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# SYNTHESIS OF 2-(METHOXYCARBONYL)METHYL-7-PHENYLACETAMIDO-3-THIACEPHAM-4-CARBOXYLATES

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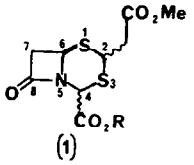
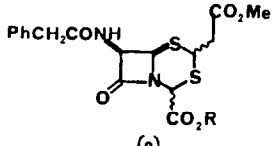
**Summary:** Representatives of the title compounds have been prepared from a benzylpenicillin-derived intermediate.

Recently, we reported[1] the synthesis, in racemic form, of compound **(1a)** - the first representative of the 3-thiacepham family. The derived sodium salt **(1b)** showed no antibacterial activity - a result of no surprise since the presence of a 7β-acylamino-substituent is mandatory for such activity in related systems. We now describe the preparation, in optically active form, of the thiacepham **(2a)** and note that its sodium salt **(2b)** is endowed with weak antibacterial properties.




(1)

**a: R = *t*-Bu**
**b: R = Na**




(2)

**a: R = *t*-Bu**
**b: R = Na**
**c: R = H**

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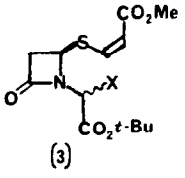
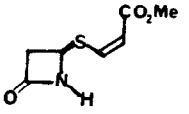
Previously, the thiacepham **(1a)** was obtained as a single diastereoisomer from the reaction of the chloro-compound **(3a)** with hydrogen sulphide/triethylamine or, preferably, of the thioester **(3b)** with cyclohexylamine. The carbinoalamide **(3c)**, which served as a precursor of compounds **(3a)** and **(3b)**, was prepared from the azetidinone **(4)** and *tert*-butyl glyoxylate. It was expected that the thiacepham **(2a)** would be derivable by a similar route and therefore the azetidinone **(5)** became a key intermediate.

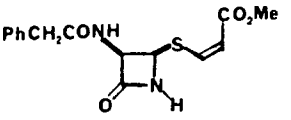



(3)

**a**: X = Cl
**b**: X = SAc
**c**: X = OH



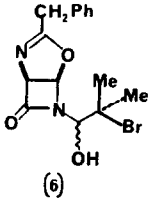

(4)



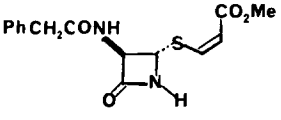

(5)

Although several routes to compound **(5)** were investigated, the only successful one involved treatment of the bromohydrin **(6)**[2] in dichloromethane with *cis*-β-(methoxycarbonyl)vinylisothiouronium chloride[3] (3 mol equiv.) followed by triethylamine (6 mol equiv.). After silica-gel purification, the azetidinone **(5)**, m.p. 171–173°C, $[\alpha]_D$ -58° ($CHCl_3$), was isolated in 35% yield and its diastereoisomer **(7)**, $[\alpha]_D$ -30° ($CHCl_3$), in 33% yield.

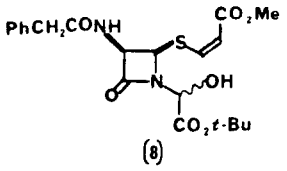
The carbinolamide **(8)**, obtained as a 1:1 mixture of diastereoisomers (84% yield after $SiO_2$ chromatography) from the reaction of the azetidinone **(5)** with *tert*-butyl glyoxylate ($THF/Et_3N$), underwent sequential reactions with thionyl chloride/2,6-lutidine and hydrogen sulphide/triethylamine to give the thiacepham **(2a)** (46% yield after $SiO_2$ chromatography), m.p. 182–183°C, $[\alpha]_D$ +170° ($CHCl_3$), as a single diastereoisomer. By using a similar reaction sequence, the azetidinone **(7)** was transformed into the thiacepham **(9)**, m.p. 163–164°C, $[\alpha]_D$ -24° ($CHCl_3$), as a single diastereoisomer in 20% overall yield.



