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7-[2-HYDROXYETHYL]CEPHALOSPORANIC ACID DERIVATIVES

H. E. Applegate, C. M. Cimarusti, and W. A. Slusarchyk*

The Squibb Institute for Medical Research
P. O. Box 4000, Princeton, New Jersey 08540

Summary. The preparation of cis and trans 7-[2-hydroxyethyl]cephalosporanic acid salts, as well as their corresponding O-sulfate analogs, is described. A very useful method for preparing large quantities of 7-oxocephalosporanates from 7-ACA is also described.

The family of antibiotics circumscribed by general formula 1 includes 128 potential entities with 5R stereochemistry. To date, no less than eight of these have been isolated from various Streptomyces: thienamycin,[1,2] epithienamycins A-D[3,4] and the 1-sulfooxyethyl-substituted antibiotics, MM4550[5,6] (MC 696-SY2-A),[7] MM13902,[6,8] and MM17880.[9,10] Although structure-activity relationships have not been described in detail, reported activities include potent antibacterial activity as well as potent β-lactamase inhibitory activity. Several cephalosporanic acid derivatives 2 substituted at C-7 with the 1-hydroxyethyl moiety have been reported; however, they were found to be essentially devoid of antibacterial activity.[11] We now report the synthesis of cis and trans 7-[2-hydroxyethyl]- and 7-[2-sulfooxyethyl]-cephalosporanic acid salts 3c-6c, as well as 7-formylmethylidene and 7-hydroxymethylidene salt derivatives 9c and 10c.

1-Oxo cephem 13[12] was obtained in 55% yield from 7-ACA via sequential sulfenylation of the trimethylsilyl ester of 7-ACA, hydrolysis and esterification (Ph_2CN_2) to 12,[13,14] rearrangement (Ph_3P, SilicAR CC-4) to 14,[14,15] and finally $HgCl_2$ mediated hydrolysis[16] in DME-H_2O with EtOAc workup. Treatment of 13 with formylmethylidene triphenylphosphorane[17] (1 eq., RT, benzene, 30 sec.) followed by quenching with dilute HCl afforded 9a (85%), which was reduced (Pd/C, H_2, EtOAc, 30 h) to give cis aldehyde 7a (21%) and trans aldehyde 8a (35%) after preparative tlc on silica gel using CH_2Cl_2-EtOAc (19:1).[18,19] Subsequent reduction of 7a with $NaBH_4$ (1 eq., 1-PrOH-DME, 15 min., 0°) gave cis alcohol 3a (90%), which was deprotected (CF_3COOH, CH_2Cl_2, anisole, 0°) to give acid 3b (79%) and finally salt 3c. In a similar manner, trans aldehyde 8a was converted via alcohol 4a (98%) and acid 4b [10% after preparative tlc on silica gel, acetone-AcOH (12:1)] to salt 4c.

Hydroxy acids 3b and 4b were converted to sulfoxy salts 5c (27%) and 6c (12%), respectively, by sequential treatment with pyridine·SO_3 complex (2 eq., DMF-CH_2Cl_2, 3 h, 25°),

removal of solvents, adjustment to pH 7-7.5 (aq. $NaHCO_3$), and purification on an XAD-2 column (H_2O-CH_3OH gradient).

When aldehyde 9a was reduced with $NaBH_4$ (1 eq.), cis alcohol 3a (21%) and Z-isomer alcohol 10a (10%) were obtained along with their Δ^2-isomers. Analogous treatment of crude samples of 9a gave 3a and 10a along with small amounts of E-isomer alcohol 11a. Spectral examination (pmr, ir) of isomers 10a and 11a allowed their structural assignments and confirmed the assignment of aldehyde 9a. Alcohol 10a, which was eventually obtained in 58% yield by reduction of 9a with DIBAL (DME, 0°, 30 min.), was deprotected to give acid 10b (83%) and finally salt 10c. Similarly, aldehyde ester 9a was converted to acid 9b (78%) and subsequently to salt 9c.

Compounds 3c-6c, 9c, and 10c exhibited no significant antibacterial activity and no significant activity against the β-lactamases tested (types I, III, IV, and staphylococcal penicillinase).

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Reference and Notes

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(15) Tolylthioamine 14 had: pmr ($DCCl_3$) δ 2.00 (3H, s, OAc), 2.30 (3H, s, CH_3), 3.40 (2H, broad s, C-2), 4.80 (1H, s, C-6), 4.77, 5.08 (2H, ABq, J=14 Hz, C-3').

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(17) S. Trippett and D. M. Walker, J. Chem. Soc., 1266 (1961).

(18) All new compounds gave pmr and ir spectra consistent with assigned structures; all crystalline compounds and precipitated salts gave satisfactory elemental analyses.

