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Studies on Prodrugs. III. A Convenient and Practical Preparation of Ampicillin Prodrugs

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In order to prepare ampicillin prodrugs conveniently for practical use, a new synthetic method for 6β-aminopenicillanic acid (6-APA) esters as key intermediates of various ampicillin prodrugs has been developed. Acylation of 6-APA esters to ampicillin esters was achieved in good yields by using phenylglycyl chloride hydrochloride in dichloromethane in the presence of sodium bicarbonate and amide, or ammonium bicarbonate alone. KBT-1585, bacampicillin, talampicillin and pivampicillin have been obtained in good yields by this procedure.

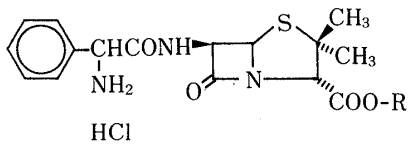
Keywords——6β-aminopenicillanic acid ester; ampicillin ester; prodrug; KBT-1585; phenylglycylchloride; acylation

As a part of our studies on prodrugs, we have reported that some ampicillin acyloxyallyl esters function as ampicillin prodrugs. Among these acyloxyallyl esters, ampicillin (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester hydrochloride (KBT-1585) was found to have excellent properties as a prodrug.

In our previous paper,[1] syntheses of ampicillin esters (prodrugs) from ampicillin (ABPC) were described. More efficient and practical methods for the preparations of ABPC esters from 6β-aminopenicillanic acid (6-APA) are reported in this paper.

Several methods to prepare ABPC prodrugs such as pivampicillin (PVPC),[2] talampicillin (TAPC)[3] and bacampicillin (BAPC)[4] are known. For example, enamine-protected ABPC was found to react with phthalidyl bromide and subsequent removal of the enamine group was shown to give TAPC.[5] Potassium benzylpenicillinate was transformed into phthalidyl ester, which, upon treatment with phosphorus pentachloride, methanol, phenylglycyl chloride hydrochloride and water successively, afforded TAPC.[3a] Benzylpenicillin pivaloyloxymethyl ester was deacylated by treatment first with phosphorus pentachloride, then with methanol and water, affording 6-APA ester, which was again acylated with phenylglycyl chloride hydrochloride to give PVPC.[2] If the 6-APA ester can be obtained conveniently, the synthetic route to ABPC prodrugs *via* acylation of the 6-APA ester with phenylglycine derivatives is considered to be the most economical.

6-APA esters can be prepared from benzylpenicillin as mentioned above, but the hitherto known deacylation of benzylpenicillin ester is rather tedious. Daehne *et al.* synthesized 6-APA pivaloyloxymethyl ester *p*-toluenesulfonate by treating 6-APA triethylammonium salt with chloromethyl pivalate in 80% yield.[2] We could not, however, obtain the desired 6-APA (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester *p*-toluenesulfonate (**4a**) in the same manner by treatment of 6-APA triethylammonium salt with 4-bromomethyl- or 4-chloromethyl-5-methyl-1,3-dioxolen-2-one. In this reaction, not only the 3-carboxyl group but also the 6-amino group appears to react with the halides and hence complex mixtures were found on thin layer chromatography (TLC). Consequently, it is necessary to protect the 6-amino group prior to the esterification.



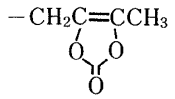
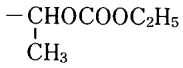
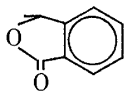
	R
KBT-1585 (**8a**)	
pivampicillin (**8d**)	$-CH_2OCOC(CH_3)_3$
bacampicillin (**8e**)	
talampicillin (**8f**)	

