[Chem. Pharm. Bull. 24(12)3058—3064(1976)]

UDC 547.466.1.04 : 615.334.011.5

Conversion of Acylamidopenicillins to Phosphoramidopenicillins, and Removal of Their Phosphoryl Side Chain

Masataka Fukumura, Noritaka Hamma and Takenari Nakagome

Research and Development Center, Pharmaceuticals Division, Sumitomo Chemical Co., Ltd.[1]

(Received April 2, 1976)

On sequential treatment of benzylpenicillanates (**1**) or their sulfoxides (**7**) with phosphorus pentachloride, methanol, and sodium bicarbonate or dimethylaniline, 6-(dimethylphosphoramido)penicillins (**5**) or their sulfoxides (**8**) were obtained. 6-(Dimethylphosphoramido)penicillin sulfoxides (**8**) were rearranged thermally to their corresponding desacetoxycephalosporins (**10**). The dimethylphosphoryl group of 7-(dimethylphosphoramido)desacetoxycephalosporins (**10**) was removed by either a 85% phosphoric acid or polyphosphoric acid, which caused the degradation of β-lactam ring in 6-(dimethylphosphoramido)penicillins (**5**) and their sulfoxides (**8**). The dimethylphosphoryl group of penicillins and desacetoxycephalosporins was also removed by phosgene and pyridine to give 6-isocyanatopenicillins (**16**) and 7-isocyanatodesacetoxycephalosporins (**15**), respectively.

The chemical deacylation procedure in penicillin and cephalosporin series by use of phosphorus pentachloride has been reported.[2,3] The reaction proceeds through an iminochloride to an iminoether at the C-6 (C-7) amide linkage. The intermediate penicillin iminochlorides have been isolated,[4] and their reactivity investigated.[5] On the other hand, little is known about the chemistry of penicillin iminoethers (**3**).[6,7]

We attempted to isolate the penicillin iminoether (**3a**) in basic media to investigate its reactivity, and found that the 6β-phosphoramidopenicillin (**5a**) instead of **3a** was isolated as a sole product. Treatment of the benzylpenicillin ester (**1a**) with phosphorus pentachloride and dimethylaniline in methylene chloride resulted in a clean and smooth reaction. Methanol was then added with cooling, followed by sodium bicarbonate to give an amorphous solid. This substance was considered to possess the structure (**5a**) on the basis of its spectral data. Disappearance of the infrared (IR) absorption at 1690 cm^{-1} indicated complete rupture of the secondary acylamide. Evidence for the dimethylphosphoryl group was provided in the loss of phenylacetyl protons in the nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) and the presence of six protons at δ 3.76 and 3.79 (d,d, J=12 Hz) which indicated that diastereotopic methoxy groups were attached to a phosphorus atom. Compound (**5a**) was also obtained in inferior yield when dimethylaniline was used instead of sodium bicarbonate in an anhydrous condition. In this reaction monomethylphosphoryl derivative such as **6** could not be detected,

1) Location; *4–2–1, Takatsukasa, Takarazuka, Hyogo, 665, Japan.*
2) B. Fechtig, H. Peter, H. Bickel, and E. Vischer, *Helv. Chim. Acta*, **51**, 1108 (1968).
3) H.W.O. Weissenburger and M.G. Van Der Hoever, *Rec. Trav. Chim.*, **89**, 1081 (1970).
4) J. Abe, T. Watanabe, T. Take, K. Fujimoto, T. Fuji, K. Takemura, and K. Nishiie, Ger. Offen. 2016892 [*Chem. Abstr.*, **74**, 13169*q*, (1971)].
5) *a*) R.D. Carrol, E.S. Hamanaka, D.K. Pirie, and W.M. Welch, *Tetrahedron Letters*, **1974**, 1515; *b*) R.D. Carrol and L.M. Smith, *J. Het. Chem.*, **12**, 445 (1975); *c*) R.D. Carrol and L.L. Reed, *Tetrahedron Letters*, **1975**, 3435.
6) The isolation of cephalosporin iminoethers was reported as the intermediate of 7-methoxycephalosporins, but no detail was given. G.G. Hazen and N.J. Westfield, U.S. Patent 3780033 [*Chem. Abstr.*, **80**, 95995*s*, (1974)].
7) *a*) A. Koda, K. Takanobu, I. Isaka, T. Kashiwagi, K. Takahashi, S. Kawahara, and M. Murakami, *Yakugaku Zasshi*, **92**, 459 (1972); *b*) W.H.W. Lunn, *Tetrahedron Letters*, **1974**, 1307.

although trimethylphosphate was separated as a side product. It is assumed that the formation of **5a** may involve the reaction of **3a** with dimethylphosphorylchloride, produced by the methanolysis of phosphorus oxychloride which was produced by the reaction of **1a** with phosphorus pentachloride. However, in the reaction where sodium bicarbonate was used instead of dimethylaniline after the methanolysis step, the pathway through **4a** and dimethylphosphoryl chloride could not be disproved, although the main pathway would follow the same one as in an anhydrous condition. Compound (**5a**) was also obtained by the reaction of **4a** with dimethylphosphoryl chloride.

