Tetrahedron Letters No.45, pp. 3993-3996, 1969. Pergamon Press. Printed in Great Britain.

EPIMERIZATION OF SOME CEPHALOSPORIN SULFOXIDES

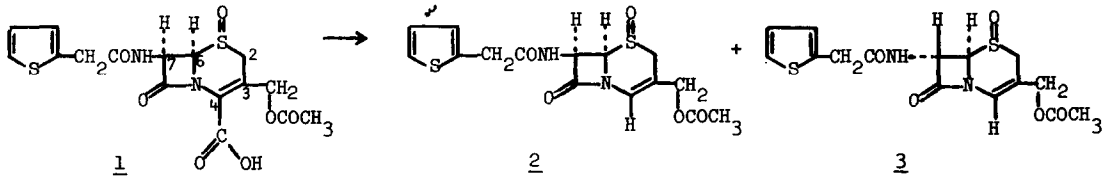
M. L. Sassiver and R. G. Shepherd

Organic Chemical Research Section, Lederle Laboratories,
American Cyanamid Company, Pearl River, N. Y.

(Received in USA 14 August 1969; received in UK for publication 29 August 1969)

Recently some examples of epimerization at the 6-position of penicillin derivatives (1,2,3) have been reported. We have observed a similar phenomenon in the cephalosporin field.

The decarboxylation of cephalosporin sulfoxides in pyridine has been previously reported (4). In our concurrent study of this reaction decarboxylation of the known (5) sulfoxide 1 was initially effected with one equivalent of triethylamine in refluxing chloroform. Inspection of the n.m.r. spectrum of the reaction product revealed the presence of two compounds,



1 2 3

the expected 6H,7H-cis isomer 2 and the trans isomer 3, present in a 1:4 proportion after 16 hours' reaction. Pure 2 was obtained in 71% yield by decarboxylation of 1 with one equivalent of N-methylmorpholine (6) in refluxing tetrahydrofuran; m.p. 176-177°; $[\alpha]_D^{25}$ +38° (c 1.0, MeOH); λ_{max}^{KBr} 5.63 μ (β-lactam), 5.79 μ (ester), 6.05 and 6.57 μ (amide), 9.75 μ (S=O); λ_{max}^{MeOH} 240 mμ (15,100); n.m.r. (see chart I); Anal. for $C_{15}H_{16}N_2S_2O_5$ calc./ found C, 49.0/49.3; H, 4.4/4.6; N, 7.6/7.5; S, 17.4/17.3. Complete isomerization of 2 to 3 was achieved with one equivalent of triethylamine in dimethylsulfoxide (48 hr., 50°). Compound 3 was obtained in 30% yield as an amorphous powder identical to 2 by thin-layer chromatography, infrared and ultraviolet spectroscopy and microanalysis (Found: C, 48.9; H, 4.3; N, 7.7). It has not yet been obtained crystalline and probably is contaminated by traces of 2 (not detectable in the n.m.r. spectrum). Properties distinguishing 3 from 2 are: m.p. ca. 100°, $[\alpha]_D^{25}$ +116° (c 0.88, MeOH) and, most informatively, its n.m.r. spectrum (see Chart I). It is apparent from a comparison of the n.m.r. spectra of 2 and 3 that the 7-H and N-H have undergone the most change in environment in the

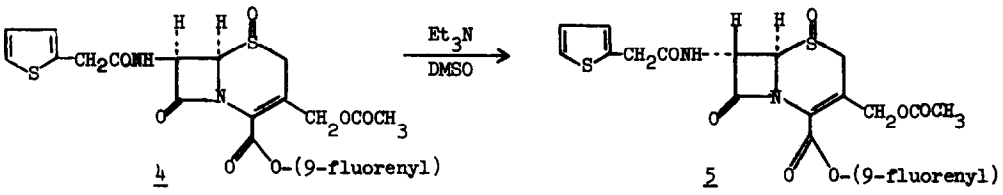
CHART I. N.M.R. Spectra of Cephalosporins[a]

Compound	O_2CCH_3	2-CH_2	thiophene-CH_2	3-$CH_2O_2CCH_3$	6-H	7-H	4-H	NH
2	122	214[b]	231	274	288(d) $J_{6,7}$=5	316(q) $J_{7,6}$=5 $J_{7,NH}$=8.5	428	501(d) $J_{NH,7}$=8.5
3	121	217	227	273	294[c]	290(q) $J_{7,6}$=2.5 $J_{7,NH}$=8.5	429	537(d) $J_{NH,7}$=8.5
4	121	228	232	280(d) 318(d) J_{gem}=13	293(d) $J_{6,7}$=5	352(q) $J_{7,6}$=5 $J_{7,NH}$=9	-	503(d) $J_{NH,7}$=9
5	121	243(d) 217(d) J_{gem}=18	227	276(d) 312(d) J_{gem}=13	300[c]	304(q)[d] $J_{7,6}$=3 $J_{7,NH}$=8.5	-	542(d) $J_{NH,7}$=8.5

a. In D_6-dimethylsulfoxide; Hz from T.M.S.; aromatic protons are omitted for clarity.
b. Poorly resolved AB pattern.
c. $J_{6,7}$ not discernible due to overlapping with downfield portion of 7-H quartet.
d. Downfield doublet overlaps 6-H doublet; upfield doublet at 308 Hz.

