Intramolecular Nucleophilic Attack in 7α-Aminophenylacetamido-cephalosporin Esters

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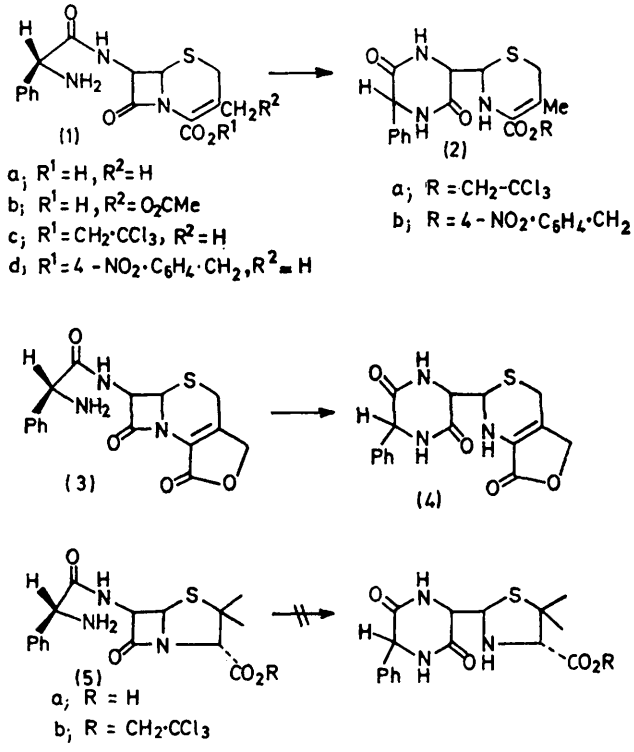
Summary 7α-Aminophenylacetamido-Δ³-cephalosporin esters cyclize to 3-dihydrothiazinyl-6-phenylpiperazine-2,5-diones by an intramolecular nucleophilic attack of the side-chain α-amino-function while under the same conditions the analogous 6α-aminophenylacetamidopenicillin ester does not cyclize, because of steric hindrance to intramolecular attack.

THE α-aminophenylacetamido-β-lactam compounds cephalexin (**1a**), cephaloglycin (**1b**), and ampicillin (**5a**) are clinically useful broad spectrum antibiotics, effective orally against both Gram-positive and Gram-negative bacteria. The β-lactam part of penicillins and cephalosporins is readily susceptible to attack by a variety of nucleophiles. The penicillins ring-open to penicilloic acids[1] (esters, amides, or polymers),[2] while the cephalosporins form the analogous unstable "cephalosporoates" which rapidly fragment in aqueous solution.[3]†

The intramolecular nucleophilic attack of a side chain α-amino-function has not been demonstrated but was suggested as a decomposition mechanism for cephaloglycin by Hoover and Stedman[5] and for ampicillin by Jusko.[6] We now report results that demonstrate intramolecular nucleophilic attack of the α-aminophenylacetamido-side chain on cephalexin trichloroethyl (**1c**) and *p*-nitrobenzyl (**1d**) esters and cephaloglycin lactone (**3**). The analogous reaction does not occur with the corresponding penicillin system, *i.e.* ampicillin trichloroethyl ester (**5b**).‡

Compounds (**2a**) (decomp. 179°), (**2b**) (decomp. 165°), and (**4**) (decomp. 145°) were obtained by heating the corresponding β-lactams in dilute benzene under reflux overnight and recovering the resulting crystalline piperazinediones by filtration. The yields ranged from 10—49%. In contrast, ampicillin trichloroethyl ester (**5b**) was recovered unchanged under these reaction conditions.

The amido-protons in the ^{1}H n.m.r. spectra of (**2a**), (**2b**), and (**4**) were easily recognized by comparison with the ^{1}H n.m.r. spectrum of cyclic GlyPh-Gly dipeptide,[7] and the remainder of the spectra were consistent with the suggested structures.§ In view of the structural similarity of the cephalosporin and penicillin esters, this difference in reactivity was surprising. Inspection of molecular models reveals intramolecular attack on the β-lactam of these compounds must occur from the β-face, *i.e. cis* to the amide side chain. The models also show that steric hindrance by



the gem-dimethyl group and the 3-hydrogen might prevent "*cis*" attack in the penicillin, while the cephalosporins are not sterically hindered to "*cis*" attack.

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† Under non-aqueous conditions penicilloate-like derivatives have been isolated from cephalosporins.[4]

‡ 7-Aminodeacetoxycephalosporanic trichloroethyl ester dimerizes in benzene to the symmetrical 3,6-bisdihydrothiazinylpiperazine-2,5-dione. (Personal communication with Dr. L. D. Hatfield.)

§ The new piperazinediones were also characterized by elemental analysis, and i.r., and mass spectra. Compound (**4**) gave an unsatisfactory elemental analysis due to occluded benzene.

[1] E. P. Abraham, *Pharmacol. Rev.*, 1962, **14**, 473.
[2] J. R. Johnson, R. B. Woodward, and R. Robinson in 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and B. Robinson, Princeton University Press, Princeton, N.J., 1949, ch. 15, pp. 440—454; H. Smith and A. C. Marshall, *Nature*, 1971, **232**, 45.
[3] J. M. T. Hamilton-Miller, E. Richards, and E. P. Abraham, *Biochem. J.*, 1970, **116**, 385.
[4] S. H. Eggers, V. V. Kane, and G. Lowe, *J. Chem. Soc.*, 1965, 1262, and J. Bradshaw, S. Eardley, and A. G. Long, *J. Chem. Soc.* (*C*), 1968, 801.
[5] J. R. E. Hoover and R. J. Stedman in 'Medicinal Chemistry,' ed. A. Burger, Wiley-Interscience, New York, 1970, ch. 18, p. 399.
[6] W. J. Jusko, *J. Pharm. Sci.*, 1971, **60**, 728.
[7] K. D. Kopple and M. Ohnishi, *J. Amer. Chem. Soc.*, 1969, **91**, 962.