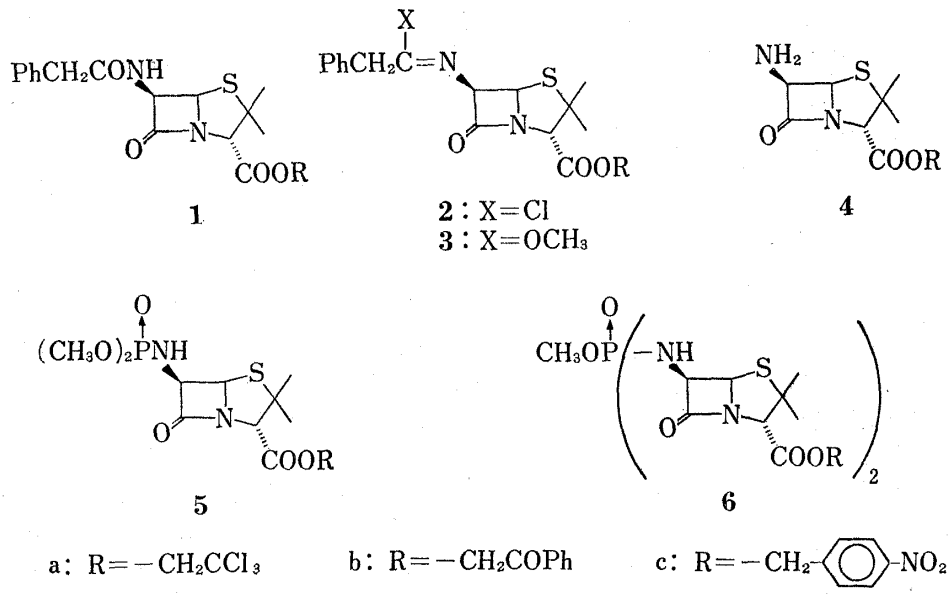

Chart 1

The phosphoramidopenicillin (**5**, R=H) has been known as one of a few penicillins which possess a significant antibacterial activity without having a secondary acylamide side chain.[8] The use of phosphorus oxychloride in addition to phosphorus pentachloride or excess phosphorus pentachloride in the chlorination step gave a better yield of **5a**. In a similar manner, either **7a** or **7b** gave **8a** and **8b** respectively. Compound (**9c**) was obtained when methanol was replaced by ethanol in the alcoholysis step. The penicillin sulfoxide rearrangement of **8** and **9** was then carried out. Since discovery of the penicillin sulfoxide rearrangement by Morin, *et al.*, many experiments have been performed using several C-6 substituted penicillins under a variety of conditions.[9] By the treatment with pyridinium dichloromethanephosphonate in refluxing dioxane, either **8a** or **8b** gave **10a** and **10b** respectively. Compound (**11c**) was also formed by the treatment of **9c** with pyridinium 2,2,2-trichloroethylphosphate in refluxing toluene. When **8a** was treated with pyridinium phenylphosphate in refluxing toluene, the isothiazolone (**13a**) was formed in addition to **10a**.

Removal of the dimethylphosphoryl group was then investigated. Although it has been pointed out that P–N bond of phosphoramidates is in general cleaved easily under acidic

8) *a*) B.K. Koe, T.A. Seto, A.R. English, and T.J. Mcbride, *J. Med. Chem.*, **6**, 653 (1963); *b*) A.B. Simmonds, ed., "Advances in Drug Research," Vol. 7, p. 68. J.H.C. Nayler, "Advances in Penicillin Research," Academic Press, New York, N.Y. 1973, p. 1.

9) *a*) R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon, and S.L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969): *b*) N.V. Ellerton, W.F. Paradise, and P.E. Sanford, Brit. Patent 1312235 [*Chem. Abstr.*, **79**, 53547*w*, (1973)]; *c*) M. Murakami, K. Takahashi, and T. Kozasa, Japanese Patent 72-22829 [*Chem. Abstr.*, **77**, 101637*h* (1972)]; *d*) J.P. Clayton, J.H.C. Nayler, M.J. Pearson, and R. Southgate, *J. Chem. Soc. Perkin Trans I.* **1974**, 22; *e*) S.B. Davis, K. Bohme, and J.E. Dolfini, Ger. Offen., 2153600 [*Chem. Abstr.*, **77**, 75211*t*, (1972)].

