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SYNTHESIS OF 2-OXO-BISNORPENICILLIN G ESTERS

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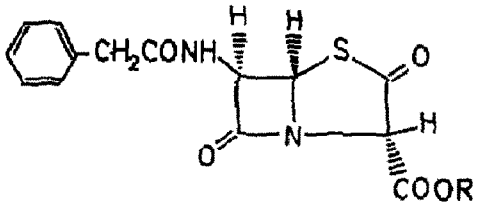
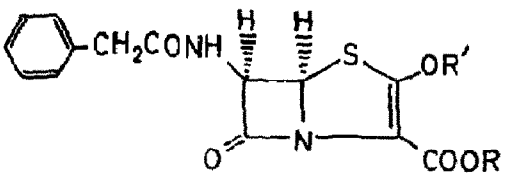
Summary : Using penicillin G as starting material, a synthetic route for the novel 2-oxo-bisnorpenicillin G esters 1 has been developed. These oxopenams are precursors of 2-alkoxy-penems 2.

The isolation of thienamycin[1] a broad spectrum β-lactam antibiotic with unusual structural features[2] has prompted considerable synthetic efforts toward structures possessing the penem[3] or carbapenem[4] nuclei.

In this communication we wish to describe our efforts toward the synthesis of the new 2-oxo-bisnorpenicillin G esters 1 which are potential precursors of 2-alkoxypenems 2.



1

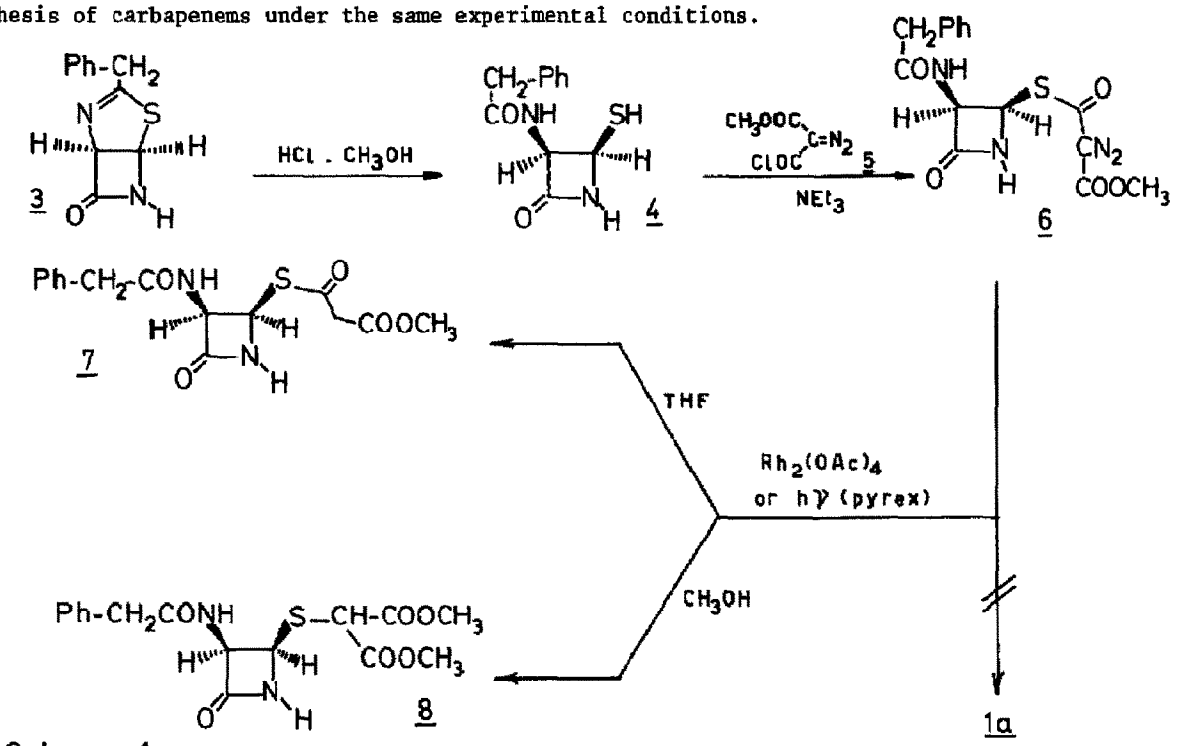


2

In considering synthetic approaches to 1, we were intrigued by the possibility to construct the bicyclic nucleus by forming the N-C_3 bond by a carbene insertion reaction[5].

