REARRANGEMENT OF EXOMETHYLENECEPHAMS TO HOMOCEPHAMS

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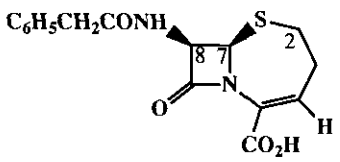
Abstract - Exomethylenecephams rearrange by reaction with diazo compounds in the presence of cupric sulfate to generate the homocepham ring-system.

The homocephem class of compounds was originally examined by Woodward and co-workers, derivative (1) was found to be devoid of antimicrobial activity.[1] More recently, Baldwin and co-workers have described the preparation of this type of ring-system (compound 2) utilizing structurally modified tripeptides in the presence of isopenicillin N synthetase (IPNS).[2] It has been suggested that study of derivatives containing this ring system might prove fruitful in the discovery of new antibiotic substances.[3] This paper describes a simple one-step ring expansion of exomethylenecephams to the corresponding exomethylenehomocephams, which in principle allows the preparation of a wide variety of modified homocephem derivatives.[4]



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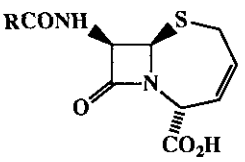
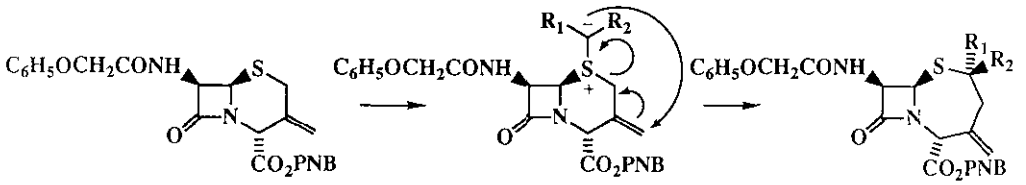


2

A refluxing slurry of exomethylenecepham-4-carboxylate ester (3, 5.0 mmol) and anhydrous cupric sulfate (3.0 mmol) in either diethyl carbonate or methylene chloride when treated with slow addition with a diazo reagent afforded the desired rearranged products (5) in moderate yield (Table I). The structures of the rearranged products were determined on the basis of ^{1}H nmr spectra in combination with other spectral and analytical data.[5] For example, mass spectral (m/z = 597) and combustion analysis indicated a molecular formula of $C_{29}H_{31}N_3O_9S$ for compound (5c). The ir spectrum showed absorption at 1770 (β-lactam), 1740 (ester), and 1690 (amide) cm^{-1}. The ^{1}H nmr spectrum (270 MHz, DMSO-d_6) displayed signals at δ 9.27 (d, J = 10.1 Hz, 1H), 8.26 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 8.9 Hz, 2H), 7.29 (m, 2H), 6.94 (m, 3H), 5.77 (dd, J = 10.1, 4.6 Hz, 1H), 5.46

(d, J = 4.6 Hz, 1H), 5.35, 5.32 (ABq, J = 13.1 Hz, 2H), 5.27 (s, 2H), 5.21 (s, 1H), 4.58, 4.56 (ABq, J = 15.6 Hz, 2H), 3.77 (dd, J = 7.3, 3.0 Hz, 1H), 3.12 (dd, J = 14.7, 7.3 Hz, 1H), 2.86 (dd, J = 14.7, 3.0 Hz, 1H), and 1.44 (s, 9H) clearly indicating a formal insertion of the $CH(CO_2{}^tBu)$ function between the 1-sulfur/2-carbon bond of the starting cepham (3). The cis relationship between H_8 (5.77 ppm) and H_7 (5.46 ppm) was evident from the coupling constant of 4.6 Hz and a difference NOE observed upon irradiation of either proton. In addition, difference NOEs were also observed between H_7 (5.46 ppm) and H_2 (3.77 ppm) indicating a cis relationship for these two protons. The ester configuration at C-5 could not be absolutely assigned on the basis of spectral data. It was assumed to be alpha as this center does not appear to be involved in the rearrangement reaction.

