminomethylphosphonate, diethyl DL-1-aminobenzylphosphonate and 6-aminopenicillanic acid; N-(ethyl phthalimidomethylphosphonyl)-L-methionine methyl ester, N-(ethyl phthalimidomethylphosphonyl)-L-valine ethyl ester, N-[ethyl N-(methoxycarbonylmethyl)benzylphosphonamido]-2-phthalimidoacetamide, N-[ethyl N-(diethyl phosphonylbenzyl)methylphthalamido] phthalimide, N-[ethyl {ethyl N-(diethyl phosphonylbenzyl)aminomethylphosphonamido} phosphonylmethyl] phthalimide, N-[ethyl N-(diethyl phosphonylbenzyl)methylphosphonamido]-2-phthalimidoacetamide, N, N'-bis (ethyl phthalimidomethylphosphonyl)ethylene diamine, 6-(ethyl DL-1-aminobenzylphosphonamido) penicillanic acid, ethyl N-(ethoxycarbonylmethyl)-1-aminobenzylphosphonamide, ethyl N-(diethyl phosphonylbenzyl)aminomethylphosphonamide and N,N'-bis (ethyl aminomethylphosphonyl) ethylene diamine.

Introduction

It is well known that penicillins have been one of the most useful and least toxic antibiotics, since it was isolated in 1929 by Fleming.

All of naturally occuring penicillins contains the bicyclic ring, 6-aminopenicillanic acid (6-APA) as main structure, but they have different substituents at C-6.[1-2]

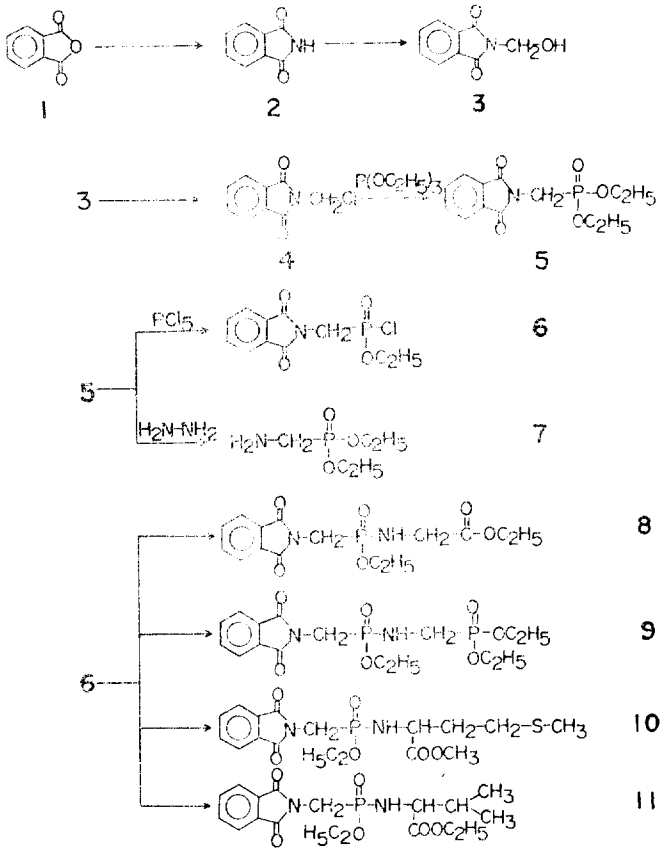
Although these drugs have revolutionized the medical world, still they have some serious problems. One of these is the lowering of activity against gram-negative bacteria on long term application in chemotherapy.[3] Hence many medicinal chemists have attempted to modify these compounds through the introduction of amido group into C-6 position in the penicillin nucleus. Consequently many semisynthetic penicillins were reported in the literatures.

So far the authors have published a series of papers on the syntheses of peptides containing aminophosphonic acids as well as phosphonamides.[4-7]

This paper is reporting the syntheses of new 9 compounds containing phosphonamido group and particulary the compound which has phosphonamido group at C-6 position of 6-APA expecting to improve the antimicrobial activity of this compound against gram-negative bacteria in further study.

