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TOTAL SYNTHESIS OF β-LACTAM ANTIBIOTICS III. (±)-CEFOXITIN

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Cefoxitin (10)[1] is a new, broad spectrum, semi-synthetic cephalosporin which exhibits high stability toward β-lactamases, as well as good activity against gram-positive and gram-negative bacteria.[2] The antibiotic is chemically unique in that it possesses a 7α-methoxy substituent and a 3-carbamoyloxymethyl group. Cefoxitin has been prepared from cephamycin C[3] *via* a novel acyl exchange reaction.[4] We now wish to report the total synthesis of (±)-cefoxitin, as well as (±)-7α-methoxy cephalothin (7).

Successive treatment of racemic Schiff base 1[5] in THF at -78° with PhLi, DMF, and CH_3SCl,[6] followed by warming to room temperature, afforded 42% of methylthio Schiff base 3: ir ($CHCl_3$) 5.63, 5.78, and 6.12μ; nmr ($CDCl_3$) τ 7.98 (s, $COCH_3$), 7.77 (s, SCH_3), 6.73 and 6.36 (ABq,[7] 2, J = 18 Hz, SCH_2), 6.22 (s,3, OCH_3), 5.23 and 4.88 (ABq, J = 14 Hz, CH_2OAc), 4.90 (s, H6), 4.73 (s, CH_2Ar), 3.11 (d, J = 9Hz, MeOArH), 2.61 (d, J = 9Hz, MeOArH), 2.03 (d, J = 8Hz, O_2NArH), 1.73 (d, J = 8Hz, O_2NArH), and 1.10 (s, N = CH). The same product was obtained in 59% yield from epimeric 6(R),7(R)-Schiff base 2.[5] Evidence that the methylthio group was introduced from the less-hindered α-face of 1 or 2 has been amply provided by other workers.[8]

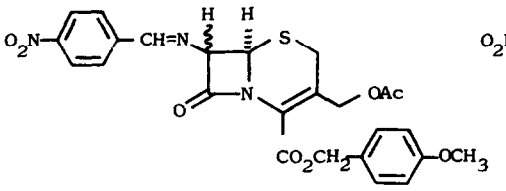
Removal of the p-nitrobenzylidene group by exchange with 2,4-DNPH·TsOH in THF gave the free amine 4: ir (neat) 2.98, 5.62, and 5.78μ; nmr ($CDCl_3$) τ 7.70 (s, SCH_3) and 5.22 (s, H6); m/e 438 (M^+). Acylation of this material with 2-thienylacetyl chloride-pyridine in CH_2Cl_2 provided a 70% overall yield of amide 5: ir ($CHCl_3$) 5.60, 5.75, and 5.90μ; nmr ($CDCl_3$) τ 7.80 (s, SCH_3), 6.60 (s, SCH_2), 6.12 (s, thienyl-CH_2), 5.06 (s, H6), and 3.45 (s, NH); m/e 562 (M^+). Methanolysis of 5 in the presence of one equivalent of thallium trinitrate gave, after chromatographic purification, 50% of 7α-

methoxy amide 6[9]: ir ($CHCl_3$) 5.61, 5.78, and 5.90μ; nmr ($CDCl_3$) τ 6.85 and 6.48 (ABq, J = 18 Hz, SCH_2), 6.55 (s,3, OCH_3), 5.25 and 4.95 (ABq, J = 14 Hz, CH_2OAc), and 4.97 (s, H6); m/e 546 (M^+). None of the epimeric 7β-methoxy derivative was detected in the crude product. The methoxylation reaction presumably involves elimination of the methylthio group by Tl(III) to give a carbonium ion or N-acylimine,[10] which then reacts with solvent from the less-hindered α-face.

The p-methoxybenzyl ester group of 6 was cleaved in 5:1 TFA-PhOMe at 0° for 5 minutes to give (±)-7α-methoxy cephalothin (7) in near quantitative yield. This material, as well as its sodium salt 8, were identical (ir, nmr, uv) with authentic samples prepared[11] from 7-ACA.

