NOTE

PREPARATION OF 7-EPI-CEPHALOSPORIN DERIVATIVES

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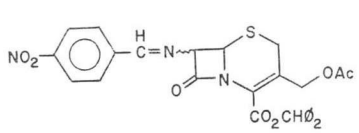
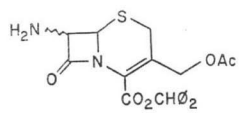
Although there has been considerable interest in the epimerization of penicillins at position 6,[1~4] the preparation of 7-epi-aminocephalosporanic acid (7α-ACA) has thus far not been reported. Some 7-epi-cephalosporins have been prepared by base-catalyzed epimerization of cephalosporin sulfoxides[5] or acid-catalyzed ring expansion of 6-epi-penicillins.[6] Both procedures, however, are not convenient for the preparation of 7-epi-cephalosporin derivatives. We wish to report the direct preparation of benzhydryl 7α-aminocephalosporanate which should be useful for the synthesis of a wide variety of 7-epi-cephalosporin derivatives.

In the penicillin series, treatment of the *p*-nitrobenzaldehyde SCHIFF base **7** with diisopropylethylamine in DMF afforded a 1:3 mixture of **7** and **8**, from which the pure 6α-aminopenicillanic acid ester **9** was obtained.[2] In the cephalosporin series, however, the treatment of the SCHIFF base **1**[7] under these conditions produced substantial amounts (up to 30 %) of Δ^2-isomers in addition to a mixture of **1** and **2** in approximately equal amounts. We found that when tetrahydrofuran or diethyl ether was used as a solvent, almost no trace of the Δ^2-isomers could be detected (by 100 MHz nmr) in the reaction mixture. Pure benzhydryl 7α-aminocephalosporanate (**4**) was obtained after hydrolysis of the mixture of **1** and **2** followed by silica gel chromatography. Although epimerization of the SCHIFF base **7** gave predominantly **8**[2] which is thermodynamically more stable, the SCHIFF base **1** produced almost equal amounts of epimers **2** and **1**, regardless of reaction temperature, reaction time, or reaction solvent, indicating approximately equal thermodynamic stability for **1** and **2**. The 7α-isomer **4** was converted to sodium 7α-[α-(4-pyridylthio)acetamido] cephalosporanate (**6**),[3] *via* **5** by standard procedures.

Experimental

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The nmr spectra were run on a Varian HA 100 MHz spectrometer with tetramethylsilane as



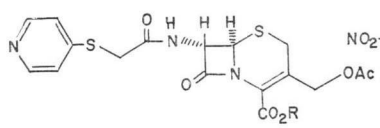


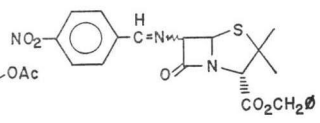
1 7β-N=C-NO_2

2 7α-N=C-NO_2

3 7β-NH_2

4 7α-NH_2



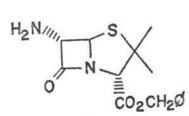


5 R = $CH\phi_2$

6 R = Na

7 6β-N=C-NO_2

8 6α-N=C-NO_2



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the internal standard.

Epimerization of Benzhydryl 7β-(*p*-Nitrobenzylidenimino) cephalosporanate (**1**)

To a solution of 589 mg (1.00 mmol) of SCHIFF base **1**[7] in 10 ml of THF (distilled from sodium) was added at 0°C, 0.16 ml (0.90 mmol) of diisopropylethylamine under a nitrogen atmosphere. After 30-minute stirring the solution was poured into 20 ml of ice-cold 5% aqueous phosphoric acid and extracted with two 30-ml portions of methylene chloride. The combined organic layers were dried ($MgSO_4$), filtered and evaporated, leaving 580 mg (98%) of a 1:1 (by nmr) mixture of **2** and **1**.

