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A NEW TOTAL SYNTHESIS OF (±)-DESACETYLCEPHALOTHIN LACTONE. A SYNTHESIS OF NOVEL FURO[3,4-c]CEPHAMS.[1]

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The synthesis of β-lactams is readily achieved by the cycloaddition of a ketene to a Schiff's base, a reaction discovered by Staudinger[3] in 1907, and utilized by Bose, et al.[4] as a route to 6-epi-penicillins.

This communication describes the synthesis of a series of β-lactams of the cephalosporin type utilizing the reaction of azidoacetyl chloride/triethylamine with 4H-furo[3,4-d]-1,3-thiazine (1) to construct the biologically important cepham nucleus.[5,6]

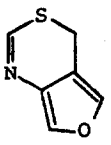
The synthesis of the intermediate thiazine was achieved as follows. Partial saponification (1 equiv. NaOH in MeOH) of diethyl furan-3,4-dicarboxylate (2) gave the monoester 3[7], mp 137° (95%), which was converted into the acid chloride 4, mp 65° (84%) by heating with purified thionyl chloride in benzene. Treatment of 4 with sodium azide in aqueous ether (0-5°) furnished the unstable azide 5, mp 58-60° (dec.), which was transformed via the isocyanate to the N-formyl ester 6, mp 164-165° (75% from monoacid 3) by heating in boiling benzene (30 min.), followed after cooling by exposure to anhydrous formic acid. The N-formyl ester 6 was reduced with $LiAlH_4$ in glyme (0°; 15 min.) and the resulting carbinol 7, mp 122-124° (68%), in turn treated with triphenylphosphine-CCl_4 in DMF[8] to yield 3-chloromethyl-4-formamidofuran (8), mp 109.5-111° (dec.) (54%).

When a solution of the chloride 8 in dry THF under nitrogen was allowed to react with P_2S_5 (42°, 1.25 hr), followed after cooling by stirring with 10% NaOH

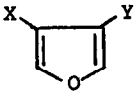
and isolation with ether, the crystalline thiazine 1 was obtained. This substance rapidly polymerized in the solid state ($t_{\frac{1}{2}}$ ca. 15 min.) but solutions of 1 in CH_2Cl_2 or ether could be kept for several days without deterioration. The structure of the thiazine 1 is based on its nmr spectrum, (CCl_4) δ: 4.15 (d, J 1Hz, 4-H), 7.10 (dd, J 1Hz, 5-H), 7.51 (d, J 1Hz, 7-H), 7.87 ppm (s, 2-H), and subsequent chemical transformations.