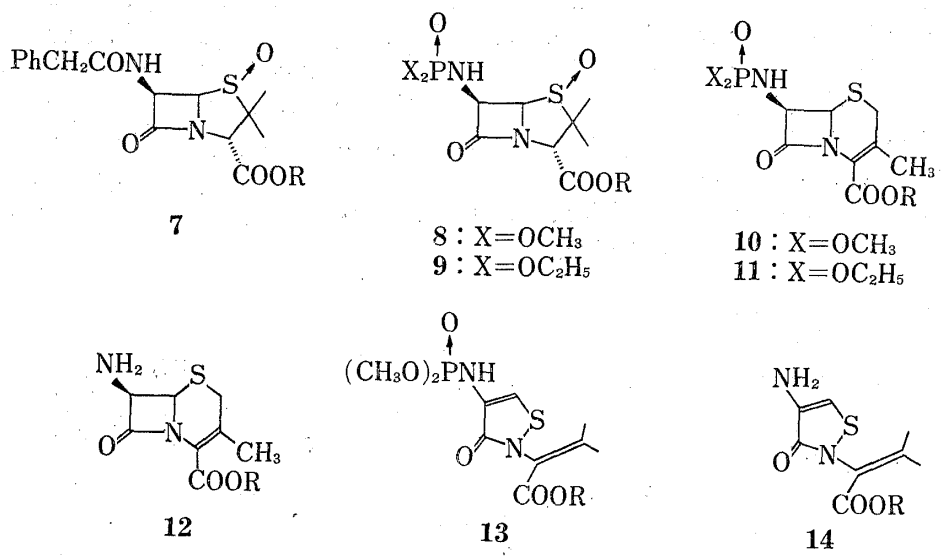

Chart 2

conditions,[10-12] removal of the dimethylphosphoryl group of **5**, **8** and **10** without rupture of β-lactam ring was not successful under similar conditions. For example, the P–N bond of phosphoramidic diester (**19**, R′=Bu, R″=Me, Bu) was conveniently cleaved in a refluxing 25% formic acid solution,[11] whereas **10b** was recovered almost quantitatively under the same conditions. In dilute hydrochloric acid,[12] no reaction occurred at room temperature, and the degradation of β-lactam ring mostly occurred on heating. In nucleotide synthesis, nucleoside 5′-phosphoramidates have been allowed to react with phosphoric acid or its monoesters to afford nucleoside diphosphate.[13] The reaction was applied to remove the dimethylphosphoryl group in penicillins and cephalosporins in the present study. By the treatment with a 85% phosphoric acid at room temperature, either **10a** or **10b** was converted to 7-aminodesacetoxycephalosporanates (**12a**) and (**12b**) respectively in high yields. However, the rate of reaction was slow and it took 40—50 hr for the completion of the reaction. The fact that the rate of reaction of **10** was fairly slow compared with the case of nucleotide synthesis suggests that the reaction of nucleoside 5′-phosohoramidate would proceed with a unimolecular solvolysis *via* metaphosphate, while the reaction of **10** would involve a bimolecular displacement at phosphorus atom,[14] since the diesters of phosphoramidic acid such as **10** could not follow the former process.

The rate of reaction was increased considerably when phosphoric acid was replaced by polyphosphoric acid, and **12a** and **12b** were obtained almost quantitatively. In a similar manner, **11c** was converted to **12c** in polyphosphoric acid. In contrast, **5a** and **8a** were unstable in either a 85% phosphoric acid or polyphosphoric acid, and the degradation of β-lactam ring occurred. On the other hand, **13a** was converted to 4-aminoisothiazolone (**14a**) on treatment with polyphosphoric acid.

Another successful method to cleave the P–N bond of phosphoramidates by use of phosgene was found. It has been reported that by the reaction with phosgene and without the addition of an acid acceptor, N-unsubstituted phosphoramidic diesters (**17**) were converted to phos-

10) V.M. Clark, *Proc. Chem. Soc.*, **1964**, 129.
11) J.A. Stock, W.J. Hopwood, and P.D. Regan, *J. Chem. Soc.* (*C*), **1966**, 637.
12) *a*) I. Öney and M. Caplow, *J. Am. Chem. Soc.*, **89**, 6972 (1967); *b*) A.W. Garrison and C.E. Boozer, *ibid.*, **90**, 3486 (1968).
13) *a*) R.W. Chambers, *J. Am. Chem. Soc.*, **81**, 3032 (1959); *b*) J.G. Moffat and H.G. Khorana, *ibid.*, **83**, 649 (1961).
14) V.M. Clark and S.G. Warren, *J. Chem. Soc.*, **1965**, 5509.

phorisocyanatidic diesters (**18**),[15] whereas N-monosubstituted phosphoramidic diesters (**19**) were converted to phosphoramidochloridic esters (**20**), or N-chloroformyl phosphoramidic diesters (**21**).[16]

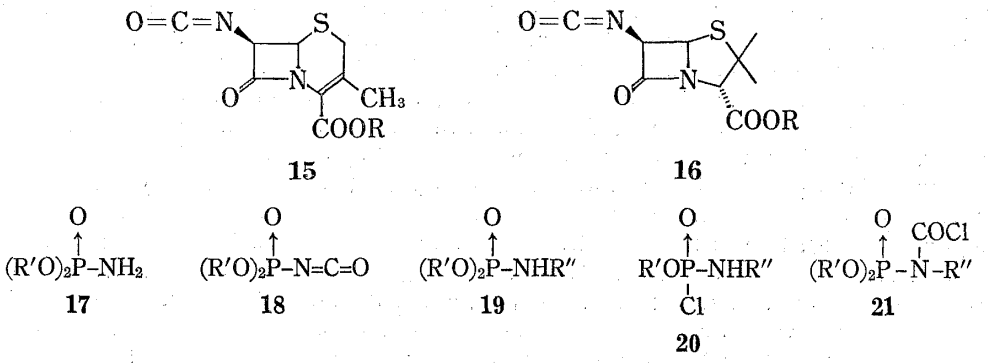

Chart 3

In contrast, when either **10a** or **10b** was treated with excess phosgene and pyridine as an acid acceptor at 0° for 5—6 hr, 7-isocyanotocephalosporins (**15a**) and (**15b**) were obtained respectively. One of the possible mechanisms was described in Chart 4. In penicillins, **5a** was also converted to 6-isocyanatopenicillin (**16a**) under the same conditions. Compounds **15** and **16** have also been obtained by the reaction of **12** and **4** with phosgene and triethylamine, and several methods to prepare the corresponding acylamido derivatives from the isocyanates have been accomplished.[17–19]

