

Synthesis of Racemic 3-Thiacepham-4-carboxylates and their 1,1,3,3-Tetroxides

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Representatives of the title compounds have been prepared from 4-(*cis*- β -methoxycarbonylvinylthio)azetidin-2-one.

Sulbactam sodium salt (1) is a powerful inactivator of a number of β -lactamases produced by pathogenic bacteria.¹ The

inactivation process is believed² to be associated with further reactions of a species of the type (3), formed from a primary

intermediate of the type (2) by a spontaneous β -elimination reaction. Recently, we described³ the preparation of the isopenam (4). This material failed to inactivate the β -lactamase from *Pseudomonas aeruginosa*. In the hope that they would act as β -lactamase inhibitors, we have been interested in the synthesis of 3-thiacephams of the type (5). We now describe our efforts to prepare such compounds.

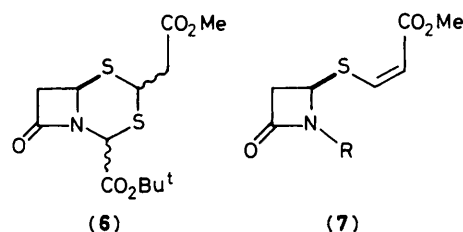
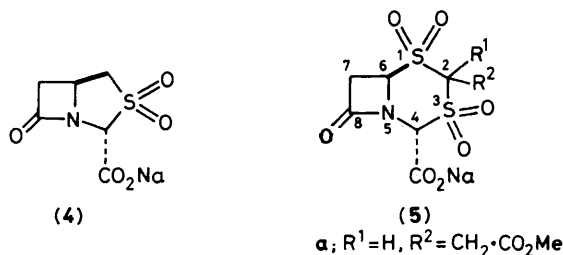
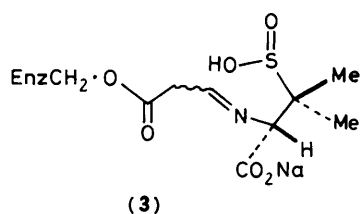
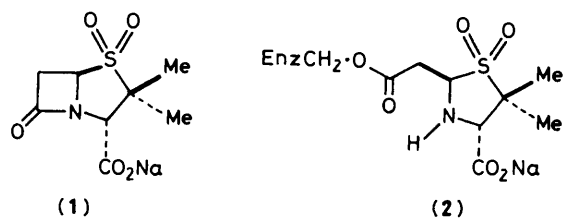
It was envisaged that the 3-thiacepham (6), from which it was hoped to derive the target (5a), would be available from the reaction of hydrogen sulphide with the precursor (7c). Treatment of the readily available azetidinone (7a)⁴ with *t*-butyl glyoxylate and triethylamine in tetrahydrofuran afforded the carbinolamide (7b)[†] (80% yield after SiO₂ chromatography) as a 1:1 mixture of diastereoisomers. Conversion of the carbinolamide (7b) into the chloride (7c) was achieved at -20 °C by the action of 2,6-lutidine and thionyl chloride. Following treatment of the chloride (7c) in dichloromethane at 0 °C with hydrogen sulphide and triethylamine and silica-gel purification of the product, the 3-thiacepham (6), m.p. 124–127 °C, ν_{\max} (KBr) 1765 cm⁻¹, was isolated as a single diastereoisomer. The yield of the compound (6) from the aforementioned procedure was somewhat variable and a more reliable route involved the two-step method of Huffman and his co-workers.⁵ Thus treatment of the chloride (7c) with potassium thioacetate in *N,N*-dimethylformamide gave the thioacetate (7d) (72% yield after SiO₂ chromatography) as a 1:1 mixture of diastereoisomers. In the presence of cyclohexylamine in dichloromethane, the thioacetate (7d) afforded the 3-thiacepham (6) (63% yield after recrystallisation).

