From Penicillin to Penem and Carbapenem. 1. 

Racemization of 6,6-Dibromo Secopenicillin, and Synthesis of 2-Oxo Penam Derivative

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Abstract -- From 6-APA the azetidinone derivative (2) which has (R)-hydroxyethyl substituent at C-6 was prepared effectively. From dibromoseco derivative (10) the same type of compounds, 17 and 18 which has (S) type substituent were prepared, however these were proved to be optically inactive dl-form. Racemization occurred during the process of the formation of the secopenicillin (10) with excess CH3I and 2.5 eq. of NaH or KO2Bu in THF via the acyliminium intermediate (22). The 2-oxo penam derivative (27) was prepared from 17 as shown in Fig. 4.

After the discovery of thienamycin [1], and the pioneering work of the syntheses of penem derivatives by Woodward and co-workers [2], many efforts have been focused on the synthesis and the structure-activity relationship of the above antibiotics. Our current interest in these antibiotics prompted us to describe here some of our preliminary results of the degradation work of penicillin and the synthesis of 2-oxo penam derivative [3].

In 1976 Merck chemists reported the introduction of the (R)-hydroxyethyl substituent at the C-6 position of benzyl 6,6-dibromopenicillanate [4]. At the beginning of the work we followed the same reaction using methyl 6,6-dibromopenicillanate (2), and found that the desired product 3, which had hydroxyethyl group of (R)-configuration at the C-6 position of the penicillin nucleus, was very easily obtained as crystal, mp 102°C. After protection of the hydroxy group by tert-butyldimethylsilyl chloride and imidazole the brom atom of the product (4), mp 54°C, was removed reductively using Zn powder in methanol in
the presence of 2 eq. of acetic acid to give methyl 6α-((R)-1'-tert-butyldimethylsilyloxyethyl)-penicillanate (5), NMR (60 MHz) (CDCl₃) 6: 3.80 (1H, dd, $J=5$ and 1.5 Hz, C₆-H), 5.16 (1H, d, $J=1.5$ Hz, C₅-H).

![Chemical Structures]

**Fig. 1**

The conversion of 5 to the monocyclic β-lactam (6) which has an acetoxy group at the C-4 position of azetidinone ring was effectively achieved by heating 5 with 2 eq. of Hg(OAc)₂ in acetic acid (90°C) for 2 hr to give exclusively 3,4-trans-azetidinone (6), whose side chain at N-1 position was oxidatively removed (1.5 eq. KMnO₄ in aqueous acetone for 24 hr at 25°C) to afford the desired monocyclic β-lactam (7), mp 104°C, $[\alpha]_{D}^{20} +48^\circ$, identical with the standard sample previously prepared by Oida (6). Monocyclic β-lactam (7): NMR (CDCl₃) 6: 0.08 (CH₂ x 2), 0.84 (₂Bu), 1.19 (CH₃, d, $J=6$ Hz), 2.01 (OAc), 3.04 (1H, dd, $J=4$ and 1.5 Hz), 4.12 (1H, m), 5.75 (1H, d, $J=1.5$ Hz), 6.73 (NH).
During the study of the reactivity of the compound 5 an interesting reactivity difference between 4 and 5 was found. Namely the thiazolidine ring in 5 was cleaved within 5 min by treating with CH₂I / NaH or KO⁻Bu at room temperature to the seco derivative (9) cleanly, but the compound 4 which has Br atom instead of H in 5 was stable enough not to give seco derivative (9) even in prolonged reaction time. Presumably the steric effect by the substituents at C-6 prevented the attack of CH₂I to the S atom in 4 to give the seco derivative (9).