Discussion

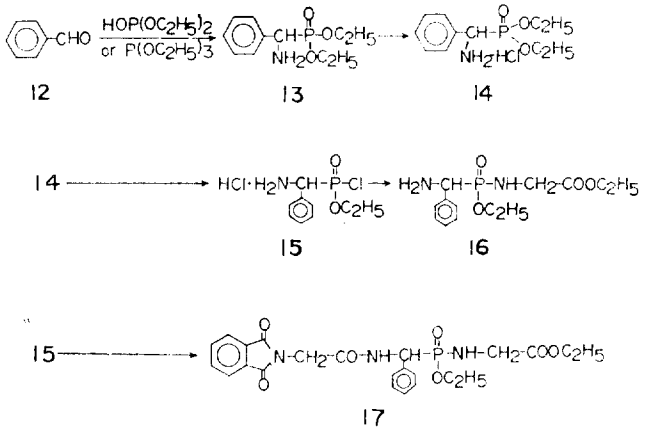
The following scheme 1 has been applied to the syntheses of some phosphonamides containing diethyl aminomethylphosphonate and diethyl DL-1-aminobenzylphosphonate.



Scheme 1.

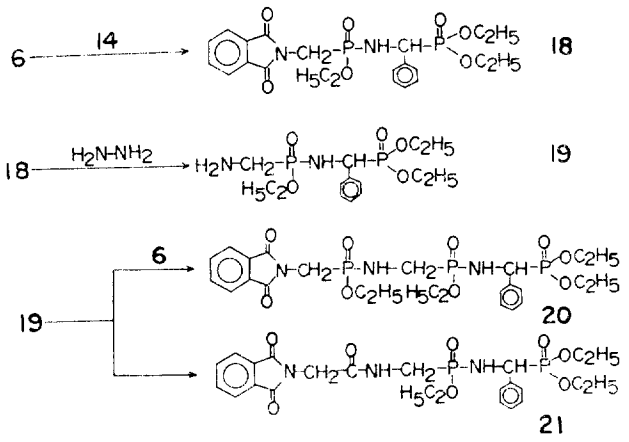
Phosphonamide **8** was prepared by the reaction of chloridate **6** and glycine ethyl ester hydrochloride; Phosphonamide **9**, by the reaction of chloridate **6** and compound **7**; phosphonamide **10**, by the reaction of chloridate **6** and L-(+)-methionine methyl ester hydrochloride and also phosphonamide **11**, by the reaction of chloridate **6** and L-(+)-valine ethyl ester hydrochloride.

The IR spectra and melting point of **8** and **9** showed good accordance with the literature listed.[8-9] The IR spectra of **8, 9, 10** and **11** showed the characteristic absorption band of P-NH- at 3200, 3150, 3240 and 3150 cm^{-1} respectively. The specific rotations of **10** and **11** were found to be $[\alpha]_{589.3}^{23} = +2.25$ and $[\alpha]_{589.3}^{23} = +2.5$ in chloroform respectively.



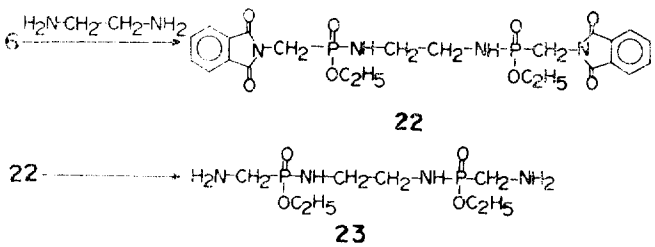
Scheme 2.

Compound **15** was prepared form compound **14** by a procedure similar to that reported by Penetta.[10] The phosphonamide **17** was obtained in 38 % yield from compound **16** with positive ninhydrin test.



Scheme 3.

Compound **19** was obtained by the dephthalation of compound **18.** The IR spectrum of the compound did not show the characteristic absorption band of phthalyl C=O at 1780 and 1720 cm^{-1} which was observed in compound **18.** The phosphonamide **20** and **21** was prepared form compound **19** in 24 % and 13 % yield respectively.

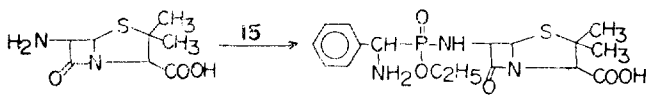


Scheme 4.

