STEREOSPECIFIC C_6-HYDROXYETHYLATION OF THE PENICILLIN NUCLEUS

Sir:

Recent discoveries of potent β-lactam antibiotics possessing a hydroxyethyl moiety instead of the usual amido side chain at C_6 have stimulated the interest in synthetic methods for obtaining hydroxyethyl penicillanates.[1] Convenient method for the preparation of 6-hydroxyethyl penicillanate by using metal-halogen exchange reaction was reported earlier by DI-NINNO, *et al.*[2] As an extension of their work, we studied the effect of halogen atom size on the stereochemistry of the incoming hydroxyethyl moiety.

Methyl 6-chloro-6-iodo- (**1**), 6,6-dibromo- (**2**) and 6,6-diiodo- (**3**) penicillanate were reacted with methylmagnesium iodide and acetaldehyde followed by protic quenching. (Fig. 1) The products were isolated by column chromatography (benzene - ethyl acetate, 5: 1, Rf 0.5~0.55) and their physico-chemical and spectral properties were determined.

4a, **4b**,**c**: IR (NaCl) ν_{max} (cm^{-1}) 3700~3100 (m), 1785 (vs), 1755 (vs); ^1H NMR (60 MHz, $CDCl_3$) δ 1.38 (6/3H, d, J=6 Hz, 8-CH_3), 1.45 (3/3H, d, J=6 Hz, 8-CH_3), 2.90 (1H, m, OH), 4.55 (1H, m, 8-H), 5.52 (1/3H, s, 5-H), 5.78 (2/3H, s, 5-H); *Anal* Calcd for $C_{11}H_{16}NO_4SCl$: C 44.98, H 5.49, N 4.77; Found: C 44.98, H 5.72, N 5.05.

5a, **5b**,**c**: IR (NaCl) ν_{max} (cm^{-1}) 3700~3200 (m), 1780 (vs), 1755 (vs); ^1H NMR (60 MHz, $CDCl_3$) δ 1.26 (9/4H, d, J=6 Hz, 8-CH_3), 1.45 (3/4H, d, J=6 Hz, 8-CH_3), 2.60 (1H, m, OH), 4.25 (1H, m, 8-H), 5.25 (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.

6a: IR (NaCl) ν_{max} (cm^{-1}) 3600~3200 (m), 1780 (vs), 1750 (vs); ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (3H, d, J=6 Hz, 8-CH_3), 2.55 (1H, d, J=4 Hz, OH), 3.30 (1H, dd, J_1=6 Hz, J_2=4 Hz, 8-H), 5.77 (1H, s, 5-H); *Anal* Calcd for $C_{11}H_{16}NO_6SI$: C 34.30, H 4.19, N 3.64; Found: C 34.68, H 4.32, N 3.88.

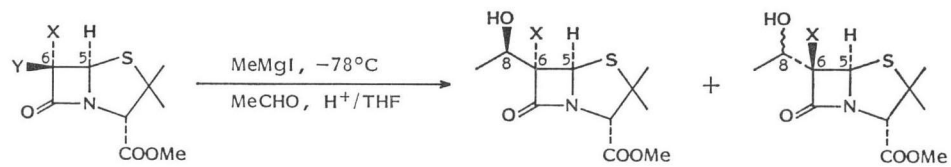
In the metal-halogen exchange reaction, the yield of each isomer was determined by the integration of the H_5 peak in the ^1H NMR spectra. The H_5 peak of the 6β-hydroxyethylated product is further down-field than that of the 6α-hydroxyethylated product because the halogen atom and H_5 are in *cis* stereochemistry.[3] Table 1 shows a consistent trend in composition as the reactants vary from **1** to **3**, which appears product related to the size of the halogen atoms. Once the anion is formed at C_6, two factors should be important in determining the stereochemistry at C_6 of the penicillin nucleus. One is the tendency to attack the less hindered α-face, and the other is the preference for *trans* stereochemistry between the penicillin ring and the remaining halogen atom, *i.e.*, β-face attack. The β-face attack always yields a single 8*R* isomer under the above reaction conditions.[2] As shown in Table 1, the β-face attack was increased as the size of remaining halogen atom was increased.

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	—	82

* The reactants and products are those shown in Fig. 1.

Fig. 1. Hydroxyethylation at C_6 of the methyl 6,6-dihalopenicillanates.



1 X = Cl, Y = I — **4a** — **4b, c**

2 X = Br, Y = Br — **5a** — **5b, c**

3 X = I, Y = I — **6a** — **6b, c**

In the case of methyl 6,6-diiodopenicillanate (**3**), only β-face attack was observed yielding a single isomer (**6a**).

From the 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 of the penicillin nucleus. Therefore, methyl 6,6-diiodopenicillanate[4] is superior to other 6,6-dihalo derivatives[5] in the stereospecific hydroxyethylation at C_6 of the penicillin nucleus.

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