Tetrahedron Letters No. 46, pp 4649 - 4652, 1973. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESIS OF β-LACTAM ANTIBIOTICS II. (±)-CEPHALOTHIN

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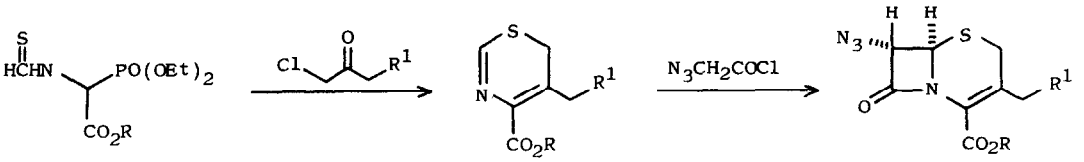
(Received in USA 29 August 1973; received in UK for publication 9 October 1973)

α-Thioformamido-diethylphosphonoacetates (I) have been found to condense with 1-chloro-2-propanones in the presence of base to give 6H-1,3-thiazine-4-carboxylates (II). These compounds react smoothly with azidoacetyl chloride and triethylamine, providing 7α-azido cephems of general structure III. One of these cephem derivatives has been converted to racemic cephalothin (14), a clinically important, semi-synthetic cephalosporin.



I II III

Condensation of 1-chloro-2-propanone with thioformamide 1a[1] in acetone containing 1.1 equivalents of K_2CO_3 at room temperature afforded a 4:1 mixture of thioformimidate 2 and thiazine 3 in quantitative yield: 2 has ir (CCl_4) 5.71, 5.76, 6.25, 7.91, 9.48, and 9.73μ; nmr ($CDCl_3$) τ 7.66 (s, $COCH_3$), 6.20 (s, CO_2CH_3), 6.16 (s, $COCH_2S$), 5.36 (d, J_{HP} = 21 Hz, CHP), and 1.59 (d, J_{HP} = 4Hz, N=CH). The mixture was converted solely to 3 by NaH in DME, or better, with K_2CO_3 in acetone: ir (CCl_4) 5.80μ; nmr ($CDCl_3$) τ 7.75 (s, CH_3), 6.67 (splintered s, SCH_2), 6.15 (s, OCH_3) and 1.73 (s, N=CH); m/e 171 (M^+). Alternatively, thiazine 3 was obtained in 83% yield by stirring 1a and 1-chloro-2-propanone in acetone containing 3 equivalents of K_2CO_3. Dropwise addition of azidoacetyl chloride[2] to an ice-cold solution of 3 and Et_3N provided, after chromatography,[3] 52% of crystalline 7α-azido cephem 4: mp 87-88°; ir (CCl_4) 4.73, 5.59, and 5.76μ; nmr ($CDCl_3$) τ 7.90 (s, CH_3), 6.89 and 6.49 (ABq[4], J = 18 Hz, SCH_2), 6.15 (s, OCH_3),

5.49 (d, J = 1.8 Hz, H6 or H7), and 5.40 (d, J = 1.8 Hz, H7 or H6); m/e 254 (M^+).