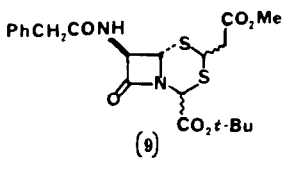

(6)




(7)



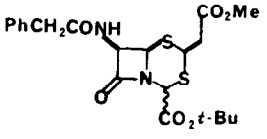

(8)



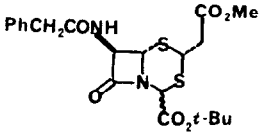

(9)

When treated with trifluoroacetic acid, the ester **(2a)** was converted into the acid **(2c)** (96% yield after recrystallisation), m.p. 196–197°C (decomp.), $[\alpha]_D$ +85° (EtOH), which reacted with sodium hydrogen carbonate to give the salt **(2b)**. The salt **(2b)**, which underwent *ca.* 50% decomposition in deuterium oxide over a 24 hour period, had limited activity against certain bacteria. Thus it showed MIC values of 50 μg $cm^{-3}$ against *Streptococcus pyogenes* and of 12.5 μg $cm^{-3}$ against *Bacillus subtilis*.

The formation of the thiacephams **(1a)**, **(2a)** and **(9)** as single diastereoisomers, from precursors that were mixtures of diastereoisomers, implies that the cyclisation reactions are thermodynamically controlled. On the basis of nuclear Overhauser effect difference (n.O.e.d.) spectroscopy, the thiacephams **(2a)** and **(9)** are considered to possess the same relative arrangement of the 2-, 4- and 6-protons; unequivocally, the 2-and 6-protons are *cis* orientated. Thus, in the case of the thiacepham **(2a)**, irradiation of $H_6$ [a doublet ( $J$ 4 Hz) at δ 5.69 ($CDCl_3$)] caused a 12.5% enhancement of $H_2$ [ a triplet (separation 7 Hz) at δ 5.00 ] and a 1.7% enhancement of $H_4$ (a singlet at δ 5.34). With the thiacepham **(9)**, irradiation of $H_2$ [a triplet (separation 7 Hz) at δ 4.97 ($CDCl_3$)] caused a 8.5% enhancement of $H_6$ [a doublet ( $J$ 2 Hz) at δ 5.35 ] and a 1.3% enhancement of $H_4$ (a singlet at δ 5.37). Clearly, the thiacephams **(2a)** and **(9)** possess the stereostructures **(10)** and **(11)**.



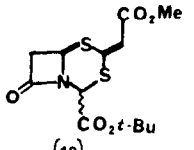

(10)




(11)

On the basis of the foregoing evidence, it is clear that the geometry of the thiacephams **(10)** and **(11)** at positions 2 and 4 is not influenced by the stereochemistry of the 7-substituent.[4] Accordingly, the 7-unsubstituted thiacepham **(1a)** must possess the

stereostructure **(12)**; whether the 4-alkoxycarbonyl group is *endo* orientated, as tentatively suggested earlier,[1] remains an issue.[5]




**(12)**

**Acknowledgements:** We thank Dr. M. Kinns for the n.O.e.d. spectra and the S.E.R.C. for a CASE Studenship (to P.H.C.).

## References and Footnotes

1 P. H. Crackett, C. W. Greengrass and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1983, 917.

2 A. C. Kaura, C. D. Maycock and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1980, 34.

3 H. R. Pfaendler, J. Gosteli and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6306.

4 The enantiomer of the thiacepham **(11)** is the 7-epimer of compound **(10)**.

5 The previous stereochemical assignment was also based upon n.O.e.d. spectroscopic studies. Thus irradiation of $H_2$ [a triplet (separation 6 Hz) at $\delta$ 4.99 ($CDCl_3$)] caused a 4% enhancement of $H_6$ [a double doublet ( $J$ 4 and 2 Hz) at $\delta$ 5.43] and a similar enhancement of $H_2$ (a singlet at $\delta$ 5.41).

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