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SUBSTITUTED PENICILLINS AND CEPHALOSPORINS III.[1] PARTIAL SYNTHESIS OF 7α-METHOXYCEPHALOSPORIN C

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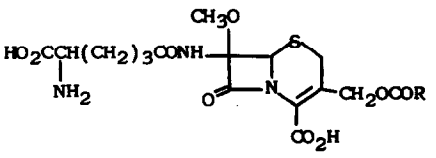
Recently two groups[2,3] have reported the isolation and structure elucidation of four new β-lactam antibiotics (1a-d) related to cephalosporin C. Each member of this group contains a 7-methoxyl substituent, for which the α-orientation may be suggested on the basis of bioactivity.[4] In this report we describe the partial synthesis of 7α-methoxycephalosporin C (5c) from benzhydryl 7-amino-7α-methoxycephalosporinate (2).[5] The identity of the natural and synthetic antibiotics confirms the α-configuration of the methoxyl group in compound 1a.

D-α-Aminoadipic acid (3a)[6] was converted as described below to BOC-α-trichloroethyl-D-α-aminoadipoyl chloride (4). Esterification of 3a with 60% aqueous H_2SO_4 and benzyl alcohol[7] afforded the δ-benzyl ester 3b: mp 173-4°; $[\alpha]_D$ -20.1 (c 1.0, 1N HCl). When 3b was treated with excess t-butyloxycarbonyl (BOC) azide and Et_3N in DMF,[8] oily BOC-derivative 3c was obtained: dicyclohexylamine (DCA) salt mp 123-4°; $[\alpha]_D$ -7.8 (c 1.1, MeOH). Dicyclohexylcarbodiimide mediated esterification of 3c with 2,2,2-trichloroethanol in pyridine--CH_2Cl_2 gave the fully protected compound 3d which was hydrogenated with 10% Pd/C in 4:1 EtOH--EtOAc to yield monoacid 3e as a clear, viscous oil: DCA salt mp 173° (dec); $[\alpha]_D$ +17.0 (c 1.2, MeOH). Treatment of 3e with excess oxalyl chloride in cold PhH containing a catalytic amount of DMF afforded acid chloride 4 as a clear oil: ir (CCl_4) 1800, 1760, and 1720 cm^{-1}; nmr (60 MHz) ($CDCl_3$) τ8.53 (s, 9, CH_3), 8.4-8.0 (m, 4, CH_2CH_2), 7.2-

6.9 (m, 2, CH_2CO), 5.7-5.4 (m, 1, CH), 5.35, 5.09 (dd, 2, J=12 Hz, Cl_3CCH_2), and 5.0-4.8 (m, 1, NH).