From the aspect of the stereochemistry it is interesting to know the difference of the reactivity between the dibromopenicillanate (2) and the secoone (10) towards Grignard reagent (Me₂MgBr) to generate the hydroxyethyl moiety. At first dibromo seco derivative (10) was prepared from 2 by adding NaH (2.5 eq.) or KO⁻Bu (2.5 eq.) to a solution of 2 with 7.5 eq. of CH₂I in THF at room temperature. The progress of the reaction was monitored by silica-gel TLC (seco derivative (10): Rf = 0.3, benzene ). After the reaction completed (h, 7.5 eq. CH₂I, 2.5 eq. NaH (or KO⁻Bu) ; i, nBu₃SnH, cat. cat. AIBN / C₆H₆, 65°C  

Fig. 2

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usually 4-20 hr) the product 10 was purified by chromatography. The introduct
of the hydroxyethyl group to the 3-position of the azetidinone molecule
was performed analogously by the procedure for the preparation of 2 from 1.
The hydroxyethyl group was introduced in 10 in 76% isolated yield after
chromatography. The brom atom of the silylated product (12), mp 68-69°C, was
smoothly removed (Zn in MeOH in the presence of 2 eq. of acetic acid) to give a
mixture of 3,4-trans and cis azetidinone derivative, 12 and 14 in a ratio of
62 : 38 in 50% isolated yield. The assignment of the trans and cis configura-
tion was deduced from the coupling constants between C\_2-H and C\_4-H, J=3 Hz in
13 and J=5.5 Hz in 14 respectively. These two compounds were easily separated
on preparative TLC\(^3\)), 12 : Rf = 0.48, and 14 : Rf = 0.32 (benzene : ethyl
acetate = 10 : 1). On the other hand debromination using 2 eq. of \(\text{Bu}_2\text{SnH}
and catalytic amount of AIBN at 65°C in benzene gave the same products 12 and
14 in a ratio of 70 : 30 in 80% isolated yield. Each separated products 12
and 14 gave 3,4-trans compounds 15 and 16 by treating with Hg(OAc)_2 in acetic
acid. These results mean that the acyliminium intermediate (19) was attacked
by the acetoxy anion to generate the sterically less-hindered 3,4-trans prod-
uct 15 and 16 respectively. The substituent at N-1 of 15 was oxidatively re-
moved by KMnO\(_4\) to give the azetidinone derivative 17, mp 78°C. The comparison
of the NMR of the standard 2 and 17 revealed that 17 had the (8)-configured
hydroxyethyl substituent at C-3 position as depicted in 17. 17 : NMR (CDCl\(_3\))
6 : 0.08 (CH\(_3\)_2x2), 0.84 (\(\text{Bu}\)), 1.26 (CH\(_2\), d, J=6.5 Hz), 2.02 (OAc), 3.07 (1H,
dd, J=4 and 1.5 Hz), 4.13 (1H, m), 5.61 (1H, d, J=1.5 Hz), 6.9 (NH). By the
same reaction compound 16 gave the corresponding product 18, mp 75°C, which
showed identical NMR of compound 2. Furthermore to confirm the configura-
tion compound 12 was treated with \(\text{BuLi}\) in THF at -60°C to give compound 20, whose
NMR showed CH\(_3\) doublet (J=7 Hz) at 2.0 ppm in CDCl\(_3\). The foregoing results
indicated that the dibromo secopenicillanate (10) which had no thiazolidine
ring fused to the \(\beta\)-lactam ring yielded mainly \(\alpha\)-orientated hydroxyethyl prod-
uct (as depicted in 11) with \(S\)-type configuration.

At this stage we measured the \([\alpha]_D\) values of 11, 12, and 17 in CHCl\(_3\). To
our surprise they did not show any of the value! We checked the blank test
with the dibromo compound (2), \([\alpha]_D^{20\circ} +190^\circ\) (c 1.27, CHCl\(_3\)) by treating with
KO\(_2\)Bu (2.5 eq.) in THF, and got a 1:1 mixture of 2 and monobromo compound 21,
(α)_D^{20} +157° (c 1.23, CHCl_3). By the same reaction in the presence of 7.5 eq. of CH_3I the seco derivative (10), which showed (α)_D^{20} +18.3°, was obtained after TLC separation. In case of using NaH the sample of seco derivative (10) which had (α)_D^{20} +7.5° was obtained and this value was reduced to +4.6° after one more

\[
\text{Br} \quad \text{SCH}_3 \quad \text{Br} \quad \text{SCH}_3 \quad \text{Br} \quad \text{SCH}_3 \quad \text{Br} \quad \text{SCH}_3
\]

