

ON THE TRANSFORMATION OF PENICILLINS TO 3-METHYL OR 3-METHYLENE CEPHAMS

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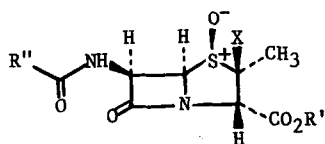
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Methylene cephams are useful synthetic intermediates for the preparation of semi-synthetic cephalosporin antibiotics.<sup>1,2</sup> A recent paper by Maki and Sako<sup>3</sup> reports on the photocyclization of 4-heterocyclic dithioazetidinones to 3-methylene cephams. We have independently investigated similar transformations, and at this time would like to communicate some recent results which confirm and extend the observations of Maki and Sako.

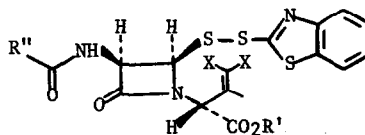
Disulfide 2 was prepared in high yield from penicillin sulfoxide 1 using the procedure of Kamiya, *et al.*<sup>4</sup> Irradiation of 2 ( $\text{CH}_2\text{Cl}_2$ , Pyrex filter, argon, 450 W. Hanovia medium pressure arc lamp,  $3 \times 10^{-3}$  M, 2 hrs) afforded 2-mercaptobenzothiazole and a mixture of  $\beta$ -lactam containing materials which was separated with difficulty by silica gel chromatography. The major component (40%, mp 149-152° d) was assigned structure 3 based on spectroscopic evidence;  $\nu_{\text{KBr}}$  1765, 1760, 1670  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ ) 3.18 and 3.66 (2H, AB<sub>q</sub>, J=14 Hz, SCH<sub>2</sub>), 5.14 and 5.26 ppm (2H, br. s, =CH<sub>2</sub>); m/e 462 M<sup>+</sup>; uv (MeOH) absence of cephem chromophore. Supporting chemical evidence for this assignment is derived by deesterification of 3 (Zn/HCO<sub>2</sub>H) and treatment of the resulting acid 5 with diphenyldiazomethane (DDM). The resulting benzhydryl ester 6 so obtained was identical with an authentic sample.<sup>5</sup> In addition, brief treatment of 3 with triethylamine initiated isomerization to the  $\Delta^3$ -analogue.

The minor product 4 (22%) was a crystalline mixture of two diastereoisomers present in approximately equal amounts;  $\nu_{\text{KBr}}$  1770, 1760, 1680  $\text{cm}^{-1}$ ; pmr ( $\text{CDCl}_3$ ) 1.06 and 1.24 ppm (3H, d, J=7 Hz,  $\text{X} \begin{array}{c} \text{H} \\ \diagup \\ \text{CH}_3 \end{array}$ ); m/e 464 M<sup>+</sup>. Although 4 was not observed by Maki and Sako, similar compounds have been previously prepared.<sup>6</sup> Difficulty in chromatographic separation of 3 and 4 was overcome by prior oxidation of the mixture of their respective sulfoxides (MCPBA,  $\text{CH}_2\text{Cl}_2$ , 0°).

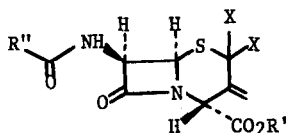
Significant amounts (>5%) of  $\Delta^3$ - and  $\Delta^2$ -cephems were not detected in the crude photo-



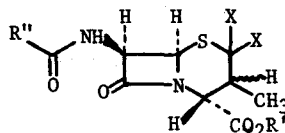
	<u>X</u>	<u>R'</u>	<u>R''</u>
<u>1</u>	CH <sub>3</sub>	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -
<u>7</u>	CH <sub>3</sub>	H	-OCH <sub>2</sub> -
<u>13</u>	CD <sub>3</sub>	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -



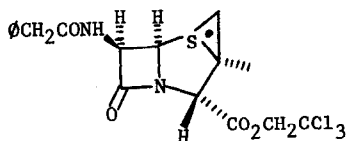
	<u>X</u>	<u>R'</u>	<u>R''</u>
<u>2</u>	H	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -
<u>8</u>	H	H	-OCH <sub>2</sub> -
<u>14</u>	D	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -



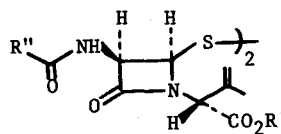
	<u>X</u>	<u>R'</u>	<u>R''</u>
<u>3</u>	H	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -
<u>5</u>	H	H	-CH <sub>2</sub> -
<u>6</u>	H	CH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	-CH <sub>2</sub> -
<u>12</u>	H	CH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	-OCH <sub>2</sub> -
<u>15</u>	D	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -



