# A 7-[2-(2-AMINOIMIDAZOL-4-YL)-ACETAMIDO]CEPHALOSPORANIC ACID

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(Received for publication July 29, 1982)

Variations in the substituents in the cephalosporin series of antibiotics, either at the C-3 of the dihydrothiazine ring or the C-7 of the azetidinone ring, have been found to have major effects upon their antibacterial activity.[1] The spectrum of this activity has been much improved recently by the introduction of the 7-[2-(2-aminothiazol-4-yl)acetamido]cephems (**5**).[2,3]

We sought to prepare a 7-[2-(2-aminoimidazol-4-yl)acetamido]cephalosporin (**4**) in order to compare its activity with the related 2-aminothiazole compounds. 2-Aminoimidazoles are readily prepared by the reaction of $\alpha$-aminoketones with cyanamide.[4] The required $\alpha$-aminoketones may be prepared by a variety of hydrolytic or chemical reductive methods.[5] However, most of these methods seemed inappropriate as our target aminoketone (**3**) contains several other chemically sensitive groups. We therefore adopted the approach of preparing an $\alpha$-azidoketone, then reducing the azide catalytically to an amine. This synthetic strategy has been rarely used to our knowledge,[5,6] and offers a simple method for the preparation of $\alpha$-aminoketones in the presence of other sensitive functional groups.

Table 1. Antibacterial activity of 7-[2-(heterocyclyl)-acetamido]cephems (MIC: $\mu$g/ml).

| | **5** | **4** | **6** |
|---|---|---|---|
| *S. aureus* 663 | 0.2 | 1 | 2.5 |
| *E. coli* 1850E | 0.5 | 4 | 62 |
| *S. typhimurium* 804 | 0.5 | 1 | 31 |
| *P. aeruginosa* 850 | >250 | >250 | >250 |
| *P. mirabilis* 431E | 0.2 | 4 | 31 |

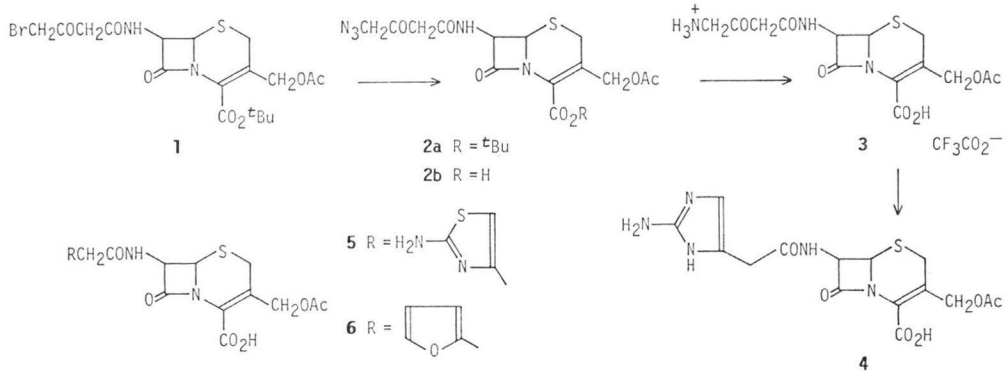
Treatment of the bromoester (**1**) with sodium azide in aqueous tetrahydrofuran gave the azido ester (**2a**). The ester (**2a**) was deprotected with trifluoroacetic acid (TFA) and the azido group of the resulting acid (**2b**) was reduced by hydrogenolysis over palladium on carbon, in the presence of one equivalent of TFA to prevent dihydropyrazine formation. The resulting amino ketone (**3**) was reacted with aqueous cyanamide at pH 4.5 to give, after purification on XAD-2 resin, the required aminoimidazole (**4**).

The antibacterial activity of the aminoimidazole (**4**) is poorer than that of the corresponding aminothiazole (**5**) (Table 1), but was notably better than that of other typical 7-[2-(heterocyclyl)acetamido]cephems (*e.g.* **6**).

## Experimental

*tert*-Butyl (6*R*,7*R*)-3-Acetoxymethyl-7-(4-bromo-3-oxobutanamido)ceph-3-em-4-carboxylate (**1**)

A solution of bromine (1.02 ml, 20 mmole) in dry dichloromethane (10 ml) was added dropwise to a cooled, stirred solution of redistilled diketene (1.68 g, 20 mmole) in dichloromethane (10 ml) at −40°C. After addition was complete, the mixture was added dropwise to a stirred, ice-



cooled solution of *tert*-butyl 7-aminocephalosporanate (6.56 g, 20 mmole) and triethylamine (2.8 ml) in dichloromethane (100 ml). The mixture was stirred for 10 minutes, then allowed to warm to room temperature over a further 15 minutes. The reaction mixture was washed with water (3×100 ml), then dried ($Na_2SO_4$) and concentrated. The residue was chromatographed on silica gel (Merck kieselgel 60; 100 g), using ethyl acetate - petroleum ether (bp 40~60°C) (3: 2) eluent, to give 5.7 g (58%) of the ester (**1**); IR ($CHBr_3$) 1785, 1725, 1685 and 1520 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 1.50 (s, *tert*-butyl), 2.05 (s, $-OCOCH_3$), 3.44 and 3.70 (ABq, $J$=18Hz, 2-$CH_2$-), 3.66 (s, $-COCH_2CO-$), 4.42 (s, $-CH_2Br$); resonances for H-6 ($\delta$ 5.14), H-7 ($\delta$ 5.76) and the amide proton ($\delta$ 9.15) were split due to keto-enol tautomerization of the side chain.

