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SYNTHESIS OF 2-METHOXY- AND 2-PHENOXYPENEMS

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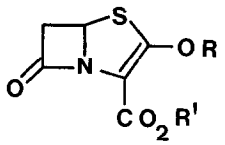
Summary: The 2-methoxy- and the novel 2-phenoxypenems 1b and 1a were synthesised from the corresponding 4-allylsulphinylazetidinones 2b, 2a by thermolysis in the presence of triphenylphosphine.

We have previously described[1] the synthesis of 2-alkylpenems using a phosphine-mediated desulphurisation of a 2-thiacephem, and of a 2-acylthiopenem from a 3-acetylthio-2-thiacephem, itself prepared by means of an allylic sulphoxide - allyl sulphenate rearrangement[2]. As part of our studies on the use of this allyl sulphoxide - sulphenate rearrangement for the synthesis of bicyclic β-lactams we wish to describe a one-pot conversion of the 4-allylsulphinylazetidinones 2a and 2b to the corresponding penems 1a and 1b.



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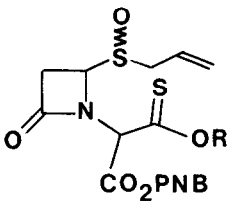
1a: R = Ph R' = PNB
1b: R = CH_3 R' = PNB
1c: R = Ph R' = Na
1d: R = CH_3 R' = Na

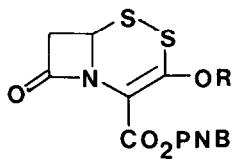
PNB = p-nitrobenzyl

Some 2-alkoxypenems 1 are reported as being prepared by treatment of 2-oxopenams with diazoalkanes[3], or by ring closures of a 2-(4-(O-alkylxanthyl)azetidinon-1-yl)-2-triphenylphosphoranyl)-acetate[4].

The thionoesters 2a and 2b (as the thioenol tautomers) possess both the thiol and latent sulphenate ester moities; we hoped that thermolysis in an inert solvent would yield the desired 2-thiacephems 3a and 3b, which could then be desulphurised with a phosphine to the corresponding penems.

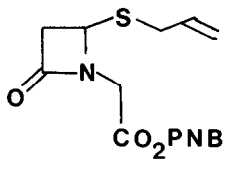


2a: R = Ph
2b: R = CH_3



3a: R = Ph
3b: R = CH_3

Treatment of the previously reported 4-allylthioazetidinonyl acetate 4[2] with $LiN(SiMe_3)_2$ (2.25 eq., THF, -78°) followed by ClCSOPh afforded a solution of the lithium salt 5a. Protonation with acetic acid gave in 69% yield the thionomalonate 6a[7] which was somewhat unstable and was purified by rapid silicagel chromatography only with difficulty ν_{max} ($CDCl_3$) 1770 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) 3.10 (dd, J 16 and 3 Hz, H-3), 3.28 (d, J 7 Hz, SCH_2), 3.55 (dd, J 16 and 5 Hz, H-3), 4.9-6.5 (7H, m, H-4, $CH{=}CH_2$, CO_2CH_2 and $CHCO_2$), 6.8-7.8 (9H, m, aromatic). Oxidation of 6a with m-chloroperbenzoic acid (1 eq., ethyl acetate, -20°C) and subsequent rapid chromatography afforded the corresponding allylsulphinyl compound 2a as a somewhat unstable yellow oil (90%) ν_{max} ($CDCl_3$) 1787 cm^{-1}. Thermolysis (60-120°) of 2a in a range of solvents (dioxane, DMF, toluene, xylene) gave, however, no trace of the desired 2-thiacephem 3a (by ^{1}H-n.m.r.); instead the only isolable material was the thiazepinone 7[8].