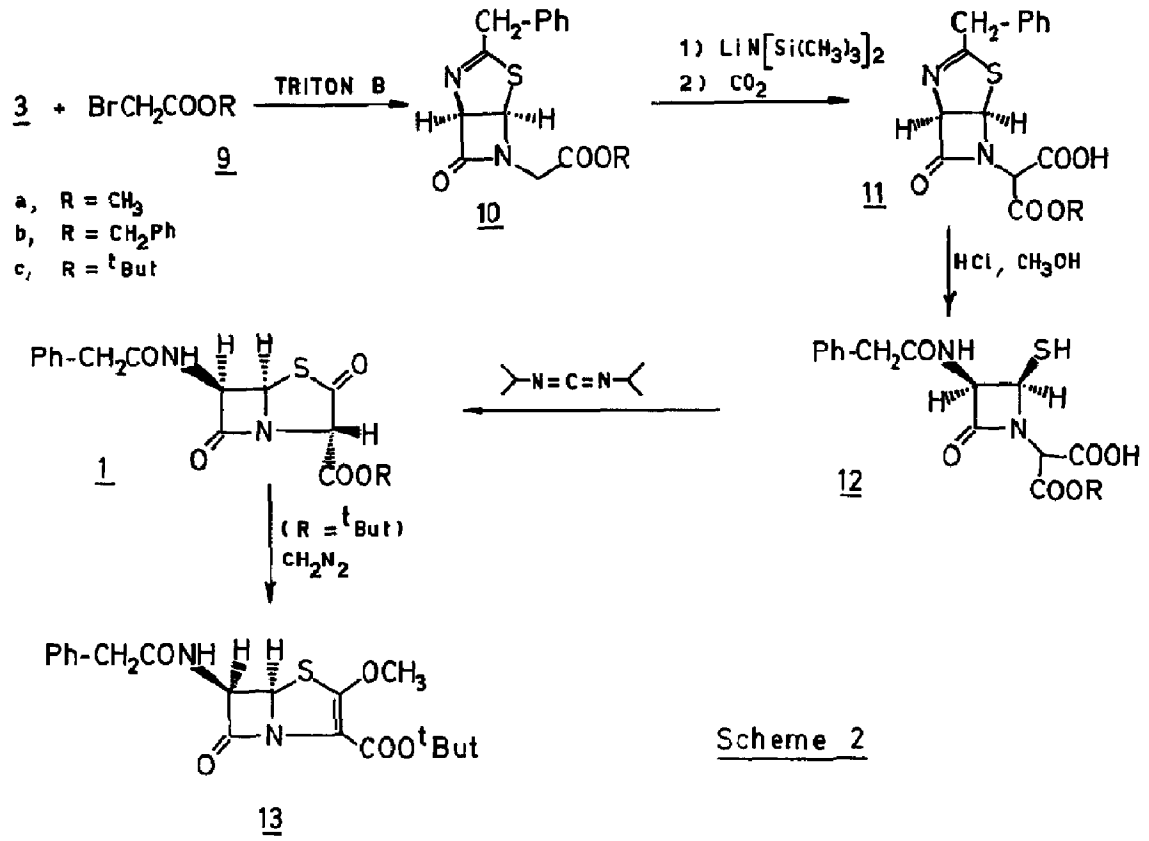
Treatment of the known[6] bicyclic β-lactam 3 with 1 N HCl in methanol (2 equiv. HCl, 20°C, 30 min) yielded the monocyclic β-lactam 4[7] (90%) which readily reacted with 5[8] (1 equiv. Et_3N, 0°C, CH_2Cl_2) to give the carbene precursor 6 (97 % crude). The decomposition of 6 was examined under a large variety of conditions. The expected cyclization leading to 1a (R=CH_3) was never observed. Both photolysis (Pyrex filter) or rhodium (II) acetate catalyzed decomposition (Scheme 1) gave identical products : in tetrahydrofuran, 7 was obtained as a result of hydrogen abstraction from the solvent. In methanol, 8 was formed via Wolff rearrangement to a ketene which is trapped by the solvent.

Rhodium (II) acetate catalysed decomposition in benzene gave a very complex mixture of products. These results sharply contrast with a recent report[4c] describing a successful synthesis of carbapenems under the same experimental conditions.