(19) 3a: m.p. 135-136°; δ ($DCCl_3$) 1.8-2.4 (2H, m, C-7'), 3.80 (2H, t, J=6, $HOCH_2$), 3.95 (1H, m, J=2.5, 5.5, 7, C-7), 4.84 (2H, q, J=13, C-3'), 4.91 (1H, d, J=5.5, C-6). 3b: δ($DCCl_3$-CD_3OD) 3.73 (2H, t, J=6, $HOCH_2$), 3.80 (1H, m, C-7), and 4.97 (1H, d, J=5, C-6). 3c: m.p. 125° dec. 4a: δ ($DCCl_3$) 3.30 (1H, m, C-7), 3.75 (2H, t, J=6, $HOCH_2$), 4.53 (1H, d, J=2, C-6). 4b: δ (acetone-d_6) 4.80, 5.13 (2H, q, J=13, C-3'), 4.75 (1H, d, J=2, C-6). 4c: m.p. 100° dec. 5c: hemihydrate; m.p. 134° dec.; δ (D_2O) 2.1 (3H, s, OAc), 2.16 (2H, m, C-7'), 4.15 (2H, t, J=6, O_3SOCH_2), 5.05 (1H, d, J=5, C-6); ν (KBr) 1760 (sh), 1740, and 1610 cm^{-1}. 6c: dihydrate; m.p. 92° dec.; ν (KBr) 1755 (sh), 1735 and 1605 cm^{-1}. 7a: δ ($DCCl_3$) 2.93 (2H, d, J=7, C-7'), 4.17 (1H, m, C-7), 4.92 (1H, d, J=5, C-6), and 9.83 (1H, s, CHO); ν ($CHCl_3$) 1780, 1740, and 1728 cm^{-1}. 8a: m.p. 100-102°; δ ($CDCl_3$) 2.9-3.1 (2H, m, C-7'), 3.60 (1H, m, C-7), 4.42 (1H, d, J=2, C-6), and 9.80 (1H, s, CHO); ν ($CHCl_3$) 1780 and 1735 (b) cm^{-1}. 9a: m.p. 125-126°; δ ($DCCl_3$) 5.48 (1H, d, J=1.5, C-6), 6.62 (1H, q, J=6, 1.5, C-7'), 9.82 (1H, d, J=6, CHO). 9c: hemihydrate; m.p. 125° dec.; δ (D_2O) 5.34 (1H, d, J=1.5, C-6), 6.34 (1H, q, J=1.5, 6, C-7'), 9.61 (1H, d, J=6, CHO). 10a: δ ($CDCl_3$) 4.37 (2H, d, J=4, $HOCH_2$), 5.27 (1H, d, J=1.5, C-6), 6.47 (1H, sextet, J=1.5, 4, C-7'); ν ($CHCl_3$) 1775 and 1735 (b) cm^{-1}. 10c: hemihydrate; m.p. 135° dec.; δ (D_2O) 4.36 (2H, d, J=4, $HOCH_2$), 5.38 (1H, d, J=1, C-6), 6.55 (1H, sextet, J=1, 4, C-7'). 11a: δ ($DCCl_3$) 4.52 (2H, d, J=4, $HOCH_2$), 5.12 (1H, d, J=1, C-6), 6.27 (1H, sextet, J=1, 4, C-7'); ν ($CHCl_3$) 1760, 1740 (b) cm^{-1}.

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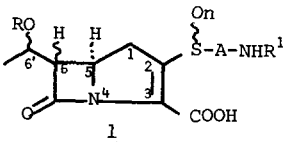
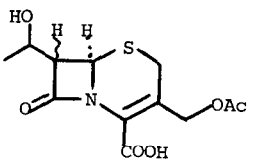


1

R = H, SO_3H; n = 0, 1, 2;

A = $-CH_2-CH_2-$, -CH=CH-(E);

R^1 = H, $CH_3C{=}O$



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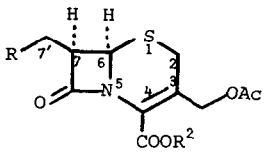
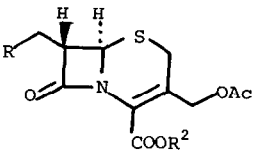


3, R = CH_2OH

5, R = CH_2OSO_3Na

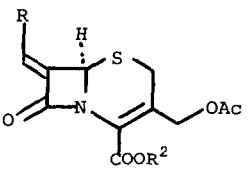
7, R = CHO



4, R = CH_2OH

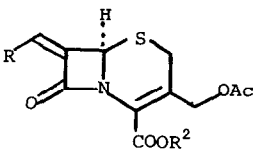
6, R = CH_2OSO_3Na

8, R = CHO



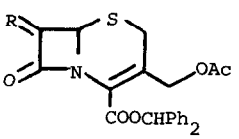
9, R = CHO

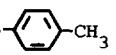
10, R = CH_2OH



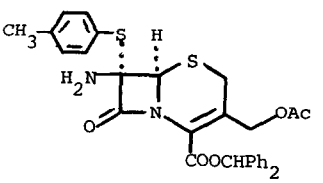
11, R = CH_2OH

a, R^2 = $CHPh_2$; b, R^2 = H; c, R^2 = Na



12, R = N-S- 

13, R = O



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