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CEPHAMS-STEREOCHEMISTRY OF 3-EXOMETHYLENECEPHAM

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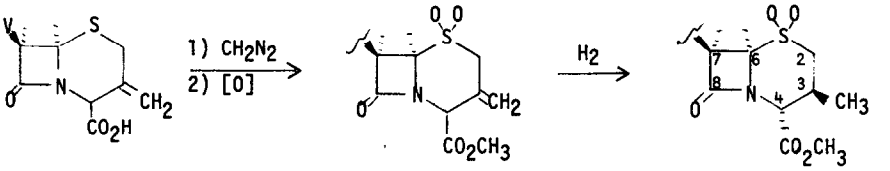
Recent interest in the C_4 stereochemistry of 3-exomethylenecephams[1,2] prompts us to report our studies involving its elucidation using cepham derivatives.

Treatment of 1[3] with diazomethane followed by 2.5 equiv m-chloroperbenzoic acid (m-CPBA) gave the sulfone ester 2. Low pressure hydrogenation of 2 using palladium on carbon followed by silica gel chromatography gave 75% of a single isomer 3.



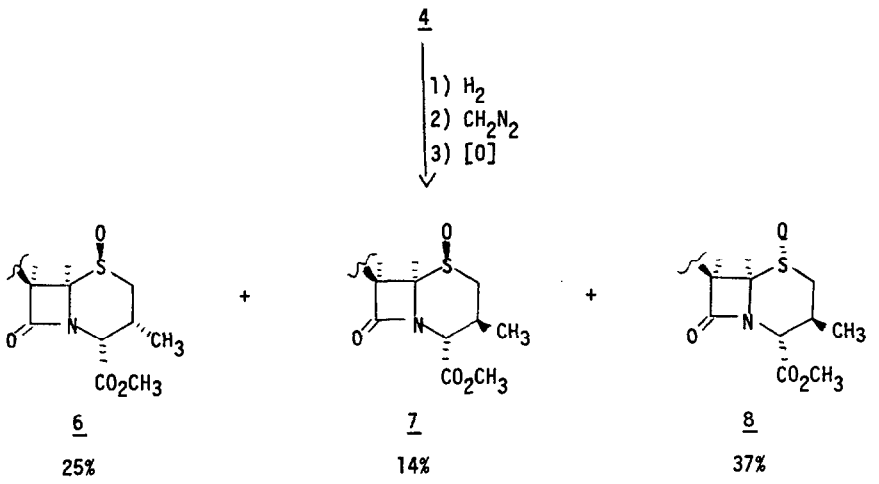
1 2 3

V= $C_6H_5OCH_2CONH$

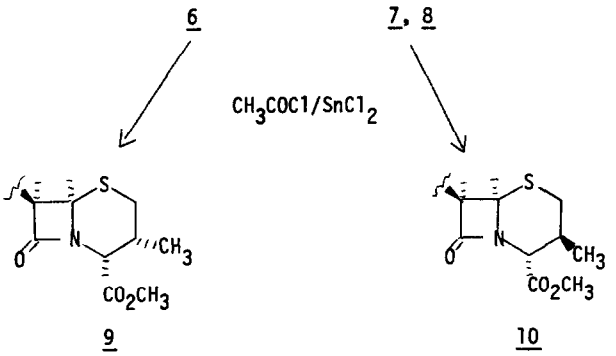
The stereochemistry of 3 at C_3 and C_4 is provided in hydrogenation studies of 4 and 5.

4 5

Van Heyningen and Ahern[4] have previously reported the hydrogenation of 4 and subsequent degradation of the C_3 isomer mixture to D-valine thus establishing the C_4-α-carboxyl configuration of Δ^2 cephems. Hydrogenation of 4 according to the procedure of Van Heyningen and Ahern followed by esterification and oxidation with 1.1 m-CPBA equiv gave 6 (163-164°)[5], 7 (152-155°), 8 (184-185°) after silica gel chromatography; the yields indicate a preferential approach of the catalyst from the back or α side of the molecule.

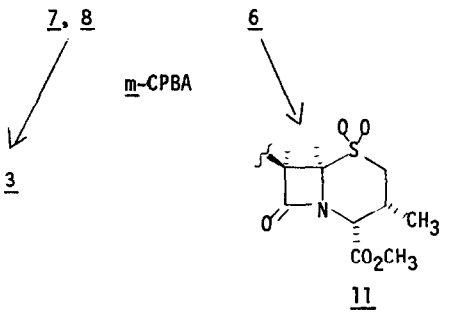


The sulfoxides 6, 7 and 8 can be reduced[6] to two different sulfides 9 and 10.

