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 believed[2] 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 described[3] 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 SiO_2 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) 1 765 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 SiO_2 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 ($CDCl_3$), 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) 1 805 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 D_2O 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 SiO_2 chromatography), ν_{max} (film) 1 785 cm^{-1}. Evidently, a β-elimination had occurred to give the sulphinate (**11b**) which had undergone a spontaneous desulphinylation.

(**1**)

(**2**)

(**3**)

(**4**)

(**5**)
a; R^1=H, R^2=CH_2·CO_2Me

(**6**)

(**7**)
a; R = H
b; R = CH(OH)CO_2Bu^t
c; R = CH(Cl)CO_2Bu^t
d; R = CH(S·COMe)CO_2Bu^t

(**8**)
a; R = Bu^t
b; R = H
c; R = Na

(**9**)
a; R = CO_2Bu^t
b; R = CO_2H
c; R = CO_2Na
d; R = H

(**10**)

(**11**)
a; X = H
b; X = SO_2^-

† 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 D_2O 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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References

1 A. R. English, J. A. Retsema, A. E. Girard, J. E. Lynch, and W. E. Barth, *Antimicrob. Agents Chemother.*, 1978, **14**, 414.
2 D. G. Brenner, J. R. Knowles, and G. Rihs, *Biochemistry*, 1981, **20**, 3680.
3 C. M. Pant and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1980, 928.
4 H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6306.
5 W. F. Huffman, R. F. Hall, J. A. Grant, and K. G. Holden, *J. Med. Chem.*, 1978, **21**, 413.