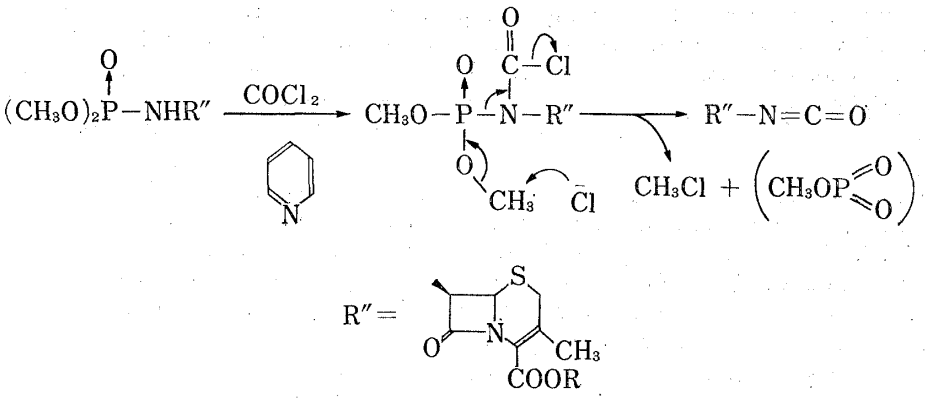

Chart 4

The described dephosphorylation using polyphosphoric acid or phosgene is relatively simple and high yielding. This fact suggests the usefulness of the phosphoryl group as the amino protecting group. The applicability is now under investigation and will be published elsewhere.

Experimental

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were measured with a JASCO IRA-1 and NMR spectra were recorded with a

15) L.I. Samaraj, O.I. Kolodjaznij, and G.I. Derkatsch, *Angew. Chem.*, **80**, 620 (1968).
16) L.I. Samaraj, O.I. Kolodyazhnyi, and G.I. Derkack, *J. Gen. Chem.*, **40**, 730 (1970).
17) Koninklijke Nederlandsche Gisten Spiritusfabriek N.V. Ger. Offen. 1931097 [*Chem. Abstr.*, 72, 79035*h* (1970)].
18) Koninklijke Nederlandsche Gisten Spiritusfabriek N.V. Ger. Offen. 2062296 [*Chem. Abstr.*, **75**, 88627*s* (1971)].
19) G.A. Koppel, *Tetrahedron Letters*, **1974**, 2427.

Varian T-60 instrument. All TLC was done using silica gel plates, benzene–ethyl acetate (1: 1) as eluent (unless otherwise stated), and iodine chamber to develop the spots.

2,2,2-Trichloroethyl 6-(Dimethylphosphoramido)penicillanate (5a)——a) A solution of 2,2,2-trichloroethyl 6-(phenylacetamido)penicillanate (5.0 g, 10.7 mmole) in CH_2Cl_2 (50 ml) was cooled to −30°, treated with dimethylaniline (1.56 g, 12.8 mmole), and stirred while a solution of phosphorus pentachloride (2.68 g, 12.8 mmole) in CH_2Cl_2 (20 ml) was added during 10 min. The mixture was stirred for 3 hr, while the temperature was maintained at −30° to −40°, and treated with dry methanol (50 ml). After stirring for 1 hr at −30°, the temperature was raised to 0°, and sodium bicarbonate (5.4 g, 64.2 mmole) was added. The mixture was stirred overnight at the same temperature, filtered, and the filtrate was washed with 1 N hydrochloric acid, then with water, and dried ($MgSO_4$). The solvent was removed by evaporation *in vacuo*. The residue was taken up in benzene for several washes with water. An oil (3.7 g), obtained after drying, evaporation of solvents, and trituration with petroleum ether, was column chromatographed over silica gel using a gradient of benzene–ethyl acetate (10: 1 to 1: 1) as eluant. The product weighed 1.87 g (38.7%): IR (Nujol) cm^{-1}: 3600, 3150 (NH), 1790 (β-lactam C=O), 1770 (ester): NMR ($CDCl_3$) δ: 1.58 (3H, s), 1.70 (3H, s), 3.76, 3.79 (6H, d,d J=12 Hz), 4.55 (1H, s), 4.80 (2H, s), 4.87 (1H, m), 5.58 (1H, d, J=5 Hz). Recrystallization from CH_2Cl_2–petroleum ether gave an analytical sample; colorless needles, mp 107—108.5° (*Anal.* Calcd. for $C_{12}H_{18}O_6N_2SCl_3P$: C, 31.63; H, 3.98; N, 6.15; S, 7.04; Cl. 23.34; P, 6.80. Found: C, 31.37; H, 4.02; N, 5.76; S, 6.66; Cl, 22.80; P, 6.93).

b) In a similar experiment, where dimethylaniline (7.78 g, 64.2 mmole) was employed instead of sodium bicarbonate in an anhydrous condition, 0.64 g (13.1%) of the product was obtained, and the starting material was recovered in 20.8% yield by column chromatography over silica gel using a gradient of benzene–ethyl acetate as eluant.

c) A solution of 2,2,2-trichloroethyl 6-(phenylacetamido)penicillanate (50 g, 0.107 mole) in CH_2Cl_2 (200 ml) was cooled to −30°, treated with dimethylaniline (25.9 g, 0.214 mole), and stirred while phosphorus oxychloride (32.8 g, 0.214 mole) and phosphorus pentachloride (26.8 g, 0.129 mole) were added consecutively. The mixture was stirred for 3 hr, while the temperature was maintained at −30° to −40°, and treated with dry methanol (500 ml). After stirring for 1 hr at −30°, the temperature was raised to 0°, and sodium bicarbonate (108 g, 1.29 mole) was added. The mixture was stirred overnight at the same temperature, filtered, and the filtrate was diluted with CH_2Cl_2 and washed with 1 N hydrochloric acid. The CH_2Cl_2 layer was separated, washed with water, and dried. The solvent was removed by evaporation *in vacuo*. The residue was taken up in benzene for several washes with water. The benzene solution was dried, and evaporated *in vacuo* to give an oil (51.2 g), which was crystallized from CH_2Cl_2–petroleum ether. The product (36.3 g, 74.2%) was one spot material on TLC and gave NMR and IR spectral data identical with those of the sample prepared by procedure a).

