STUDIES ON THE S_1-C_2 BOND CLEAVAGE REACTION OF PENICILLINS BY CARBENE REACTION : SYNTHESIS OF PENICILLIN DERIVATIVE

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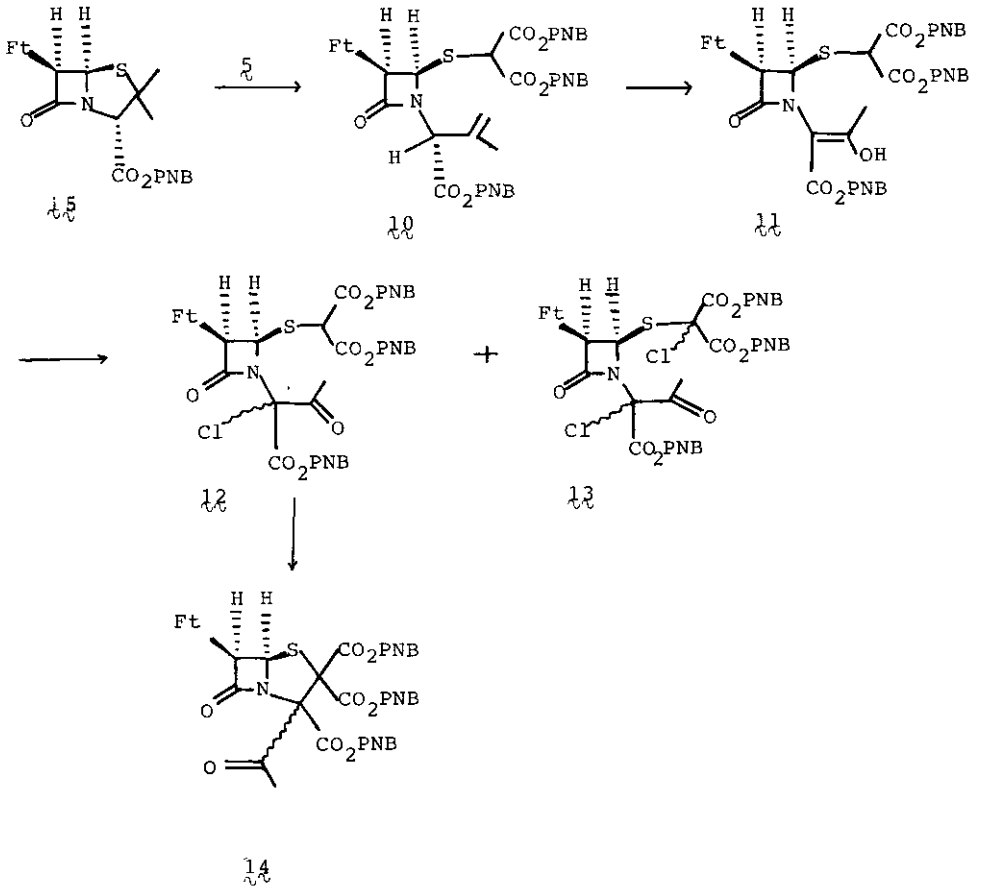
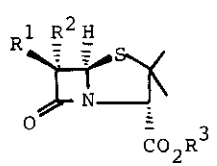
Abstract —— Treatment of α-diazomalonate (5) with penicillin derivative (1 - 4) in the presence of a catalytic amount of rhodium acetate brought about the facile S_1-C_2 bond cleavage reactions in moderate yields. 2-Dicarboxylated penicillin derivative was synthesized by employing the above reaction as a key step.

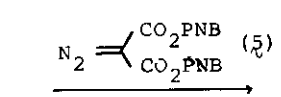
The interaction of carbenes or carbenoids to sulfur atom has been well-known reactions and has been sometimes utilized to construct an intricate molecule. This types of reactions have already been applied to the conversion of penicillin nucleus into cephalosporin derivatives by Sankyo[1] and Takeda groups[2], independently. We have also been investigating the application of this carbene reaction[3-5] for the synthesis of carbapenem derivatives, and have reported[3] the new carbon-introducing reaction at the C_4-position of azetidinones by the reaction of α-diazomalonate with the monocyclic β-lactams in the presence of a catalytic amount of rhodium acetate. In continuation of our work on the synthesis of new types of β-lactam antibiotics, the extention of the above reaction was further investigated. Treatment of di-*p*-nitrobenzyl α-diazomalonate (5) with penicillin G methyl ester (2) in benzene-methylene chloride (1 : 1 v/v) in the presence of a catalytic amount of rhodium acetate yielded the bond-cleaved product which was, without isolation, converted to 7 by treatment with triethylamine in 20.7 % yield from 2. The structure of the product (7) was determined based on its spectral data (see Table). Similarly penicillin V benzyl ester (3) was reacted with 5 to give 8 in 24.3 % yield. When this reaction was applied to 6-phthalimidyl derivatives (1 and 4) which had no NH group at the C_6-position, the yields of the products (6 and 9) increased to 81 % and 78.5 % yield, respectively. The spectroscopic data, microanalyses and yields for all the new compounds obtained are summarized in Table.