The compound **22** was prepared by the reaction of ethylene diamine and chloridate **6** in 80.7 % yield. Diamine **23** was obtained in a oily state by the dephthalation of compound

22. It is expected that diamine **23** can be used as the monomer of a polyamide.

The IR spectra of all above phosphonamides showed the characteristic absorption band of P–NH–at 3100–3250 cm^{-1}.



24

Scheme 5.

The compound **24** was prepared from chloridate **15** by the similar method used in the synthesis of 6-sulfobenzylpenicillin.[11] The IR spectrum of the compound also showed the characteristic band P–NH–at 3200 cm^{-1}.

It has been reported by Green[12] that the IR spectrum of β-lactam antibiotics show characteristic absorption band of C=O in β-lactam ring at 1790–1770 cm^{-1}. Morin and coworkers[13] have proposed that the higher IR frequency of the β-lactam C=O is, the better the antimicrobial activity is. Since the IR spectra of compound **24** showed the higher absorption band of β-lactam C=O at 1797cm^{-1} as compared with that of ampicillin at 1760cm^{-1}, we expect compound **24** to have considerable high antimicrobial activity in further study.

Experimental

1. *Synthesis of Starting Materials.* Diethyl N-phosphonylmethylphthalimide **5** was prepared from N-chloromethyl phthalimide **4**[14] adapting the procedure of Imoto and his coworkers: mp 65–67°C (lit.[18] mp 68°C). Glycine ethyl ester hydrochloride was obtained from glycine: mp 143–144°C (lit.[16] 144°C). Methionine methyl ester hydrochloride and Valine ethyl ester hydrochloride were synthesized from L-methionine and L-valine by the same procedure which we used for glycine ethyl ester hydrochloride: mp 149–151°C (lit.[17] 151–153 °C), $[\alpha]_{589.3}^{23} = +20.85$ (C=4, H_2O) and 100–102 °C (lit.[18] 102–104 °C), $[\alpha]_{589.3}^{23} = +6.8$ (C=4, H_2O) respectively. Ethyl phthalimidomethylphosphonochloridate **6** was prepared from compound **5** by the same method used by Imoto and his coworkers; mp 90–92 °C (lit.[19] 92–94° C). Diethyl DL-1-aminobenzylphosphonate hydrochloride **14** (ABP. HCl) was prepared from benzaldehyde and diethyl phosphite[20] or triethyl phosphite[6]: mp 160°C (lit.[21] 159–160°C).

2. *Synthesis of Phosphonamide* **8.** Glycine ethyl ester hydrochloride (0.93g, 0.0066 mol) was suspended in 16m*l* of chloroform and the suspension was cooled to 0–5 C° in ice water bath. Three m*l* of triethylamine was added into the suspension and mixture was stirred for 30 min. The mixture was slowly added to the solution of compound **6** (1.9g) which were dissolved in 4m*l* of tetrahydrofuran.

The reaction mixture was stirred at room temperature for 10 h. The final solution was filtered to remove triethylamine hydrochloride ($Et_3N \cdot HCl$). The filterate was concentrated by a rotary evaporator under the reduced pressure of water aspirator and then the residue was dissolved in 16m*l* of chloroform. The solution was washed repeatedly with 10m*l* of aqueous saturated sodium bicarbonate solution and water. The organic layer was dried over drierite for overnight. After filtering the drierite, the filterate was evaporated under the reduced pressure of water aspirator. To the residue 20m*l* of ethyl ether was added and then the solution was allowed to stand at room temperature. The resulting white crystals of **8** were obtained in 85 % (2.0g) yield. The compound was recrystalized from ether–tetrahydrofuran mixture: mp. 130–132 °C (lit.[22] 132–133 °C).