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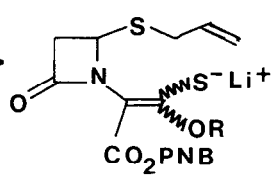
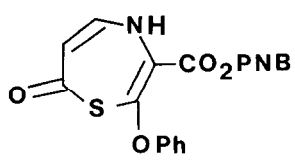
(i) $LiN(SiMe_3)_2$
(ii) ClCSOR



5a: R = Ph
5b: R = CH_3



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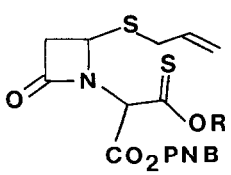
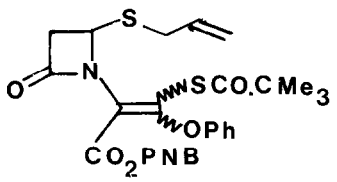


6a: R = Ph
6b: R = CH_3

Reasoning that the desired 3-phenoxy-2-thiacephem might be unstable to the reaction conditions, we repeated the thermolysis (100°, dioxane, 15 min.) in the presence of a trapping agent triphenylphosphine (1.1 eq.) and obtained as the sole β-lactam product the desired 2-phenoxypenem 1a in 18% yield after silicagel chromatography {m.p. 112-114° dec., ν_{max} ($CDCl_3$) 1794 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) 3.43 (dd, J 16 and 1.8 Hz, H-3), 3.87 (dd, J 16 and 3.4 Hz, H-3), 5.43 (2H, AB, J_{gem} 14 Hz, CO_2CH_2), 5.70 (dd, J 3.4 and 1.8 Hz, H-5), 7.0-7.5 (5H, m, C_6H_5), 7.7 and 8.3 (4H, AB, J 9 Hz, p-C_6H_4)}.

In order to overcome the instability and purification difficulties associated with the thionomalonates 6a and 2a, it was found to be more convenient if 5a was treated *in situ* (0 to 20°) with pivaloyl chloride to afford the S-pivalate 8[9]. Subsequent oxidation with m-chloroperbenzoic acid (1 eq., ethyl acetate, -20°) afforded the corresponding mixture 9[10]. Treatment of 9 with imidazole (1 eq., dioxane/water (9/1 v/v), 5°) and subsequent partition of the crude product between ethyl acetate and 0.1M HCl gave in 90% yield 2a pure without the need for chromatography.



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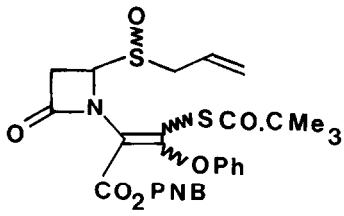

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To confirm the applicability of our sequence also for a 2-alkoxypenem, methyl chlorothionoformate was used to form analogously 6b {26%, ν_{max} ($CDCl_3$) 1755, 1770 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) 3.07 (dd, J 16 and 3 Hz, H-3), 3.24 (d, J 7 Hz, SCH_2), 3.50 (dd, J 16 and 6 Hz, H-3), 4.13 (OCH_3), 5.02 (dd, J 6 and 3 Hz, H-4), 5.31 (s, $CHCO_2$)}, which was by the above procedures converted to the corresponding 2-methoxypenem 1b {48%, ν_{max} ($CDCl_3$) 1790 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) 3.45 (dd, J 12 and 2 Hz, H-6), 3.80 (dd, J 12 and 4 Hz, H-6), 4.03 (OCH_3), 5.27 (2H, AB, J 14 Hz, CO_2 CO_2CH_2), 5.62 (dd, J 4 and 2 Hz, H-5), 7.4-8.3 (4H, AB, p-C_6H_4)}.

Finally, the esters 1a and 1b were deprotected in high yield (80-95%) by hydrogenolysis (H_2 (3 atm) Pd/C, $NaHCO_3$, ethyl acetate/water (1/1 v/v)) to the corresponding sodium salts 1c and 1d[11] which displayed significant antibacterial activity against Gram +ve and Gram -ve bacteria[12].