Scheme 1

Our second approach toward the oxopenam nucleus 1 involved a ring closure by formation of the S-C_2 bond. Treatment of 3 with the bromoacetates 9 (1 equiv. Triton B, DMF, - 30° to 0°C, then addition of 1,2 equiv. 9, -30°C to 20°C, work-up with H_2O - ethylacetate and column-chromatography) yielded 10 a-c[9]. The N-substituted β-lactams 10 were reacted successively with lithium hexamethyldisilazide (4 eq. in THF, - 60°C, 30 min) and dry CO_2 (bubbling for 2 hrs, -60°C to 0°C) to give 11 after work-up (0.1 N HCl, ethylacetate, 0°C, and washing the crude solid with ether, 80 - 90%). Acids 11 are mixtures of diastereoisomers. Mild hydrolysis (1N HCl in CH_3OH + 10% ethylacetate, 20° C, 30 min) liberated the acylamino side chain and the thiol group without effecting the decarboxylation of the malonic halfester. The final step was directly effected on crude 12 (1 eq. diisopropylcarbodiimide, CH_2Cl_2, - 60°C to 20°C). Pure 2-oxo-bisnorpenicillin G esters 1 a-c[10] were obtained after column-chromatography(silica-gel, ethylacetate-benzene 20 : 80) and recrystallization from ether. Spectral data[11] supported the proposed structures. The short-wavelength stretching absorption (1800 cm^{-1}) is characteristic[3a] of a strained β-lactam. We found no evidence for the enol tautomer in either the crystalline or solution state.



Treatment of the 2-oxo-bisnorpenicillinate 1c with diazomethane (20 equiv. in ether-CH_2Cl_2, 20°C, 4h) yielded the 2-methoxypenem derivative 13[12] (60% after column-chromatography on silica-gel, ethylacetate-benzene 30:70; m.p. 49-51°C, after crystallization in ether/petroleum ether).

The extension of this methodology to the synthesis of novel antibiotics will be reported in due course.

Acknowledgements:

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9. 10a : 73% ; mp : 51°C.
10b : 47% ; mp : 113.5°C.
10c : 75% ; mp : 127.5°C.

10. 1a ; 36% ; mp : 148.5°C ; α_D = + 308.2° ($CHCl_3$; c = 0,28%).
1b : 31% ; mp : 107°C ; α_D = + 265.4° ($CHCl_3$; c = 0.59%).
1c : 65% ; mp : 123°C ; α_D = + 276.4° ($CHCl_3$; c = 0,53%).

11. 1a : $\nu(CH_2Cl_2)$: 3400, 1800, 1753, 1725, 1685 cm^{-1}
$\delta(CDCl_3)$: 3.61 (s,2,$PhCH_2$); 3.83 (s,3, $COOCH_3$); 4.91 (s,1,H-3); 5.78 - 6 (mult.,2,H-5+H-6); 6.30 (broad d,1,NH) and 7.30 (broad s,5,Ph).
Mass : 334 (M^+, 43%); 274 (M-COS, 15%); 160(M-$PhCH_2CONH$-CH=C=O, 100%); 175 (50%).

1b $\nu(CH_2Cl_2)$: 3400, 1800, 1755, 1730, 1690 cm^{-1}
$\delta(CDCl_3)$: 3.60 (s, 2, $PhCH_2$); 4.93 (s,1,H-3); 5.21 (s,2 $COOCH_2Ph$); 6-5.76 (mult, 2,H-5 + H-6); 6.4 (broad d,1, NH); 7.33 (broad s,10, Ph)
Mass : 410 (M^+, 31%); 350 (M-COS, 9%); 236(M-$PhCH_2CONH$-CH=C=O, 58%); 175 (62%)

1c $\nu(CH_2Cl_2)$: 3400,1800, 1738 (broad), 1687 cm^{-1}
$\delta(CDCl_3)$: 1.50 (s,9, tBut) ; 3.60 (s,2, $PhCH_2$); 4.82 (s,1,H-3); 6.03-5.83 (mult, 2, H-5 + H-6); 6.36 (broad d, 1,NH); 7.33 (broad s,5 Ph).
After D_2O exchange (100 MHz) : 1.50 (s,9,tBut), 3.60 (s,2,$PhCH_2$); 5.82 (ABq, J=4Hz, 2,H-5 + H-6)
Mass : 376 (M^+, 63%); 316 (M-COS, 2%); 202 (M-$PhCH_2CONH$-CH=C=O, 49%), 175 (53%)

12. $\nu(CH_2Cl_2)$: 3400, 1795, 1690 (broad)cm^{-1}
$\delta(CDCl_3)$: 1.50 (s,9 tBut); 3.63 (s,2,$PhCH_2$); 3.97(s,3,OCH_3); 5.6 - 5.83 (mult. 2, H-5 + H-6; 6.5 (broad, 1, NH); 7.33 (s,5,Ph).

Note added in proof :

Structures related to 1 and 2 have been recently reported in a Japanese Patent : Jpn. Kokai Tekkyo Koho 79 66, 695 - C.A. 91 193300 h (1979).

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