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AN EFFICIENT NEW SYNTHESIS OF 7-PHTHALIMIDO-8-t-BUTOXY-5,8-seco-DESACETYLCEPHALOSPORANIC ACID LACTONE, - A KEY INTERMEDIATE IN A TOTAL SYNTHESIS OF THE CEPHALOSPORINS.

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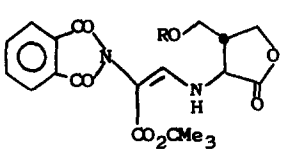
The subject compound was first synthesized by chemists at Roussel[1] in an original sequence subsequently providing a novel route to the cephalosporins. A similar pathway was also pursued by chemists at Squibb[2] in a variant of the Roussel procedure. Both routes are predicated on the incorporation of the center of unsaturation in the initial lactonic species, subsequently elaborated to the end product. The inherent instability of these precursor butenolides[3] presents transformational limitations reflected in relatively low yields as well as isomer formation in the end product.

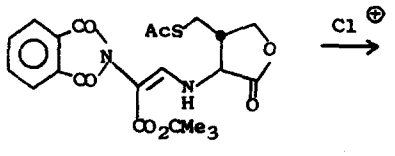
We have devised a relatively simple and efficient synthesis of 7-phthalimido-8-t-butoxy-5,8-seco-desacetylcephalosporanic acid lactone 5 in excellent overall yield (50-55%) and obtained as a single isomeric species. Condensation of α-phthalimidomalonaldehydic acid t-butyl ester[4] with γ,γ'-dihydroxyvaline lactone[5] in methanol at 25° in the presence of sodium acetate yielded the enamine 1[6] $\lambda_{max}^{CHCl_3}$ 2.7-3.10, 5.59, 5.80, 5.92, 6.0-6.2, 8.70 and 11.28μ. The latter was converted directly to its tosylate derivative ($C_7H_7SO_2Cl$, Py, 0°) and thence with potassium thioacetate in refluxing acetone to the acetylthioenamine 2 obtained in 71% overall yield from starting compounds. The enamine 2 was separable by chromatography on silica gel (EtOAc-C_6H_6/40:60) into a cis-form, m.p. 175-177°, λ_{max}^{MeOH} 280 nm (ε, 21800), Calcd for $C_{22}H_{24}O_7N_2S$: C, 57.38; H, 5.25; N, 6.08; Found: C, 57.69; H, 5.40; N, 5.88, and a trans-form, m.p. 192-194°, λ_{max}^{MeOH} 273 nm (ε, 25800), Found: C, 57.63; H, 5.59; N, 5.83. Structural assignment was based on the lower U.V. extinction associated

with the cis-isomer[7] wherein cis and trans denote the relationship of the ester and amine groups. The two isomers are thermally interconvertible. For purposes of



1 R = H

1a R = $C_7H_7SO_2$



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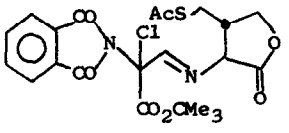

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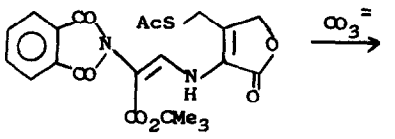

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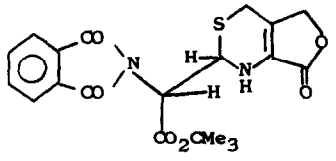

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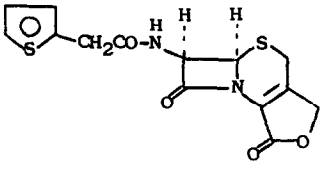

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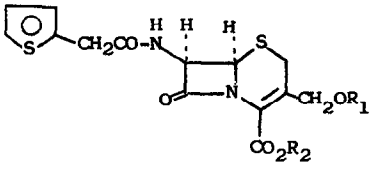

