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6α-METHYLSULPHINYL PENICILLINS: USEFUL INTERMEDIATES FOR THE INTRODUCTION OF 6α-SUBSTITUENTS INTO PENICILLINS

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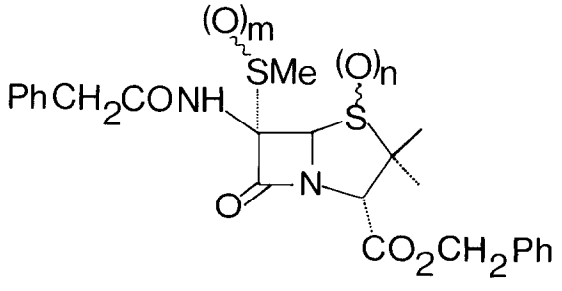
Abstract: A new method for the conversion of 6α-methylthiopenicillins into 6α-methoxy and 6α-formamido penicillins is described.

Over the last decade a wide variety of methods have been developed for the introduction of a 6(7)-α-methoxy group into penicillins and cephalosporins.[1] The insertion of such functionality involves the generation of an electrophilic centre at C-6(7) which is attacked by methanol (or methoxide). In some derivatives this is done directly[2]; in others it is done indirectly by first generating a nucleophilic centre which is reacted with a suitable electrophile to introduce an alkylthio group.[3,4] The sulphur substituent is then replaced by methoxy in a subsequent mercury (II)-mediated reaction[3,4] or by chlorinolysis.[5] In the course of our studies into methods of introducing a 6α-substituent into penicillins, we found a new procedure for the replacement of a 6α-methylthio group by methoxy and other functional groups.

Oxidation of benzyl 6α-methylthio-6β-phenylacetamidopenicillanate (1a) with m-chloroperbenzoic acid (1.1eq., CH_2Cl_2, 0°C) was not selective and after chromatography, the mono- and bis-sulphoxides (1b) (54%) and (1c) (25%) respectively were obtained.[6] The n.m.r. spectrum (250 M Hz) revealed that the mono-oxide (1b) was a 3:1 mixture of isomers and the bis-oxide (1c) a mixture of all possible isomers. As expected, oxidation at sulphur of the 6α-methylthio group caused a downfield shift by 0.5 ppm of the adjacent methyl protons relative to their position in (1a). The C-5 hydrogen is shifted downfield in (1b) and upfield in (1c) relative to its position in the precursor (1a).



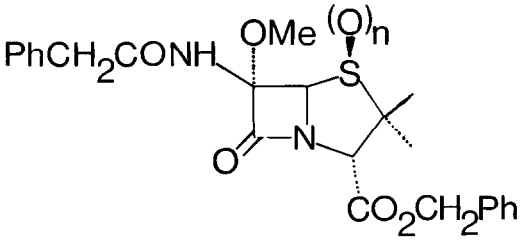
(1a) m = n = 0

(1b) m = 1, n = 0

(1c) m = n = 1

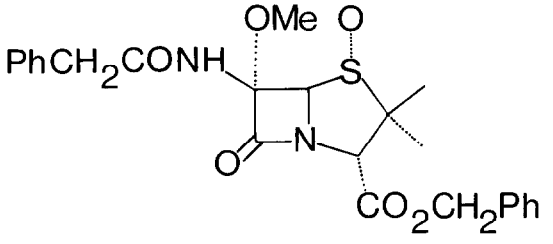
When the mono-sulphoxide (1b) was heated in refluxing methanol for 2h, the 6α-methoxy penicillin (2a) was isolated in 54% yield. Methyl methanethiosulphinate was formed concomitantly, presumably by dehydrative dimerisation of methanesulphinic acid eliminated during the reaction.[7] Alternatively, prolonged treatment (12 days) of (1b) with methanol at ambient temperature afforded (2a) in quantitative yield.

The bis-sulphoxide (1c), when treated with methanol at room temperature, gave the 6α-methoxy penicillin-β-oxide (2b) and the corresponding α-oxide (3) in 47% and 5% yields respectively. However, heating a methanolic solution of (1c) under reflux led to the exclusive formation of the β-oxide (2b) (87%), reflecting the greater thermodynamic stability of (2b) relative to (3).[8] The same product (2b) was obtained (40%), along with the corresponding methyl ester (4) (23%), by treatment of a methanolic solution of (1c) with triethylamine (1 eq., RT,24 h).

