Stereospecific C_6-Hydroxyethylation of the Penicillin Nucleus

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6, 6-Diiodopenicillanic acid was prepared from 6-aminopenicillanic acid using iodine-sodium iodide systems in good yield (60%). Enolates derived from 6-chloro-6-iodo-, 6,6-diiodo-penicillanate have been generated in situ by a metal-halogen exchange process at −78°C using methylmangnesium iodide and reacted with acetaldehyde to yield aldols. As the size of remaining halogen atom increases, the proportion of β-face attack was increased. In the case of 6,6-diiodopenicillanate, only β-face attack was observed yielding a single isomer (6S, 8R).

Introduction

Recent discoveries of portent β-lactam antibiotics lacking the usual amido side chain at C_6 and possessing a hydroxyethyl moiety[1] have stimulated the development of methods for obtaining the corresponding hydroxyethyl penicillanates. Successful method for preparation of 6,6-dibromo-, 6-chloro-6-iodo-, 6-bromo-6-iodo-penicillanic acid was reported recently[2] and 6, 6-diiodopenicillanic acid was prepared in good yield (60%) in our laboratory by modifying the reported methods.[2,4] Chemists at Merck attempted the hydroxyethylation at C_6 of the penicillin nucleus starting from benzyl 6,6-dibromopenicillanate by using a metal-halogen exchange reaction.[3] With above method, the C-C bond formation at C_6 of the highly strained penicillin nucleus was somewhat efficient but the stereochemistry at C_6 was not controlled successfully. In our research the behavior of anions generated at C_6 was examined with varying the halogen atoms at C_6 position.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were recored on a Perkin-Elmer 283B Spectrophotometer using potassium bromide pellets or sodium chloride cells. Only selected adsorptions are reported. Nuclear magntic resonance spectra were recorded on a Varian FT-80A Spectrometer using tetramethysilane as internal standard. Chemical shift values are reported in parts per million (δ) relative to tetramethylsilane. Column chromatgraphy was conducted with Kieselgel 60 (70-230 mesh).

Tetrahydrofuran was refluxed over sodium metal and distilled prior to use. Methylmagnesium iodide was prepared from the reaction of magnesium metal and methyl iodide in ether soltion. Small amount of iodine was used as an initiator. Methyl 6,6-dibromopenicillanate and methyl 6-chloro-6-iodopenicillanate were prepared according to the known procedure.[2]

Preparation of Methyl 6, 6-Diiodopenicillanate. A 1-L three necked round bottomed flask was equipped with a magnetic stirrer and thermometer. Dichlormethane (250m*l*) was added and cooled to about 5°C and iodine (64g, 0.25 mole), sodium iodide (37.5g, 0. 5 mole), 2.5*N* sulfuric acid .100 ml), and sodium nitrite (17.3g, 0.5 mole) were added, 6-Aminopenicillanic acid (27.0g, 0.12 mole) was added portionwise over a period of 30 min. The pot temperature was maintained at 5-10°C. The resultant dark red solution was stirred keeping the same temperature for 1 hr. A solution of 1*M* sodium bisulfite (250 m*l*) was added dropwise over the period of 20 min until the iodine color was discharged, forming a light yellow solution. The organic layer was separated and the aqueous layer was extrated with dichloromethane (2×60 m*l*). The combined organic extract was washed with brine (2×100 m*l*), dred over magnessium sulfate, and concentrated in vacuo to get dark yellow crystal, The dark yellow crystal obtained above was dissolved in dimethylformamide (70 m*l*) and to this solution were added sodium carbonate (14g, 0.1 5*M*) and methyl iodide (7.6 ml, 0.125M). The reaction mixture was stirred for 3 hr at room temperature. Then the mixture was poured into ice-cold water (500 ml) and extacted with dichloromethane (4×70 m*l*). The organic extract was washed with brine (2×50 m*l*), dried over magnesium sulfate, and evaporated to dryness yielded 33.3g (60%) of light yellow crystal.