d) A solution of 2,2,2-trichloroethyl 6-aminopenicillanate (0.35 g, 1 mmole) in CH_2Cl_2 (10 ml) was cooled to 0°, treated with pyridine (0.08 g, 1.05 mmole), and stirred while dimethylphosphorylchloride (0.15 g, 1.05 mmole) was added. The mixture was stirred for 1.5 hr at room temperature, and washed with 1 N hydrochloric acid, water, and dried. The solvent was removed by evaporation *in vacuo* to give an amorphous solid (0.31 g, 68%). This product was one spot material on TLC and gave NMR and IR spectral data identical with those of the sample prepared by procedure a).

2,2,2-Trichloroethyl 6-(Dimethylphosphoramido)penicillanate 1-Oxide (8a)——A solution of 2,2,2-trichloroethyl 6-(phenylacetamido)penicillanate 1-oxide (60 g, 0.125 mole) in CH_2Cl_2 (300 ml) was allowed to react with phosphorus oxychloride and phosphorus pentachloride in the presence of dimethylaniline in a similar fashion as for the preparation of **5a** (procedure C). The reaction mixture was poured into dry methanol (300 ml) over 30 min, treated with sodium bicarbonate, and worked up in a similar way. The dried CH_2Cl_2 solution was evaporated *in vacuo*, and the residue triturated with ether to give a crystalline solid (53.1 g, 90.7%); mp 128—9.5°; recrystallization from isopropyl alcohol gave an analytical sample; mp 131—134°, IR (Nujol) cm^{-1}: 3290 (NH), 1800 (β-lactam C=O), 1765 (ester): NMR ($CDCl_3$) δ: 1.33 (3H, s), 1.80 (3H, s), 3.77 (6H, d, J=11 Hz), 4.55 (1H, s), 4.77 (2H, s), 4.93—5.20 (2H, m). (*Anal.* Calcd. for $C_{12}H_{18}O_7N_2SCl_3P$: C, 30.56; H, 3.85; N, 5.94; S, 6.80; Cl, 22.55; P, 6.57. Found: C, 31.28; H, 3.83; N, 6.00; S, 6.68; Cl, 22.35; P, 6.60).

Phenacyl 6-(Dimethylphosphoramido)penicillanate 1-Oxide (8b)——A solution of phenacyl 6-(phenylacetamido)penicillanate 1-oxide (50 g, 0.11 mole) in CH_2Cl_2 (300 ml) was allowed to react with phosphorus oxychloride and phosphorus pentachloride in the presence of quinoline (42.7 g, 0.33 mole) in a similar fashion as for the preparation of **5a** (procedure C). The reaction mixture was poured into dry methanol (300 ml) over 30 min, treated with sodium bicarbonate, and worked up in a similar way. The dried CH_2Cl_2 solution was evaporated *in vacuo*, and the residue was taken up in ethyl acetate for several washes with water. Evaporation of the dried ethyl acetate solution and trituration of the residue with petroleum ether gave an amorphous solid (45.7 g, 90.6%). This product was one spot material on TLC (using ethyl acetate–methanol–c. hexane 120: 15: 15 system) and can be used directly in the next step without further purification: IR (Nujol) cm^{-1}: 3330 (NH), 1780 (β-lactam C=O), 1760, 1710 (ester): NMR ($CDCl_3$) δ: 1.45 (3H, s), 1.78 (3H, s), 3.75 (6H, d, J=12 Hz), 4.73 (1H, s), 4.5—5.3 (2H, m), 5.25, 5.68 (2H, d,d, J=17 Hz), 7.3—8.1 (5H, m). Recrystallization

from ethyl acetate–hexane gave an analytical sample; colorless needles; mp 101—103° (*Anal.* Calcd. for $C_{18}H_{23}O_8N_2SP$: C, 47.16; H, 5.06; N, 6.11; S, 6.99. Found: C, 47.68; H, 5.05; N, 5.97; S, 7.21.)

***p*-Nitrobenzyl 6-(Diethylphosphoramido)penicillanate 1-Oxide (9c)**——A solution of *p*-nitrobenzyl 6-(phenylacetamido)penicillanate 1-oxide (10 g, 20.6 mmole) in CH_2Cl_2 was allowed to react with phosphorus oxychloride and phosphorus pentachloride in the presence of quinoline in a similar fashion as for the preparation of **8b**. The reaction mixture was treated with dry ethanol (100 ml), sodium bicarbonate, and worked up in a similar way. Evaporation of dried ethyl acetate solution and crystallization of the residue from ethyl acetate–hexane gave a crystalline solid (6.4 g, 61.5%). An analytical sample was obtained by recrystallization from ethyl acetate–hexane; colorless leaflets, mp 99.5—101.5°; IR (Nujol) cm^{-1}: 3260 (NH), 1790 (β-lactam C=O), 1755 (ester): NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.35 (6H, t, $J=7$ Hz), 1.70 (3H, s), 4.20 (4H, q, $J=7$ Hz), 4.72 (1H, s) 4.93—5.23 (2H, m), 5.35 (2H, s), 7.4—8.3 (4H, m). (*Anal.* Calcd. for $C_{19}H_{26}O_9N_3SP$: C, 45.32; H, 5.21; N, 8.35; S, 6.37; P, 6.15. Found: C, 45.23; H, 5.28; N, 8.25; S, 6.50; P, 6.0.)