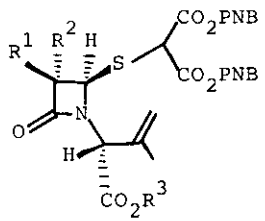
We next turned our attention to the utilization of the product for the synthesis of penicillin derivative, because the preparation of additional members of this class is of interest from the biological point of view. Ozonolysis of 10, followed by reductive work-up with dimethyl sulfide afforded the corresponding enol (11) in 93 % yield. N-Chlorosuccinimide treatment of 11 in methylene chloride gave the monochloro-β-lactam (12) and dichloro derivative (13) in 69.2 % yield in the ratio of 3 : 2. The former compound was then treated with potassium tert-butoxide to give rise to 2-dicarboxylated penicillin derivative (14) in 54 % yield.

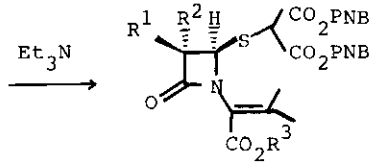
Scheme











(1) R^1 = Ft, R^2 = H, R^3 = CH_2Ph
(2) R^1 = G, R^2 = H, R^3 = Me
(3) R^1 = V, R^2 = H, R^3 = CH_2Ph
(4) R^1 = H, R^2 = Ft, R^3 = CH_2Ph

Table

(6) R^1 = Ft, R^2 = H, R^3 = CH_2Ph
(7) R^1 = G, R^2 = V, R^3 = Me
(8) R^1 = Ft, R^2 = H, R^3 = CH_2Ph
(9) R^1 = H, R^2 = Ft, R^3 = CH_2Ph

Data / Compd.	NMR ($CDCl_3$) δ:	IR ν $^{CHCl_3}_{max}$ cm^{-1}:	$[\alpha]_D$ ($CHCl_3$)	Anal. (%) calcd	Anal. (%) Found	yield (%)
6	2.26 (6H, s, 2 x CH_3), 4.13 (1H, s, SCH), 5.13 (2H, s, CH_2Ar), 5.20 (4H, s, 2 x CH_2Ar), 5.66 (1H, d, J = 7 Hz, C_4-H), 5.83 (1H, d, J = 7 Hz, C_3-H)	1785, 1770 1730, (C=O) 1355 (NO_2)	- 19.25° (c = 0.136)	$C_{40}H_{32}O_{13}N_4S$ C, 59.02 H, 3.86 N, 6.85	C, 59.40 H, 3.99 N, 6.93	81
7	2.0 (3H, s, CH_3), 2.2 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 3.78 (2H, s, CH_2Ar), 4.33 (1H, s, SCH<), 5.55 (1H, d, J = 7.3 Hz, C_4-H), 6.93 (1H, d, J = 13 Hz, NH)	3400 (NH), 1760, 1740, 1735, 1710, 1670, (C=O), 1345 (NO_2)	+ 6.5° (c = 0.062)	$C_{34}H_{32}O_{12}N_4S$ $1.5H_2O$ C, 54.99 H, 4.22 N, 7.42	C, 54.62 H, 4.72 N, 7.49	20.7
8	2.0 (3H, s, CH_3), 2.21 (3H, s, CH_3), 4.4 (1H, s, SCH<), 4.90 (2H, s, OCH_2CO), 5.65 (1H, d, J = 7.0 Hz, C_4-H), 6.86 (1H, d, J = 13.3 Hz. NH)	34oo (NH), 1770, 1735, 1685 (C=O) 1345 (NO_2)	- 8.7° (c = 0.062)	$C_{40}H_{36}O_{13}N_4S$ $1.5H_2O$ C, 57.27 H, 4.21 N, 6.48	C, 57.21 H, 4.68 N, 6.67	24.3
9	2.09 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.31 (1H, s, SCH<), 5.41 (1H, d, J = 2.9 Hz, C_4-H), 5.75 (1H, d, J = 2.9 Hz, C_3-H)	1790, 1775, 1735 (C=O) 1355 (NO_2)	+ 47.92° (c = 0.084)	$C_{40}H_{32}O_{13}N_4S$ C, 59.53 H, 3.88 N, 6.76	C, 59.40 H, 3.99 N, 6.93	78.5

EXPERIMENTAL SECTION

Melting points are not corrected. IR spectra were measured with a Hitachi 260-10 spectrophotometer, NMR spectra with JEOL PMX-60 and JNM-FX100 spectrometers using tetramethylsilane as an internal reference. Mass spectra were taken with a JEOL JMX-D300 spectrometer. All optical rotations were measured in chloroform solution on a JASCO DIP-181 polarimeter using a 1-dm cell.

