

A STEREoselective Oxidative Cyclization of
D-MANDELAMIDO-3-CARBAMOYLOXYMETHYL-3-CEPHEM-4-CARBOXYLIC ESTER

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
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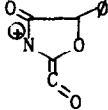
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The isolation of a new family of antibiotics¹ (1a-d) has stimulated interest in a synthetic route to 7- α -methoxycephalosporins.² Baldwin³ has reported the general synthesis of α -methoxyamides by generation of an acylimine followed by addition of methanol to this highly reactive functionality. He also demonstrated its great utility by the successful conversion of penicillin sulfoxide to the 6- α -methoxypenicillin sulfoxide.³ Whereas his conditions require protection of the penicillin thiazolidine sulfur as its sulfoxide, conditions for the successful direct synthesis of 6- α -methoxypenicillin from penicillin were developed by us utilizing the acylimine concept.⁴ The acylimine approach has also been extended to include the conversion of cephalosporins to the 7- α -methoxy derivatives (2 \rightarrow 4) via intermediate 3.⁴

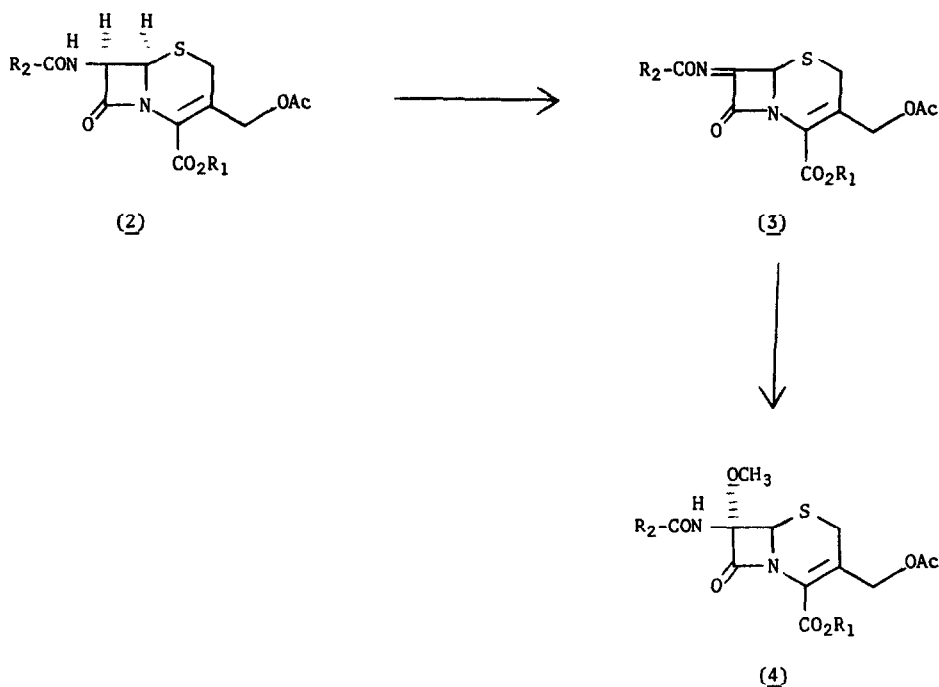
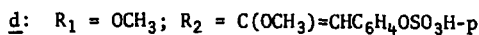
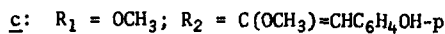
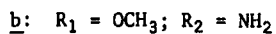
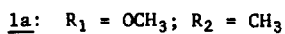
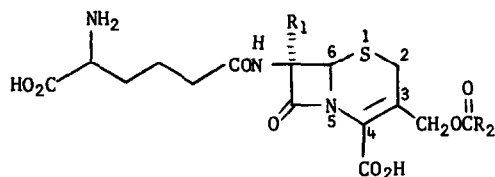
The possibility of intercepting such an acylimine intermediate with an internal nucleophile prompted us to investigate the reaction of 5,^{5,6} ir (CHCl₃) [(1780, 1740, 1695, 1610) cm⁻¹] and nmr τ (DMSO d₆) [C₇, 4.13 (doublet of doublets), C₆ (4.83, doublet, J = 4 Hz)] in a similar manner.