12 (dl) 20 2 21

j, tBuLi, -60°C / THF ; k, 2.5 eq. KOtBu / THF

\[
\begin{align*}
\text{Br} & \quad \text{S} & \quad \text{N} & \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \text{S} & \quad \text{N} & \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \text{S} & \quad \text{N} & \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \text{S} & \quad \text{N} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

2-sulfonium 2'-sulfonium

\[
\text{Br} \quad \text{SCH}_3 \quad \text{Br} \quad \text{SCH}_3
\]

10 (dl)

TLC purification. On silica-gel TLC the seco derivative (10) and the monobromopenicillanate (21) showed almost the same Rf value (0.3, benzene), but the NMR of the isolated seco derivative, (α)_D +18.3°, clearly showed that this sample was contaminated with about 11 % of monobromopenicillanate (21) which corresponded to the above value of +18.3°. The situation was the same for the sample of seco derivative of (α)_D +7.5° (about 4 % contaminated with 21). By the above results it is reasonably concluded that the racemization occurred during the process of the formation of the seco product 10, and the process was interpreted by the analogous mechanism which included the acyliminium intermediate (22) proposed by Denerley and Thomas. Because of the almost same possibility to attack the acyliminium intermediate (22) by intramolecular sulfide a 1:1 mixture of 2- and 2'-sulfonium should be formed, and by the result of which dibromo seco compound (10) was formed as a dl form (Fig. 3).
With the important material (17) in hand we tried to get the 2-oxo penam derivative (27). Displacement of the acetoxyl group in 17 was effected by reaction with 1.1 eq. of sodium $\sim$-butylthio-thioacetate to afford 23. The azetidinone derivative (23) was then coupled with $p$-nitrobenzylglyoxylate in refluxing benzene to give the aminal (24), which was chlorinated with thionyl chloride and 2,6-lutidine, and then the ylide was formed successfully with triphenyl phosphine and pyridine. The intramolecular Wittig reaction in toluene at 90°C in the presence of catalytic amount of hydroquinone for 5 hr gave the expected penem derivative (25), mp 107°C, NMR (CDCl$_3$) δ : 4.12 and 3.84 (2H, AB quartet, J=15.5 Hz, -CH$_2$S$\sim$-). The crucial step for the isomerization of the double bond to the exo-one was performed satisfactorily with one equivalent of triethylamine in CH$_2$Cl$_2$ at room temperature for 1 hr to afford the penem derivative (26), mp 117°C, NMR (CDCl$_3$) δ : 5.18 (1H, C$_2$-H) and 6.22 (1H, -CH$_2$S$\sim$-), and then by ozonolysis in CH$_2$Cl$_2$ at -40°C the desired $p$-nitrobenzyl-(6, 1')-erythro-5,6-trans-6-(1'-t-butyldimethylsilyloxyethyl)-2-oxo-penam-3-carboxylate (27) was obtained smoothly. Rf = 0.55 (benzene : ethyl acetate = 5 : 1). NMR (CDCl$_3$) δ : 0.09 (CH$_3$ x 2), 0.85 ($^t$-Bu), 1.36 (CH$_2$, d, J=6 Hz), 3.56 (1H, dd, J=4 and 2 Hz ), 5.06 (1H, s ), 5.26 (2H, s ), 5.40 (1H, d , J=2 Hz), 7.4-8.4 (4H ). IR ν (liq.) cm$^{-1}$: 1798, 1763, 1730, 1610, 1522.

1, NaSCOCH$_2$S$^t$Bu/ dioxane:H$_2$O; m, CHCO$_2$PBN / C$_6$H$_6$ ; n, SOCl$_2$/THF:dioxane, -10°C ; o, P(C$_6$H$_5$)$_3$/py./ dioxane:DMF (4:1), 70-80°C, 3hr ; p, toluene, 90°C, 5 hr ; q, NET$_3$/ CH$_2$Cl$_2$ ; r, O$_3$, MeSMe

Fig. 4

PNB : $p$-nitrobenzyl
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REFERENCES


8) (Preparative) thin layer chromatography (TLC) was carried out on Merck TLC plate, silica-gel, F₂₅₄ pre-coated, layer thickness : (2 mm) 0.25 mm .

They described this type of intermediate [22] as azetidinyl cation.

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