Sequential addition of triethylamine (5.5 equiv.) and azidoacetyl chloride (5 equiv.) in CH_2Cl_2 in 5 portions[9] to a solution of the thiazine 1 [from 8 (1 equiv.)] in CCl_4/CH_2Cl_2, followed after workup by silica gel chromatography furnished the trans-azido-β-lactam 9, mp 94-96° (45% from 8); ir (KBr) 2125, 1765 cm^{-1}; nmr ($CDCl_3$) δ: 3.84 (broad s, 2-H), 4.69, 4.84 (two d, J 2Hz, 6-H and 7-H), 7.28 (broad d, J 1.5Hz, 3a-H), 7.61 ppm (d, J 1.5Hz, 4a-H). Reduction of azide 9 with 22% ammonium sulphide solution in methanol (20°) furnished the amine 10, mp 105° (95%); ir (KBr) 3400, 1760 cm^{-1}; nmr ($CDCl_3$) δ: 3.76 (broad s, 2-H), 4.28, 4.64 (two d, J 2Hz, 6-H and 7-H), 7.20 (broad s, 3a-H), 7.58 ppm (d, J 1.5Hz, 4a-H), which was converted into the cis-amide 13 in the following manner. Treatment of 10 with p-nitrobenzaldehyde in benzene[10] afforded the Schiff base 11[11], mp 202-204° (73%), ir (KBr) 1770, 1515 cm^{-1}; nmr ($CDCl_3$) δ: 3.87 (broad s, 2-H), 4.97 (t, J 2Hz, 7-H), 5.11 (d, J 2Hz, 6-H), 7.27 (broad d, J 1.5Hz, 3a-H), 7.63 (d, J 1.5Hz, 4a-H), 7.8-8.4 (m, AA'BB' pattern, aromatic-H), 8.60 ppm (d, J 2Hz, CH=N), which was equilibrated to a 1:4 mixture of 7β- and 7α-Schiff bases, respectively, on treatment with DBN in benzene.[14] Hydrolysis of this mixture with Girard's reagent P[15] afforded a mixture of amines which was acylated directly with thiophene-2-acetyl chloride in $CHCl_3$-NEt_3. Purification by preparative tlc on SiO_2 (EtOAc/C_6H_6 1:5) furnished the desired cis-lactam 13, mp 255-257° (10% based on 11), ir (KBr) 1775, 1660 cm^{-1}; nmr (acetone-d_6) δ: 3.85 (s, α-CH_2), 3.91 (s, 2-H), 5.27 (d, J 4.5Hz, 6-H), 5.85 (dd, J 4.5, 9Hz, 7-H), 6.8-7.4 (m, thienyl-H), 7.44 (d, J 1.5Hz, 3a-H), 7.59 ppm (d, J 1.5Hz, 4a-H), and the trans-lactam 12, mp 204-206° (42% based on 11), ir (KBr) 1775, 1660 cm^{-1}; nmr (DMSO-d_6) δ: 3.75 (s, α-CH_2), 3.90 (s, 2-H), 4.81 (dd, J 2, 8Hz, 7-H), 4.99 (d, J 2Hz, 6-H), 6.8-7.4 (m, thienyl-H), 7.56 (d, J 1.5Hz, 3a-H), 7.78 ppm (d, J 1.5Hz, 4a-H).

Transformation of the furan 13 into racemic desacetylcephalothin lactone (14)[6c] was achieved by bromination of 13 in acetic acid in the presence of KOAc to yield the mixture of isomeric diacetates 15, which was rearranged without purification to 14[16], (40% from 13); ir 1800, 1765 cm^{-1}; nmr (acetone-d_6) δ: 3.78 (AB_q, J_{AB} 18Hz, 2-H), 3.85 (s, α-CH_2), 4.98 (s, 3'-H), 5.12 (d, J 5Hz, 6-H), 5.87 (dd, J 5, 9Hz, 7-H), 6.8-7.4 ppm (m, thienyl-H), by brief treatment with p-toluenesulphonic acid in boiling chloroform. The racemic lactone 14 was identical (tlc, uv, ir, nmr and ms) with authentic (+)-14, mp 230-234° (lit.[17] reports mp 230-232°), prepared by exposure of Keflin to dioxane-hydrochloric acid.[17]



1



2 X = Y = CO_2Et

3 X = CO_2H, Y = CO_2Me

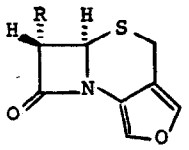
4 X = COCl, Y = CO_2Me

5 X = CON_3, Y = CO_2Me

6 X = NHCHO, Y = CO_2Me

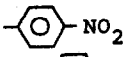
7 X = NHCHO, Y = CH_2OH

8 X = NHCHO, Y = CH_2Cl

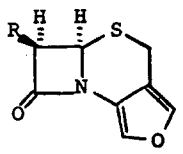


9 R = N_3

10 R = NH_2

11 R = N=CH- 

12 R = $NHCOCH_2$- 



13

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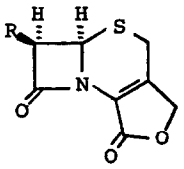

14

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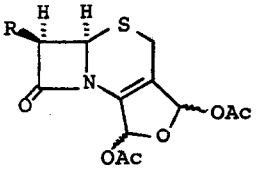

15

R = $NHCOCH_2$- 

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2. Syntex Postdoctoral Fellow; (a) 1971-1972; (b) 1972-1973; (c) 1973-1974.

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