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PHOTOCHEMICAL FORMATION OF 3-METHYLENECEPHAM

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The chemical conversion of the penicillins into cephalosporins is the object of much courrent research.[2,3] The efficient methods of the penam-cepham conversion involve primarily interaction between an electrophilic sulfur of 4-sulfenic acid group or its equivalent groups and an appropriately situated isopropenyl double bond of the N-side chain in the azetidinone intermediate which can be produced *via* an 1-2 bond cleavage of penicillin sulfoxides.

We now wish to report the first photochemical formation of the cepham nucleus from the azetidinone intermediate *via* a radical process. An important special feature of this new type of conversion is the preferential formation of 3-methylenecepham[4,5] by virtue of irradiation of dithioazetidinones, which involves the intramolecular attack of a generated thiyl radical to an isopropenyl double bond followed by hydrogen abstraction.

On the basis of accumulation of a number of facts, some biosynthetic pathways of β-lactam antibiotics have been proposed and also pursued *in vitro*.[2,6] The present result shows that a speculative biosynthetic route to a cephams from a dithioazetidinone intermediate, which presumably attaches to a protein surface by the S-S linkage, is chemically reasonable.

Kamiya *et al*.[3] have shown that 4-heterocyclic dithioazetidinones can be prepared by intermolecular trapping of the sulfenic acid intermediate produced thermally from penicillin sulfoxides with heterocyclic thiols.

According to Kamiya's procedure, 4-(2'-benzoxazolyl and benzothiazolyl)dithioazetidinones((2a), mp 47-49°, and (2b), mp 138-141°)[7] were obtained quantitatively upon heating of penicillin G sulfoxide methyl ester(1) with 2-mercaptobenzoxazole(5a) or 2-mercaptobenzothiazole(5b) in toluene. Synthesis of 4-(2'-pyridyl)-dithioazetidinone(2c, oil) was achieved by employing 2,2'-pyridyl disulfide instead of 2-mercaptopyridine(5c) as a trapping agent of the intermediary sulfenic acid.

Dithioazetidinone(2a)(2×10^{-3}M) in acetonitrile was irradiated by a 400W high pressure mercury arc lamp surrounded by a water-cooled jacket through Pyrex filter under nitrogen for about 1 hr. Chromatographic separation allowed to isolate 3-methylenecepham methyl ester(3), 3-methyl-2-cephem methyl ester(4) and (5a) in 60%, 15% and 58% yields, respectively.[8] The NMR spectrum of the reaction mixture did not show the presence of detectable amount of other products.

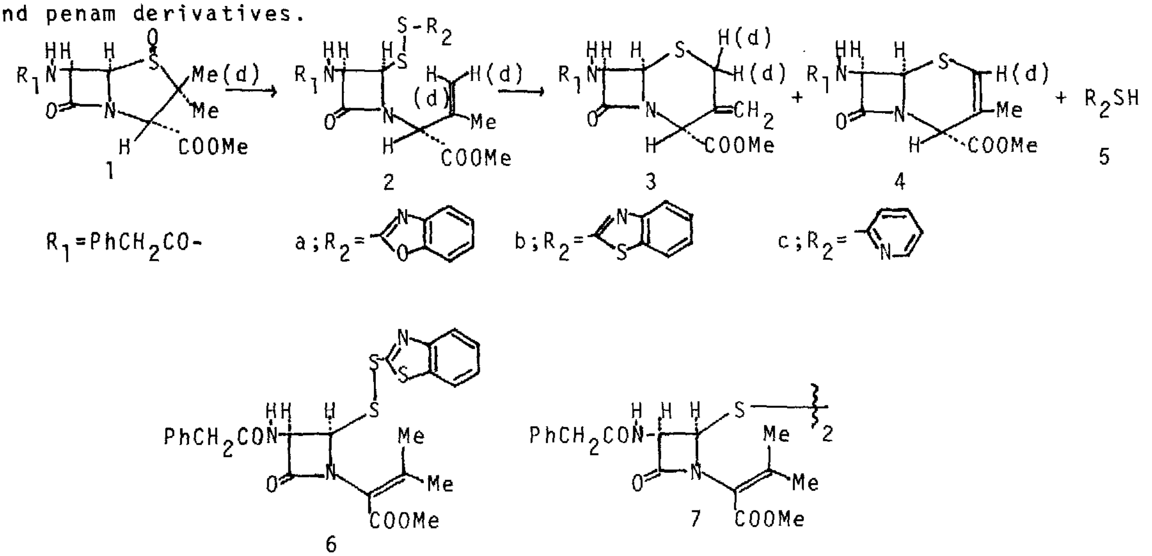
The spectral data, microanalytical results and base-catalyzed conversion into 3-methyl-3-cephem derivative[4] established the structure of (3). 2-Cephem (4) and (5a) were identical in every respect with authentic samples.

Analogous irradiation of (2b) and (2c) in acetonitrile gave (3) in 45% and 18% isolated yields, respectively.

Photointerconversion between (3) and (4) was not realized under the similar conditions, indicating the competing formation of both the products.

It is notable that 3-methyl-3-cephem derivative was not formed in the present photoreaction. Contrary to (3) and (4), 3-cephem derivatives are labile to uv light to take place the complete destruction of the β -lactam dihydrothiazine nucleus.[9] However, since the destruction requires a considerable long-period irradiation under the employed conditions, the possibility of photodegradation of the initially formed 3-cephem derivative during the irradiation is negligible.