IR (KBr): 3450 (N–H), 3200 (P–NH–), 1770, 1710 (phthalyl C=O), 1220 (P=O), 1070cm^{-1}(P–OEt)

3. *Synthesis of Phosphonamide* **9.** Diethyl aminomethylphosphonate (1.2g, 0.0066 mol) was dissolved in 16m*l* of chloroform and the solution was cooled to 0–5°C in a ice water bath. Two m*l* of triethylamine was added into this solution and the mixture was treated as decribed above for the preparation of **8.** The resulting white crystals of **9** were obtained in 55 % (1.6g): mp 105–108 °C (lit.[9] 108–109 °C)

IR (KBr): 3500 (N–H), 3150 (P–NH–), 1780, 1720 (phthalyl C=O), 1210 (P=O), 1030 cm^{-1} (P–OEt)

4. *Synthesis of Phosphonamide* **10.** L-Methionine methylester hydrochloride (7.9g) was suspended in 90m*l* of chloroform and the suspension was cooled to 0–5°C in a ice–water bath. To the suspension was added 22m*l* of triethylamine and the mixture was stirred for 30 min. To the reaction mixture a solution of compound **6** in 24m*l* of tetrahydrofuran was slowly added over 30 min. The reaction mixture was treated by the same procedure as used in the preparation of compound **8.** Finally the compound **10** was obtained in 40 % (6.6g) yield; mp 120–122°C. The specific rotation of this compound was found to be $[\alpha]_{589.3}^{24.3} = +2.25°$ (C=4, $CHCl_3$)

IR (KBr): 3520 (N–H), 3240 (P–NH–), 1775, 1715 (phthalyl C=O), 1215 (P=O), 1055cm^{-1} (P–OEt)

Anal. Calcd for $C_{17}H_{23}N_2O_6PS$: N, 6.76 %; P, 7.49 % Found: N, 6.58 %; P, 7.40 %

5. *Synthesis of Phosphonamide* **11.** Compound **11** was prepared form L-valine ethyl ester hydrochloride (7.2g) by adopting the same procedure as used in the preparation of compound **10.** The compound **11** was obtained in 35 % (5.5g): mp 104–106 °C. The specific rotation of the compound was $[\alpha]_{589.3}^{23.5} = +2.5°$(C=4, $CHCl_3$)

IR (KBr): 3450 (N–H), 3150 (P–NH–), 1780, 1720 (phthalyl C=O), 1210 (P=O), 1060cm^{-1} (P–OEt).

Anal. Calcd for $C_{10}H_{23}N_2O_4P$: N, 10.53 %; P, 11.7 % Found: N, 10.4 %; P, 11.5 %

6. *Ethyl Aminobenzylphosphonochloridate Hydrochloride* **15.** Diethyl DL-1-aminobenzylphosphonate hydrochloride (5.1 g) was suspended in 15m*l* of benzene and to the suspension was added a phosphorous pentachloride (4.0g). After the mixture had been stirred for 15h at room temperature, it was allowed to cool to room temperature and was concentrated by rotary evaporator under the reduced pressure of water aspirator. The resulting white semisolid was suspended in 10m*l* of tetrahydrofuran and the suspension was used in following reaction.

7. *Synthesis of Phosphonamide* **16.** Glycine ethyl ester hydrochloride (2.6g) was suspended in 16m*l* of chloroform and the suspension was cooled to 0–5°C in a ice-water bath. Sixteen m*l* of triethylamine was added to the suspension and was stirred for 30 min. at room temperature. The reaction mixture was mixed slowly with the suspension of compound **15** at room temperature. Then, the mixture was filtered to remove the resulting triethylamine hydrochloride, and the filterate was concentrated by rotary evaporator under the reduced pressure of water aspirator. The resulting residue was taken up in 15m*l* of chloroform and the solution was washed repeatedly with each 10m*l* of saturated sodium bicarbonate solution and also water. The organic layer was dried over drierite for overnight. After filtering the drierite, the filterate was evaporated under the reduced pressure of water aspirator. The resulting residue was dissolved 10m*l* of ethyl alcohol and the solution was treated by activated charcoal. After filtering the charcoal, the solvent was removed by rotary evaporator under the reduced pressure of water aspirator. The resulting syrup of **16** was obtained in 39 % (2.2g) yield and gave positive ninhydrin test.

