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TOTAL SYNTHESIS OF β-LACTAM ANTIBIOTICS V.[1] (±)-3'-METHYL-CEPHALOTHIN

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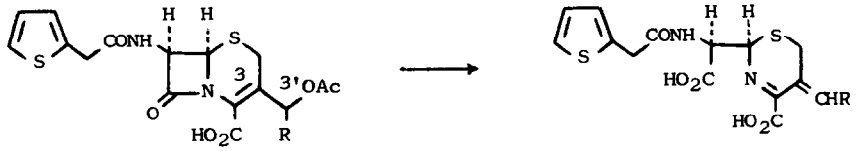
We recently reported on a simple and unique total synthesis[2] of the cephalosporin antibiotics cephalothin and cefoxitin. In addition to providing pharmacologically important compounds, our interest in structure-activity relationships dictated a route which would provide new nuclear analogs of the basic cephem system. For simplicity of analog synthesis, a common route was required that permits the insertion of different fragments during the synthesis. We believe that these criteria are fully realized in that synthetic scheme.[2,3]

It has been observed that cleavage of the β-lactam ring of cephalosporins bearing a 3'-substituent capable of accepting an electron occurs with expulsion of that substituent[4] (c.f. 1 ⟶ 2). Electronic considerations lead to the prediction that additional alkyl substitution at 3' would stabilize the postulated transition state and thus provide a more reactive β-lactam ring. Such compounds are not presently available by modification of naturally-occurring cephalosporins. In this paper we describe application of the basic scheme to the total synthesis of (±)-3'-methyl-cephalothin (3) and discuss its solvolytic behavior.



1, R = H

3, R = CH_3

2, R = H

The requisite component for introduction of the 3'-methyl group was prepared from 2-acetoxypropionyl chloride (4).[5] Dropwise addition of 4 to ice-cold, ethereal CH_2N_2 and Et_3N provided the crude diazoketone 5 which, without isolation, was treated with anhydrous HCl. Work-up and distillation afforded 1-chloro-3-acetoxy-2-butanone (6) in 52% yield: bp 43-44° (0.2 mm); ir (neat) 5.72μ; nmr ($CDCl_3$) τ 8.53 (d, J = 7 Hz, $CHC\underline{H}_3$), 7.84 (s, $COCH_3$), 5.64 (s, $ClCH_2$), and 4.65 (q, J = 7 Hz, $C\underline{H}CH_3$).

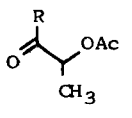
Condensation of 6 with thioformamide 7[2a] in acetone containing three equivalents of K_2CO_3 at room temperature provided 92% of crude thiazine 8: ir ($CHCl_3$) 5.75μ; nmr ($CDCl_3$) τ 8.55 (d, J = 6.5 Hz, $CHC\underline{H}_3$), 7.98 (s, $COC\underline{H}_3$), 6.67 (ABq, J = 15 Hz, SCH_2), 6.20 (s, $ArOCH_3$), 4.73 (s, CH_2Ar), 3.75 (q, J = 6.5 Hz, $C\underline{H}CH_3$), 2.87 (ABq, J = 9 Hz, ArH), and 1.65 (s, N=CH). Immediate dropwise addition of azidoacetyl chloride to an ice-cold solution of 8 and Et_3N in CH_2Cl_2 gave a mixture of Δ^2- and Δ^3- cephems 9 and 10, which were readily separated by column chromatography.[6] Pure 10 was obtained in 14% yield: ir ($CHCl_3$) 4.73, 5.60, and 5.79μ; nmr ($CDCl_3$) τ 8.59 (d, J = 6.5 Hz, $CHC\underline{H}_3$), 7.98 (s, $COCH_3$), 6.58 (s, SCH_2), 6.18 (s, $ArOCH_3$), 5.47 (d, J = 1.5 Hz, H6 or H7), 5.38 (d, J = 1.5 Hz, H7 or H6), 4.74 (s, CH_2Ar), 4.02 (q, J = 6.5 Hz, $C\underline{H}CH_3$), and 2.85 (ABq, J = 9 Hz, ArH); m/e 432 (M^+). The azido group was then reduced by hydrogenation over PtO_2 in benzene solution to give amino cephem 11: ir ($CHCl_3$) 2.91, 5.61, and 5.76μ; nmr ($CDCl_3$) τ 6.65 (s, SCH_2), 5.92 (d, J = 2 Hz, H7), 5.58 (d, J = 2 Hz, H6), and 4.12 (q, J = 6.5 Hz, $C\underline{H}CH_3$).