mp; 132-134°C

IR (KBr); ν_{max} (cm^{-1}) 1775 (vs), 1760 (vs), 1300 (*vs*), 1223 (vs) ^1H NMR ($CDCl_3$/TMS); δ(ppm) 1.45 (3H, *s*, 2-CH_3), 1.70 (3H, *s*, 2-CH_3), 3.80 (3H, *s*,-$COOCH_3$), 4.55 (1H, *s*, 3-H), 6.25 (1H, *s*, 5-H)

Preparation of Methyl 6-(1-Hydroxyethyl)-6-iodopenicillanate. A 2.2 m*M* ethereal solution of methylmagnsium iodide (2.2 m*l*, 1m*M*/m*l*) was added dropwise to a solution of methyl 6, 6-diiodopenicillanate (0.965g, 2m*M*) in THF (10 m*l*) at −78°C with stirring. The mixture was stirred for 20 min at the same temperature and acetaldehyde (0.6 ml, 10 m*M*) was added. The stirring was continued for 20 min with cooling. After addition of saturated ammonium chloride solution (6 m*l*), the mixture concentrared in vacuo to its half volume and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was exracted with ethyl acetate (3×10 m*l*). The combined organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness in vacuo. Separation by chromatography (C_6H_6: EtOAc=5; 1) gave 0.655g (82 %) of methyl

6-(1-hydroxyethyl)-6-iodopenicillanate as an oil.

IR (NaCl); ν_{max} (cm^{-1}) 3600-3200 (m), 1780 (*vs*) 1750(*vs*) ^1H NMR($CDCl_3$/TMS); δ(ppm) 1.25 (3H, *d*, *J*=6Hz, 8-CH_3), 1.53(3H, *s*, 2-CH_3), 1.73 (3H, *s*, 2-CH_3), 2.55 (1H, *d*, *J*=4Hz,-OH), 3.30 (1H, *dd*, J_1=6Hz, J_2=4Hz, 8-H), 3.85 (3H, *s*,-$COOCH_3$), 4,55 (1H, *s*, 3-H), 5.77 (1H, *s*, 5-H)

Anal. Calcd for $C_{11}H_{16}NO_4SI$: C, 34.30; H, 4.19; N, 3.64 Found: C, 34.68; H, 4.32; N, 3,88

The following compounds were prepared by the same method as adove.

Methyl 6-Chloro-6-(1-hydroxyethyl)penicillanate from methyl 6-chloro-6-iodopenicillanate

IR (NaCl); ν_{max}(cm^{-1}) 3700-3100(m), 1785 (vs), 1755 (vs) ^1H NMR ($CDCl_3$/TMS); δ(ppm) 1.38 (6/3H, *d*, J=6Hz, 8-CH_3), 1.45 (3/3H, *d*, J=6Hz, 8-CH_3), 1.58 (3H, *s*, 2-CH_3), 1.76 (3H, *s*, 2-CH_3), 2.90 (1H, *m*,-OH), 3.90 (3H, *s*,-$COOCH_3$), 4.55 (1H, *m*, 8-H), 4.60 (1/3H, *s*, 3-H), 4.62(2/3H, *s*, 3-H), 5.52(2/3H, *s*, 5-H), 5.78 (1/3H, *s*, 5-H)

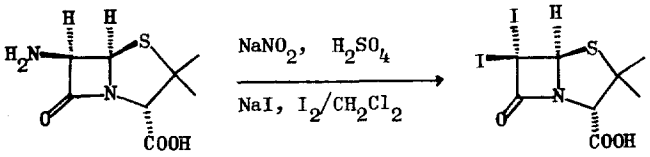
Anal. Calcd for $C_{11}H_{16}NO_4SCI$: C, 44.98; H, 5,49; N, 4.77 Found: C, 44.98: H, 5.72; N, 5.05

Methyl 6-bromo-6-hydroxyethyl penicillanate from methyl 6, 6-Bibromopenicillanate