*Anal.* Calcd. for $C_{15}H_{23}BrN_2O_7S$:
C 44.0, H 4.7, N 5.7, S 6.5
Found: C 44.6, H 5.0, N 5.4, S 6.4.

*tert*-Butyl (6*R*,7*R*)-3-acetoxymethyl-7-(4-azido-3-oxobutanamido)ceph-3-em-4-carboxylate (**2a**)

A solution of sodium azide (66 mg, 1 mmole) in water (1 ml) was added to a solution of the bromide (**1**) (0.50 g, 1 mmole) in THF - water (3: 1, 8 ml). After stirring for 2 hours, the mixture was partitioned between ethyl acetate and water. The organic phase was dried and concentrated to yield 0.34 g (74%) of the ester (**2a**); IR (Nujol) 2100, 1786, 1728 and 1686 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.34 and 3.62 (2H, ABq, 2-$CH_2$), 4.52 (2H, s, $-CH_2N_3$), 4.93 (1H, d, $J$=5 Hz, 6-H), 5.88 (1H, d of d, $J$=5 and 8 Hz, 7-H), 7.76 (1H, d, $J$=8 Hz, –CONH).

(6*R*,7*R*)-3-Acetoxymethyl-7-(4-amino-3-oxobutanamido)ceph-3-em-4-carboxylic Acid Trifluoroacetate (**3**)

A solution of the ester (**2a**) (4.5 g, 10 mmole) in TFA-anisole (4: 1, 50 ml) was allowed to stand at room temperature for 20 minutes, then concentrated *in vacuo*. The residue was triturated with ether (50 ml) and the insoluble material filtered off, washed with ether (2×50 ml) and dried to yield 3.8 g of the azido acid (**2b**); IR (Nujol) 2100, 1784, 1753, 1713 and 1663 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 3.32 and 3.62 (2H, ABq, 2-$CH_2$), 4.63 (2H, s, $-CH_2N_3$), 5.04 (1H, d, $J$= 5Hz, 6-H), 5.62 (1H, d of d, $J$=5 and 8Hz, 7-H), 9.06 (1H, d, $J$=8Hz, –CONH–).

The acid (**2b**) (3.6 g) was dissolved in ethanol - ethyl acetate (3: 2, 50 ml) and added to a suspension of palladium on carbon (10%, 7.0 g) in ethyl acetate (30 ml). TFA (1.0 ml) was added to the mixture, which was then shaken vigorously on a hydrogenator for 25 minutes. The mixture was filtered through Kieselguhr and the filtrate concentrated *in vacuo*. The residue was triturated with ether (50 ml) and the insoluble material filtered off and dried to yield 1.6 g (33%) of the amino acid (**3**); IR (Nujol) 1770, 1740, 1678 and 1540 $cm^{-1}$; UV (pH 6 phosphate buffer) $\lambda_{max}$ 262 nm ($\varepsilon$ 8,800); NMR (DMSO-$d_6$) $\delta$ 2.04 (3H, s, $-CH_3$), 4.02 (2H, s, $-CH_2NH_3^+$), 4.69 and 5.02 (2H, ABq, $J$=15Hz, $-CH_2OCOCH_3$), 4.86 (1H, d, $J$=5Hz, 6-H) and 9.15 (1H, d, $J$=9Hz, –CONH–).

*Anal.* Calcd. for $C_{14}H_{17}N_3O_7S \cdot CF_3CO_2H$:
C 39.6, H 3.7, N 8.65, S 6.6.
Found: C 39.1, H 3.95, N 8.8, S 6.7.

(6*R*, 7*R*)-3-Acetoxymethyl-7-[2-(2-aminoimidazol-4-yl)acetamido]ceph-3-em-4-carboxylic Acid (**4**)

A solution of the amino acid (**3**) (2.1 g, 4.3 mmole), cyanamide (1.0 g, 24 mmole) and sodium bicarbonate (0.30 g) in water (25 ml) was warmed at 45°C for 2 hours. The mixture was then acidified to pH 2 with 2 N aqueous hydrochloric acid and the precipitated material filtered off. The filtrate was neutralized (pH 6) with sodium bicarbonate, then passed down a column of XAD-2 resin using water as eluent. After all cyanamide had been washed out (negative cyanamide test), the eluent was changed to water - ethanol (3: 1) and 500 ml of eluate collected. The ethanolic eluate was concentrated to *ca.* 10 ml. The deposited crystals were filtered off and dried over $P_2O_5$ to yield 0.25 g (15%) of the aminoimidazole (**4**); IR (Nujol) 3544, 3360, 1760, 1741, 1699, 1655 and 1535 $cm^{-1}$; UV (pH 6 phosphate buffer) 261 nm ($\varepsilon$ 8,700); NMR ($D_2O$/DCl) $\delta$ 3.52 and 3.76 (2H, ABq, $J$=16Hz, 2-$CH_2$), 3.77 (2H, s, $-CH_2$-CONH–), 5.18 (1H, d, $J$=5Hz, 6-H), 5.70 (1H, d, $J$=5Hz, 7-H), 6.72 (s, imidazole 5-H).

*Anal.* Calcd. for $C_{15}H_{17}N_5O_6S \cdot H_2O$:
C 43.6, H 4.6, N 16.95.
Found: C 43.8, H 4.4, N 16.9.

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