127.25, 138.14, 157.31. 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether(**1**); mp 36-39°C; IR(NaCl, neat) 3000, 1600, 1100, 850, 700 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.32(s, 6H), 1.42(t, 3H, J=7Hz), 3.42(s, 2H), 4.00(q, 2H, J=7Hz), 4.44(s, 2H), 6.75-7.42(m, 13H).

13. The p-isomer **4** was identified on the basis of the proton decoupled ^{13}C-NMR spectrum. For the p-isomer **4**, there are four different kinds of aromatic carbon present(Fig. 2). The shifts for C-1 and C-4 are nearly identical with lower intesity, whereas C-3 has a chemical shift near that of benzene, and C-2 is shielded, as expected for carbon ortho to an oxygen function (Figure 2).
14. 3-Phenoxybenzyl bromide was easily prepared from 3-phenoxybenzyl alcohol by treatment with aqeous HBr and a catalytic amount of H_2SO_4.
15. Mitsui Toatsu Chemicals, Inc. *Jpn. Kokai Tokkyo JP* 58 32, 840 (1983) (CA **99**;53343q).

Synthetic Studies on Penems and Carbapenems (V)[1]. Preparation of 6-Acetylpenicillanate Derivatives

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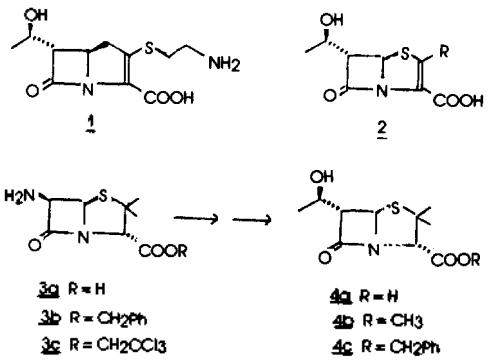
6-Aminopenicillanic acid (6-APA, **3a**) is regarded as one of the best starting materials for preparation of thienamycin (**1**)[2,3] and penems (**2**)[4], since it provides their necessary stereochemistry at C-5 and C-6 positions. Synthesis of thienamycin or penems from 6-APA requires stereospecific transformation of the amino group to a hydroxyethyl group[2] (Scheme 1). During these processes, it is necessary to retain the stereochemistry at C-5[5] and to invert that at C-6[4]. *Trans* configuration of the hydroxyethyl group at C-6 position relative to the sulfur atom at C-5 in the penicillin ring is easily achieved during alkylation since the *trans* analog is energetically preferred to the *cis*. After fixing the configuration at the C-6 position with a hydroxyethyl group, stereospecific formation of a new carbon-carbon or carbon-sulfur bond at the C-5 position can be achieved[6].

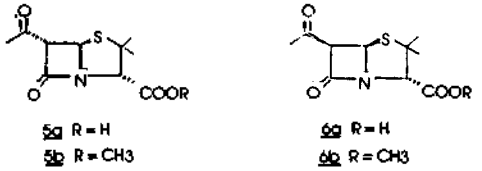
The hydroxyethyl chain of thienamycin was found to have *R*-configuration[7]. Stereospecific formation of the hydroxyethyl chain was primarily achieved by two methods. 6-APA is diazotized in the presence of bromine[1,8] or iodine[9] to give 6,6-dibromo- or 6,6-diiodopenicillanic acid, which is methylated with diazomethane. Methyl 6,6-dibromo- or 6,6-diiodopenicillanate is then converted to methyl 6-bromo- or 6-iodo-6-(1-hydroxyethyl)penicillanate by treating with methylmagnesium bromide or iodide and condensing with acetaldehyde. They are then reduced with Zn-AcOH or Zn-NH_4Cl-NH_4OH[1] to give methyl 6-(1-hydroxyethyl)penicillanate. The best crystallized yield for methyl (6*S*)-6-[(1*R*)-1-(β,β,β-trichloroethoxycarbonyloxy)ethyl] penicillanate from 6-APA was 47%[1]. Also, derivatives of optically enriched benzyl 6-(1-hydroxyethyl)penicillanate (**4c**) was obtained by stereospecific reduction of benzyl 6-acetylpenicillanate (**5c**) with diisopropylamineborane in the presence of magnesium trifluoroacetate[3]. Benzyl 6-acetylpenicillanate was prepared by reaction of benzyl 6-diazopenicillanate with acetaldehyde.

In order to develop the stereospecific reduction of 6-acetylpenicillanates, we examined various methods for preparation of 6-acetylpenicillanates (**5**, **6**) from 6-APA. In the course of synthesis of thienamycin or its analogs, several workers examined oxidation of 3-(1-hydroxyethyl)azetidin-2-one derivatives to 3-acetyl analogs and their stereospecific reduction[10], but extensive studies on the preparation of 6-acetylpenicillanates were not carried out at all.