IR (KBr): 3400 (N–H), 3250 (P–NH–), 1750 (ester C=O), 1220 (P=O), 1040cm^{-1} (P–OEt)

8. *Synthesis of Phosphonamide* **17.** A mixture of **16** (2.3g) phthalylglycine (0.77g) and dicyclohexylcarbodiimide (1.6g) in 15m*l* of tetrahydrofuran, was prepared and it was stirred for 10h. Further 0.8m*l* of acetic acid and 1.6m*l* of water were added to it and again was stirred for 2h at room temperature. The resulting precipitate was filtered, and the filterate was concentrated as before. The residue was taken up in 15m*l* of chloroform and was washed with 8m*l* of water, 8m*l* of aqueous saturated sodium bicarbonate solution and 2m*l* of water. The organic layer was dried over drierite for overnight and the solvent was removed by rotary evaporator under the reduced pressure of water aspirator. The residue was dissolved in the least amount of benzene and the solution was allowed to stand in a refrigerator for overnight. The resulting white crystals of **21** were obtained in 38.2 % (0.7g) yield: mp 174–176 °C.

IR (KBr) 3350 (N–H), 3070 (P–NH–), 1780, 1720 (phthalyl C=O), 1650 (peptide C=O), 1240 (P=O), 1080cm^{-1} (P–OEt)

Anal. Calcd for $C_{23}H_{26}N_3O_7P$; N, 8.62 %; P, 6.37 % Found: N, 8.4 %; P, 6.3 %

9. *Synthesis of Phosphonamide* **18.** Diethyl DL–1–aminobenzylphosphonate hydrochloride (11. 1g) was suspended in 90m*l* of chloroform and the suspension was cooled to 0–5 °C in a ice-water bath. To the suspension 22m*l* of triethylamine was added and the mixture was stirred for 30 min. A solution of **6** (11. 4g) in 24m*l* of tetrahydrofuran was mixed with the above reaction mixture. After stirring the mixture for 10h at room temperature, it was further treated by the procedure of experiment **2.** Compound **18** was obtained in white crystalline form having 61 % (12g) yield: mp 162–164 °C.

IR (KBr): 3400 (N–H), 3200 (P–NH–), 1780, 1720 (phthalyl (C=O), 1200 (P=O), 1070 (P–OEt)

Anal. Calcd for $C_{22}H_{28}N_2O_7P_2$: N, 5.7 %; P, 12.6 % Found: N, 5.6 %; P,12.4 %

10. *Synthesis of Phosphonamide* **19.** Compound **18** (5.3g) in 20m*l* of ethyl alcohol was mixed with 1.1m*l* of hydrazine (100 %), and the mixture was stirred for overnight at room temperature. The resulting precipitate was filtered, and the filterate was concentrated by rotary evaporator under the reduced pressure of water aspirator. The residue was treated according to the same procedure as in experiment **7** to give the syrup of **19** in 77.5 % (3g) yield. The syrup gave positive ninhydrin test.

IR (KBr): 3400 (N–H), 3240 (P–NH), 1220 (P=O), 1045cm^{-1} (P–OEt)

11. *Synthesis of Phosphonamide* **20.** Compound **19** (3.6g) was suspended in 25m*l* of tetrahydrofuran and the suspension was cooled to 0–5°C in a ice-water bath. To the suspension was added 3m*l* of triethylamine and the mixture was stirred for 30min. To this reaction mixture compound **6** (2.9g) in 5m*l* of tetrahydrofuran was slowly added. The mixture was stirred for 10h at room temperature and was filtered to remove the resulting triethylamine hydrochloride. The filterate was treated further by the procedure of experiment **2.** Compound **21** was obtained in 13.1 % (0.8g) yield; mp 204–206°C.