Chart 1

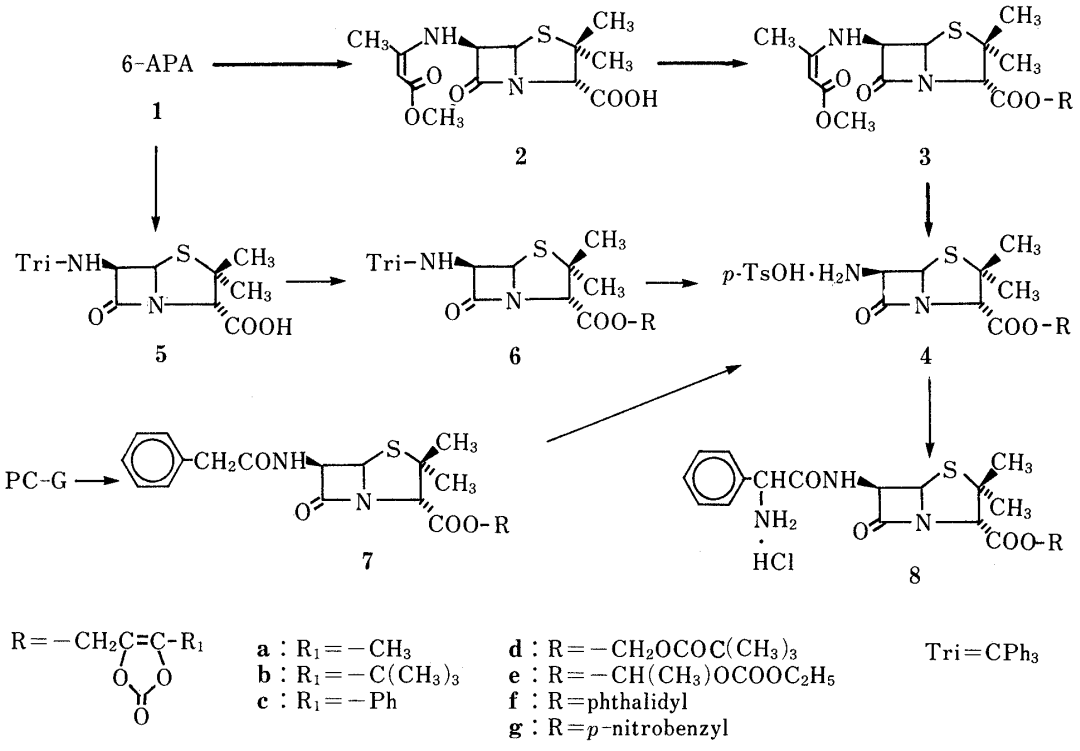


Chart 2

The trityl group is often used to protect an amino goup, and the 6-amino group of 6-APA is known to be well protected by the trityl group.[6] Thus, 6-tritylaminopenicillanic acid (**5**) was allowed to react with 4-bromomethyl-5-methyl-1,3-dioxolen-2-one and then the trityl group was removed with *p*-toluenesulfonic acid monohydrate to afford crystalline 6-APA (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester *p*-toluenesulfonate (**4a**) in 81% yield. However, it is not practical to use the trityl group for a large scale preparation of 6-APA esters, and the total yield of **4a** from 6-APA was not sufficient (53%) as shown in Chart 2.

A β-dicarbonyl compound such as the methyl acetoacetate has been used to protect an amino group, and is also known to protect the side chain amino group of ABPC.[7] Accordingly we applied this method to protect the 6-amino group of 6-APA as shown in Chart 2. 6-APA was allowed to react with methyl acetoacetate in the presence of triethylamine