Benzhydryl 7α-Aminocephalosporanate (**4**)

The procedure of FIRESTONE[2] was followed. To a mixture of 198 mg (1.00 mmol) of 2, 4-dinitrophenylhydrazine and 190 mg (1.00 mmol) of *p*-toluenesulfonic acid monohydrate in 30 ml of ethanol was added a solution of 589 mg (1.00 mmol) of a 1:1 mixture of **1** and **2** in 3 ml of chloroform. After 45-minute stirring the mixture was filtered and the precipitate was washed with ethanol. The combined filtrate and washing was concentrated to a yellow oil which was taken into 50 ml of ethyl acetate and washed with 50 ml of phosphate buffer (pH 9). The solution was dried over $MgSO_4$, then concentrated to give a yellow oil which was chromatographed over 50 g of silica gel. Elution with methylene chloride-ethyl acetate (4:1) produced 180 mg (21%) of pure 7α-isomer **4** as white amorphous powder: Nmr ($CDCl_3$) δ 1.98 (s, 3H) 3.30 (d, J=9.0 Hz, 1H), 3.58 (d, J=9.0 Hz, 1H), 4.72 (d, J=7.5 Hz, 1H), 4.80 (d, J=1.8 Hz, 1H), 4.92 (d, J=1.8 Hz, 1H), 5.01 (d, J=7.5 Hz, 1H) 6.95 (s, 1H), 7.2~7.6 (m, 10H).

Anal. Calcd. for $C_{23}H_{22}N_2O_5S$:
C, 62.80; H, 5.02; N, 6.38.
Found: C, 62.96; H, 5.05; N, 6.24.

Benzhydryl 7α-[α-(4-Pyridylthio)acetamido] cephalosporanate (**5**).

To a solution of 200 mg (0.46 mmol) of **4** and 101 mg (1.00 mmol) of N-methylmorpholine in 10 ml of methylene chloride was added at 0°C 104 mg (0.46 mmol) of 4-pyridylthioacetyl chloride hydrochloride under a nitrogen atmosphere. After 2-hour stirring the reaction was poured into 20 ml of ethyl acetate and 20 ml of phosphate buffer (pH 4). The organic layer was separated, washed with 5% sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated, leaving 240 mg (90%) of **5** as white amorphous powder.

Anal. Calcd. for $C_{30}H_{27}N_3O_6S_2$:
C, 61.25; H, 4.58; N, 7.13.
Found: C, 60.99; H, 4.68; N, 7.42.

Sodium 7α-[α-(4-Pyridylthio)acetamido] cephalosporanate (**6**)

To a solution of 3 ml of trifluoroacetic acid and 0.1 ml of anisole was added at 0°C 330 mg (0.55 mmol) of **5**. After 10 minutes the solution was poured into 100 ml of ether to obtain a white precipitate. This was dissolved in a solution of 3 ml of methylene chloride and 0.15 ml of triethylamine and treated with 0.55 mmol of sodium 2-ethylhexanoate in 0.2 ml of *t*-butanol. After 15 minutes, 30 ml of acetone-ether (1:1) was added. The white precipitate was collected, washed with acetone and air-dried to give 114 mg (47%) of pure **6**. Nmr (DMSO-d_6-D_2O) δ 1.95 (s, 3H), 3.24 (d, J=11.0 Hz, 1H), 3.58 (d, J=11.0 Hz, 1H), 3.90 (s, 2H), 4.68 (d, J=2.0 Hz, 1H), 4.70 (d, J=7.0 Hz, 1H), 4.75 (d, J=2.0 Hz, 1H), 4.82 (d, J=7.0 Hz, 1H), 7.3(m, 2H), 8.4(m, 2H).

Anal. Calcd. for $C_{17}H_{16}N_3O_6S_2Na \cdot 1\frac{1}{2} H_2O$
C, 43.35; H, 4.02; N, 8.91.
Found: C, 43.31; H, 3.64; N, 9.02.

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Anal. Calcd. for $C_{30}H_{25}N_3O_7S$:
C, 63.25; H, 4.38; N, 7.36.
Found: C, 63.45; H, 4.60; N, 7.37.

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