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SYNTHESIS OF THE 3-ACETOXY-7-OXO-1-AZABICYCLO [3.2.0]HEPT-2-ENE-2-CARBOXYLATE SYSTEM

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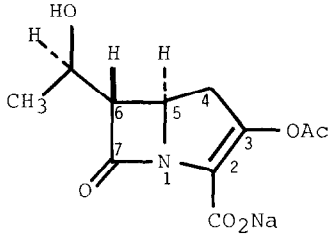
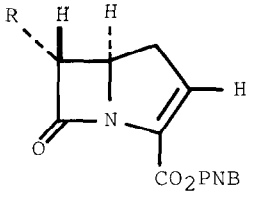
Summary: Lead tetraacetate oxidation of the carbapenem derived ethanethiol adducts (4-6) gave the corresponding 3-acetoxy-3-ethylthio derivatives (7-9). Oxidation to sulphone and elimination of ethylsulphinic acid furnished the 3-acetoxy-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate ester (12). Alternatively, elimination of acetic acid from (7) and (8) provided a new route to alkylthiocarbapenems.

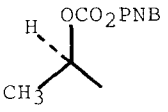
Interest in the preparation of 3-hydroxycephems[1,2] and, more recently, the related penems[3,4] prompted us to consider the synthesis of a comparable derivative (1) in the olivanic acid series. We now report an oxidative functionalisation of alkylthiocarbapenams which permits the introduction of the required acetoxy group.



(1)



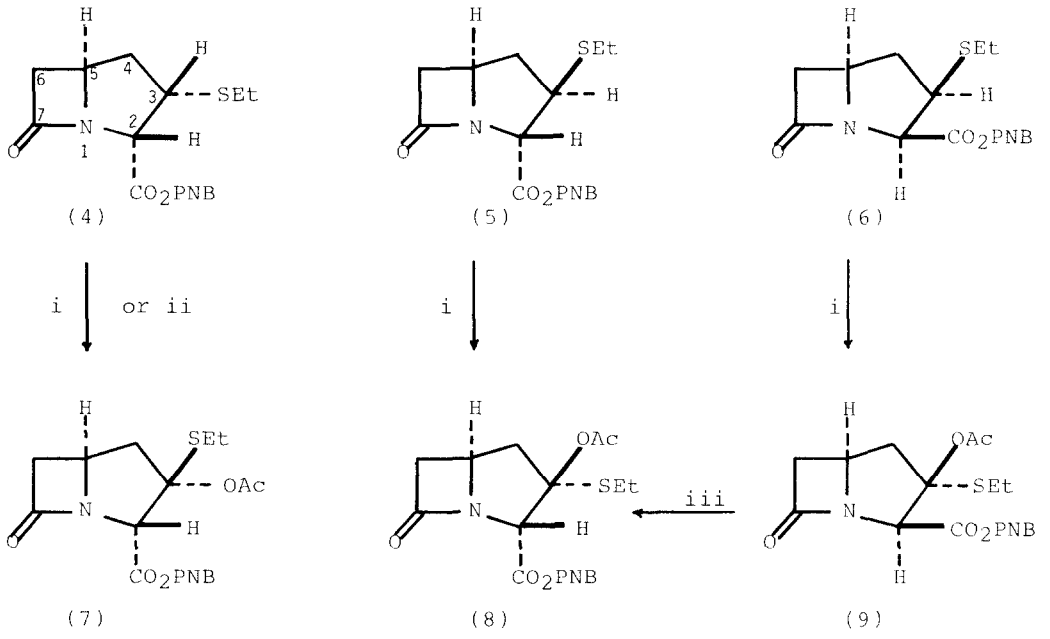
(2) R = H

(3) R = 

PNB = $CH_2C_6H_4NO_2$-p

We have described[5] the preparation and structure assignments of Michael adducts (4-6), obtained by reaction of ethanethiol with the parent Δ^2-ester (2). When a mixture (3:2 ratio) of isomers (4) and (5) was oxidised with lead tetraacetate (2 equiv.) in anhydrous benzene under irradiation (W-lamp, 24h), the 3-acetoxy derivatives (7)[6] and (8) were isolated (3:2, 76%). The reaction also proceeded thermally in refluxing benzene (2h) in comparable yield; pure 2α, 3α-isomer (4) gave (7) exclusively. Although we were unable to obtain samples of (5) uncontaminated by traces of isomer (4), we conclude from the material balance that (8) arises solely from (5). The 2β, 3β-isomer (6) afforded (9)

SCHEME 1



Reagents: i, $Pb(OAc)_4$ (2 equiv.), PhH, Δ, 2h; ii, $PhI(OAc)_2$ (1.2 equiv.), pyridine (2.4 equiv.), CH_2Cl_2, Δ, 4h; iii, DBU (0.1 equiv.), CH_2Cl_2, room temp., 16h.

as the only thermal product (43%). The transformation (4)→(7) was also effected using iodobenzene diacetate - pyridine (60%).

The structures of the acetoxy derivatives (7-9) followed from LIS studies on the individual isomers (7) and (9)[7]. These indicated a 3β-orientation of the ethylsulphinyl group in (7), and of the acetoxy substituent in (9). Isomer (9) was epimerised to (8) by the action of a catalytic quantity of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). We note that in contrast to our related iodobenzene dichloride-mediated α-chlorosulphoxidations of these substrates, for which retention of C-3 stereochemistry is favoured,[5] the lead tetraacetate acetoxylation is seen to proceed with inversion.