in dichloromethane/methanol (10/1, v/v) at room temperature for 2 h, yielding a clear solution. The solvent was removed *in vacuo*, and the enamine-protected 6-APA triethylammonium salt (**2**) was obtained as a syrup in a quantitative yield. The syrupy enamine (**2**) obtained was treated with 4-chloromethyl-5-methyl-1,3-dioxolen-2-one in ethyl acetate/*N*,*N*-dimethylformamide (3/1, v/v) in the presence of sodium iodide or tetrabutylammonium iodide (0.1 mol eq) to obtain the enamine ester (**3a**). *p*-Toluenesulfonic acid monohydrate in ethyl acetate was added to the ethyl acetate solution of **3a** without isolation under stirring at 0—5 °C, and the crystalline *p*-toluenesulfonate (**4a**) precipitated out. The desired **4a** was obtained from 6-APA in 88% yield by this method. 6-APA pivaloyloxymethyl ester *p*-toluenesulfonate (**4d**) was obtained similarly in 83% yield from 6-APA. The reaction with α-chlorodiethylcarbonate, however, gave 6-APA 1-ethoxycarbonyloxyethyl ester *p*-toluenesulfonate (**4e**) in very low yield (2%) because of the low reactivity of the chloride. However, when α-iododiethylcarbonate, which was prepared by halogen exchange reaction with sodium iodide in acetonitrile, was used instead of the chloride in this reaction, 6-APA 1-ethoxycarbonyloxyethyl ester *p*-toluenesulfonate (**4e**) was obtained in 81% yield. Enamine-protected 6-APA phthalidyl ester (**3f**) was also obtained quantitatively by treatment of 6-APA enamine (**2**) with phthalidyl bromide. However, when the phthalidyl ester (**3f**) was treated with *p*-toluenesulfonic acid in the same manner, the *p*-toluenesulfonate (**4f**) could not be obtained in crystalline form. Other crystalline *p*-toluenesulfonates were synthesized similarly in high yields as shown in Table I. This procedure is convenient and practical for the preparation of 6-APA esters which are important intermediates of β-lactam derivatives.

6-APA ester *p*-toluenesulfonate (**4a**) was also obtained from benzylpenicillin in 60% total yield according to the conventional method[2] *via* deacylation under carefully controlled reaction conditions. Our method to prepare 6-APA ester (**4**) from 6-APA is superior to the conventional procedure. After this work was complete, M. S. Manhas *et al.* also reported a similar result with simple 6-APA esters.[8]

The next important step for the synthesis of ABPC prodrugs is the acylation of 6-APA esters (**4**) with a phenylglycine moiety.

Phenylglycyl chloride hydrochloride or enamine-protected phenylglycine can be used for the acylation. The use of phenylglycyl chloride is better, since the reaction does not require any deprotection process. There have been few reports on the reaction of 6-APA esters with phenylglycyl chloride hydrochloride, except for the reaction of 6-APA pivaloyloxymethyl ester and phenylglycyl chloride in dichloromethane in the presence of sodium bicarbonate.[2] A

TABLE I. 6-APA Ester *p*-Toluenesulfonates (**4**) Prepared from 6-APA

Compd. No.	Yield (%)	mp (dec.) (°C)	Analysis (%)					
			Calcd			Found		
			C	H	N	C	H	N
4a	88	157—160	47.99	4.83	5.60	47.99	4.96	5.68
4b	89	163—168	50.91	5.57	5.16	50.72	5.57	5.27
4c	90	156—161	53.37	4.66	4.98	53.35	4.60	5.11
4d	83	149—152	50.18	6.02	5.57	50.10	6.03	5.67
4e	81	140—142	47.61	5.59	5.55	47.60	5.60	5.66
4f[a]	90	—	53.07	4.65	5.38		—	
4g	80	138—140	50.47	4.81	8.03	50.34	4.90	7.83

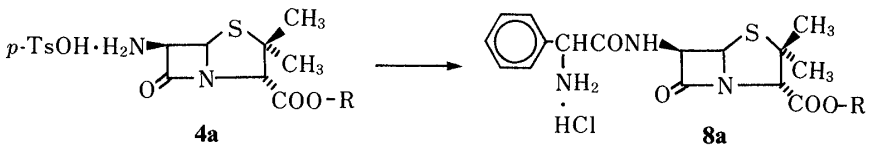
a) This compound did not crystallize and a yellow amorphous solid was obtained in *ca.* 90% yield. Elemental analysis values for **4f** were not within 0.5% of the calculated ones.

general organic base such as triethylamine or pyridine cannot be used in this acylation because they are relatively so basic as to cause some undesired side reactions. Thus sodium bicarbonate, *N*, *N*-dimethylaniline or a weak tertiary amine was used as the base. Prior to the acylation, free 6-APA ester has to be formed by treating the *p*-toluenesulfonate (**4**) with a weak base. In this work, a simplified method without the removal of *p*-toluenesulfonic acid has been examined.