Having demonstrated the applicability of our synthetic scheme, we turned our attention to the construction of a cephem derivative suitable for conversion to useful cephalosporin antibiotics. Treatment of thioformamide 1b[1] with 1-chloro-3-acetoxy-2-propanone[5] and excess K_2CO_3 in acetone for 3 hours at room temperature gave crude thiazine 5: ir (CCl_4) 5.71 and 5.82(sh)μ; nmr ($CDCl_3$) τ 7.95 (s, $COCH_3$), 6.63 (s, SCH_2), 6.20 (s, OCH_3), 4.86 (s, CH_2OAc), 4.75 (s, CH_2Ar), 3.13 (d, J = 9Hz, ArH), 2.63 (d, J = 9Hz, ArH) and 1.65 (s, N=CH). Addition of azidoacetyl chloride to 5 and Et_3N in ice-cold CH_2Cl_2 afforded a 1:2 mixture of Δ^2- and Δ^3-cephems 6 and 7, which were easily separated by column chromatography. The Δ^2-isomer arises from Et_3N initiated double bond isomerization of the initial Δ^3-product. This difficulty was surmounted by simply allowing an equimolar mixture of thiazine 5, azidoacetyl chloride, and Et_3N in CH_2Cl_2 at -78° to gradually warm to room temperature, affording 7α-azido-Δ^3-cephem 7 in 56% yield: ir (CCl_4) 4.73, 5.58, and 5.73μ; nmr ($CDCl_3$) τ 6.75 and 6.35 (ABq, J = 19 Hz, SCH_2), 5.47 (d, J = 1.8 Hz, H6 or H7), 5.40 (d, J = 1.8 Hz, H7 or H6) and 5.27 and 4.98 (ABq, J = 13 Hz, CH_2OAc); uv (EtOH) 228 (ε 32,400) and 268 (ε 18,100)mμ; m/e 418 (M^+). Compound 7 contains the requisite functionality for conversion to cephalothin.

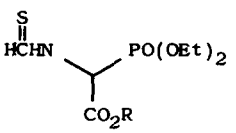
Hydrogenation of 7 in benzene solution over PtO_2 afforded amino cephem 8: ir ($CHCl_3$) 2.94, 5.62, and 5.75μ; nmr ($CDCl_3$) τ 8.18 (br s, NH_2), 5.87 (d, J = 2Hz, H7), and 5.57 (d, J = 2Hz, H6); m/e 392 (M^+), which was converted to crystalline 7α-Schiff base 9 with p-nitrobenzaldehyde in CH_2Cl_2 containing $MgSO_4$: 74% overall yield; ir ($CHCl_3$) 5.61, 5.76, and 6.10μ; nmr ($CDCl_3$) τ 6.67 and 6.28 (ABq, J = 18 Hz, SCH_2), 5.22 and 4.93 (ABq, J = 13 Hz, CH_2OAc), 5.08 (d, J = 2Hz, H6), 4.72 (d, J = 2Hz, H7), and 1.41 (s, N=CH); m/e 525 (M^+). The Schiff base anion, generated from 9 and one equivalent of PhLi in THF at -78°, was treated with DMF and quenched with aqueous HOAc.[6] Work-up afforded a 92% yield of a 55:45 mixture of epi and normal Schiff bases 9 and 10, respectively.

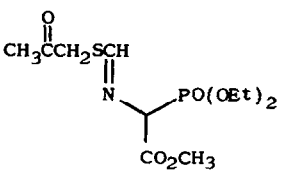
It was observed that the pure normal Schiff base 10 gave on epimerization the same 55:45 epi-normal mixture as did pure epi Schiff base 9. Pure 6(R),7(R)-Schiff base 10 was obtained as follows. Cephalothin (14)[7] was converted to its acid chloride with oxalyl chloride in CH_2Cl_2 containing 0.1 equivalent of DMF, and the crude product was treated with p-methoxybenzyl alcohol and d,l-α-pinene in CH_2Cl_2. Chromatography and recrystallization provided 41% of p-methoxybenzyl cephalothin (11), mp 148-149.5°; ir