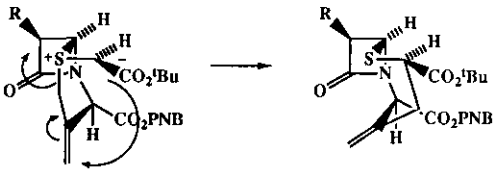
Table I



3 4 5

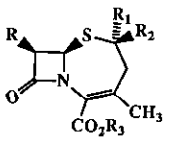
Substrate	Diazo reagent [solvent]	Product (yield)
3	dimethyl diazomalonate [$(EtO)_2CO$]	5a: $R_1 = R_2 = CO_2Me$ (74%)
3	ethyl diazoacetate [CH_2Cl_2]	5b: $R_1 = H, R_2 = CO_2Et$ (45%)
3	t-butyl diazoacetate [CH_2Cl_2]	5c: $R_1 = H, R_2 = CO_2{}^tBu$ (45%)
3	diphenyl diazomethane [$(EtO)_2CO$]	5d: $R_1 = R_2 = C_6H_5$ (73%)

A plausible mechanism for this rearrangement would involve carbenoid addition to the sulfur atom followed by [2,3] sigmatropic rearrangement of the intermediate ylide (4) resulting in the ring expansion to give (5).[6-8] The stereochemistry at C-2 observed for compound (5c) is consistent with a mechanism that involves formation of the alpha-ylide[9] and subsequent rearrangement via a transition state with the ester function assuming a conformation situated away from the six-membered ring (i):

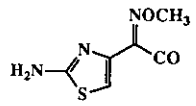


i 5c

These homocepham analogs obtained could then be converted by olefin isomerization and appropriate side-chain modification to homocephem derivatives for biological testing. The olefin of triester (5a) was isomerized (Et_3N, CH_2Cl_2, 92%) and the *p*-nitrobenzyl ester was removed by hydrogenolysis (H_2, Pd/C MeOH-THF, 84%) to afford the acid (6a). Compound (5b) was isomerized (Et_3N, CH_2Cl_2, 78%) to ester (6b) and the phenoxyacetyl side-chain was removed (PCl_5, py, CH_2Cl_2, $^{i}BuOH$, 58%)[10] to afford amine (6c). Acylation with ^{t}BOC-D-phenylglycine (EEDQ, THF, 81%)[11] followed by *p*-nitrobenzyl ester cleavage (H_2, Pd/C, MeOH, 81%) and removal of the BOC group (HCO_2H, Et_3SiH, 50%) afforded derivative (6d). Compound (6e) was prepared from (6c) by acylation with trityl protected 2-aminothiazol-4-yl-methoximinoacetic acid[12] (DCC, CH_2Cl_2, 63%), followed by removal of the *p*-nitrobenzyl ester (H_2, Pd/C, EtOH, 32%) and removal of the trityl protecting group (HCO_2H, Et_3SiH, 28%). Derivatives (6a, 6d, and 6e) exhibited no antimicrobial activity against a variety of microorganisms at concentrations as high as 128 μg/ml.



6a:[13] R = $C_6H_5OCH_2CONH$, R_1 = R_2 = CO_2Me, R_3 = H
6b: R = $C_6H_5OCH_2CONH$, R_1 = H, R_2 = CO_2Et, R_3 = PNB
6c: R = H_2N, R_1 = H, R_2 = CO_2Et, R_3 = PNB
6d: R = $C_6H_5CH(NH_2)CONH$, R_1 = H, R_2 = CO_2Et, R_3 = H
6e:[14] R = ATMONH, R_1 = H, R_2 = CO_2Et, R_3 = H

ATMO = 

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. R. Scartazzini, J. Gosteli, H. Bickel, and R. B. Woodward, *Helv. Chim. Acta*, 1972, 55, 2567.
2. J. E. Baldwin, R. M. Adlington, A. Basak, S. L. Flitsch, A. K. Forrest, and H.-H. Ting, *J. Chem. Soc., Chem. Commun.*, 1986, 273.
3. R. Kirrstetter and W. Durckheimer, *Pharmazie*, 1989, 44, 177.
4. The 3-exomethylenecepham system has been shown to be a key intermediate in the preparation of a variety of 3-substituted cephalosporin analogs; S. Kukolja, R. R. Chauvette, "Chemistry and Biology of Beta-Lactam Antibiotics", eds. by R. B. Morin and M. Gorman, Vol. 1, Academic Press: New York, 1982, p. 93.