The general procedure is as follows. One eq of triethylamine was added to a suspension of 6-APA ester *p*-toluenesulfonate (**4a**) in dichloromethane under cooling (*ca.* 5 °C) to afford a clear solution, to which a base and phenylglycyl chloride hydrochloride were added. First, the acylation was carried out using sodium bicarbonate as the base in dichloromethane at 5—10 °C for 1 h. However the acylation reaction was not complete and the yield of KBT-1585 (**8a**) was poor (35%). The yield of **8a** was 68% when *N*, *N*-dimethylaniline was used as the base, but it was rather difficult to remove a trace of *N*, *N*-dimethylaniline from the product. The low yield of KBT-1585 in the reaction with sodium bicarbonate is due to the insolubility of this inorganic base in dichloromethane, but since *N*, *N*-dimethylaniline is soluble in dichloromethane, it can smoothly trap the hydrochloride generated.

Amides, which are generally more soluble in dichloromethane and can trap the hydrochloride, were found to be effective bases, when used together with sodium bicarbonate.[9] The amides tested in the acylation reaction and the yields of **8a** are shown in Table II. It is apparent that urea, methylurea, ethylurea, ethyleneurea, acetamide and *N*, *N*-

TABLE II. Acylation of 6-APA Ester *p*-Toluenesulfonate (**4a**)[a]



4a **8a**

Exp. No.	Inorganic base	Amide	Yield of **8a**[d] (%)
1	$NaHCO_3$	—	35
2	$NaHCO_3$	Urea	73
3	$NaHCO_3$	Methylurea	73
4	$NaHCO_3$	Ethylurea	71
5	$NaHCO_3$	Ethyleneurea	70
6	$NaHCO_3$	Acetamide	72
7	$NaHCO_3$	*N*, *N*-Dimethylformamide	70
8	$NaHCO_3$	Imidazole	b)
9	$NaHCO_3$	4-Dimethylaminopyridine	b)
10	NH_4HCO_3	—	76
11	NH_4HCO_3	Urea	75
12	NH_4HCO_3	Methylurea	75
13	NH_4HCO_3	Ethylurea	72
14	NH_4HCO_3	Ethyleneurea	74
15	NH_4HCO_3	Acetamide	75
16	$(NH_4)_2CO_3$	—	c)
17	$(NH_4)_2HPO_4$	—	c)

a) Acylation was carried out using 1.2 eq of phenylglycyl chloride hydrochloride, 2.5 eq of inorganic base and 1 eq of amide in dichloromethane at 5—10 °C for 1 h.
b) Yield and purity were not satisfactory.
c) Side reaction occurred to give complex mixtures.
d) The purity of **8a** was over 98% in HPLC (*μ*-Bondapak C_{18} column, 0.1 M acetate buffer (pH 4)/methanol (50/50, v/v)).

dimethylformamide are quite effective in the acylation reaction. However, imidazole and 4-dimethylaminopyridine, which are effective catalysts in acylation or esterification reactions, were ineffective. In this acylation reaction, the use of a mixture of sodium bicarbonate with an amide is quite effective. The acylation with an amide alone gave relatively poor yield and the purity of the product was insufficient.

Next, we examined the catalytic abilities of inorganic bases alone without any amide, and found that ammonium bicarbonate was effective (Exp. 10 of Table II). Other ammonium salts such as ammonium carbonate or diammonium hydrogen phosphate were ineffective in the acylation because they are more basic than ammonium bicarbonate and hence gave complex mixtures. Thus, acylation in the presence of sodium bicarbonate and an amide, or with ammonium bicarbonate as the base and in dichloromethane alone as the solvent, is quite useful for the practical synthesis of an ABPC prodrug, KBT-1585.