	<u>X</u>	<u>R'</u>	<u>R''</u>
<u>4</u>	H	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -
<u>11</u>	H	CH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	-OCH <sub>2</sub> -
<u>16</u>	D	CH <sub>2</sub> CCl <sub>3</sub>	-CH <sub>2</sub> -



17



	<u>R'</u>	<u>R''</u>
<u>9</u>	H	-OCH <sub>2</sub> -
<u>10</u>	CH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	-OCH <sub>2</sub> -

lysis mixture (NMR). Under similar reaction conditions  $\Delta^3$ -cephems are not photostable and have been shown to rearrange to thiazole derivatives;<sup>7</sup> however, we have found that this process is slow relative to conversion of 2 to 3 to 4. A systematic investigation of reaction variables revealed that the conversion is solvent dependent, methylene chloride, methanol, or acetonitrile being preferred with respect to 3. In contradistinction, photolysis of 3 in absolute ethanol led to high yields of 3-methyl cepham 4 with little or no 3.

Heating penicillin V sulfoxide (7) in *tert*-butanol with an equivalent amount of 2-mercaptobenzothiazole yielded disulfide acid 8.<sup>4</sup> Dissolution of 8 in aqueous sodium bicarbonate effected rearrangement to the symmetrical disulfide 9,<sup>4</sup> which was esterified with DDM to give 10. Substance 10 was inert to the described photolytic conditions. However, photosensitization by benzophenone induced cyclization to a mixture containing epimeric cephams 11, but not 12. The heterothiol moiety is thus implicated in formation of 3.

Deuterium-labelled penicillin sulfoxide 13 ( $\approx 84\%$  by NMR),<sup>8</sup> after heating in toluene for 4 hrs with thio-deuterated 2-mercaptobenzothiazole afforded crystalline, regiospecifically-labelled disulfide 14. The site of deuteration was determined by PMR and CMR. Photolysis of 14 yielded a 2:1 mixture of cephams 15 and 16, which clearly contained deuterium only at C-2 (PMR, CMR). Again, separation of the mixture was best achieved by oxidation to the sulfoxide prior to silica gel chromatography.

The above data suggest alkylthiyl, anti-Markownikoff radical addition to olefin as the likely pathway for the production of both 3 and 4, in accord with the mechanism proposed earlier.<sup>6</sup> Homolytic cleavage of disulfide 2 must be initiated by the benzothiazole ring, since the dialkyl disulfide 10 is photostable in the absence of photosensitizers.

The above mechanistic interpretation is consistent with the fact that the conjugated isomer of 2 (obtained from 2 by brief treatment with triethylamine) does not undergo similar photocyclization to  $\Delta^3$ -cephems. Maki and Sako suggest that the highly regioselective production of methylene cephem 3 might be attributable to the fact that the C-H bond orbital at position 2 or 4 and the spin orbital of the radical carbon are not co-planar and therefore hydrogen abstraction at methyl is preferred. While we essentially agree with their interpretation, an alternative explanation could be due to the formulation of the  $\beta$ -lactam thiyl moiety as a bridged radical such as 17. Bridged radicals are putative intermediates in the addition of thiyl radicals to alkenes.<sup>9</sup> If stereoelectronic constraints dictate that the

hydrogen atom abstracted to produce olefin must be anti-periplanar to the carbon-sulfur bond in 17 undergoing fission, then an explanation for the observed regioselectivity is at hand. Inspection of Dreiding models clearly demonstrates that only the C-3' hydrogens can assume the requisite anti-periplanar relationship with one of the carbon-sulfur bonds of the bridged radical, irrespective of whether the bridge is disposed with  $\alpha$ - or  $\beta$ -stereochemistry. 2-Mercaptobenzothiazoyl radicals are likely involved in hydrogen atom abstraction from C-3', perhaps in an initially formed solvent cage. The ratio of diastereoisomers of 4 produced may reflect the proportion of  $\alpha$  and  $\beta$  isomer of 17 (stereospecific hydrogen atom transfer) or the incursion of classical radical (non-stereospecific hydrogen atom transfer). The high yields of cepham 4 obtained by photolysis in ethanol may be attributed to a facile donation of hydrogen atoms by solvent.

#### Acknowledgement

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#### References

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