Benzyl and β,β,β-trichloroethyl 6-acetylpenicillanates (**5c**, **6c** and **5d**, **6d**) were found to be very unstable[2,3]. The only



Scheme 1

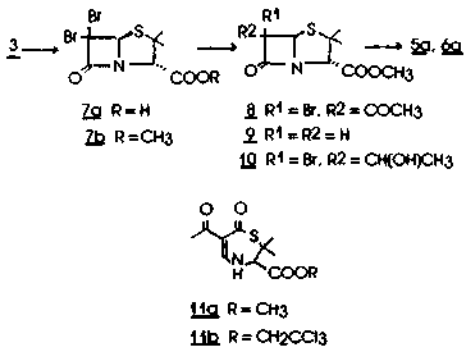


reported method for preparation of these 6-acetyl penicillanates was by diazotization of the corresponding 6-aminopenicillanates with N_2O_3 and by condensation with acetaldehyde[2]. We wish to report here four methods examined for preparation of methyl 6-acetylpenicillanate (**5b**, **6b**) and 6-acetylpenicillanic acid (**5a**, **6a**).

The first approach we attempted was substitution one bromine atom of methyl 6,6-dibromopenicillanate (**7b**) by acetyl group, followed by elimination of the other bromine atom by reduction as shown in Scheme 2. Methyl 6,6-dibromopenicillanate was prepared by treatment of diazomethane on 6,6-dibromopenicillanic acid (**7a**) which was synthesized from 6-APA[1]. When methyl 6,6-dibromopenicillanate (500 mg, 1.3 mmol) was treated with etherial methylmagnesium bromide (0.42 m*l*, 1.6 mmol)[11] in THF and with 1.2 equivalent of acetyl chloride, acetyl imidazole, ethyl acetate or acetic anhydride in THF solution at −78°C, only acetyl chloride and acetyl imidazole gave the acetylated product (**8**). Further purification of the crude product on silica gel column gave the pure one (**8**, 160 mg, yield: 36%), which showed a R_f value at 0.26 (benzene), IR(KBr) bands at 1760 and 1740 cm^{-1}, and ^1H NMR ($CDCl_3$) peaks at 1.47(s, 3H), 1.67(s, 3H), 2.50(s, 3H), 3.73(s, 3H), 4.50(s, 1H) and 5.79(s, 1H) ppm. However, the attempt to reduce **8** to 6-acetylpenicillanates (**5b**, **6b**) by stirring either with zinc in acetic acid[3] or in ammonium hydroxide-ammonium chloride solution[4] completely failed.

The second method attempted for preparation of 6-acetylpenicillanates was direct acetylation on methyl penicillanate (**9**) (Scheme 2). Thus, **7b** (500 mg, 1.34 mmol) was stirred at −9°∼−10°C with zinc powder (262 mg, 4.02 mmol) in acetone (2.0 m*l*). Ammonia water (28%; 0.36 m*l*) and amonium chloride solution (272 mg in 1 m*l* of water) were added and stirred for 30 min. Extraction of the reaction mixture with methylene chloride gave a light yellow crystal, methyl penicillanate (**9**, 275 mg, yield: 96%) which showed a R_f value at 0.27 (benzene–ethyl ether = 95:5), mp 44-45°C, IR bands (KBr) at 1780 and 1760 cm^{-1}, and ^1H NMR peaks at 1.43(s, 3H), 1.67(s, 3H), 2.90–3.75(q, 2H), 3.77(s, 3H), 4.47(s, 1H) and 5.30(d, 1H) ppm[12]. To **9** (275 mg, 1.29 mmol) in THF at −78°C was added lithium 1,1,1,3,3,3-hexamethyldisilazide (1.55 mmol) and the mixture was stirred for 60 min, followed by addition of acetyl chloride (0.11 m*l*, 1.55 mmol) in THF, and stirred further for 80 min. The reaction mixture was extracted with ethyl acetate, worked up and chromatographed on silica gel column to give methyl 6-acetylpenicillanate (**5b** and **6b**, 60 mg, yield: 18%) which showed a R_f value at 0.55 (chloroform–ethyl acetate = 9:1), IR(KBr) bands at 1775 and 1750 cm^{-1}, and ^1H NMR peaks at 1.47(s, 3H), 1.67(s, 3H), 2.17 and 2.21 (two peaks, 3H), 2.95–3.72(1d, 4d, 6H), 3.77(s, 3H), 4.47(s, 1H) and 5.27 (d, 1H) ppm. Two isomers with almost equal amounts were noticed as indicated by the peaks at 2.17 and 2.21 ppm in its ^1H NMR spectrum.

