SYNTHESIS OF METHYLENE (R)-6-ACETONYLIDENE-3-METHYL-7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPT-2-ENE-CARBOXYLATE PIVALATE

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Abstract——Methylene (Z)-6-acetonylidenepenicillanate pivalate (1 b) a powerful inhibitor of β-lactamases, is converted efficiently into the title compound.

Reports from our laboratories have described the synthesis and the exceptional β-lactamase activity of 6-acetylmethylenepenicillanic acid (1 a)[1-6]. This compound was shown to be more potent than clavulanic acid and sulbactam. As part of a programme directed towards the synthesis of nuclear analogs, we now report the transformation of (1 b) into the analogous penem (11).

Treatment of methylene (Z)-6-acetonylidenepenicillanate pivalate (1 b) with m-chloroperbenzoic acid (1.1 equiv., tetrahydrofuran, 20°C) gave the β-sulfoxide (2)[7] (90%). Reaction of (2) with thiophenol (1 equiv.) in the presence of catalytic amounts of DBN in dichloromethane at 20°C, followed by flash chromatography, gave the adducts (3) (35%) and (4) (30%). Compound (3) was obtained as a diastereomeric mixture. When (4) was heated with 2-mercaptobenzothiazole (1 equiv., toluene, reflux 7h), using the Kamiya[8] procedure, disulfide (5) was obtained in almost quantitative yield. Base-catalysed isomerisation[9,10] (triethylamine, 0.1 equiv., dichloromethane, 4h, 20°C) gave (6 a). Crude disulfide (6 a) was dissolved in a mixture of acetic acid-acetic anhydride (ratio 1:3) and treated at -20°C with triphenylphosphine (1 equiv.) followed by pyridine. The crystalline acetylthio derivative (6 b) was then isolated, after flash chromatography (73%). The isopropylidene compound (6 b) was then ozonised, in dichloromethane at -78°C, to give the oxalyl derivative (7). Reduction of (7) with Zn and acetic acid in dichloromethane at 5°C gave the hemiaminal (8 a) which was subsequently converted by thionyl

chloride-pyridine (1.5 equiv.) in dichloromethane at -20°C to an oily chloride (8 b). The phosphorane (9) was obtained in 80% yield when (8 b) was treated with triphenylphosphine (dichloromethane, reflux 20h). When heated in toluene under reflux (12h) (9) cyclised to the oily penem (10) which was isolated, after flash-chromatography, in 60% yield. The ^{1}H n.m.r. spectra showed the expected resonances for the pivaloyloxymethyl group together with signals at δ ($CDCl_3$) 2.18 (=-Me), 2.27 (CO-Me), 3.18 and 3.38 (C(8)-H,2xd, J 18Hz), 5.62 (C(5)-H) and 7.5 (Ar). The double bond at C(6) was reintroduced in the following manner: (10) was treated with m-chloroperbenzoic acid (1 equiv.) in tetrahydrofuran at -15°C and the mixture was allowed to warm-up to ambient temperature (2h). The (Z)-acetylmethylene penem[11] (11) formed smoothly and was isolated, after flash chromatography, as an orange oil in 80% yield. No (E) isomer was detected. The ^{1}H n.m.r. spectra showed the expected resonances for the pivaloyloxymethyl group together with signals at δ ($CDCl_3$) 2.36 (=-Me and CO-Me), 6.21 (C(5)-H quite a d J 1Hz), 6.61 (C(8)-H); ν_{max} ($CHCl_3$) 1793, 1752, 1725 and 1715 cm^{-1}.

Penem (11) was found to inhibit a number of cell-free β-lactamases derived from both Gram-positive and Gram-negative organims; it turned out to be more potent against the β-lactamase of Proteous vulgaris 1028 than the corresponding penam (1 b). Compound (11) was devoid of any antibacterial activity.

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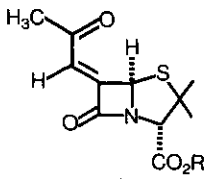
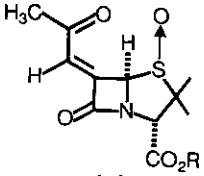


(1)

a; R = H

b; R = $-CH_2OCOC(CH_3)_3$



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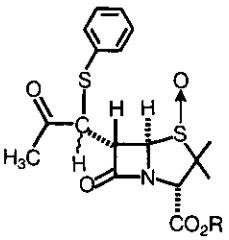

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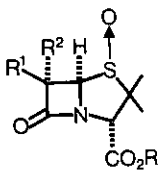

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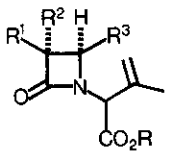

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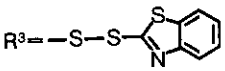

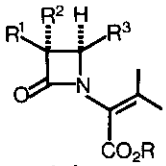

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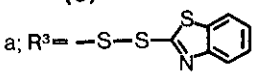
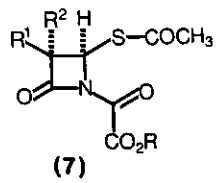


a; $R^3 = -S-S-$

b; $R^3 = -S-COCH_3$



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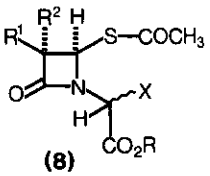
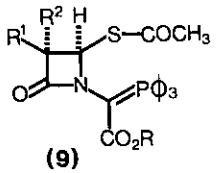


(8)

a; X = OH

b; X = Cl



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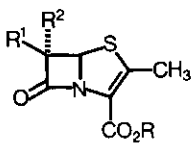

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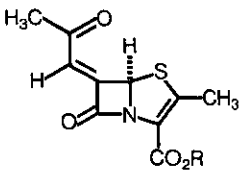

(11)

R = $-CH_2OCOC(CH_3)_3$

$R^1 = -CH_2COCH_3$

$R^2 = -S-$ 

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11. Stereochemical assignment for (11) is based on comparison of its n.m.r. properties with those of related compounds: (1 b) and the corresponding 6 (E) isomer.

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