Bis(p-nitrobenzyl)-2-diazomalonate (5) —— To a stirred solution of bis(p-nitrobenzyl)malonate (10 g) and p-toluenesulfonyl azide (5.62 g) in dry acetonitrile (60 ml) was added dropwise dry triethylamine (2.8 g) at 0°C. After the mixture had been stirred at room temperature for 12 h, the solid precipitated was collected by filtration and washed with methanol to give bis(p-nitrobenzyl)-2-diazomalonate (9 g, 84.2 %) as a crystalline precipitate; IR $\nu_{max.}^{CHCl_3}$ cm^{-1}: 2150 (N_2), 1750, 1725 (C=O), and 1340 (NO_2); NMR ($CDCl_3$) δ : 5.42 (4H, s, 2 x CH_2Ar), 7.40 and 8.23 (each 4H, each d, J = 7 Hz, ArH).

Benzyl 6α-Phthalimidylpenicillanate (4) —— To a solution of benzyl 6β-phthalimidylpenicillanate (1 g) in dry dimethyl formamide (20 ml) was added 60 % sodium hydride (93 mg) under nitrogen at 0°C. After stirring for 1 h at room temperature, a saturated aqueous ammonium chloride solution and benzene was added. The benzene layer separated was washed with brine, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was chromatographed on silica gel using methylene chloride-acetone (98 : 2 v/v) as eluant to afford the trans-compound (4) (890 mg, 89 %); $[\alpha]_D$ +140.66° ($CHCl_3$, c = 0.148); IR $\nu_{max.}^{CHCl_3}$: 1780, 1740 and 1730 (C=O); NMR ($CDCl_3$) δ : 1.4 (3H, x, CH_3), 1.6 (3H, s, CH_3), 4.5 (1H, s, C_3-H), 5.1 (2H, s, CH_2Ar), 5.2 (1H, d, J = 2.6 Hz, C_5-H), 7.1 ∿ 7.9 (9H, m, 9 x ArH); MS m/e 436.1073 [M^+]. $C_{23}H_{20}N_2O_5S$ requires 436.1091.

General Procedure for the Conversion of Penicillins to 1,2-Secopenicillins —— To a stirred solution of penicillin derivative (1 - 4) (1 eq.) and diazo compound (1.2 ∿ 1.3 eq.) in dry benzene and dry methylene chloride (1 : 1 v/v) was added a catalytic amount of rhodium acetate at room temperature. The mixture was then heated at 70 ∿ 80°C for 10 ∿ 15 h. Removal of the solvent gave an oily residue, which was purified by column chromatography to give the 1,2-secopenicillins, whose solution in dry methylene chloride was treated with dry triethylamine (1.1 eq.) at 0°C for 2 h. Evaporation of the solvent gave an oily residue, which was purified by column chromatography to give the compounds (6 - 9) whose S_1-C_2 bond was cleaved. The spectroscopic data for all the new compounds prepared (6 - 9) were summarized

in Table.

p-Nitrobenzyl 2-[(3R,4R)-4-Bis(p-nitrobenzyloxycarbonyl)methylthio-2-oxo-3-phthalimido-1-azetidinyl]-3-hydroxycrotonate (11) ——— To a stirred solution of p-nitrobenzyl 6β-phthalimidylpenicillanate (15) (200 mg) and the above diazo compound (5) (170 mg) in dry benzene (10 ml) and dry methylene chloride (10 ml) was added a catalytic amount of rhodium acetate at room temperature. The mixture was then heated at 70 ∿ 80°C for 10 h. Removal of the solvent gave an oil, which was chromatographed on silica gel using benzene-acetone (97/3 ∿ 96/4 v/v) as eluant to afford the compound (10) (306 mg, 86 %); IR $\nu_{max.}^{CHCl_3}$ cm^{-1} : 1780, 1745, 1730 (C=O), and 1350 (NO_2); NMR ($CDCl_3$) δ : 1.95 (3H, s, CH_3), 4.5 (1H, s, $SCH\langle$), 4.76 ((1H, s, N-$CH\langle$), 5.4 (1H, d, J = 4.5 Hz, C_4-H), 5.50 (1H, d, J = 4.5 Hz, C_3-H).