5. Satisfactory spectral and analytical data were obtained for all new compounds.

6. Carbenoid addition to the sulfur atom of penams has been reported: M. Yoshimoto, S. Ishihara, E. Nakayama, E. Shoji, H. Kuwano, and N. Soma, *Tetrahedron Lett.*, 1972, 4387; M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Lett.*, 1972, 5097; T. Kametani, N. Kanaya, T. Mochizuki, and T. Honda, *Heterocycles*, 1982, 19, 1023; T. Kametani, N. Kanaya, T. Mochizuki, and T. Honda, *Tetrahedron Lett.*, 1983, 24, 221, 1511; T. Kametani, N. Kanaya, A. Nakayama, T. Mochizuki, S. Yokohama, and T. Honda, *J. Org. Chem.*, 1986, 51, 624; C.-P. Mak, G. Schulz, and H. Flirí, *Heterocycles*, 1987, 26, 1001; I. Ernest, *Tetrahedron*, 1977, 33, 547; and J. Kang, W. B. Im, S.-G. Choi, D. Lim, Y. R. Choi, H. G. Cho, and J. H. Lee, *Heterocycles*, 1989, 29, 209.

7. Carbenoid addition to the sulfur atoms of Δ-3-cephems and subsequent [2,3] sigmatropic rearrangement have been reported: M. Yoshimoto, S. Ishihara, E. Nakayama, and N. Soma, *Tetrahedron Lett.*, 1972, 2923.

8. [2,3] Sigmatropic rearrangement of exomethylene cepham sulfoxides has been reported: H. Yanagisawa and A. Ando, *Tetrahedron Lett.*, 1982, 23, 3379 and R. D. G. Cooper, M. D. Kinnick, L. R. Peters, J. M. Morin, Syn. Comm., 1988, 18, 763.

9. This explanation assumes that product (**5c**) is a kinetic product, however, the possibility for epimerization of the corresponding alpha-product to the beta-product (**5c**) cannot be ruled out on the basis of this study. These results are also consistent with the product observed from a similar reaction of the Δ-3-cephem with ethyl diazoacetate, see reference 7. See also, R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1979, 18, 563, for an explanation of the stereochemistry observed in reference 7.

10. L. D. Hatfield, W. H. W. Lunn, B. G. Jackson, L. R. Peters, L. C. Blaszczak, J. W. Fisher, J. P. Gardner, and J. M. Dunigan, "Recent Advances in the Chemistry of Beta-Lactam Antibiotics", G. I. Gregory, The Royal Society of Chemistry: Burlington House, London, 1980, p 109.

11. B. Belleau, R. Martel, G. Lacasse, M. Menard, N. L. Weinberg, and Y. G. Perron, *J. Am. Chem. Soc.*, 1968, 90, 823.

12. W. Duerckheimer, J. Blumbach, R. Lattrell, and K. H. Scheuenemann, *Angew. Chem., Int. Ed. Engl.*, 1985, 29, 105.

13. (6a): m/z 479; nmr ($CDCl_3$) δ 7.75 (d, J = 8 Hz, 1H), 7.05 (m, 2H), 6.7 (m, 3H), 5.55 (dd, J = 5, 8 Hz, 1H), 5.18 (d, J = 5 Hz, 1H), 4.35 (s, 2H), 3.56 (s, 3H), 3.53 (s, 3H), 3.18, 3.10 (ABq, J = 15 Hz, 2H), 1.95 (s, 3H).

14. (6e): m/z 484; ir ν (KBr) 1767 cm^{-1}; nmr (DMSO-d_6)δ 9.56 (d, J = 9 Hz, 1H), 7.18 (s, 2H), 6.70 (s, 1H), 5.47 (m, 1H), 5.13 (d, J = 4 Hz, 1H), 4.10 (m, 2H), 3.79 (s, 3H), 2.77 (m, 2H), 2.46 (s, 1H), 1.99 (s, 3H), 1.16 (m, 3H).

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