Epimerization[1] at position 7 to the thermodynamically less stable and desired β-isomer was accomplished by kinetic protonation of the anion derived from Schiff base 12. Compound 12 was obtained in 80% yield by simply stirring amine 11, p-nitrobenzaldehyde, and $MgSO_4$ in CH_2Cl_2: ir ($CHCl_3$) 5.61, 5.76, and 6.10μ; nmr ($CDCl_3$) τ 6.54 (s, SCH_2), 5.14 (d, J = 1.5 Hz, H6 or H7), 5.08 (d, J = 1.5 Hz, H7 or H6), 4.00 (q, J = 6.5 Hz, $C\underline{H}CH_3$), 1.90 (ABq, J = 9 Hz, ArH), and 1.47 (splintered s, CH=N). Successive treatment of 12 in THF at -78° with PhLi, DMF, and aqueous HOAc afforded a 1:1 mixture of epi and normal Schiff bases 12 and 13, respectively. The normal isomer displayed a characteristic signal in the nmr spectrum at τ 1.28 (d, J = 1.5 Hz, CH=N).

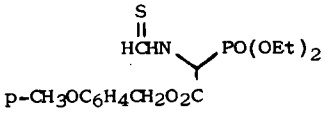
The Schiff base mixture afforded the corresponding mixture of amino cephems 11 and 14 in 97% yield by exchange with 2,4-DNPH·TsOH in EtOH. Acylation of this mixture

with 2-thienylacetyl chloride and pyridine in CH_2Cl_2 at 0° gave amides 15 and 16 which were resolved by column chromatography. Pure, normal isomer 16 was obtained in 17% yield: ir ($CHCl_3$) 5.60, 5.79, 5.93, and 6.64μ; nmr ($CDCl_3$) τ 6.63 (s, SCH_2), 6.18 (s, thienyl-CH_2), 5.12 (d, J = 5 Hz, H6), 4.26 (dd, J = 5 Hz and J = 9 Hz, H7), 3.98 (q, J = 7 Hz, $CHCH_3$), 3.55 (d, J = 9 Hz, NH), and 3.2-2.5 (m, ArH); m/e 530 (M^+). The p-methoxybenzyl ester group of 16 was cleaved in 5:1 TFA-PhOMe at 0° for 5 minutes to yield (±)-3'-methyl-cephalothin (3) in near quantitative yield: ir ($CHCl_3$) 5.60, 5.78, 5.94, and 6.64μ; nmr ($CDCl_3$) τ 8.58 (d, J = 7 Hz, $CHCH_3$), 7.97 (s, $COCH_3$), 6.60 (s, SCH_2), 6.12 (s, thienyl-CH_2), 5.02 (d, J = 5 Hz, H6), 4.14 (dd, J = 5 Hz and J = 9 Hz, H7), 3.85 (q, J = 7 Hz, $CHCH_3$), 3.51 (d, J = 9Hz, NH), and 3.05-2.45 (m, ArH).