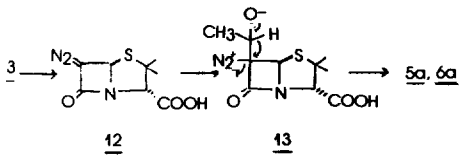
Direct acetylation of methyl penicillanate gave poor yield, so we persued third method to obtain methyl 6-acetylpenicillanate by direct oxidation of methyl 6-(1-hydroxyethyl)-penicillanate (Scheme 2). Methyl 6,6-dibromopenicillanate (**7b**) was treated with methylmagnesium bromide followed by addition of acetaldehyde to give methyl 6-bromo-6-(1-hydroxyethyl)penicillanate (**10**)[1]. Reduction of **10** was done with zinc in acetic acid[3] or in ammonium hydroxide-ammonium chloride solution[1,12] to give methyl 6-(1-hydroxyethyl)penicillanate. Oxidation of the hydroxyethyl group in methyl 6-(1-hydroxyethyl)penicillanate to the 6-acetyl analog was attempted by two methods. The first method was the DMSO-dicyclohexylcarbodiimide oxidation. Methyl 6-(1-hydroxyethyl)penicillanate (0.5 g, 2.2 mmol) was dissolved in a solution of 20 m*l* of anhydrous benzene and DMSO (1:1), and pyridine (0.17 m*l*, 2.2 mmol), trifluoroacetic anhydride (0.09 m*l*, 1.1 mmol), and dicyclohexylcarbodiimide (1.9 g, 9 mmol) were added in sequences, and the reaction mixture was stirred at room temperature for 18 hr. The mixture was diluted with benzene, filtered, washed with water, and evaporated to give a residue (0.4 g). The second method was the Collins' oxidation. Methylene chloride solution of chromic trioxide (18 g, 0.18 mmol) and pyridine (28.4 m*l*, 0.36 mol) was added to methyl 6-(1-hydroxyethyl)penicillanate (7.9 g, 0.03 mol) in methylene chloride (50 m*l*) at 0°C and the mixture was stirred for 30 min. It was neutralized with sodium bicarbonate (5%, 100 m*l*), and the organic layer was separated and evaporated to give a residue (7.2 g). Each residue was chromatographed through silica gel very fast to give 0.3 g (yield: 60%) or 5.77 g (yield: 73%) of the pure product, respectively. Both products showed the identical IR, ^1H NMR and mass spectra[14]. These spectral data confirmed a rearranged product, **11a**, which is a similar product (**11b**) reported by Sheehan *et al.*[2]



Scheme 2

The fourth method attempted for the preparation of 6-acetylpenicillanates was acetylation on diazotized 6-APA by reaction with acetaldehyde. Thus, 6-APA was diazotized, by reaction with nitrous acid, to give 6-diazopenicillanic acid (**12**), which would further react with acetaldehyde to afford 6-acetylpenicillanic acid (**5a**, **6a**) through a betaine intermediate (**13**). To a solution of 10.4 m*l* of methylene chloride-acetonitrile-sulfuric acid (2.5 N) saturated with sodium sulfate (4:4:2.4) was added sodium nitrite (420 mg, 6 mmol). 6-APA (440 mg, 2.0 mmol) and acetaldehyde (2 m*l*) were added in sequences. After stirring for 5 hr at 0–5°C the organic layer was separated and evaporated to give an amorphous solid (**5a** and **6a**, 530 mg), showing IR (thin film) bands at 3400–2500, 1795, 1750, and 1730 cm^{-1} and ^1H NMR (THF-d_8) peaks at 1.39(s, 3H), 1.40(s, 3H), 1.46(s, 3H), 1.47(s, 3H), 1.71(s, 3H), 1.78(s, 3H), 4.72(s, 2H), 5.09(d, 1H, J = 5Hz), 5.22(d, 1H, J = 5Hz), 5.66(d, 1H, J = 1.0Hz) and 6.03(d, 1H, J = 1.0Hz) ppm. The ^1H NMR spectrum implies the existence of two isomers **5a** and **6a** (46.3:53.7), but no other products at all. Similar results were reported also on acetylation of β,β,β-trichloroethyl or benzy 6-diazopenicillanate which was obtained by treatment of N_2O_3 on **3c**[2,3].

The attempt to separate these isomers by chromatography on silica gel column completely failed due to instability. However they were pretty stable under dried condition at low temperature to store for a few months without decomposition. As reported by others[2,3], esterfication of 6-acetylpenicillanic acid with diazomethane and attempt to purify the product did not give any noticeable β-lactam compounds, which seemed to imply the instability of the ester analogs. Stereospecific formation of **5a** from 6-APA and stereospecific reduction of **5a** to **4a** are currently under investigation.



Scheme 3

Acknowledgement. The financial support from The Korean Traders Scholarship Foundation is acknowledged.

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