Acylation of benzhydryl 7-amino-7α-methoxycephalosporanate (2)[5] with excess 4 and pyridine in CH_2Cl_2 at 0° afforded, after chromatography on silica gel, 48% of 5a contaminated with ca. 14% of Δ^2-isomer 6. 5a: ir (CCl_4) 1779, 1751, and 1724 cm^{-1}; nmr (100 MHz) ($CDCl_3$) τ8.60 (s, 9, CH_3), 8.4-8.0 (m, 4, CH_2CH_2), 8.04 (s, 3, $COCH_3$), 7.9-7.4 (m, 2, CH_2CO), 6.72, 6.53 (dd, 2, J=18 Hz, 2-CH_2), 6.52 (s, 3, OCH_3), 5.8-5.4 (m, 1, CH), 5.31, 5.21 (dd, 2, J=12 Hz, Cl_3CCH_2), 5.21, 5.01 (dd, 2, J=13 Hz, 3-CH_2), 4.91 (s, 1, H-6), 4.74 (d, 1, J=8 Hz, NH), 3.05 (s, 1, $CHPh_2$), and 2.66 (s, 10, ArH). The Δ^2-isomer 6, which was prepared in moderate yield from mixed anhydride 3f and amine 2 in THF containing triethylammonium chloride, was readily identified by characteristic bands[9] in its nmr spectrum at τ5.42 (s, 2, 3-CH_2), 4.88 (m, 1, H-4), and 3.62 (m, 1, H-2). The trichloroethyl ester of 5a was smoothly cleaved using zinc in 90% aqueous HOAc[10] at 0° to yield 5b: ir ($CHCl_3$) 1783, 1736, and 1709 (sh) cm^{-1}; nmr (100 MHz) ($CDCl_3$) τ8.61 (s, 9, CH_3), 8.4-8.0 (m, 4, CH_2CH_2), 8.05 (s, 3, $COCH_3$), 7.9-7.5 (m, 2, CH_2CO), 6.74, 6.56 (dd, 2, J=18 Hz, 2-CH_2), 6.51 (s, 3, OCH_3), 5.9-5.5 (m, 1, CH), 5.21, 5.00 (dd, 2, J=14 Hz, 3-CH_2), 4.91 (s, 1, H-6), 3.06 (s, 1, $CHPh_2$), and 2.66 (s, 10, ArH). Removal of the remaining protecting groups with TFA--anisole at room temperature readily gave crude 7α-methoxycephalosporin C (5c). Preparative paper electrophoresis using 10% AcOH as buffer afforded pure 5c as a white powder; $[\alpha]_D$ +146° (c 0.9, H_2O), which was identified through comparison of its ir, uv, nmr[2] and CD spectra[11] with those reported for the natural material. The mass spectrum of N-chloroacetyl dimethyl ester derivative 5d exhibited a molecular ion at m/e 549 as well as a fragmentation pattern identical to that reported[2] for the corresponding derivative of 1a.

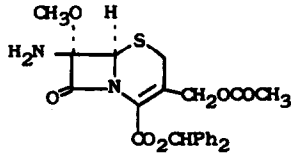


1 a, R = CH_3

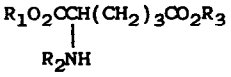
b, R = NH_2

c, R = $C(OCH_3)=CH-C_6H_4-OH-p$

d, R = $C(OCH_3)=CH-C_6H_4-OSO_2OH-p$



2



3 a, $R_1 = R_2 = R_3 = H$

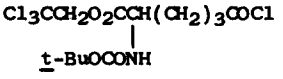
b, $R_1 = R_2 = H$, $R_3 = CH_2Ph$

c, $R_1 = H$, $R_2 = t$-BuOCO, $R_3 = CH_2Ph$

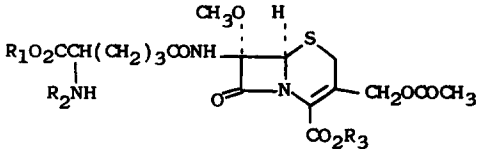
d, $R_1 = Cl_3CCH_2$, $R_2 = t$-BuOCO, $R_3 = CH_2Ph$

e, $R_1 = Cl_3CCH_2$, $R_2 = t$-BuOCO, $R_3 = H$

f, $R_1 = Cl_3CCH_2$, $R_2 = t$-BuOCO, $R_3 = CO_2Et$



4

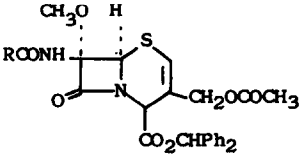


5 a, $R_1 = Cl_3CCH_2$, $R_2 = t$-BuOCO, $R_3 = CHPh_2$

b, $R_1 = H$, $R_2 = t$-BuOCO, $R_3 = CHPh_2$

c, $R_1 = R_2 = R_3 = H$

d, $R_1 = R_3 = CH_3$, $R_2 = ClCH_2CO$



6, R = $Cl_3CCH_2O_2CCH(CH_2)_3$ (t-BuOCONH)

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(4) 6-Epipenicillins and 7-epicephalosporins are appreciably less active than their counterparts in which the side-chain has the β-configuration. These observations intimate the 7α-configuration for the added methoxyl functionality in the natural products.

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