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SYNTHESIS OF FURO[3,4-c]CEPHAMS[1]

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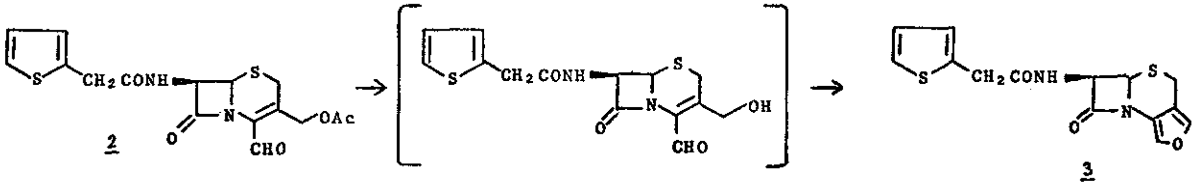
Previously we reported a total synthesis of racemic desacetylcephalothin lactone[2]. A key intermediate in this synthesis was the novel furo[3,4-c]cepham (3). This communication describes the synthesis of optically-active 3 starting with the commercially available cephalosporin antibiotic cephalothin (1).

Dilute hydrochloric acid/dioxane treatment of cephalothin (1) readily converts it to the corresponding lactone[3], presumably by way of the 3-hydroxymethyl intermediate. An analogous process involving the aldehyde (2)[4] instead of 1 would be expected to lead to the desired furan (3).



Initial experiments were carried out using the sulfoxyaldehyde (6)[4,5]. When 6 was stirred for six hours at room temperature in 1:1 dioxane/2N hydrochloric acid and the product isolated by extraction with ethyl acetate and chromatography on silica gel, a 60% yield of the furan 10[6] was obtained: mp$>300^\circ$, $[\alpha]_D$ $+211^\circ$ (C=0.5, DMSO); nmr (DMSO-d_6): 3.75, 4.40[7] (2H, ABq, J 15.5 Hz, 2-CH_2); 3.83 (2H, bs, thiophene methylene); 4.99 (1H, d, J 4.5 Hz, 6-H); 5.84 (1H, dd, J 4.5, 8.5 Hz, 7-H) 6.8-7.0 (2H, m, thiophene); 7.2-7.5 (1H, m, thiophene); 7.65 (1H, bt, J ca. 1.5 Hz, furan); 7.87 (1H, d, J 1.5 Hz, furan); 8.45 (1H, d, J 8.5 Hz, NH).

On account of the lower stability of the aldehyde (2), the above procedure was attempted using crude aldehyde obtained directly from the Moffatt oxidation of the alcohol (4)[4,8], and the desired furan (3) obtained in about 15% yield (based on alcohol (4)): mp 281-283°, $[\alpha]_D$ + 161° (C=0.5, dioxane); nmr (DMSO-d_6): 3.74 (2H, s, thiophene methylene); 3.90 (2H, bs, 2-CH_2); 5.27 (1H, d, J 4.5 Hz, 6-H); 5.74 (1H, dd, J 4.5, 8.5 Hz, 7-H); 6.8-7.0 (2H, m, thiophene); 7.2-7.5 (1H, m, thiophene); 7.59 (1H, bd, J 1.5 Hz, furan); 7.8 (1H, d, J 1.5 Hz, furan); 9.15 (1H, d, J 8.5 Hz, NH). Purified aldehyde (2), obtained by way of the diethyl acetal[4], led to only slightly higher yields of the furan (3) when the above reaction was applied, the remainder being unidentified polar material.

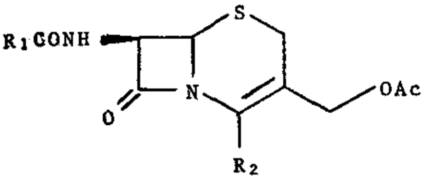
When the furan (3) in dry DMF was treated with N,O-bis(trimethylsilyl) acetamide and DBN, isomerization at the 7-position occurred, and a 25% yield of the trans-furan (14) was obtained: mp 130-135°; $[\alpha]_D$+ 23° (C=0.5, $CHCl_3$): nmr ($CHCl_3$): 3.73 (2H, bs, 2-CH_2); 3.81 (2H, s, thiophene methylene); 4.78 (1H, dd, J 2, 7 Hz, 7-H); 4.91 (1H, d, J 2 Hz, 6-H); 6.67 (1H, d, J 7 Hz, NH); 6.8-7.1 (2H, m, thiophene); 7.1-7.4 (2H, m, thiophene + furan); 7.58 (1H, d, J 1.5 Hz, furan). The furan derivatives (3) and (14) were identical (nmr, ir, uv and TLC) to the corresponding racemic compounds prepared previously by total synthesis.

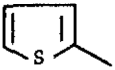
Moffatt oxidation of the alcohol (7)[9], followed by treatment of the crude aldehyde with 1:1 dioxane/2N hydrochloric acid as above, afforded in 20% overall yield the furan (11): mp 208-210°, $[\alpha]_D$ + 53° (C=0.5, dioxane); nmr (DMSO-d_6): 3.80 (2H, bs, 2-CH_2); 4.80 (2H, s, CH_2CCl_3); 5.19 (1H, d, J 4.5 Hz, 6-H); 5.43 (1H, d, J 8.5 Hz, CH Ph); 5.77 (1H, dd, J 4.5, 8 Hz, 7-H); 7.1-7.6 (6H, m, phenyl + furan); 7.78 (1H, d, J 1.5 Hz, furan); 8.42 (1H, d, J 8.5 Hz, NH) 9.28 (1H, d, J 8 Hz, NH).

