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HYDROLYTIC CLEAVAGE OF THIAZOLINE SULFOXIDES BY A RADICAL CHAIN PROCESS SELECTIVE TRANSFORMATION OF COOPER'S β-LACTAM THIAZOLINES INTO PENICILLIN SULFOXIDES

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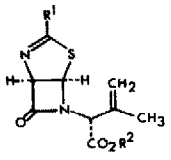
We recently reported a biogenetic-type synthesis of penam- and cephem-derivatives from an acyclic precursor.[1,2] Related to this synthesis, we studied selective transformation of the β-lactam thiazoline sulfoxide 2 into penicillin sulfoxide 3. This communication reports that such transformation can efficiently be effected by a radical chain process.

Cooper first reported[3] that the β-lactam thiazoline 1a, a degradation product of penicillin,[4] yielded a mixture of penicillin sulfoxide 3a, deacetoxycephalosporin sulfoxide 4a and other substances on *m*-chloroperbenzoic acid oxidation *in the presence of* trifluoroacetic acid. This procedure was applied to our synthesis of penam- and cephem-derivatives.[1] However, the results were not completely satisfactory in our case because of its poor selectivity and low overall yields and also because of lack of information about its intermediate(s) and reaction mechanism. Concerning the reaction mechanism, Cooper suggested that the reaction would proceed *via* sulfenic acid intermediate 5a[3], but the sulfur atom in 1a is very inert to oxidants such as *m*-chloroperbenzoic acid *in the absence of* trifluoroacetic acid and therefore, it was impossible to examine the reaction in a stepwise manner. This difficulty was overcome as follows; namely, when the substituent R^1 in the β-lactam thiazoline system is modified,[5] the sulfur atom is readily oxidized to the corresponding sulfoxide. Thus,

the sulfoxides 2b[6] (mp 102-3°), 2c[6] (mp 112-4°), 2d[6] (mp 169-172°), and 2e[6] (mp 113-5°) were synthesized in 80-90% yield from the corresponding β-lactam thiazolines 1b-e[7] by *m*-chloroperbenzoic acid in methylene chloride.[5] The peracid oxidation took place stereospecifically to yield a simple sulfoxide. The α-configuration was tentatively assigned to the sulfoxides 2b-e for steric reasons.



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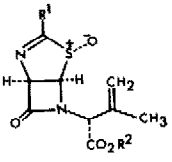

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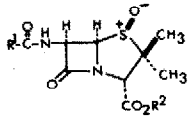

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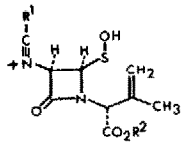
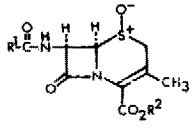


5a



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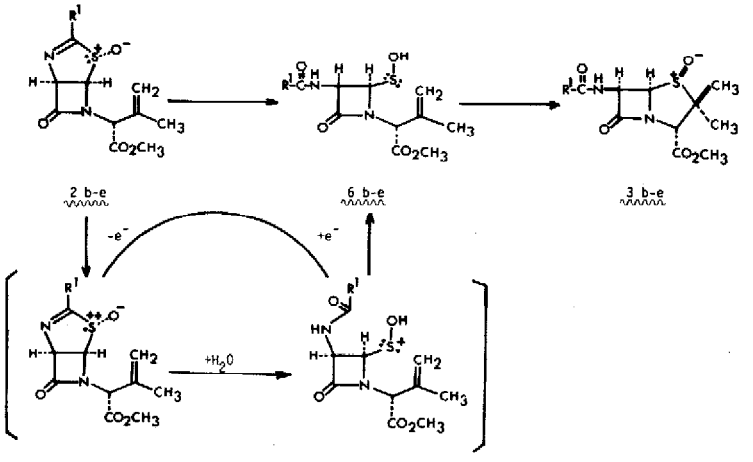
a : $R^1=CH_2OC_6H_5$, $R^2=CH_2CCl_3$
b : $R^1=C_6H_4OCH_3$-*p*, $R^2=CH_3$
c : $R^1=C_6H_5$, $R^2=CH_3$
d : $R^1=C_6H_4NO_2$-*p*, $R^2=CH_3$
e : $R^1=C(CH_3)_3$, $R^2=CH_3$
f : $R^1=CH_3$, $R^2=CH_3$