2 → 3 isomerization. Assignment of the trans-6H,7H configuration to 3 was made primarily because of the decrease in $J_{6,7}$ from 5 Hz in 2 to 2.5 Hz in 3 as expected for cis and trans vicinal coupling of β-lactam protons, respectively (7). Moreover, such coupling constants of 2.5-3 Hz have been observed in the 6H,7H-trans 7-chlorocephalosporanic acid resulting from deamination-chlorination of 7-aminocephalosporanic acid (8), and in the synthesis of dl-6H,7H-trans-7-aminocephalosporanic acid lactone (9). Other portions of the spectra are assigned in a manner consistent with known cephalosporin spectra (10). Strong additional evidence for the 7-epimerization was obtained from a deuterium-labelling experiment. Epimerization of 2 to 3 was performed with one equivalent of triethylamine in D_6-dimethylsulfoxide with added D_2O (100-fold molar excess). Isolation of 3 showed nearly complete exchange at the 7-position, leading to singlets for the 6-H (294 Hz) and NH (537 Hz) protons. In addition, nearly complete exchange at the C-2 and thienylacetyl methylenes occurred.

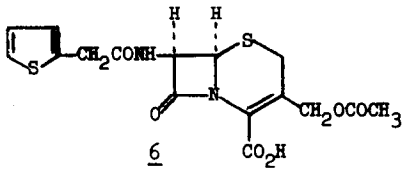
We have also observed another case of 7-epimerization. The ester 4 was converted to 5 with 0.2 equivalents of triethylamine in dimethylsulfoxide (48 hr., 50°). The lesser amount of base was necessary to minimize a β-lactam cleavage side-reaction. Compound 4 was prepared from diazofluorene and the sulfoxide 1: m.p. 229-230°; λ_{max}^{KBr} 5.58 (β-lactam), 5.72 μ (acetate), 5.81 μ (4-ester), 6.04 and 6.52 μ (amide), 9.75 μ (S=O); $[\alpha]_D^{25}$ +3.3° (c 0.55, dimethylsulfoxide); n.m.r.



4 5

(see Chart I); Anal. for $C_{29}H_{24}N_2S_2O_7$ calc./found C, 60.5/60.8; H, 4.2/4.7; N, 4.9/4.7; S, 11.1/11.2. Isomer 5 was obtained crystalline, m.p. 213-215°; λ_{max}^{KBr} same as 4; $[\alpha]_D^{25}$ +265° (c 0.2, dimethylsulfoxide); n.m.r. (see Chart I); Anal. (found C, 60.2; H, 4.3; N, 4.7). It is apparent from comparison of the n.m.r. spectra that the relationship of 5 to 4 is the same as that of 3 to 2.

We have found that cephalothin, 6, lacking a 1-oxide function, does not epimerize at C-7 under conditions which transform 1 to 2 and 3. Similarly, methyl 6-phthalimidopenicillinate was epimerized with NaH-THF, whereas Et_3N-CH_2Cl_2 was sufficient for isomerization of the cor-



6

responding sulfoxide (1). The sulfoxide function may facilitate epimerization by allowing homoenolic stabilization of the anion (at C-7 in cephalosporins or at C-6 in penicillins), permitting formation of the less hindered trans-epimers. Alternatively, the sulfoxide group may be acting inductively, in much the same way as electronegative groups at C-6 in penicillins have been recently reported to facilitate anion formation (11). Our failure to observe deuterium exchange at C-6 in cephalosporin sulfoxides 2 and 3 is probably due to the sterically unfavorable 1,6-double bond required for sulfoxide resonance-stabilization of the anion as well due to the sulfoxide group's inductive effect being overcome by repulsion between the 6-anion and the adjacent cis lone-pair on the thiazine nitrogen atom. These latter factors are not involved with 2-anionization; deuterium exchange is observed at this position.

Acknowledgements: We are indebted to Mr. W. Fulmor and associates for spectra and rotations, to Mr. G. Morton for aid in interpreting n.m.r. spectra, and to Mr. L. Brancone and coworkers for microanalyses.

References

1. D. A. Johnson, D. Mania, C. A. Panetta and H. H. Silvestri, Tetrahedron Letters, 1903 (1968).

2. S. Wolfe and W. S. Lee, Chem. Commun., 242 (1968).

3. R. D. G. Cooper, P. V. DeMarco and D. O. Spry, J. Am. Chem. Soc., 91, 1528 (1969).

4. J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall and A. G. Long, J. Chem. Soc. (C), 1142 (1966).

5. J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly and G. A. Sommerfield, J. Chem. Soc., 5015 (1965).

6. G. W. Anderson, J. E. Zimmerman and F. M. Callahan, J. Am. Chem. Soc., 89, 5012 (1967), have used this base to avoid racemization in peptide synthesis.

7. (a) K. D. Barrow and T. M. Spotswood, Tetrahedron Letters, 3325 (1965);
   (b) A. Vigevani and G. G. Gallo, J. Heterocyclic Chem., 4, 583 (1967).

8. R. B. Morin, B. G. Jackson, E. H. Flynn, R. W. Roeske and S. L. Andrews, J. Am. Chem. Soc., 91, 1396 (1969).

9. R. Heymes, G. Amiard and G. Nomini, Compt. Rend., Ser. C, 263, 170 (1966). Details given in French Patent 1,480,288 (1966).

10. G. F. H. Green, J. E. Page and S. E. Staniforth, J. Chem. Soc., 1595 (1965).

11. J. P. Clayton, J. H. C. Nayler, R. Southgate and E. R. Stove, Chem. Commun., 129 (1969).