2,2,2-Trichloroethyl 7-(Dimethylphosphoramido)desacetoxycephalosporanate (10a)——a) A solution of **8a** (3.0 g, 6.4 mmole) and pyridinium dichloromethanephosphonate (0.16 g, 0.64 mmole) in dry dioxane (40 ml) was heated under reflux for 7 hr, during which the condensed liquor was returned to the reaction system through a Soxhlet extractor packed with molecular sieves. The solvent was removed by evaporation *in vacuo*, and the residue was taken up in benzene for several washes with water. The benzene solution was dried, and evaporated to dryness *in vacuo* to give a foam which was percolated through Florisil, with chloroform as eluant. An amorphous solid (2.21 g, 76.5%) was obtained. This product was one spot material on TLC and could be used directly in the next step without further purification: IR (Nujol) cm^{-1}: 3190 (NH), 1785 (β-lactam C=O), 1740 (ester): NMR ($CDCl_3$) δ: 2.20 (3H, s), 3.28, 3.55 (2H, d,d, $J=19$ Hz), 3.78 (6H, d, $J=11$ Hz), 4.79, 4.97 (2H, d,d, $J=12$ Hz), 4.63—5.23 (2H, m). In an identical preparation, the product was better characterized following a purification by recrystallization from ether: mp 86—89° (*Anal.* Calcd. for $C_{12}H_{16}O_6N_2SCl_3P$: C, 31.75; H, 3.53; N, 6.17; S, 7.06; Cl, 23.48; P, 6.84. Found: C, 31.72; H, 3.53; N, 6.12; S, 6.80; Cl, 22.92; P, 6.97).

b) To a solution of **8a** (3.0 g, 6.4 mmole) in toluene (20 ml) was added phenylphosphate (0.11 g, 0.64 mmole) and pyridine (0.05 g, 0.64 mmole), and the mixture was heated under reflux for 5 hr with stirring, during which the water formed was separated. After the evaporation of the solvent, the residue was column chromatographed over silica gel using chloroform as eluant. Initial fraction gave **10a** (1.51 g, 52.2%) on evaporation of solvent. The second fraction gave (13a) (0.25 g, 8.7%). An analytical sample of **13a** was obtained by recrystallization from CH_2Cl_2–petroleum ether: mp 131—132°; *m/e* 452 (M^+): IR (Nujol) cm^{-1}: 3210 (NH), 1735 (ester), 1640 (thiazolone carbonyl): NMR ($CDCl_3$) δ: 1.97 (3H, s), 2.43 (3H, s), 3.80 (6H, d, $J=12$ Hz), 4.72 (2H, s), 5.68 (1H, d, $J=12$ Hz), 7.52 (1H, s). (*Anal.* Calcd. for $C_{12}H_{16}O_6N_2SCl_3P$: C, 31.77; H, 3.56; N, 6.17; S, 7.07; Cl, 23.44; P, 6.83. Found: C, 31.82; H, 3.63; N, 6.15; S, 7.36; Cl, 23.40; P, 7.06.)

Phenacyl 7-(Dimethylphosphoramido)desacetoxycephalosporanate (10b)——A solution of (8b) (20 g, 43.7 mmole) and pyridinium dichloromethanephosphonate (1.1 g, 4.5 mmole) in dry dioxane (200 ml) was heated under reflux for 7 hr, during which the condensed liquor was returned to the reaction system through a Soxhlet extractor packed with molecular sieves. The solvent was removed by evaporation *in vacuo*, and the residue was taken up in CH_2Cl_2 for several washes with water. The CH_2Cl_2 solution was dried, and evaporated to dryness *in vacuo* to give a solid. After trituration with ethyl acetate, a crystalline solid (9.7 g, 50.4%) was obtained: mp 164—166.5°. Recrystallization from isopropyl alcohol afforded colorless needles: mp 180—181°: IR (Nujol) cm^{-1}: 3130 (NH), 1780 (β-lactam C=O), 1730, 1685 (ester): NMR ($CDCl_3$) δ: 2.22 (3H, s), 3.30, 3.57 (2H, d,d, $J=18$ Hz), 3.80 (6H, d, $J=12$ Hz), 4.80—5.28 (2H, m), 5.42, 5.65 (2H, d,d, $J=16$ Hz), 7.45—8.05 (5H, m). (*Anal.* Calcd. for $C_{18}H_{21}O_7N_2SP$: C, 49.09; H, 4.81; N, 6.36; S, 7.28; P, 7.03. Found: C, 48.94; H, 4.77; N, 5.96; S, 7.28; P, 7.0.)