7 $R_1 = R_2 = H$

8 R_1 = Ac; $R_2 = CH_3$

further transformation, however, both isomers serve the same end. Treatment of 2 with one equivalent of t-butylhypochlorite in methylene chloride at 0° quantitatively afforded the chloroimine 3.[8] The latter was treated directly without isolation with 1,4-diazabicyclo[2:2:2]octane (DABCO) in benzene solution at 0° to afford the dienamine 4 in 90-95% yield separable by chromatography on silica gel (EtOAc-C_6H_6/ 30:70): cis-form, m.p. 170-173°, λ_{max}^{MeOH} 310 nm (ε, 26500), 264 nm (ε, 8350), nmr ($CDCl_3$) δ 1.42 [s, 9H, $OC(CH_3)_3$], 2.42 (s, 3H, CH_3COS), 3.89 (s, 2H, $SCH_2C{=}C$), 4.77 (s, 2H, $OCH_2C{=}C$), 7.87 (m, 4H, aromatic), 8.05 (d, 1H, J = 12.5Hz, CH=C) and 10.12 (d, 1H, J= 12.5Hz, NH), Calcd for $C_{22}H_{22}O_7N_2S$: C, 57.63; H, 4.84; N, 6.11; Found: C, 57.29; H, 4.73; N, 5.79; trans-form, m.p. 192-194°, λ_{max}^{MeOH} 304 nm (ε, 29700), 265 nm (ε, 12800), nmr ($CDCl_3$) δ 1.47 [s, 9H, $OC(CH_3)_3$], 2.16 (s, 3H, CH_3COS), 3.69 (s, 2H, $SCH_2C{=}C$), 4.67 (s, 2H, $OCH_2C{=}C$), 7.71 (d, 1H, J= 13.5Hz, NH), 7.85 (m, 4H, aromatic) and 8.84 (d, 1H, J = 13.5Hz, CH=C), Found: C, 57.79; H, 4.99; N, 6.07. Both isomers are interconvertible on melting.

Finally, treatment of the dienamine 4 with one equivalent of potassium carbonate in aqueous methanol at 0° evoked selective hydrolysis of the thiol acetyl group followed by ring closure to give 5 in 80% yield. Compound 5 was obtained exclusively as the erythro isomer from $CHCl_3$-hexane, m.p. 181-5°, single spot tlc (EtOAc-C_6H_6/20:80) R_F 0.64, λ_{max}^{EtOH} 268 nm (ε, 5200), λ_{max}^{chf} 2.70-2.80, 2.93, 5.67, 5.77, 5.82, 5.91, 6.20 and 11.41μ, nmr ($CDCl_3$) δ 1.44 [s, 9H, $OC(CH_3)_3$], 3.40 (q, 2H, J = 18Hz, $SCH_2C{=}C$), 4.70 (d, 1H, J = 10Hz, CHCO), 4.82 (q, 2H, J = 15Hz, $OCH_2C{=}C$), 5.37 (d, 1H, J = 5Hz, NH, exchanges with CD_3OD), 5.59 (q, 1H, J = 5 and 10Hz, CHS, collapses to a doublet on exchange) and 7.87 (m, 4H, aromatic), Calcd for $C_{20}H_{20}O_6N_2S$: C, 57.68; H, 4.84; N, 6.73; Found: C, 58.00; H, 4.77; N, 6.42. Compound 5 thus obtained was found to be identical with material prepared by the Roussel procedure which in our hands likewise melted at 181-185°. Compound 5 appears prone to polymorphism as adjudged by the fact that previous workers have reported different melting points for this substance (215°[1] and 193°[2]). We also have observed on occasion m.p. 191-192.5° which was lowered on recrystallization; the separate samples were otherwise identical.[9]

Since 5 has been converted via desacetylcephalothin lactone (6)[1] to desacetylcephalothin (7) and cephalothin methyl ester (8),[10] the present work accordingly

constitutes a formal total synthesis of these cephalosporins.

References

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6. The groups about the lactone ring were assigned the trans orientation on the assumption that this represents the thermodynamically more stable group dispositions in association with the following equilibration result: γ,γ'-dihydroxyvaline lactone as its N-phthaloyl derivative [m.p. 157-160°; nmr δ 5.17 (d, J = 10 Hz) -N-CH-C=O] after O-silylation and equilibration [$(Me_3Si)_2$ N-Li/THF] was recovered predominantly unchanged (85-90%) as determined by the nmr ratio of the α-H doublets at δ 5.17 (d, J = 10 Hz) and δ 5.25 (d, J = 9.5 Hz).

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8. Substantiation for the chlorimine structure 3 was derived from its nmr spectrum which exhibited a singlet proton at δ 8.46. Aqueous hydrolysis of 3 yielded the corresponding chlorophthalimidoaldehydic ester with a singlet aldehyde proton at δ 9.75.

9. Erythro 5 can be equilibrated with its threo isomer. Further, removal of the blocking phthaloyl and ester groups enroute to 6 has been demonstrated to proceed equally from either the erythro or threo isomer to give the desired threo amino acid intermediate (cf. ref. 1c).

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