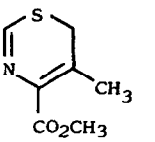
($CHCl_3$) 5.60, 5.77, and 5.93μ; nmr ($CDCl_3$) τ 6.77 and 6.43 (ABq, J = 18 Hz, SCH_2), 6.18 (s, thienyl-CH_2), 5.25 and 4.86 (ABq, J = 13 Hz, CH_2OAc), 5.10 (d, J = 4.5 Hz, H6), and 4.20 (d of d, J = 4.5 Hz and J = 9Hz, H7); uv (EtOH) 229 (e 23,460) and 266 (e 8,830)mμ; m/e 516 (M^+). The thienylacetyl group was cleaved by successive treatment of a cold CH_2Cl_2 solution of 11 with PCl_5-quinoline, n-propanol, and NaCl-H_2O,[8] yielding 64% of 7β-amino cephem 12: ir ($CHCl_3$) 5.62 and 5.77μ; nmr ($CDCl_3$) τ 8.19 (br s, NH_2) and 5.15 (m, H6 and H7). Crystalline 6(R),7(R)-Schiff base 10 was obtained in quantitative yield by stirring 12 with one equivalent of p-nitrobenzaldehyde in CH_2Cl_2 containing $MgSO_4$ for 6 hours at room temperature: mp 113-115°; ir ($CHCl_3$) 5.60, 5.76, and 6.09μ; nmr ($CDCl_3$) τ 6.70 and 6.34 (ABq, J = 18 Hz, SCH_2), 5.20 and 4.87 (ABq, J = 13 Hz, CH_2OAc), 4.82 (d, J = 4.5 Hz, H6), 4.50 (d of d, J = 4.5 Hz and J = 1.8 Hz, H7), and 1.25 (d, J = 1.8 Hz, N=CH); m/e 525 (M^+).

The racemic Schiff base mixture afforded the corresponding mixture of amino cephems 8 and 12 in 92% yield by exchange with 2,4-DNPH·TsOH in EtOH. Acylation of this mixture with 2-thienylacetyl chloride-pyridine in CH_2Cl_2 at 0° gave amides 11 and 13, which were separated by column chromatography. The racemic 7β-isomer 11 was identical in all respects (ir, nmr, uv, ms, and tlc) to 6(R),7(R)-11 obtained from cephalothin. (±)-Cephalothin (14) was obtained in 95% yield by treatment of (±)-11 with 5:1 TFA-$PhOCH_3$ for 5 min at 0°. Both (±)-14 and its sodium salt 15 were identified by spectral comparison (ir, nmr, uv) with authentic samples of the corresponding natural modifications. In addition, (±)-15 displayed the same antimicrobial spectrum and approximately one-half the activity of commercial sodium cephalothin.

The extension of these procedures to the synthesis of cefoxitin[9] and to nuclear modified β-lactam antibiotics[10] will be the subject of forthcoming communications.





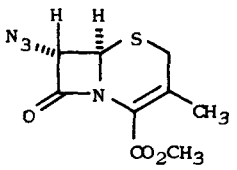


1a, R = CH_3

1b, R = CH_2-C6H4-OCH_3

2

3



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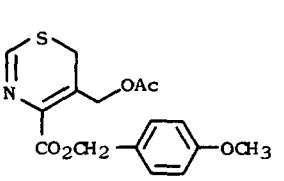

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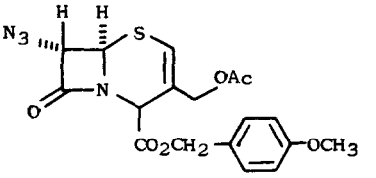
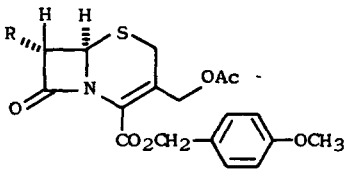
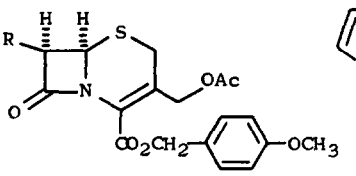
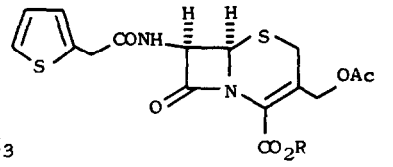


6

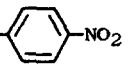




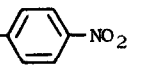


7, R = N_3

8, R = NH_2

9, R = N=CH- 

13, R = $NHCOCH_2$- 

10, R = N=CH- 

11, R = $NHCOCH_2$- 

12, R = NH_2

14, R = H

15, R = Na

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