IR (NaCl); ν_{max}(cm^{-1}) 3700-3200 (*m*), 1780 (*vs*), 1755 (*vs*) ^1H NMR ($CDCl_3$/TMS); δ(ppm) 1.26 (9/4H, *d*, *J*=6Hz, 8-CH_3), 1.45 (3/4H, *d*, *J*=6Hz, 8-CH_3), 2.60 (1H, *m*, -OH), 3.90 (3H, *s*, -$COOCH_3$), 4.25 (1H, *m*, 8-H), 4.55 (1H, *s*, 3-H), 5.25, 5.26 (1/4H, *s*, 5-H), 5,34(3/4H, *s*, 5-H) *Anal.* Calcd for $C_{11}H_{16}NO_4SBr$: C, 39.06: H, 4.77; N, 4.14 Found: C, 40.02; H, 4.87; N, 4.06

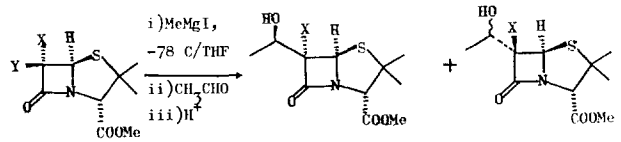
Results and Discussion

The formation of 6, 6-diiodopenicillanic acid was first reported by Clayton[4] from the reaction of 6-aminopenicillanic acid with sodium nitrite and sodium iodide. Recently, efficient synthesis of 6, 6-dihalopenicillanic acid was developed using two phase reaction sysems.[2] But 6, 6-diiodopenicillanic acid was not synthesized efficiently under the same reaction conditions. Since the iodide ion can easily be oxidized to iodine by the nitrous acid, the diazo intermediate can nat have the chance to be attacked by iodide ion. To repress the oxidation of iodide ion, we used sodium iodide and excess amount of iodine and obtaind 6, 6-diiodopenicillanic acid in moderately good yield (60%).



Methyl 6-chloro-6-iodo-, 6,6-dibromo-,6,6-diiodopenicillanate were reacted with methylmagnesium iodide and acetaldehyde and the products were analyzed with ^1H NMR spectra.

The major interest in this reaction is the stereochemistry at C_6 and C_8 of the penicillin nucleus. DiNinno and *et al.* reported the production of **5a** as a major component from



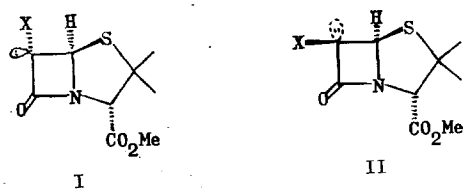
1	X=Cl, Y=I	4a	4b,c
2	X=Br, Y=Br	5a	5b,c
3	X=I, Y=I	6a	6b,c

2, but **5b**, a were existed as a diastereomeric mixture. The separation of stereoisomers in this stage is tedious and inefficient, we tried to generate a single isomer with varying the halogen atoms at C_6 position. The composition of each isomers were determined by the integration of H_5 peak in the ^1H NMR spectra. The H_5 peak of the β-hydroxthylated product is more downfield shifted than that of the α-hydryeoxyethylated product in the ^1H NMR spectrum because of the electronegative halogen atom. The compositions of each isomers were determaned ano denoted in Table 1.

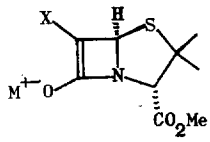
Table 1. shows some trends as the reactants change from **1** to **3.** This can explained by the specific penicillin ring structure and the size of halogen atoms. Once the anion is formed at C_6, two factors are thought to be important in determining the sterochemistry at C_6 of the penicillin nucleus. One is the tendency to attack at the less hindered α-face, the other is the preferrence of *trans* stereochemistry of the penicillin ring and the remaining halogen atom, *i.e.*, β-face attack. In Table 1, the ratio of β-face attack was increased as the size of remaining halogen atom was increased. From the above results, we can not rule out the fact that the transition state of metal-halogen exchange reaction can be the equilibrium mixture of tetrahedral carbanions[5,6] (I and II) as well as the planar enolate anion (III).