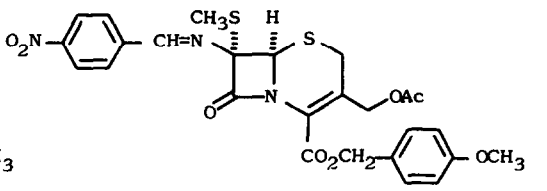
Compound 8 was deacetylated with citrus acetyl enzyme,[12] affording hydroxymethyl salt 9 in 83% yield: nmr (D_2O) τ 6.83 and 6.43 (ABq, J = 18 Hz, SCH_2), 6.52 (s, OCH_3), 6.08 (s, $ArCH_2$), 5.80 (s,2, CH_2OH), 4.90 (s, H6), 3.00 (d,2, J = 3.5 Hz, ArH), and 2.67 (t,1, J = 3.5 Hz, ArH). The corresponding free acid was treated with chlorosulfonyl isocyanate in THF at -40° followed by hydrolysis[13] to yield 65% of (±)-cefoxitin (10). Both (±)-10 and its sodium salt (±)-11 were identical spectrally with cefoxitin and sodium cefoxitin of natural configuration. In addition, the racemic sodium salt displayed the same antimicrobial spectrum and approximately one-half the activity of natural sodium cefoxitin.[14]

A more direct synthesis of the 7α-methoxy cephem nucleus was investigated. Methyl 2-chloro-2-methoxyacetate (12)[15] was converted to azido derivative 13 with NaN_3 in refluxing DME. Hydrolysis gave the free acid 14 which afforded acid chloride 15 with thionyl chloride:[16] bp 64-66° (27 mm); ir (CCl_4) 4.72 and 5.58μ; nmr ($CDCl_3$) τ 6.37 (s, OCH_3) and 5.23 (br s, CH). Addition of 15 to thiazine 16[5] and Et_3N in CH_2Cl_2 afforded a mixture of products from which a 3:1 mixture of epimeric cephems 17 and 18 were isolated in low yield: 17 shows ir (CCl_4) 4.72, 5.60, and 5.78μ; nmr ($CDCl_3$) τ 7.80 (s, CH_3), 6.76 (s, SCH_2), 6.33 (s, OCH_3), 6.13 (s, CO_2CH_3), and 5.12 (s, H6). 7α-Methoxy-7-azido cephems have previously been converted to medicinally useful antibiotics.[11]



1, 7β-H

2, 7α-H



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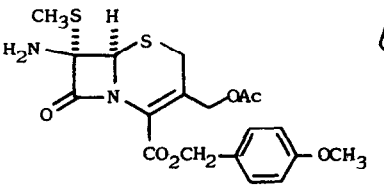

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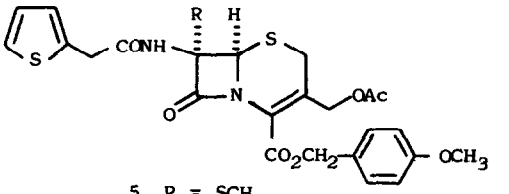
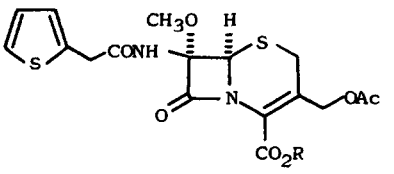


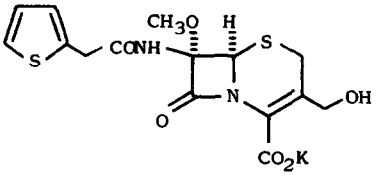
5, R = SCH_3

6, R = OCH_3



7, R = H

8, R = Na



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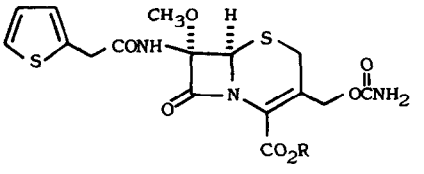
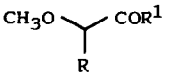


10, R = H

11, R = Na

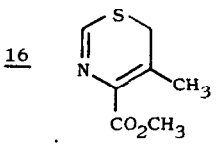


12, R = Cl, R^1 = OCH_3

13, R = N_3, R^1 = OCH_3

14, R = N_3, R^1 = OH

15, R = N_3, R^1 = Cl



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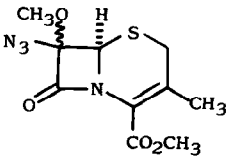

17, 7α-OCH_3

18, 7β-OCH_3

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14. We thank Dr. E. H. Thiele for these measurements.

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16. We thank W. J. Leanza for this preparative route.