Furthermore, this process has also been found to be applicable to the preparations of PVPC, BAPC and TAPC, which were obtained in 72, 68 and 65% yields, respectively. Extensions of this work to other penicillin derivatives, *e.g.*, mecillinam and sulbactam, are in progress in this laboratory.

Experimental

Melting points were determined on a capillary melting point apparatus, Yamato model MR-21. All melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Nihon Denshi model PS-100 NMR spectrometer and a Hitachi model R-24A NMR spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded with a Shimadzu model IR-440 instrument.

Triethylammonium 6β-(1-Methyl-2-methoxycarbonylvinylamino)penicillanate (2)——Triethylamine (9 ml) and methyl acetoacetate (6.5 g) were added to a suspension of 6-APA (10 g) in dichloromethane (100 ml) and methanol (10 ml) at room temperature. The mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo* to give **2** as a syrup. IR ν_{max}^{neat} cm^{-1}: 1775—1755 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (9H, t, J=7 Hz, ($C\underline{H}_3CH_2)_3N$), 1.55 (3H, s, 2-CH_3), 1.60 (3H, s, 2-CH_3), 2.01 (3H, s, $C\underline{H}_3CH$=C), 3.07 (6H, q, J=7 Hz, ($CH_3C\underline{H}_2)_3N$), 3.64 (3H, s, CH_3O), 4.35 (1H, s, $CH_3C\underline{H}$=C), 4.63 (1H, s, 3-H), 5.07 (1H, dd, J=4 and 9 Hz, 6-H), 5.68 (1H, d, J=4 Hz, 5-H), 9.0 (1H, d, J=9 Hz, NH).

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl 6β-(1-Methyl-2-methoxycarbonylvinylamino)penicillanate (3a)——Potassium bicarbonate (1.7 g), sodium iodide (1.2 g) and 4-chloromethyl-5-methyl-1,3-dioxolen-2-one (8.2 g) were added to a solution of **2** in ethylacetate (70 ml) and *N*,*N*-dimethylformamide (18 ml) at 5 °C, and the mixture was stirred at room temperature for 15 h. Then cold water (40 ml) was added, and the reaction mixture was stirred vigorously for 10 min. The organic layer was separated, washed with 5% aq. sodium chloride (40 ml × 2) and dried over anhydrous magnesium sulfate. The dried organic layer was used in the next step without further purification. IR ν_{max}^{neat} cm^{-1}: 1830, 1780, 1755 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, s, 2-CH_3), 1.61 (3H, s, 2-CH_3), 1.94 (3H, s, $C\underline{H}_3CNH$), 2.12 (3H, s, $C\underline{H}_3C$=C), 3.57 (3H, s, OCH_3), 4.41 (1H, s, HC=C), 4.57 (1H, s, 3-H), 4.87 (2H, s, $C\underline{H}_2C$=C), 5.08 (1H, dd, J=4 and 9 Hz, 6-H), 5.60 (1H, d, J=4 Hz, 5-H), 8.92 (1H, d, J=9 Hz, NH).

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4a)——A solution of *p*-toluenesulfonic acid monohydrate (8.7 g) in ethyl acetate (25 ml) was added to a stirred solution of **3a** in ethylacetate at 0—5 °C. The crystalline *p*-toluenesulfonate (**4a**) precipitated out in a few minutes and the suspension was stirred at 5—10 °C for 30 min. The *p*-toluenesulfonate was filtered off and washed with ethyl acetate to give 20.4 g of **4a** (yield 88%). mp 157—60 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1820, 1780, 1760 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.40 (3H, s, 2-CH_3), 1.59 (3H, s, 2-CH_3), 2.12 (3H, s, $C\underline{H}_3C$=C), 4.46 (1H, s, 3-H), 4.9—5.1 (3H, m, 6-H and $C\underline{H}_2C$=C), 5.41 (1H, d, J=4 Hz, 5-H), 2.24 (3H, s, $PhC\underline{H}_3$), 6.97 and 7.38 (4H, d, arom. H). *Anal.* Calcd for $C_{20}H_{24}N_2O_9S_2$: C, 47.99; H, 4.83; N, 5.60. Found: C, 47.99; H, 4.96; N, 5.68.