IR (KBr): 3250 (N–H), 3250 (P–NH–), 1780, 1720 (phthalyl C=O), 1230 (P=O), 1040cm^{-1} (P–OEt)

Anal. Calcd for $C_{25}H_{36}N_3O_9P_3$: N, 6.83 %; P, 15.1 % Found: N, 6.7 %; P, 15.4 %

12. *Synthesis of Phosphonamide* **21.** A solution of **19** (3g), phthalylglycine (1.7g) and dicyclohexylcarbodiimide (DCC) (2g) in 20m*l* of tetrahydrofuran was stirred for 10h. The reaction mixture was treated with the mixed solution of 1.6m*l* of acetic acid and 2.4m*l* of water. Then, the mixture was stirred for additional 2h, and the resulting precipitate was filtered. The filterate was concentrated by rotary evaporator under reduced pressure of water aspirator and the residue was taken up in 20m*l* of chloroform. The solution was washed repeatedly with about each 10m*l* of water, aqueous saturated sodium bicarbonate solution and again water. The organic layer was dried over drierite for overnight, and the drierite was filtered, and the filterate was concentrated by rotary evaporator under the reduced pressure of water aspirator. The residue was dissolved in the least amount of ethyl ether and the solution was allowed to stand for 2 days. White crystalline compound **20** was obtained in 24.2 % (1.1g) yield: mp 190–192 °C.

IR (KBr): 3350 (N–H), 3250 (P–NH–), 1770, 1710 (phthalyl C=O), 1630 (peptide C=O), 1190 (P=O), 1020cm^{-1} (P–OEt)

Anal. Calcd for $C_{24}H_{31}N_3O_8P_2$: N, 7.62 %; P, 11.25 % Found: N, 7.4 %; P, 11.1 %

13. *Synthesis of Phosphonamide* **22.** A solution of ethylene diamine (0.44m*l*) in 32m*l* of chloroform was cooled to 0–5°C, and mixed with triethylamine (6m*l*). After stirring for 30min, it was mixed slowly with a solution of ethyl phthaliminomethylchloridate (3.8g) in 6m*l* of tetrahydrofuran. The mixture was stirred for 10h and filtered to remove the resulting triethylamine hydrochloride. The filterate was concentrated by rotary evaporator under the reduced pressure of water

aspirator. The residue was dissolved in 30m*l* of chloroform, and the solution was washed with each 30m*l* of water, aqueous saturated sodium bicarbonate solution and water. The organic layer was dried over drierite for overnight and the solvent was removed by rotary evaporator under the reduced pressure of water aspirator. The residue was dissolved in 50m*l* of ethyl ether allowed to stand in the refrigerator for overnight. Compound **22** was obtained in white crystalline form in 80.7 % (3g) yield: mp 196–199 °C.

IR (KBr): 3450 (N–H), 3200 (P–NH–), 1780, 1720 (phthalyl C=O), 1200 (P=O), 1050cm^{-1} (P–OEt)

14. *Synthesis of Diamine* **23**. To the suspension of **22** in 8m*l* of ethyl alcohol was added a hydrazine hydrate (100 %, 2.6g), and the mixture was stirred for 10h followed by 2h of reflux. After cooling it to room temperature, the resulting precipitate so obtained was filtered.

The filtrate was concentrated by rotary evaporator under the reduced pressure of water aspirator. The light yellowish viscous oil was obtained in 72.8 % (0.22g) yield and gave positive ninhydrin test.

IR (KBr): 3400 (N–H), 3150 (P–NH–), 1210 (P=O) 1040cm^{-1} (P–OEt)

15. *6-(Ethyl DL-1-aminobenzylphosphonyl) aminopenicillanic acid* **24**. To a suspension of 6-aminopenicillanic acid (6-APA, 3.95g) in 33m*l* of water slowly added sodium bicarbonate (5.4g), and the resulting mixture was cooled to 5 °C. Dropwise a solution of compound **15** obtained from experiment **6** has added to this. The mixture was allowed to stand at 0–5 °C for 60min. Then, the organic layer was separated and the pH of aqueous layer was adjusted by a dilute hydrochloric acid solution. The aqueous mixture was allowed to stand at 0 °C for overnight. The resulting white crystals were obtained by filtering and washing with acetone. The white crystals of compound **24** were dried. The yield of the compound was obtained in 13.3 % (1g) yield and decomposed at 200 °C.

IR (KBr): 3450 (N–H), 3200 (P–NH–), 2050 ($-NH_3^+$), 1797 (β-lactam C=O), 1330 (P=O), 1140cm^{-1} (P–OEt)

Anal. Calcd for $C_{17}H_{24}N_3O_5PS$: N, 10.17 %; P, 7.51 % Found: N, 9.96 %; P, 7.3 %

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