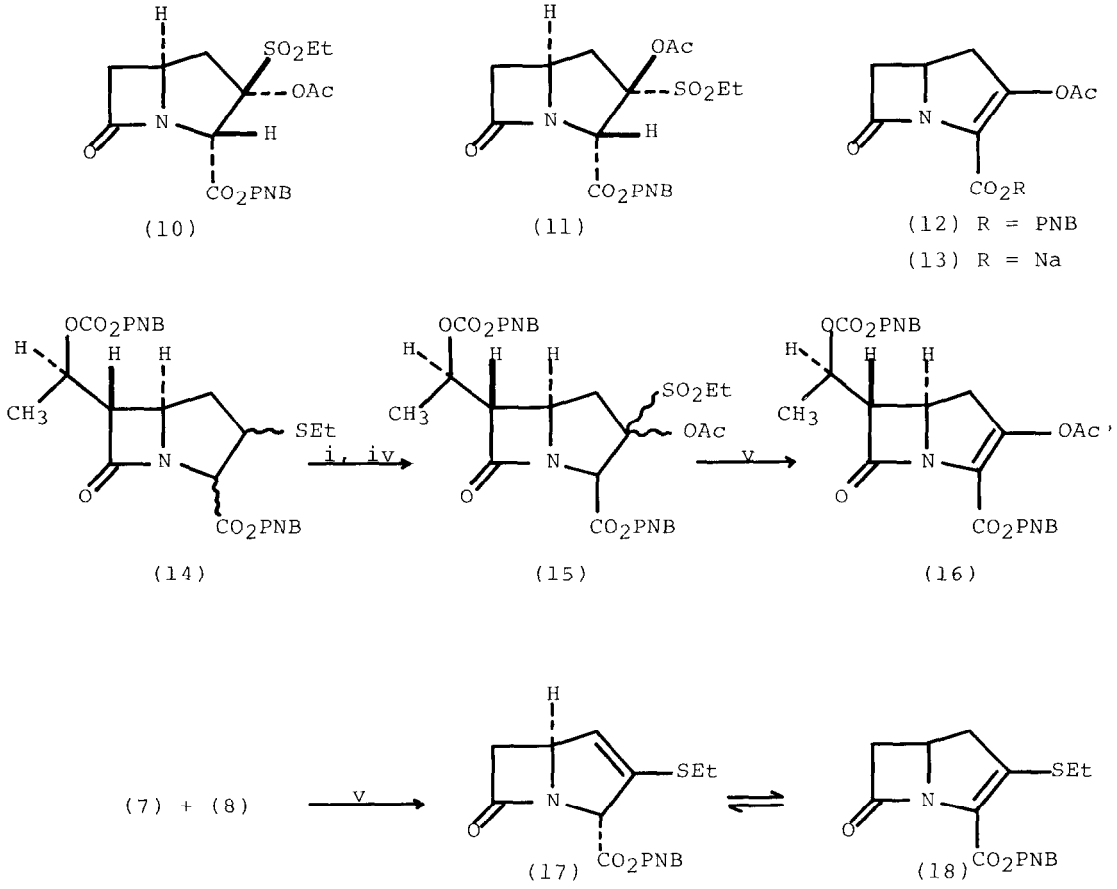
Further oxidation (m-CPBA, 2.2 equiv.) of (7) or (8) gave the respective sulphones (10) (78%) and (11) (60%). Elimination of ethyl sulphinic acid with DBU rapidly afforded the crude enol-acetate (12). Although even flash chromatography (Florisil) caused considerable decomposition, we succeeded thereby in isolating a sample of the pure material (19%).[8] The resulting 3-acetoxy-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate system may be considered as an olivanic acid analogue of the synthetic 3-acetoxy cephalosporins.[12]

Starting from the carbapenem derivative (3)[9], we obtained a mixture of ethanethiol adducts (14), containing a protected 6-hydroxyethyl substituent (thienamycin 5,6,7 - relative stereochemistry). This was subjected to the aforementioned sequence **via** sulphones (15) to provide the 6-substituted enol-acetate (16), which was closely similar in spectral properties to the unsubstituted counterpart (12).

Attempts to isolate sodium salts (1) and (13) after hydrogenolysis of esters (12) and (16), according to our established conditions[10], resulted in degradation. Sodium salts derived from esters (7)-(9) were stable but antibacterially inactive.

We have also demonstrated that lead tetraacetate oxidation provides an alternative route to Δ^2-3-alkylthio compounds related to the olivanic acids (e.g. 18). To this end, a mixture of 3-acetoxy-3-ethylthio derivatives (7) and (8) was treated with DBU in stoichiometric proportions at room temperature. Elimination of acetic acid afforded our previously described[11] equilibrium mixture of (17) and (18).

Scheme 2



Reagents: iv, m-CPBA (2.2 equiv.), CH_2Cl_2, 0°C - rt, v, and (10) or (11)→(12), DBU (1 equiv.), CH_2Cl_2, rt.

References and notes.

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6. All compounds prepared are racemic; one enantiomer is depicted throughout. New compounds were characterised by high resolution mass spectral measurements and/or microanalytical data.

7. Carried out using $Eu(fod\text{-}d_9)_3$ according to principles established in these laboratories for 1-oxadethiapenicillins: **cf.** R.G. Alexander and R. Southgate, J. Chem. Soc., Chem. Commun., 1977, 405.

8. Selected data for (12): λ_{max} (EtOH) 270nm (ε 13,100 $dm^3\ mol^{-1}\ cm^{-1}$); ν_{max} ($CHCl_3$) 1790, 1730, 1640 wk cm^{-1}; δ($CDCl_3$) 2.20 (3H, s, OAc), 3.02 - 3.12 (3H, m, 6-H8 + 4-H_2), 3.56 (1H, dd, J 16 and 6Hz, 6-H_α), and 4.26 (1H, m, 5-H).

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