Other 6-APA ester *p*-toluenesulfonates (**4b—g**) were obtained by the same procedure, and their physical properties are as follows.

(5-*tert*-Butyl-2-oxo-1,3-dioxolen-4-yl)methyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4b)——Yield 89%. mp 163—168 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1830, 1790, 1750 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (9H, s, $C(C\underline{H}_3)_3$), 1.45 (3H, s, 2-CH_3), 1.64 (3H, s, 2-CH_3), 4.59 (1H, s, 3-H), 5.10 (1H, d, J=4 Hz, 6-H), 5.14 (2H, s, $C\underline{H}_2C$=C), 5.54 (1H, d, J=4 Hz, 5-H), 2.28 (3H, s, $PhC\underline{H}_3$), 7.09 and 7.48 (4H, d, arom. H). *Anal.* Calcd for $C_{23}H_{30}N_2O_9S_2$: C, 50.91; H, 5.57; N, 5.16. Found: C, 50.72; H, 5.57; N, 5.27.

(5-Phenyl-2-oxo-1,3-dioxolen-4-yl)methyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4c)——Yield 90%. mp 156—161 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1830, 1785, 1750 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.44 (3H, s, 2-CH_3), 1.63 (3H, s,

2-CH_3), 4.60 (1H, s, 3-H), 5.09 (1H, d, J=4 Hz, 6-H), 5.34 (2H, s, $CH_2C{=}C$), 5.53 (1H, d, J=4 Hz, 5-H), 2.28 (3H, s, $PhCH_3$), 7.09 (2H, d, arom. H), 7.4—7.7 (7H, m, arom. H). *Anal.* Calcd for $C_{25}H_{26}N_2O_9S_2$: C, 53.37; H, 4.66; N, 4.98. Found: C, 53.37; H, 4.60; N, 5.11.

Pivaloyloxymethyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4d)——Yield 83%. mp 149—152 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1795, 1770, 1750 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.16 (9H, s, $C(CH_3)_3$), 1.45 (3H, s, 2-CH_3), 1.63 (3H, s, 2-CH_3), 4.56 (1H, s, 3-H), 5.10 (1H, d, J=4 Hz, 6-H), 5.52 (1H, d, J=4 Hz, 5-H), 5.75 (1H, d, J=7 Hz, OCH_2O), 5.87 (1H, d, J=7 Hz, OCH_2O), 2.29 (3H, s, $PhCH_3$), 7.10 and 7.48 (4H, d, arom. H). *Anal.* Calcd for $C_{21}H_{30}N_2O_8S_2$: C, 50.18; H, 6.02; N, 5.57. Found: C, 50.10; H, 6.03; N, 5.67.

1-Ethoxycarbonyloxyethyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4e)——A mixture of diastereomers (1 : 1). The ratio of the diastereomers was determined from the peak height ratio of 3-H, and it changed upon recrystallization. Yield 81%. mp 140—142 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1790, 1760 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, CH_3CH_2O), 1.48—1.64 (9H, m, 2-CH_3 and $CHCH_3$), 4.16 (2H, q, J=8 Hz, OCH_2CH_3), 4.51 and 4.55 (1H, s, 3-H), 5.10 (1H, d, J=4 Hz, 6-H), 5.52 (1H, d, J=4 Hz, 5-H), 6.6—6.8 (1H, m, $CHCH_3$), 2.30 (3H, s, $PhCH_3$), 7.10 and 7.49 (4H, d, arom. H). *Anal.* Calcd for $C_{20}H_{28}N_2O_9S_2$: C, 47.61; H, 5.59; N, 5.55. Found: C, 47.60; H, 5.60; N, 5.66.

Phthalidyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4f)——**4f** was not obtained as crystals, but as an amorphous solid in *ca.* 90% yield, and it was also a mixture of diastereomers (1 : 1). IR ν_{max}^{KBr} cm^{-1}: 1785 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.55 (3H, s, 2-CH_3), 1.62 (3H, s, 2-CH_3), 4.72 and 4.74 (1H, s, 3-H), 5.18 (1H, d, J=4 Hz, 6-H), 5.57 (1H, d, J=4 Hz, 5-H), 2.33 (3H, s, $PhCH_3$), 7.1—8.0 (9H, m, $COOCH$, arom. H).

***p*-Nitrobenzyl 6β-Aminopenicillanate *p*-Toluenesulfonate (4g)**——Yield 80%. mp 138—140 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1780, 1740 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.44 (3H, s, 2-CH_3), 1.65 (3H, s, 2-CH_3), 4.63 (1H, s, 3-H), 5.11 (1H, d, J=4 Hz, 6-H), 5.35 (2H, s, CH_2Ph), 5.54 (1H, d, J=4 Hz, 5-H), 2.29 (3H, s, $PhCH_3$), 7.09 and 7.50 (4H, d, arom. H), 7.69 and 8.22 (4H, d, arom. H). *Anal.* Calcd for $C_{22}H_{25}N_3O_8S_2$: C, 50.47; H, 4.81; N, 8.03. Found: C, 50.34; H, 4.90; N, 7.83.

Ampicillin (5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl Ester Hydrochloride (8a, KBT-1585)——Triethylamine (2.8 ml) and ammonium bicarbonate (4 g) were added to a stirred suspension of **4a** (10 g) in dichloromethane (100 ml) at 0—5 °C. Then phenylglycylchloride hydrochloride (5 g) was added portionwise for 15 min and the mixture was stirred at 7—10 °C for 50 min. Water (70 ml) was added and the pH was adjusted to 7.4 with 3 N sodium hydroxide at 0—5 °C. After filtration, the dichloromethane layer was separated and washed with 5% aq. sodium chloride. Saturated sodium chloride (80 ml) was added to the stirred dichloromethane solution at 0—5 °C, followed by the addition of 2 N hydrochloric acid until the pH reached to 1.5. The organic layer was separated, washed with sat. sodium chloride and dried over anhydrous magnesium sulfate. The solution was concentrated *in vacuo* to afford a syrup, which was crystallized from 2-butanone (40 ml). The crude crystals were dissolved in dichloromethane and concentrated *in vacuo* to give a syrup which was recrystallized from isopropanol (20 ml) and ethyl acetate (40 ml). The solution was allowed to stand overnight at 5 °C to give colorless crystals, which were collected by filtration and washed with cold ethyl acetate to give 7.6 g of **8a** (76%). mp 145 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1825, 1785, 1750, 1690 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.32 (3H, s, 2-CH_3), 1.47 (3H, s, 2-CH_3), 2.17 (3H, s, $C{=}CCH_3$), 4.38 (1H, s, 3-H), 5.09 (2H, s, $C{=}CCH_2$), 5.16 (1H, s, $PhCHNH_3$), 5.40—5.60 (2H, m, 5- and 6-H), 7.3—7.6 (5H, m, arom. H), 8.98 (NH_3), 9.4 (1H, d, NHCO). *Anal.* Calcd for $C_{21}H_{23}N_3O_7S \cdot HCl$: C, 50.65; H, 4.86; N, 8.44. Found: C, 50.38; H, 4.95; N, 8.24.

Other ampicillin ester hydrochlorides were obtained by the same procedure as described above and their physical properties were as follows.

Ampicillin (5-*tert*-Butyl-2-oxo-1,3-dioxolen-4-yl)methyl Ester Hydrochloride (8b)——Yield 75%. mp 133 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1830, 1785, 1755, 1690 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (9H, s, $C(CH_3)_3$), 1.33 (3H, s, 2-CH_3), 1.47 (3H, s, 2-CH_3), 4.39 (1H, s, 3-H), 5.10 (1H, s, $PhCHNH_3$), 5.12 (2H, s, $C{=}CCH_2$), 5.4—5.6 (2H, m, 5- and 6-H), 7.3—7.6 (5H, m, arom. H), 8.7 (NH_3), 9.3 (1H, d, NHCO). *Anal.* Calcd for $C_{24}H_{29}N_3O_7S \cdot HCl$: C, 53.38; H, 5.60; N, 7.78. Found: C, 52.89; H, 5.66; N, 7.45.

