Total Synthesis of N-Protected 7-Amino-7-methoxy Cephems

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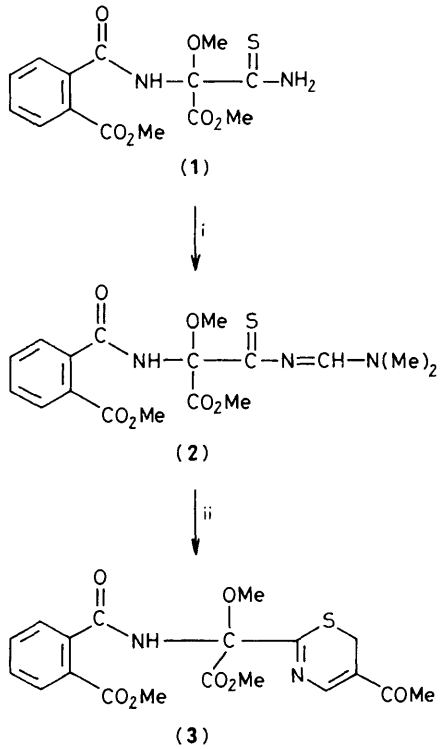
N-Protected 7-amino-7-methoxy cephems are synthesised from methyl *N*-(*o*-methoxycarbonylbenzoyl)methoxy(thiocarbamoyl)glycinate in two major steps: construction of the thiazine ring and subsequent closure of the β-lactam ring.

The 7-methoxy cephem moiety is of considerable interest as it constitutes the molecular backbone of compounds which make up the cephamycin group of antibiotics. We report herein a convenient total synthesis of N-protected 7-amino-7-methoxy epimeric cephems, the originality of which lies in the introduction of the methoxy group at the beginning of the synthesis. The subsequent reaction sequence is based on the extremely versatile Diels–Alder reaction, thus opening the way to a variety of possible structural modifications applicable to the total synthesis of cephamycins.

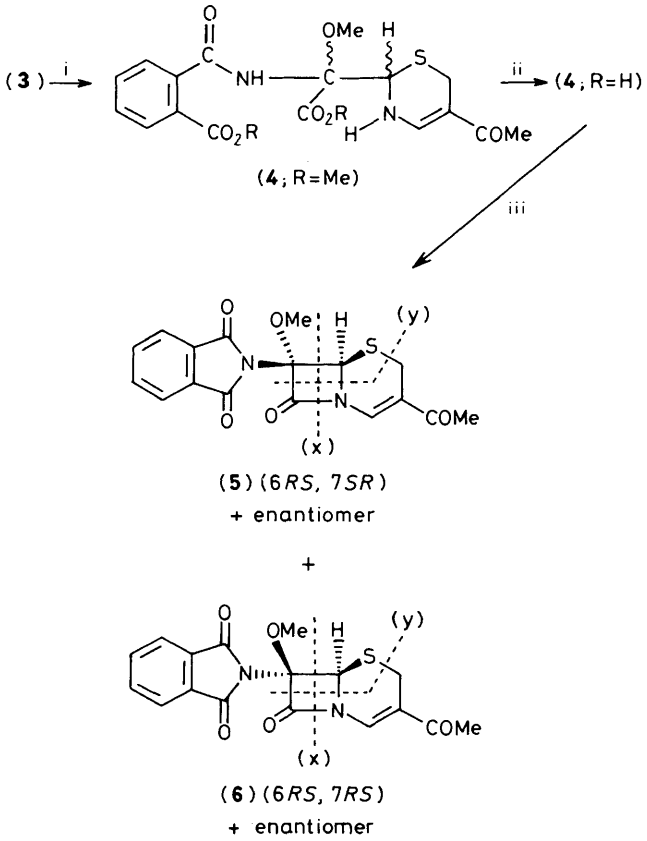
The present work builds on earlier research carried out in this laboratory on the synthesis of Δ^3-cephems.[1,2] The key intermediate, methyl *N*-(*o*-methoxycarbonylbenzoyl)-methoxy(thiocarbamoyl)glycinate (**1**)† was synthesised in several steps from a methyl cyanoglycinate in which the amine group was protected as a phthalimide.[3]‡ The ester function of the amino acid provides the carbonyl function of the future lactam.



Scheme 1. i, $(MeO)_2CHNMe_2$; ii, CH_2=CHCOMe.

Our synthetic method for the construction of the thiazine ring is outlined in Scheme 1. The *N*-disubstituted-*N'*-thioacylformamidine (**2**)† was obtained in 90% yield by condensing dimethylformamide dimethyl acetal with the thioamide (**1**). The 1,3-thiazine (**3**)† was a result of a Diels–Alder type [4 + 2]cycloaddition between the heteroatomic chain of (**2**) as diene and an acrylic dienophile, in this case methyl vinyl ketone. The amine group at position 3 was eliminated to form the carbon–carbon double bond of the thiazine ring. This procedure gave (**3**) in 85% yield.

Two steps are necessary prior to lactamisation: regioselective reduction of the imine function and deprotection of the acid group. These are outlined in Scheme 2. Reduction of the 1,3-thiazine (**3**) was carried out in methanol using aluminium amalgam. The dihydrothiazine isomers (**4**; R = Me)† thus obtained, in 70% yield, were then treated with lithium hydroxide to give, after acidification, the diacid isomers (**4**; R = H)† in 90% yield. Finally, double intramolecular coupling, *i.e.* closure of the phthalimide group and the β-lactam ring was achieved using BOP [benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate]. The



Scheme 2. i, Al–Hg, MeOH; ii, LiOH, H^+; iii, BOP.

† All new compounds gave satisfactory analytical and spectroscopic data.

‡ α-Chlorination of the N-protected methyl cyanoglycinate was carried out using t-butyl hypochlorite. Subsequent dehydrochlorination and opening of the phthalimide group to *o*-methoxycarbonylbenzamide was achieved by reaction with lithium methoxide. Addition of methanol to the acylimine intermediate afforded the methyl methoxyglycinate which on reaction with hydrogen sulphide gave (**1**) in good yield.

N-protected 7-amino-7-methoxy cephems† were thus obtained in 27% yield.

The relative configurations of the two chiral centres, C-6 and C-7, in the cephems (**5**) and (**6**) were assigned on the basis of nuclear Overhauser effects. From these results, the following ^{1}H n.m.r. chemical shifts were assigned: for (**5**) δ 3.68 (MeO), 5.39 (6-H) and for (**6**) δ 3.61 (MeO), 5.52 (6-H) (recorded in $CDCl_3$).

The mass spectrum of (**5**) and (**6**) showed the parent ion M^+ 358 and, in addition, showed the characteristic fragments of the β-lactam moiety [indicated by dotted lines: (x) M^+ 217 and (y) M^+ 234].

An A.S.P. 'PIRMED' was granted by the C.N.R.S. for the work presented in this article.

Received, 20th September 1983; Com. 1245

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