On the basis of 250 MHz nuclear Overhauser enhancement (n.O.e.) difference spectroscopy (CDCl₃), the 3-thiacepham

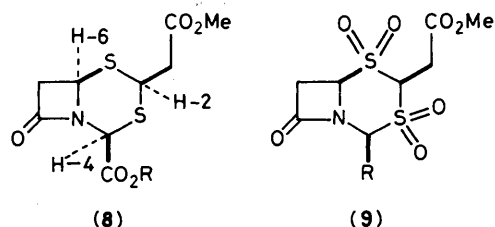
(6) was tentatively assigned the stereostructure (8a). Thus irradiation of the triplet (separation 6 Hz) at δ 4.99 (assigned to H-2) resulted in 4% enhancements of the singlet at δ 5.41 (assigned to H-4) and of the double doublet (*J* 4 and 2 Hz) at δ 5.43 (assigned to H-6).

Oxidation of the 3-thiacepham (8a) with potassium permanganate in aqueous acetic acid gave the disulphone (9a), m.p. 138–139 °C, ν_{\max} (KBr) 1805 cm⁻¹, in 82% yield after recrystallisation.

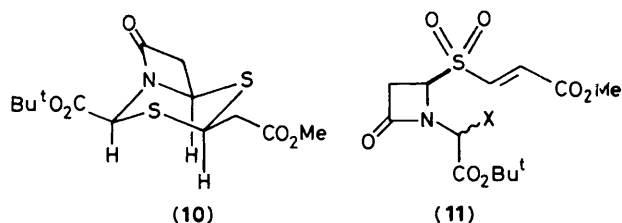
Attempts were made to epimerise the compounds (8a) and (9a) at position 4. Although the former compound was unaffected by the action of 1,5-diazabicyclo[4.3.0]non-5-ene in deuteriochloroform, exchange of the hydrogen atoms at position 4 and the side-chain methylene group occurred when D₂O was present. Evidently, the cyclisation reaction had led to the thermodynamically favoured thiacepham; the preference for the diastereoisomer (8a) is presumably a reflection of the diequatorial disposition of the 2- and 4-substituents in the conformer (10). The compound (9a) reacted readily with triethylamine in dichloromethane to give the azetidinone (11a) (61% yield after SiO₂ chromatography), ν_{\max} (film) 1785 cm⁻¹. Evidently, a β -elimination had occurred to give the sulphinate (11b) which had undergone a spontaneous desulphinylolation.



- a; R = H
b; R = CH(OH)CO₂Bu^t
c; R = CH(Cl)CO₂Bu^t
d; R = CH(S·COMe)CO₂Bu^t



- a; R = Bu^t
b; R = H
c; R = Na
a; R = CO₂Bu^t
b; R = CO₂H
c; R = CO₂Na
d; R = H



- a; X = H
b; X = SO₂⁻

[†] All new compounds were characterised by their spectroscopic properties; correct elemental analyses were obtained for crystalline compounds.

In view of the failure to effect the epimerisations, efforts were made to convert the compounds (8a) and (9a) into the salts (8c) and (9c) for biological evaluation. Trifluoroacetic acid reacted with the compound (8a) to give the acid (8b), m.p. 152—154 °C, in 79% yield after recrystallisation. The salt (8c), obtained by treating the acid (8b) with sodium hydrogen carbonate in water, was stable in D₂O over an 18 h period and showed no antibacterial activity. Although the acid (9b) appeared to be the predominant product of the reaction of the ester (9a) with trifluoroacetic acid, it was converted into the decarboxylated material (9d), m.p. 197—199 °C, when treated with sodium hydrogen carbonate in water. Evidently, the salt (9c) undergoes a spontaneous decarboxylation in aqueous solution. It is noteworthy that its counterpart (4) was stable over a 12 h period under similar conditions. The acid (9b) showed no antibacterial activity and did not act as an ampicillin synergist against β -lactamase-producing bacteria.

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