***p*-Nitrobenzyl 7-(Diethylphosphoramido)desacetoxycephalosporanate (11c)**——To a solution of **9b** (2.0 g, 3.96 mmole) in toluene (40 ml) was added pyridinium trichloroethyl phosphate (0.12 g, 0.4 mmole) and the resulting mixture refluxed for 3 hr with stirring, during which the water formed was separated. The mixture was chilled to 0°, and the crystalline precipitate formed was filtered (1.24 g, 64%). Recrystallization from ethanol gave an analytical sample: colorless needles, mp 168—169°; IR (Nujol) cm^{-1}: 3150 (NH), 1765 (β-lactam C=O), 1720 (ester): NMR ($CDCl_3$) δ: 1.35 (6H, t, $J=7$ Hz), 2.15 (3H, s), 3.25, 3.52 (2H, d,d, $J=19$ Hz), 3.90—4.35 (4H, m), 4.87—5.22 (2H, m), 5.32 (2H, s), 7.50—8.30 (4H m). (*Anal.* Calcd. for $C_{19}H_{24}O_8N_3SP$; C, 47.01; H, 4.98; N, 8.66; S, 6.60; P, 6.38. Found: C, 46.94; H, 4.92; N, 8.32; S, 6.57; P, 6.54).

2,2,2-Trichloroethyl 7-Aminodesacetoxycephalosporanate (12a)——a) In a 85% phosphoric acid (20 g) was dissolved **10a** (4.5 g, 10 mmole), and the solution was stirred for 40 hr at room temperature. Ice water (100 ml) was added to the reaction mixture which was then washed with benzene. The aqueous layer was neutralized with sodium bicarbonate and extracted with benzene. The benzene layer was washed with water, and dried. A slightly yellow solid (3.3 g, 96.5%) was obtained after evaporation of the solvent: IR ($CHCl_3$) cm^{-1}: 1780 (β lactam C=O), 1740 (ester): NMR ($CDCl_3$) δ: 2.10 br (2H, exch.), 2.18 (3H, s) 3.25, 3.55 (2H, d,d, $J=18$ Hz), 4.73 (1H, d, $J=5$ Hz), 4.93 (1H, d, $J=5$ Hz), 4.81, 4.96 (2H, d,d, $J=13$ Hz). This product (1.0 g) thus obtained was dissolved in ethyl acetate (10 ml), and a solution of *p*-toluenesulfonic acid in ethyl acetate was added thereto. The precipitated crystals were filtered to afford *p*-toluenesulfonate (**12a**) (1.3 g, 87%)

as a crystalline solid: mp 192—194° (*Anal.* Calcd. for $C_{18}H_{21}O_6N_2S_2Cl_3$: C, 40.7; H, 4.0; N, 5.3; S, 12.1. Found: C, 40.5; H, 4.1; N, 5.4; S, 11.9.)

b) A solution of **10a** (2.0 g, 4.4 mmole) dissolved in polyphosphoric acid (10 g) was stirred for 12 hr at 35° to 40°. Ice water (50 ml) was added to the reaction mixture and worked up as described in procedure a) to afford **12a** (1.5 g, 98.7%) as a slightly yellow solid. This product was one spot material on TLC and gave NMR and IR spectral data identical with those of the sample obtained by procedure a).

Phenacyl 7-Aminodesacetoxycephalosporanate (12b)——A solution of **10b** (4.4 g, 10 mmole) dissolved in polyphosphoric acid (12 g) was stirred for 15 hr at room temperature. Ice water (100 ml) was added to the reaction mixture which was adjusted to pH 6 by the addition of aqueous sodium hydroxide, and extracted with CH_2Cl_2. The separated organic layer was dried and hydrogen chloride gas introduced thereto. After stirring at 0—5° for 3 hr a colorless crystalline solid (3.5 g, 95.1%) of **12b**·HCl, was filtered: mp 179—180°: IR (Nujol) cm^{-1}: 1780 (β-lactam C=O), 1740, 1710 (ester): NMR (CD_3OD) δ: 2.32 (3H, s), 3.60 (2H, s), 5.08 (1H, d, J=5 Hz), 5.32 (1H, d, J=5 Hz), 5.62 (2H, s), 7.50—8.13 (5H, m). (*Anal.* Calcd. for $C_{16}H_{17}O_4N_2SCl$: C, 52.10; H, 4.65; N, 7.60; S, 8.69; Cl, 9.61. Found: C, 52.01; H, 4.67; N, 7.66; S, 8.85; Cl, 9.83.)

***p*-Nitrobenzyl 7-Aminodesacetoxycephalosporanate (12c)**——A solution of **11c** (0.5 g, 1.03 mmole) dissolved in polyphosphoric acid (5 g) was stirred for 15 hr at room temperature. Ice water (50 ml) was added and a colorless crystalline solid of **12c**·H_3PO_4 (0.33 g, 72.5%) that precipitated was filtered: mp 165.5—167°: IR (Nujol) cm^{-1}: 1770 (β-lactam C=O), 1730 (ester): NMR (d_6-DMSO) δ: 2.13 (3H, s), 3.53 (2H, s), 5.27—5.47 (2H, m), 7.47—8.33 (4H, m). (*Anal.* Calcd. for $C_{15}H_{18}O_9N_3SP$: C, 40.27; H, 4.05; N, 9.39; S, 7.17; P, 6.92. Found: C, 39.82; H, 3.85; N, 9.16; S, 7.16; P, 7.65.)

The filtrate was neutralized by the addition of sodium bicarbonate and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with water and dried. Evaporation of the solvents gave **12c** (0.075 g, 20.9%).