A solution of this compound (10) (306 mg) in dry methylene chloride (35 ml) was ozonized at -78°C until the solution turned bluish-green. When the excess ozone had been purged, dimethyl sulfide (1 ml) was added and the solution was allowed to stand at room temperature for 12 h. The organic layer was washed with water and with brine and dried (Na_2SO_4). Evaporation of the solvent gave an oily residue, which was purified by column chromatography using methylene chloride-acetone (98 : 2 v/v) as eluant to give the enol-compound (11) (285 mg, 93 %); $[\alpha]_D$ -61.61° ($CHCl_3$, c = 0.09); NMR ($CDCl_3$) δ : 2.33 (3H, s, CH_3), 4.15 (1H, s, $SCH\langle$), 5.60 (1H, d, J = 5.5 Hz, C_4-H), 5.75 (1H, d, J = 5.5 Hz, C_3-H); Anal. calcd for $C_{39}H_{27}N_5O_{16}S$: C, 54.70; H, 3.35; N, 7.88. Found : C, 54.74; H, 3.42; N, 8.19 %.

p-Nitrobenzyl 2-Chloro-2-[(3R,4R)-4-bis(p-nitrobenzyloxycarbonyl)methylthio-2-oxo-3-phthalimido-1-azetidinyl]acetoacetate (12) and p-Nitrobenzyl 2-Chloro-1-[(3R,4R)-4-[chloro-bis(p-nitrobenzyloxycarbonyl)methylthio]-2-oxo-3-phthalimide-4-azetidinyl]-acetoacetate (13)——— A solution of the above enol ketone (11) (1.05 g) and N-chlorosuccinimide (167 mg) in dry methylene chloride (50 ml) was stirred for 1.5 h at -78°C under nitrogen. After filtration of the reaction mixture, the filtrate was evaporated to give an oil, which was chromatographed on silica gel using methylene chloride-acetone (98 : 2 v/v) as eluant to afford the dichloro compound (13) (320 mg, 27.6 %); $[\alpha]_D$ -90.97° ($CHCl_3$, c = 0.038); IR $\nu_{max.}^{CHCl_3}$ cm^{-1} : 1800, 1750, 1730 (C=O), and 1350 (NO_2); NMR ($CDCl_3$) δ : 2.64 (3H, s, CH_3), 5.23 (2H, s, CH_2Ar), 5.29 (2H, s, CH_2Ar), 5.39 (2H, s, CH_2Ar), 5.80 (1H, d, J = 5.2 Hz, C_4-H), 5.93 (1H, d, J = 5.2 Hz, C_3-H); Anal. calcd for $C_{39}H_{27}O_{16}N_5SCl_2$: C, 51.15; H, 2.89; N, 7.37. Found: C, 50.66; H, 2.94; N, 7.58 %. Further elution with methylene chloride-acetone (97 : 3 ∿ 96 : 4 v/v) gave the monochloro compound (12) (450 mg, 41.6 %); $[\alpha]_D$ -60.34° ($CHCl_3$, c =

0.044); IR $\nu_{max.}^{CHCl_3}$ cm^{-1} : 1795, 1750, 1730 (C=O), and 1350 (NO_2); NMR ($CDCl_3$) δ : 2.60 (3H, s, CH_3), 4.33 (1H, s, SCH<); Anal. cacld for $C_{39}H_{28}O_{16}N_5SCl$: C, 52.23; H, 3.04; N, 7.62. Found : C, 52.62; H, 3.17; N, 7.86 %. Third elution with methylene chloride-acetone (96 : 4 v/v) gave the starting material (11) (300 mg).

p-Nitrobenzyl (5R,6R)-3-Acetyl-2-bis(p-nitrobenzyloxycarbonyl)-6-phthalimidylpenam-3-carboxylate (14) —— To a stirred solution of the above monochloro compound (12) (300 mg) in dry tetrahydrofuran (20 ml) was added dropwise a solution of potassium tert-butoxide (39 mg) in dry bert-butanol (10 ml) at -15°C under nitrogen. After stirring for 2 h at -10 ∿ -15°C, methylene chloride and brine were added and the mixture was allowed to stand at room temperature. The methylene chloride layer was separated and dried (Na_2SO_4). Evaporation of the solvent gave an oily residue which was purified by column chromatography using methylene chloride-acetone (98 : 2 v/v) as eluant to give the penam compound (14) (190 mg, 66 %) as a colorless plates, m.p. 249 ∿ 251°C (from methylene chloride-n-hexane); $[\alpha]_D$ +108.54° ($CHCl_3$, c = 0.019); IR $\nu_{max.}^{CHCl_3}$ cm^{-1} : 1805, 1760, 1735 (C=O), and 1350 (NO_2); NMR ($CDCl_3$) δ : 2.51 (3H, s, CH_3), 5.63 (1H, d, J = 4.3 Hz, C_5-H), 5.75 (1H, d, J = 4.3 Hz, C_6-H); Anal. calcd for $C_{39}H_{28}O_{15}N_5S\cdot CH_2Cl_2$: C, 51.17; H, 2.85; N, 7.33. Found : C, 51.18; H, 3.14; N, 7.46 %.

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