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REACTIONS OF METHYL 6β- PHENOXYACETAMIDOPENICILLANATE S- AND R- OXIDES WITH N-CHLORO-N-SODIOURETHANE LEADING TO NEW PENAMS AND CEPHEMS

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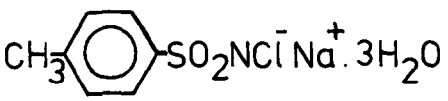
Reagents such as N-chloro-N-sodio-toluene-p-sulphonamide (1) and N-chloro-N-sodiourethane (NCNSU) (2) exhibit an interesting duality of nature in that they may react (a) as sources of chloronium cation, and (b) as sources of sulphonamidate or carbamidate anion. These properties have recently been exploited in a range of structural modifications of penicillanates[1-4] and secopenicillanates.[5] We now report that N-chloro-N-sodiourethane affords certain unique reactions with the S- and R-sulphoxides (3) and (8) of methyl 6β-phenoxyacetamidopenicillanate.



1

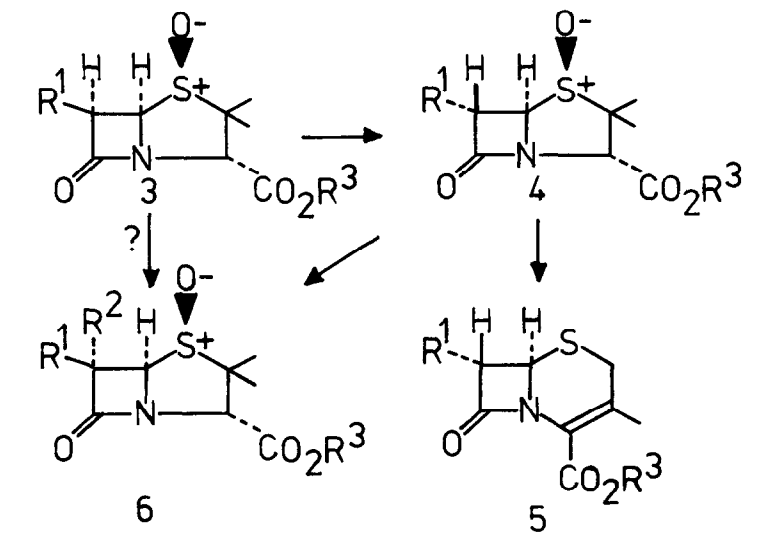
2

In a typical reaction the S- oxide (3)[6] reacted slowly at room temperature with 4 molar equivalents of (2) in N,N-dimethylformamide to give two β-lactam products which were isolated by rapid short-path column chromatography. The more polar product, obtained in 15% yield, was identified as the 6- epi penicillanate (4) by comparison with an authentic sample.[7] Compound (4) is presumably formed via anion (11) which results from carbamidate ion abstraction of 6-H. The less polar β-lactam product (22%) which on t.l.c. was identical in R_f to starting material was obtained as an amorphous solid which was shown by spectroscopic analysis to have structure (6)[≠]: $[\alpha]_D^{25}$ +193° (c. 1.0, $CHCl_3$).

This compound has also been prepared[4] as a mixture of R- and S- sulphoxides by peracid oxidation of the corresponding 6α-ethoxyformamido-6β-phenoxyacetamidopenicillanate.[8]

Compound (6) was also formed (50%) by the reaction of NCNSU with the epi-penicillanate (4). An intermediate N-chloroamide which loses HCl to form a 6-imine is probably involved. Subsequent attack of the carbamidate anion on the α- face of the imine then affords (6) in which the phenoxyacetamido group has been re-epimerised. Also isolated from the reaction mixture was phenoxyacetamidoethylcarbamate (7).[9] (17%) This non-polar product may have arisen from attack of carbamidate anion at the carbonyl group of the phenoxyacetamido side chain. These three reaction products therefore represent three different modes of attack on the penicillanate molecule by (2) and related species.

The epi-penicillanate sulphoxide (4) was converted by acetic-anhydride-dimethylformamide reflux[10] into the epi-cephalosporanate (5).[11]



$R^1 = PhOCH_2CONH-$ $R^2 = EtOCONH-$

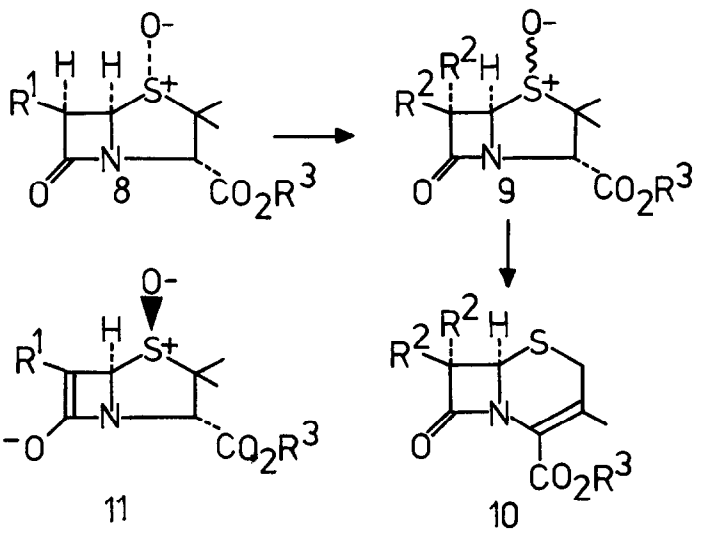
$R^3 = CH_3$

The R- sulphoxide (8) under the same reaction conditions yielded (9)≠ obtained as an oil (69%), the structure of which was conclusively established by ir, nmr and mass spectroscopy. To our knowledge this represents the first example of complete replacement of the 6-acylamino group of a penicillanate. To obtain (9) necessitates the successive formation of two different imino intermediates. Compound (9) has been transformed[10] into the new 7,7-disubstituted cephem (10)≠, obtained as an oil (36%), $[\alpha]_D^{25}+24^\circ$ (C. 0.25, $CHCl_3$).

It is apparent that the different reaction modes of (3) and (8) are a consequence of differing sulphoxide stereochemistry. In S-sulphoxide (3) formation of an N-chloroamide (and thence an imine) is possibly precluded because of proximate effects of the sulphoxide. Thus the favoured reaction involves proton abstraction from C-6 followed by epimerization to (4), which can be converted to an N-chloroamide and thus to (6). The R- sulphoxide (8) can, however, form an N-chloroamide in the first step, and thence a 6-imine and product (9). Similar products were obtained from other penicillanate sulphoxide esters but the trichloroethylpenicillanates afforded complex reactions.

$PhOCH_2CONHCO_2Et$

7



In comparison with similar reactions of penicillanates[1-4] and secopenicillanates[5] we have therefore demonstrated interesting and novel differences in reactivity at various sites in the penam nucleus.

≠ All new compounds gave correct elemental analyses and/or high resolution molecular ion mass measurements, and spectroscopic data.

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