The sulfoxides 2b-e were stable under a wide variety of acidic conditions such as formic, acetic, benzoic, trifluoroacetic, and *p*-toluenesulfonic acids in wet toluene at 115°. However, the sulfoxides 2b-e were found to be smoothly converted to their corresponding penicillin β-sulfoxides 3b[6] (mp 158-160°), 3c[6] (mp 157-9°), 3d[6] (mp 172-3°), and 3e[6] (mp 145-7°), respectively, in 60-90% yield by a treatment with a small amount (0.05-0.1 eq.) of a radical initiator in wet toluene at 115°. For instance, the sulfoxide 2e (100 mg)

was heated in 10 ml of wet toluene containing a 5 mg of α,α'-azobisisobutyronitrile at 115° for 40 minutes. Preparative tlc separation, crystallization and recrystallization gave the penicillin β-sulfoxide 3e[6] (mp 145-7°) in 70% yield in addition to 25% of recovered starting material 2e (mp 113-5°).[8]

α,α'-Azobisisobutyronitrile could be efficiently replaced with benzoyl peroxide, *t*-butyl hydroperoxide, or *m*-chloroperbenzoic acid. Photolysis was also effective, although the yield of the penicillin sulfoxide was low. Addition of radical scavenger such as 4,4'-thiobis-(6-*t*-butyl-3-methylphenol)[9] to the reaction solution containing a radical initiator caused the reaction to be completely quenched. These results clearly indicate that the transformation of the sulfoxides 2b-e into the penicillin β-sulfoxides 3b-e involves a radical chain process. One of the possibilities would be as shown in *Figure 1*. Deuterium exchange experiments suggests that the electrocyclization process[10,11] of the sulfenic acids 6b-e is involved; namely, when the reaction was run in the presence of D_2O, deuterium incorporation was observed exclusively on the 2β-methyl group of the penicillin sulfoxide.[12,13]

Figure 1



References and Footnotes

1. S. Nakatsuka, H. Tanino, and Y. Kishi, J. Am. Chem. Soc., 97, 5008 (1975).
2. S. Nakatsuka, H. Tanino, and Y. Kishi, J. Am. Chem. Soc., 97, 5010 (1975).
3. R. D. G. Cooper, J. Am. Chem. Soc., 94, 1018 (1972).
4. R. D. G. Cooper, and F. L. Jose, J. Am. Chem. Soc., 92, 2575 (1970).
5. It is still not clear why the β-lactam thiazolines 1a and 1f are not oxidized to the corresponding sulfoxides, while the β-lactam thiazolines 1b-e can be smoothly oxidized by *m*-chloroperbenzoic acid. The different reactivity towards the oxidant is not obviously related to the electronic (compare 1b with 1d) and steric (compare 1f with 1e) factors, nor to the difference of the reaction mechanism (i.e., the oxidation reaction yielding the sulfoxides 2b-e proceeds smoothly in the absence or presence of a radical scavenger[9].
6. Satisfactory spectroscopic and analytical data were obtained on this substance.
7. The β-lactam thioazolines 1b-e were synthesized from 6-aminopenicillanic acid in five steps; i.e., 1. $[(CH_3)_3Si]_2NH$, 2. R^1COCl, 3. CH_2N_2, 4. *m*-$ClC_6H_4CO_3H$, 5. $P(OCH_3)_3/\Delta^4$.
8. The reaction could be brought to completion in a longer reaction period, but the recovery of the product was low.
9. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, Chem. Commun., 64 (1972).
10. R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, Acct. Chem. Res., 6, 32 (1973).
11. This step was confirmed *not* to involve the radical chain process.
12. Deuterium incorporation due to a 6 ⇄ 3 process under this condition was confirmed to be negligible.
13. Financial assistance by Harvard University, the National Institutes of Health, the National Science Foundation, and the Pharmaceutical Division of CIBA-GEIGY is gratefully acknowledged.