2,2,2-Trichloroethoxycarbonyl α-Isopropylidene-4-amino-3-isothiazolone-2-acetate (14a)——A solution of **13a** (0.5 g, 1.1 mmole) dissolved in polyphosphoric acid (6 g) was kept for 2 days at room temperature. Ice water (30 ml) was added to the reaction mixture which was neutralized by the addition of aqueous sodium hydroxide, and extracted with CH_2Cl_2. The CH_2Cl_2 was dried and removed by evaporation to afford an amorphous solid (0.36 g, 75.6%). Recrystallization from CH_2Cl_2–petroleum ether gave an analytical sample: colorless scales: mp 133.5—135°: IR (Nujol) cm^{-1}: 1735 (ester), 1635 (isothiazolone carbonyl): NMR ($CDCl_3$) δ: 1.92 (3H, s), 2.38 (3H, s), 3.83 br (2H, exch.), 4.70 (2H, s), 6.83 (1H, s). (*Anal.* Calcd. for $C_{10}H_{11}O_3N_2SCl_3$: C, 34.75; H 3.21; N, 8.10; S, 9.28; Cl, 30.77. Found: C, 34.83; H, 3.25; N, 8.11; S, 9.01; Cl, 30.91.)

2,2,2-Trichloroethyl 7-Isocyanatodesacetoxycephalosporanate (15a)——A solution of **10a** (1.0 g, 2.2 mmole) in dry CH_2Cl_2 (10 ml) was cooled to 0°, treated with pyridine (1.04 g, 13.2 mmole), and stirred while a 30% phosgene-toluene solution (6 ml) was added. The mixture was stirred for 6 hr at 0—5°, and to quench excess phosgene, formic acid was added dropwise below 5° until the evolution of gas ceased. The solution was rapidly washed with cold 1 N hydrochloric acid, water, and dried. An oil (0.84 g) was obtained after evaporation of solvents: IR (Neat) cm^{-1}: 2270 (N=C=O), 1790 (β-lactam C=O), 1740 (ester): *m/e* 370 (M^+). In further confirmation, this oil (0.42 g) was dissolved in dry ethanol (20 ml) and kept overnight at room temperature. Evaporation of the solvent gave 2,2,2-trichloroethyl 7-ethoxycarbamidodesacetoxycephalosporanate as a crystalline solid (0.43 g, 93.5%). This product was one spot material on TLC. Recrystallization from ethanol gave an analytical sample: mp 187—189°: IR (Nujol) cm^{-1}: 3290 (NH), 1790 (β-lactam C=O), 1740 (ester), 1695 (urethane): NMR (d_6-DMSO) δ: 1.18 (3H, t, J=7 Hz), 2.13 (3H, s), 3.48 (2H, s), 4.02 (2H, q, J=7 Hz), 4.92, 5.05 (2H, d,d, J=13 Hz), 5.03 (1H, d, J=5 Hz), 5.40 (1H, d,d, J=5 Hz, 9 Hz), 8.07 (1H, d, J=9 Hz). (*Anal.* Calcd. for $C_{13}H_{15}O_5N_2SCl_3$: C, 37.38; H, 3.62; N, 6.71; S, 7.68; Cl, 25.46. Found: C, 37.44; H, 3.43; N, 6.86; S, 7.36; Cl, 25.16.)

Phenacyl 7-Isocyanatodesacetoxycephalosporanate (15b)——A solution of **10b** (1.0 g, 2.3 mmole) in dry CH_2Cl_2 (20 ml) was allowed to react with phosgene in the presence of pyridine and worked up in a similar fashion as for the preparation of **15a**. A colorless solid (0.74 g, 91%) was obtained upon evaporation of solvents: IR (Nujol) cm^{-1}: 2280 (N=C=O), 1780 (β-lactam C=O), 1745, 1700 (ester): NMR ($CDCl_3$) δ: 2.27 (3H, s), 3.30, 3.50 (2H, d,d, J=18 Hz), 5.02 (2H, m), 5.37, 5.66 (2H, d,d, J=17 Hz), 7.4—8.1 (5H, m).

2,2,2-Trichloroethyl 6-Isocyanatopenicillanate (16a)——A solution of **5a** (1.0 g, 2.2 mmole) in dry CH_2Cl_2 (10 ml) was allowed to react with phosgene in the presence of pyridine and worked up in a similar fashion as for the preparation of **15a**. An oil (0.98 g) was obtained on evaporation of solvents: IR (Neat) cm^{-1}: 2245 (N=C=O), 1790 (β-lactam C=O), 1765 (ester). In further confirmation, this oil was dissolved in a mixture of pyridine (1.0 g) and dry ethanol (20 ml) and stand overnight at room temperature. The mixture was diluted with CH_2Cl_2 and washed with 1 N hydrochloric acid, water, and dried. Evaporation of solvents gave an oil (0.75 g). Inspection of NMR and TLC revealed that this oil was a mixture of **5a** and 2,2,2-trichloroethyl 6-ethoxycarbamidopenicillanate. Column chromatography of this oil over silica gel using chloroform as eluant gave 2,2,2-trichloroethyl 6-ethoxycarbamidopenicillanate (0.57 g, 55.4%) as an oil: IR (Neat) cm^{-1}: 3320 (NH), 1790 (β-lactam C=O), 1770 (ester), 1730 (urethane): NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 1.60 (3H, s), 1.72 (3H, s), 4.17 (2H, q, J=7 Hz), 4.57 (1H, s), 4.80 (2H, s), 5.58 (2H, s).

From the second fraction, the starting material (0.18 g, 18%) was recovered.