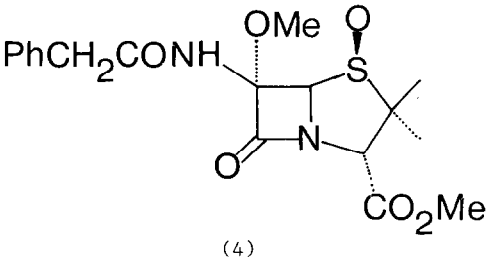


(2a) n = 0

(2b) n = 1

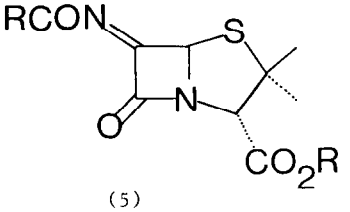


(3)



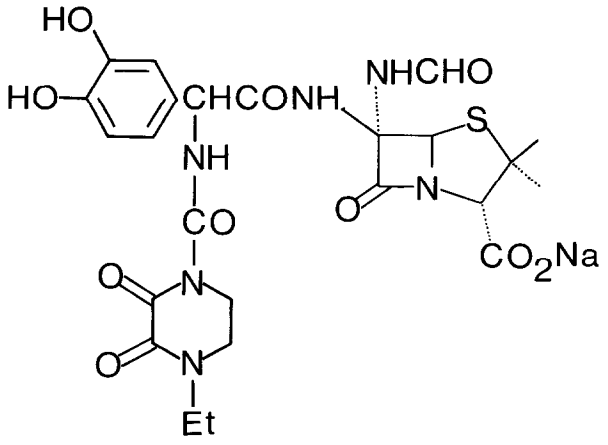
(4)

Acylimines of the type (5) have previously been postulated as the reactive intermediates in 6α-substitution reactions.[2] Indeed, the acylimine (5; R = $PhCH_2$) was detected transiently in the mass spectrum of the mono-oxide (1b). [Observed $\underline{M}^+$, 422.1299; $C_{23}H_{22}N_2O_4S$ requires 422.1300].



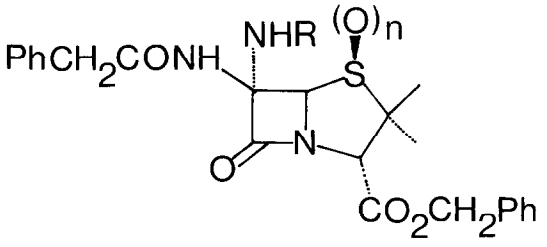
(5)

The utility of 6α-methylsulphinyl penicillins was further extended by their conversion into 6α-formamido penicillins,[9] of which BRL 36650 has been shown to possess potent antibacterial activity.[10]



BRL 36650

Successive treatment of the mono-sulphoxide (1b) with ammonia(2 eq.,CH_2Cl_2,0°C RT) and formic-acetic anhydride gave the 6α-formamido penicillin (6b) (70%) *via* the 6α-amino derivative (6a) (47%). Reaction of the bis-sulphoxide (1c) with ammonia gave only non β-lactam-containing products.



(6a) R = H, n = 0

(6b) R = CHO, m = 0

(6c) R = CHO, n = 1

6α-Formamido penicillins were also obtained by a more direct route. When the mono-sulphoxide (1b) was heated in refluxing THF containing bis-trimethylsilylformamide[11] (4 eq.), the 6α-formamido derivative (6b) (91%) was isolated. Similar treatment of the bis-sulphoxide (1c) for 6h gave a 45% yield of the 6α-formamido-β-oxide (6c).

Finally, when a solution of the mono-sulphoxide (1b) and *bis*-trimethylsilylformamide (4 eq.) was treated with triethylamine (1.1 eq.) (CH_2Cl_2,RT,1.75h), the penicillin (6b) was produced in 48% yield. However, under these conditions the bis-sulphoxide (1c) afforded non β-lactam-containing products.

The process described herein has particular utility in β-lactam ring systems lacking a second sulphur atom (e.g. oxa-cephems, monobactams). Its application in this area will be reported at a later date.

We thank Dr. G. Burton for his advice and interest during the course of this work.

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11. Bis-trimethylsilylformamide has previously been shown to undergo displacement of a 6α-methylthio group in a mercuric (II) acetate mediated reaction. See reference 9.

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