Ampicillin (2-Oxo-5-phenyl-1,3-dioxolen-4-yl)methyl Ester Hydrochloride (8c)——Yield 76%. mp 140 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1830, 1785, 1760, 1690 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, s, 2-CH_3), 1.46 (3H, s, 2-CH_3), 4.41 (1H, s, 3-H), 5.11 (1H, s, $PhCHNH_3$), 5.30 (2H, s, $C{=}C{-}CH_2$), 5.4—5.6 (2H, m, 5- and 6-H), 7.3—7.6 (10H, m, arom. H), 8.8 (NH_3), 9.3 (1H, d, NHCO). *Anal.* Calcd for $C_{26}H_{25}N_3O_7S \cdot HCl$: C, 55.76; H, 4.67; N, 7.50. Found: C, 55.26; H, 4.73; N, 7.33.

Ampicillin Pivaloyloxymethyl Ester Hydrochloride (8d, PVPC)——Yield 72%. mp 153—155 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1780, 1760, 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.13 (9H, s, $C(CH_3)_3$), 1.33 (3H, s, 2-CH_3), 1.46 (3H, s, 2-CH_3), 4.38 (1H, s, 3-H), 5.12 (1H, s, $PhCHNH_3$), 5.41 (1H, d, J=4 Hz, 5-H), 5.55 (1H, dd, J=4 Hz and 8 Hz, 6-H), 5.71 (1H, d, J=7 Hz, OCH_2O), 5.84 (1H, d, J=7 Hz, OCH_2O), 7.3—7.6 (5H, m, arom. H), 8.94 (NH_3), 9.4 (1H, d, NHCO). *Anal.* Calcd for $C_{22}H_{29}N_3O_6S \cdot HCl$: C, 52.85; H, 6.14; N, 8.14. Found: C, 52.38; H, 6.14; N, 8.14.

Ampicillin 1-Ethoxycarbonyloxyethyl Ester Hydrochloride (8e, BAPC)——A mixture of diastereomers, yield 68%. mp 140 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1780, 1760, 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.14—1.28 (3H, t, J=8 Hz, OCH_2CH_3), 1.46—1.52 (3H, d, J=6 Hz, $CHCH_3$), 1.36 (3H, s, 2-CH_3), 1.46 (3H, s, 2-CH_3), 4.07—4.26 (2H, q, J=

8 Hz, OCH_2CH_3), 4.32, 4.37 (1H, s, 3-H), 5.13 (1H, s, $PhCHNH_3$), 5.4—5.62 (2H, m, 5- and 6-H), 6.58—6.76 (1H, q, $J=6$ Hz, $CHCH_3$), 7.35—7.60 (5H, m, arom. H), 8.9 (3H, NH_3), 9.4 (1H, d, NHCO). *Anal.* Calcd for $C_{21}H_{27}N_3O_7S \cdot HCl$: C, 50.25; H, 5.62; N, 8.37. Found: C, 49.79; H, 5.68; N, 8.10.

Ampicillin Phthalidyl Ester Hydrochloride (8f, TAPC)——A mixture of diastereomers, yield 65%. mp 150 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1780, 1685 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.43 (3H, s, 2-CH_3), 1.48 (3H, s, 2-CH_3), 4.54 (1H, s, 3-H), 5.07 (1H, s, $PhCHNH_3$), 5.43—5.65 (2H, m, 5- and 6-H), 7.36—8.00 (10H, m, arom. H, $COOCHO$), 8.95 (3H, NH_3), 9.4 (1H, d, NHCO). *Anal.* Calcd for $C_{24}H_{23}N_3O_6S \cdot HCl$: C, 55.65; H, 4.67; N, 8.11. Found: C, 55.21; H, 4.85; N, 7.85.

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