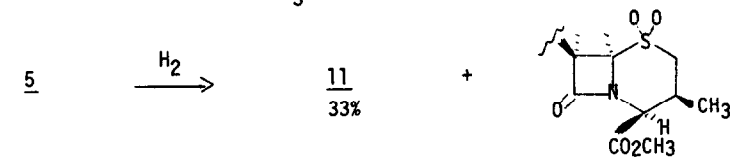


Peracid oxidation of 10 gave 8 and 7 in a 3/1 ratio as a result of the β-axial methyl hindering the approach of the peracid from the β face of the molecule. Peracid oxidation of 9 gave only 6; however, ozone oxidation provides the α sulfoxide in 80% yield[7].

The sulfoxides 6, 7 and 8 can be oxidized further to two different sulfones 3 and 11 (167-168°),



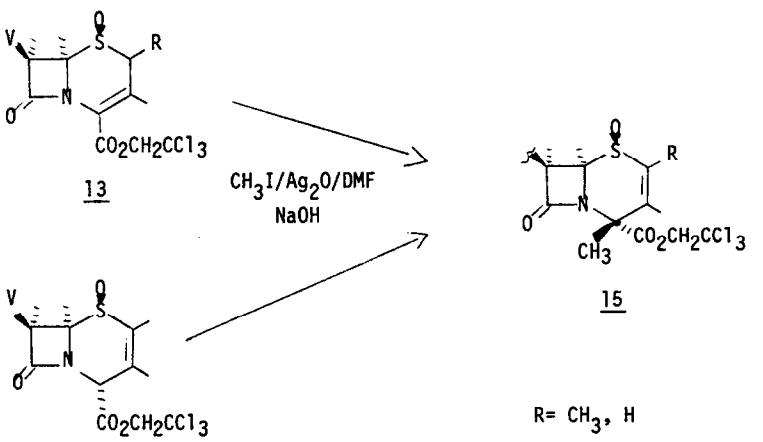
one of which (11) is also a product from the high pressure hydrogenation of 5, thus providing the key to the stereochemistry at C_3[8,9].



12
27%

Compound 12 (192-193°) exhibits 5-bonded coupling (ca. 1.0 cps) between the α-axial C_4 proton and H_7. Since such coupling is absent in 3 the presence of H_4-H_7 coupling can be used as evidence for the abnormal C_4 stereochemistry in other cepham compounds[12]. Treatment of 12 with strong base (0.1N NaOH/dioxane) results in C_4 epimerization to yield 3, thus indicating that the α configuration of the carboxyl is the base stable configuration.

In addition to the selective protonation described above, preferential alkylation from the β face of the C_4-carbanion is illustrated by the conversion of 13 and 14 to 15.



In conclusion, hydrogenation studies thus show that the C_4 carboxyl in the 3-exomethylenecepham 1 is of a normal (α) configuration and thus in agreement with prior published data[1,2].

REFERENCES

1. M. Ochiai, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Letters*, 3241 (1972).

2. M. Ochiai, E. Mizuta, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Letters*, 3245 (1972).

3. The 3-exomethylenecepham 1 was prepared in these laboratories by R. R. Chauvette. Paper in preparation.

4. E. M. Van Heyningen and L. K. Ahern, *J. Med. Chem.*, 11, 933 (1968).

5. Acetone-methylenechloride/hexane was the solvent for all crystallizations.

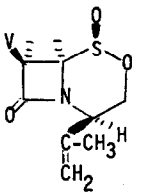
6. G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, 35, 2430 (1970).

7. D. O. Spry, *J. Org. Chem.*, 37, 793 (1972).

8. We thank J. B. Campbell for running the high pressure hydrogenation.

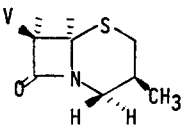
9. R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 91, 1401 (1969).

10. Prior to our studies R. D. G. Cooper noted similar H_4-H_7 coupling in A. Unpublished results of R. D. G. Cooper



A

11. We have also observed H_4-H_7 coupling in B, its β sulfoxide (183-184°), the α sulfoxide, and the corresponding sulfone.



B

12. For further discussion of H_4-H_7 coupling, see "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, N.Y. 1972 (in press)