References and Notes:

1. A. Henderson, G. Johnson, K.W. Moore and B.C. Ross, J. Chem. Soc., Chem. Comm., 1982, 809.

2. N.J. Daniels, G. Johnson, B.C. Ross and M.A. Yeomans, J. Chem. Soc., Chem. Comm., 1982, 1119.

3. J. Marchand-Brynaert and L. Ghosez, Tetrahedron Letters, 21, 3085 (1980); Japan Patent J54-66695 to Sankyo.

4. British Patent Application GB 2042 508 to Beechams.

5. A general synthesis is given by P. Reich and D. Martin, Chem. Ber., 98, 2063 (1965), and in Japan Patent J70 37968 to Mitsubishi Chemical Industries.

6. All new compounds gave satisfactory combustion analysis and/or high resolution mass measurement.

7. From the spectroscopic and chromatographic evidence it appears that 6a, 6b, 2a and 2b exist as the thionoesters rather than as the thioenols.

8. ν_{max} ($CDCl_3$) 1710(m), 1525(s) and 1351(m) cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) 5.26 (dd, J 3.7 and ~0.6 Hz, COCH=), 5.41 (s, CO_2CH_2), 6.24 (broad d, J ~3.5 Hz, NH), 6.98 (2H, d, J 7 Hz, o-H), 7.29 (t, J 7 Hz, p-H), 7.40 (2H, t, J 7 Hz, m-H), 7.55 and 8.20 (4H, AB, J 8.2 Hz, C_6H_4), 8.21 (dd, J 3.7 and 3.5 Hz, N-CH=).

9. 8 was isolated by silicagel chromatography as the partially separable E/Z mixture: ν_{max} ($CDCl_3$) 1768 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) : for 8 (major isomer) 1.01 (9H, s), 3.07 (dd, J 2.7 and 15.6 Hz), 3.3-3.5 (3H, m), 5.07-5.2 (2H, m, CH_2=), 5.23 (dd, J 2.5 and 3.5 Hz, H-4), 5.33 (2H, AB, J 13.5 Hz, CO_2CH_2), 5.78-5.94 (m, CH=), 7.02 (2H, d, J 7 Hz, o-H), 7.20 (t, J 8 Hz, p-H), 7.32 (2H, m, m-H), 7.58 and 8.23 (2H, AB, J 9 Hz, p-$C_6H_4NO_2$-); for 8 (minor isomer) 1.05 (9H, s), 3.02 (dd, J 2.8 and 15.5 Hz), 3.2-3.5 (3H, m), 5.07-5.2 (2H, m), 5.2 (dd, J 2.5 and 3.5 Hz), 5.30 (2H, AB, J 13 Hz, CO_2CH_2), 5.7-6.0 (m, CH=), 7.0 (2H, d, J 7 Hz), 7.18 (t, J 8 Hz), 7.30 (2H, m), 7.40 and 8.10 (4H, AB, J 9 Hz).

10. 9 was present as the E/Z and R/S isomer mixture: ν_{max} ($CDCl_3$) 1785 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$) 1.00, 1.02 (major pair), 1.05, 1.06 (minor pair) (9H, 4s, CMe_3), 3.1-3.8 (4H, m), 5.0-5.2 (2H, m), 5.33 (m, H-4), 5.4 (2H, m, CO_2CH_2), 5.7-5.95 (m, CH=), 6.95 and 7.05 (2H, 2d, J 7 Hz, o-H), 7.19 (t, J 7 Hz, p-H), 7.3-7.4 (2H, m, m-H), 7.45 and 8.05 (minor, 2AB, m, p-$C_6H_4NO_2$), 7.60 and 8.22 (major, 2AB, m, p-$C_6H_4NO_2$).

11. 1c: δ (D_2O) 3.48 (dd, J 18 and 1.5 Hz, H-6), 3.80 (dd, J 18 and 3.5 Hz, H-6), 5.70 (dd, J 3.5 and 1.5 Hz, H-5), 7.2-7.5 (5H, m, C_6H_5); 1d: δ (D_2O) 3.67 (dd, J 15 and 2 Hz, H-6), 4.08 (3H, s, OCH_3), 4.03 (dd, J 15 and 4 Hz, H-6), 5.83 (dd, J 4 and 2 Hz, H-5).

12. We thank Mr. J.G. Walmsley (Hoechst Pharmaceutical Research Laboratories) for performing the MIC determinations.

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