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 sulfoxides5) 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 17) under these conditions produced substantial amounts (up to 30 %) of 6α-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 6α-isomers could be detected (by 100 MHz nmr) in the reaction mixture. Pure benzhydryl 7α-aminoccephalosporanate (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 82) 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-[a-(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
the internal standard.

Epimerization of Benzhydryl 7α-(p-Nitrobenzylideniminio) cephalosporanate (1)

To a solution of 589 mg (1.00 mmol) of SCHIFF base 17) 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 (MgSO₄), 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 FIRESTONE2) 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 MgSO₄, 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 (CDCl₃) 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), 4.92 (d, J=1.8 Hz, 1H), 5.01 (d, J=7.5 Hz, 1H) 6.95 (s, 1H), 7.2-7.6 (m, 10H).


Found: C, 62.96; H, 5.05; N, 6.24.

Sodium 7α-[a-(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 (MgSO₄), filtered and evaporated, leaving 240 mg (90%) of 5 as white amorphous powder.


Found: C, 60.99; H, 4.68; N, 7.42.

References


4) CARROLL, R. D.; E. S. HAMANAKA, D. K. PIRIE & W. M. WELCH: Penicillin imino chlorides, I. Facile epimerization and keteni-


Anal. Calcd. for C_{30}H_{25}N_{3}O_{7}S:
C, 63.25; H, 4.38; N, 7.36.
Found: C, 63.45; H, 4.60; N, 7.37.