Neutralization of acid 3 with aqueous $NaHCO_3$ followed by lyophilization afforded sodium salt 17 as an amorphous white powder: ir (KBr) 2.7-4.0, 5.70, 6.01, and 6.23μ; nmr (D_2O) τ 8.59 (d, J = 7 Hz, $CHCH_3$), 7.98 (s, $COCH_3$), 6.56 (s, SCH_2), 6.13 (s, thienyl-CH_2), 4.94 (d, J = 4.5 Hz, H6), 4.44 (d, J = 4.5 Hz, H7), 4.19 (q, J = 7 Hz, $CHCH_3$), 3.00 (d, ArH), and 2.67 (t, ArH); uv (H_2O) 237 ($E^{1\%}$ 274) and 263 ($E^{1\%}$ 155)nm. Periodic examination of the nmr spectrum of 17 revealed that covalent acetate (τ 7.98) was rapidly ($t_{1/2}$ ca. 20 min. at 37°) replaced by free acetate ion (τ 8.13). In addition, new methyl doublets appeared at τ 8.75 and 8.69[8] and the SCH_2 singlet shifted downfield to τ 6.49. The remainder of the nmr spectrum, as well as a uv spectrum obtained after incubation at 37°, was not significantly different. These observations are consistent with rapid ionization without concomitant cleavage of the β-lactam ring to a stabilized carbonium ion[7] which is then trapped internally by the carboxyl function to yield the γ-lactone. The facile ionization of 3'-methyl analog 17 is most surprising in view of the demonstrated stability of corresponding 3'-hydrogen cephalosporins.



4, R = Cl
5, R = CHN_2
6, R = CH_2Cl



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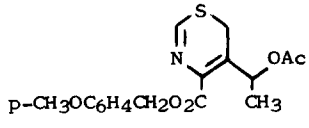

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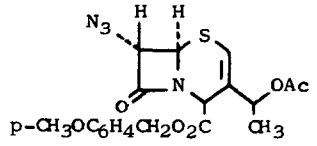

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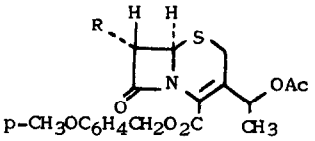
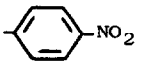
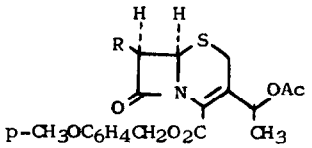


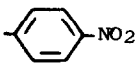
10, R = N_3

11, R = NH_2

12, R = N=CH- 

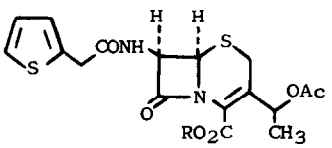
15, R = $NHCOCH_2$- 



13, R = N=CH- 

14, R = NH_2

16, R = $NHCOCH_2$- 



3, R = H

17, R = Na

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1. Part IV; R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, J. Org. Chem., 39, 437 (1974).
2. (a) R. W. Ratcliffe and B. G. Christensen, Tetrahedron Lett., 4645 (1973). (b) ibid., 4649 (1973). (c) ibid., 4653 (1973).
3. Application of the synthetic scheme to provide 3-aryl cephalosporins will appear shortly. Further modification to provide sulfur replacements at position 1 will be the subject of forthcoming communications.
4. C. H. O'Callaghan and P. W. Muggleton, in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., 1972, Academic Press, New York, p. 442.
5. E. H. Filachione, J. H. Lengel, and C. H. Fisher, J. Amer. Chem. Soc., 66, 494 (1944).
6. Column chromatographies were performed on E. Merck silica gel 60 using benzene-ethyl acetate mixtures as eluant.
7. The mechanism of acetoxy solvolysis and displacement from 3'-H cephalosporins has been discussed by others. (a) J. D. Cocker, B. R. Cowley, J.S.G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly, and G. A. Somerfield, J. Chem. Soc., 5015 (1965). (b) A. B. Taylor, ibid., 7020 (1965).
8. Pairing of the nmr signals is indicative of a diastereomeric mixture. Although such mixtures were anticipated for all other bicyclic intermediates, tlc and nmr examination indicated sample homogeneity.