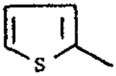
The preparation of furo[3,4-c]cephams substituted in the 4'-position was investigated both by starting with a 4-ketone group in place of the 4-aldehyde group, or by carrying out electrophilic substitution reactions on the unsubstituted furo[3,4-c]cepham.

In the first case, the known acetyl derivative 9[8] was treated as above with dioxane/2N hydrochloric acid. Obtained was a 20% yield of the 4'-methylfuran (12) mp 238-239°; $[\alpha]_D$+ 254° (C=0.5, dioxane); nmr (DMSO-d_6): 2.39 (3H, s, CH_3); 3.74 (2H, s, thiophene methylene); 3.85 (2H, s, 2-CH_2); 5.19 (1H, d, J 4.5 Hz, 6-H); 5.70 (1H, dd, J 4.5, 8.5 Hz, 7-H); 6.8-7.0 (2H, m, thiophene); 7.2-7.5 (1H, m, thiophene); 7.41 (1H, bs, furan); 9.12 (1H, d, J 8.5 Hz, NH).

In the second, the furan (3) was subjected to the Vilsmeier reaction (DMF/$POCl_3$), and a 40% yield of the aldehyde (13)[10] was obtained: mp 214-218°; uv (EtOH) 295 nm (ε 13,700); nmr (acetone-d_6): 3.88 (2H, s, thiophene methylene); 4.00 (2H, s, 2-CH); 5.47 (1H, d, J 5 Hz, 6-H); 6.04 (1H, dd, J 5, 9 Hz, 7-H); 6.8-7.4 (3H, m, thiophene); 7.82 (1H, bs, furan); 9.86 (1H, s, CHO).

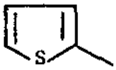


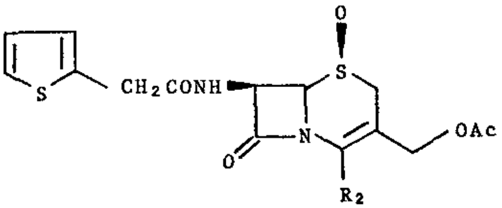
1 R_1 =  CH_2, R_2 = CO_2H

4 R_1 =  CH_2, R_2 = CH_2OH

7 R_1 = $PhCH(NHCO_2CH_2CCl_3)$, R_2 = CH_2OH

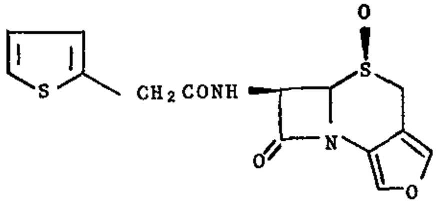
8 R_1 = $PhCH(NHCO_2CH_2CCl_3)$, R_2 = CHO

9 R_1 =  CH_2, R_2 = $COCH_3$



5 R_2 = CH_2OH

6 R_2 = CHO



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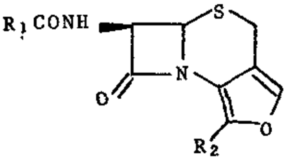
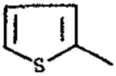
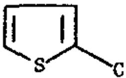
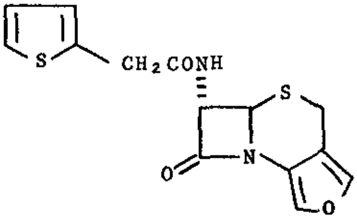


11 R_1 = $PhCH(NHCO_2CH_2CCl_3)$, R_2 = H

12 R_1 =  CH_2, R_2 = Me

13 R_1 =  CH_2, R_2 = CHO



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Compounds (3) and (13) were tested *in vitro* against several strains of gram-positive and gram-negative bacteria[11]. Compound (3) inhibited the growth of *S. Aureus* at 3 μg/ml but was inactive against the other organisms at 100 μg/ml. Substance (13) showed no antibacterial activity at the 100 μg/ml level against the test organisms.

REFERENCES

1. Syntex contribution #467 from the Institute of Organic Chemistry.
2. J. A. Edwards, A. Guzman, R. Johnson, P. J. Beeby, and J. H. Fried, *Tetrahedron Lett.*, 2031 (1975).
3. R. R. Chauvette, and E. H. Flynn, *J. Med. Chem.*, 9, 741 (1966).
4. P. J. Beeby, *J. Med. Chem.*, submitted for publication.
5. The sulfoxy-aldehyde (5) was significantly more stable than the aldehyde (2).
6. All new compounds gave correct elemental analyses.
7. The chemical shifts given are those of the midpoints of the doublets of the AB quartet, rather than the true chemical shift.
8. T. Jen, B. Dienel, J. Frazee and J. Weisbach, *J. Med. Chem.*, 15, 1172 (1972).
9. Prepared *via* reduction using lithium tris(t-butoxy)aluminum hydride of the corresponding acid chloride, available starting with cephaloglycin.
10. The 4'-isomer product was assumed on mechanistic grounds, but has not yet been definitely established.
11. The following test organisms were employed: *S. Aureus* (ATCC# 6538P), *Str. Pyogenes* (ATCC# 8668), *E. Coli* (ATCC# 25922-1), *K. Pneumoniae* (ATCC# 10031-2), *Pr. Vulgaris* (ATCC# 9484).