

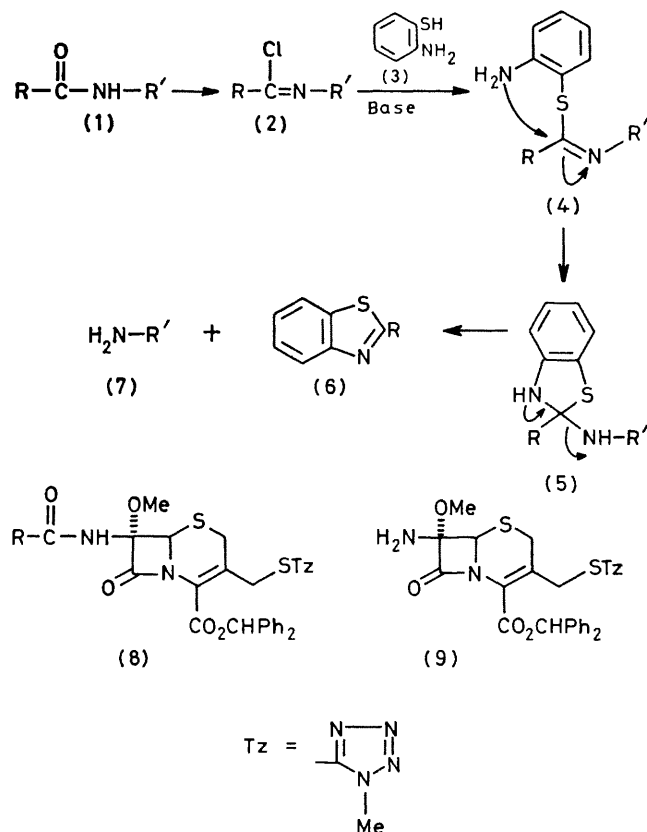
## Deacylation of Amides: Removal of the Acyl Side-chain from Cephamycin Derivatives

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**Summary** Diphenylmethyl (6*R*,7*S*)-7-amino-7-methoxy-3-[[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]- $\Delta^3$ -cephem-4-carboxylate (**9**) is obtained from a cephamycin C derivative by treatment of an imino chloride intermediate with *o*-aminobenzenethiol

APPLICATION to cephamycin derivatives of methodology that is well established for removal of the *N*-acyl side-chain at C-6(7) in penicillins (cephalosporins), *ie* imino chloride solvolysis, results in epimerization at C-7,<sup>1</sup> although a recent report in the patent literature claims that this

epimerization is reduced substantially when the solvolysis is performed at temperatures near  $-70^\circ\text{C}$ .<sup>2</sup> The imino chloride-methyl cuprate method of Karady *et al*.<sup>3</sup> maintains the chirality at C-7 but is accompanied by  $\Delta^3$ - $\Delta^2$  isomerization. The oxalyl chloride method, mentioned only briefly in an application to penicillins<sup>4</sup> but applied by Shiozaki *et al*.<sup>5</sup> to cephamycins, is the only one that avoids both epimerization and isomerization. We now report a novel method for deacylation of cephamycin derivatives that proceeds without epimerization at C-7 or  $\Delta^3$ - $\Delta^2$  isomerization.



a; R = Pr<sup>n</sup>

b; R = Ph<sub>2</sub>CHO<sub>2</sub>CCH(NHCO<sub>2</sub>Bu<sup>t</sup>)(CH<sub>2</sub>)<sub>3</sub>

It was reasoned that reaction of an imino chloride (2), derived from the corresponding amide, with *o*-amino-benzenethiol (3) in the presence of a suitable base should give an imino sulphide (4) that could undergo cyclization to the benzothiazoline (5). Subsequent base-catalysed elimination would provide the 2-substituted benzothiazole (6) and the desired amine (7).

Treatment of the *N*-butyramide (8a) sequentially with phosgene-pyridine in CH<sub>2</sub>Cl<sub>2</sub> (3 h; room temp.) and aqueous NaHCO<sub>3</sub> provided, after drying and solvent removal, the corresponding imino chloride [ $>90\%$ ; CDCl<sub>3</sub>  $\delta$  2.75 (2H, t, -CH<sub>2</sub>-CCl=N-), 3.58 (3H, s, OMe), and 5.03 (1H, s, C-6)]. Reaction of this product in CH<sub>2</sub>Cl<sub>2</sub> with 2 equiv. each of (3) and pyridine (1.5 h; room temp.) followed by work-up with aqueous NaHCO<sub>3</sub> and preparative t.l.c. on silica gel (Quantum PQ1F or Whatman PK1F) using CH<sub>2</sub>Cl<sub>2</sub>-EtOAc (9:1) afforded the 7 $\alpha$ -methoxy amine (9)<sup>6</sup> (15%), the benzothiazole (6a)<sup>7</sup> (45%), and (8a) (23%).<sup>†</sup> Similar treatment of the cephamycin derivative (8b)<sup>8</sup> provided the corresponding isolated imino chloride [ $>90\%$ , CD<sub>2</sub>Cl<sub>2</sub>  $\delta$  2.73 (2H, t, -CH<sub>2</sub>-CCl=N-), 3.48 (3H, s, OMe), and 5.00 (1H, s, C-6)] and subsequently (9) (20–25%) and (6b) {30–35%, m.p. 113–114 °C, [ $\alpha$ ]<sub>D</sub> +4° (*c* 0.205, CHCl<sub>3</sub>)}. In both examples, no products derived by epimerization at C-7 or isomerization of the  $\Delta^3$  double bond were observed. Substitution of *o*-aminophenol or *o*-phenylenediamine for (3) provided little, if any, of the desired products.

This sequence represents a novel, alternative method for *N*-deacylation of cephamycin derivatives. The yields given here do not represent optimized ones for these reactions.

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† Compounds (6a) and (9) were identified by comparisons (<sup>1</sup>H n.m.r., i.r., t.l.c.) with authentic samples.

‡ Compound (6b) gave satisfactory spectral data and elemental analysis.

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