TABLE 1: Isomer Distribution in the Metal-Halogen Exchange Reaction

Reactant	Product Ratio(%)		Isolated Yield(%)
	a	*b,c*	
1	33	67	89
2	75	25	85
3	100	trace	82



I II



III

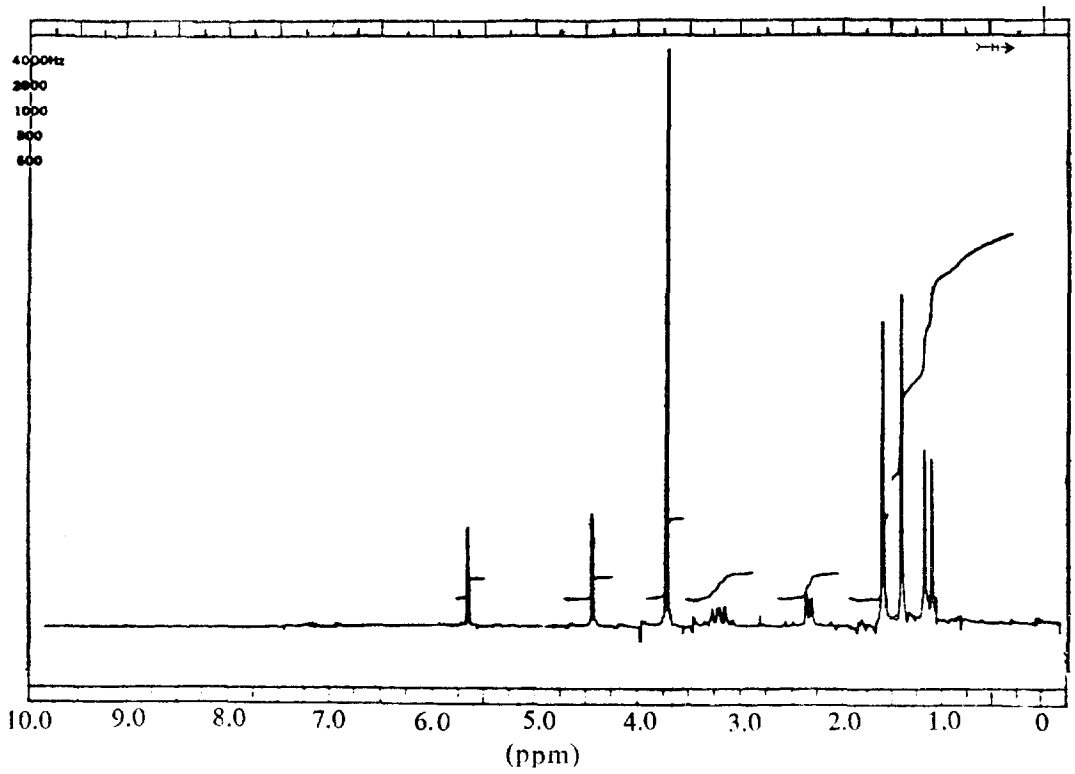
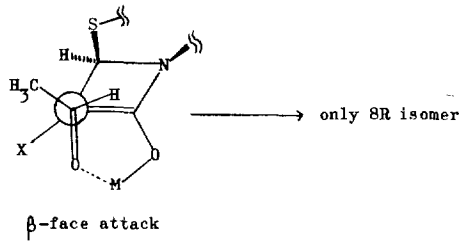


Figure 1. ^1H NMR Spectrum of methyl 6α–iodo–6β–[(R)–hydroxyethyl]penicillanate.

In the case of methyl 6,6–diiodopenicillanate (**3**), only β–face attack was observed yielding a single isomer (**6a**) with 8R stereochemistry. The 8R stereochemistry in the case of β–face attack can be explained by the following mechanism.[7,8]



The doublet of −OH proton at δ2.55(J=4Hz) and the AB quartet of the 8–H proton at δ3.30 (J_1=4Hz, J_2=6Hz) in the ^1H NMR spectrum are critical evidence of the 8R isomer (Figure 1).

From the above results, we can conclude that the size of the remaining halogen atom plays an important role in the determination of the stereochemistry at C_6 and C_8 of the penicillin nucleus. Therefore methyl 6,6–diiodopenicillanate is superior to other 6,6–dihaloderivatives in the stereorpecific hydroxyethylation at C_6 of the penicillin uneleus.

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