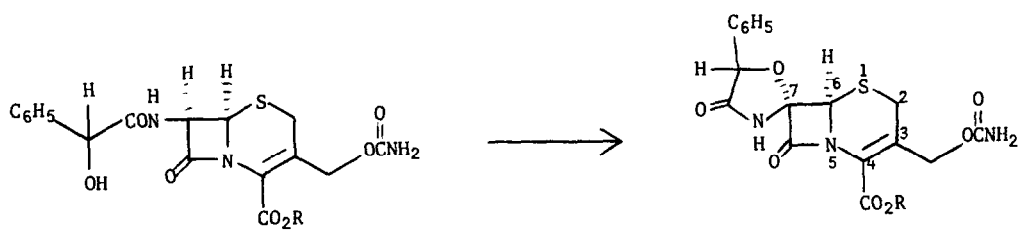
Treatment of 5 with 3.5 equivalents of lithium methoxide and 1 equivalent of t-butyl hypochlorite in tetrahydrofuran at -78° for 30 min followed by quenching with acetic acid, work up and preparative thin layer chromatography afforded 7a isolated as a foam in 63% yield. Structure assignment of 7a is based on the following spectral data: ir (CHCl₃) [1788, 1730,

and 1610 cm⁻¹], nmr τ (CDCl₃) [, 4.54 (singlet), H₆, 4.92 (singlet), C₂-methylene, 6.63 (multiplet)] and uv (MeOH) (263 m μ , ϵ = 9400).^{7a} In addition, the mass spectrum of 7a

had a strong peak, m/e 188 (, providing evidence for spiro formation about C₇.

The conversion of 7a to the free cephalosporanic acid (7b) was carried out in 70% yield using trifluoroacetic acid-formic acid. The stereochemical assignment at C₇ is based on 7b being a biologically active substance and the preferred mode of cyclization of intermediate 6.^{7b,c} In addition the chemical shift of H₆ is in complete agreement with the H₆ shifts found for 7-*a*-methoxycephalosporins.⁸



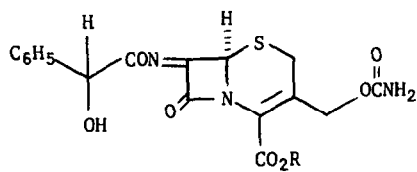


(5)

R = benzhydryl

(7a) R = benzhydryl

(7b) R = H



(6)

R = benzhydryl

REFERENCES

1. (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, 93, 2308 (1971). (b) G. Albers-Schonberg, B. H. Arison, and J. L. Smith, *Tetrahedron Lett.*, 2911 (1972).
2. (a) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, 94, 1408 (1972). (b) S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzing, *ibid.*, 1410 (1972).
3. J. E. Baldwin, F. Urban, R. D. G. Cooper, and F. Jose, *J. Amer. Chem. Soc.* (in press).
4. G. A. Koppel and R. E. Koehler, *J. Amer. Chem. Soc.* (in press).
5. All new compounds gave satisfactory elemental analyses.
6. (a) Prepared according to method of C. F. Murphy, R. E. Koehler, and J. A. Webber, *Tetrahedron Lett.*, 1585 (1972). (b) The mandelic side chain has the D-configuration. (c) The interest in a 3-carbamoyloxymethyl group is a result of the isolation of a 7- α -methoxycephalosporin with a 3-carbamoyloxymethyl group. See Reference 1.
7. (a) The shift of the amide carbonyl in the ir from 1695 cm^{-1} to 1730 cm^{-1} is consistent with a five-membered lactam. (b) The biological assay of 6b showed antimicrobial activity at 10 $\mu\text{g}/\text{ml}$. An analogy with penicillins suggests that the 7- β -methoxycephalosporins are biologically inactive. See Reference 2a. (c) If the oxygen of the mandelic side chain were to add to the β -face of the cephalosporin nucleus, there would be a severe steric interaction between the phenyl group of the side chain and the sulfur of the cephalosporin nucleus.
8. The chemical shift of H_α of a series of 7- α -methoxycephalosporins has been located in a range of 4.88-4.94 τ . The chemical shift in the corresponding 7- β -methoxycephalosporin has been at 4.76 τ . See W. H. W. Lunn, R. Burchfield, E. Mason, T. Elzey, *Chem. Commun.* (submitted for publication).