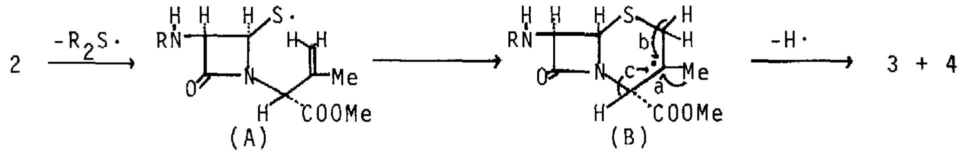
Irradiation of an isomeric 4-(2'-benzothiazolyl)dithioazetidinone(9) resulted in the formation of a disulfide(7) in 37% yield and did not give the cepham and penam derivatives.



Scheme 1

4-(2'-Benzothiazolyl)dithioazetidinone deuterated at the olefinic carbon (2b-d)(d-content ca 30%, by NMR) was prepared by reaction of 2-β-deuterated methylpenam sulfoxide(1-d)[10] (d-content 40%) with (5b). The NMR spectrum of the photoproducts,(3-d)and(4-d), derived from (2b-d) showed that deuterium retains at the 2-position of (3-d) and (4-d) in ca 30% deuterium content, respectively. Thus, origin of the carbon at position 2 of (3) and (4) was confirmed to be the olefinic carbon, but not the methyl carbon in the isopropenyl moiety of (2).

On the basis of above fact, we propose a reaction sequence as outlined in Scheme II.



Scheme 2

Homolytic cleavage of the S-S bond of (2) in an excited state gives a thiyl radical(A) and a heterocyclic thiyl radical($R_2S\cdot$).[11,12] Attack of the thiyl radical(A) on the olefinic bond occurs in the anti-Markovnikov's manner[13] to give an intermediary radical(B). Although three possible ways(a,b and c) for the loss of hydrogen in (B) can be considered, the most favorable one appears to be the hydrogen abstraction from a methyl grouping(a) mainly due to the steric reason, i.e., Dreiding model experiment of (B) showed that the C-H bond orbitals at position 2 or 4 and the spin orbital of the *radical carbon are not coplanar.*

The heterocyclic thiyl radical($R_2S\cdot$) would play a role for the hydrogen abstraction and could capture the eliminated hydrogen atom to convert into heterocyclic thiol(5). There have been many examples of five, six and seven-menbered ring formations by intramolecular addition of thiols to appropriately situated bouble bonds via the radical or ionic process. Contrary to the present photocyclization, these reactions obviously did not involve the hydrogen abstraction.[14]

The present photoreaction made possible to prepare 3-methylenecephams, which are a versatile intermediate for the modification of cephalosporin antibiotics,[4] from penams in fairly high yields.[15]

Extension of this type of the photoreaction to other systems is now in progress.

Acknowledgment

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References and Footnotes

(1) On leave from Toyo Jozo Co. Ltd, Mifuku, Ohito, Tagata, Shizuoka, Japan.
(2) For recent reviews, see (a) " *Cephalosporins and Penicillins: Chemistry and* Biology", E.H. Flynn, Ed., Academic press, New York, N. Y., 1972; (b) R.J. Stoodley, *Tetrahedron*, **31**, 2321(1975); (c) A.K. Mukerjee and A.K. Singh, *Synthesis*, 547(1975); (d) P.G. Sammes, *Chem. Reviews*, **76**, 113(1976).
(3) T. Kamiya, T. Teraji, H. Hashimoto, O. Nakaguchi, T. Oku, *Tetrahedron Lett.*, 3001(1973); *J. Am. Chem. Soc.*, **97**, 5027(1975).
(4) 3-Methylenecephams have been synthesized by an electrochemical reduction and by chrominium(II) salts, Raney nickel or zinc-formic acid reduction of the

corresponding cephalosporinic acids(cf. M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki and Y. Asahi, *J. Chem. Soc., Perkin I*, 258(1974); M.Ochiai, O. Aki, A. Morimoto, T. Okada and K. Morita, *Tetrahedron*, 115(1975); R.R. Chauvette and P.A. Penington, *J. Org. Chem.*, **38**, 2994(1973).
During preparation of this paper two thermal conversions of penams to 3-methylenecephams have been reported(cf. S. Kukolja, M.R.B. Gleissner, A.I. Ellis, D.E. Dorman and A.W. Paschal, *J. Org. Chem.*, **41**, 2276(1976); S. Kukolja, S.R. Lammert, M.R.B. Gleissner and A.I. Ellis, *J. Am. Chem. Soc.*, **98**, 5040(1976).

(5) 3-Methoxy(or Chloro)-3-cephems possessing a potential antibiotic activity have been synthesized from 3-methylenecephams by low temperature ozonolysis of the 3-exomethylene function followed by methylation(or chlorination)(cf. R.R. Chauvette and P.A. penington, *J. Medicinal Chem.*, **18**, 403(1975); *J. Am. Chem. Soc.*, **96**, 4985(1974)).

(6) (a) S. Nakatsuka, H. Tanino and Y. Kishi, *J. Am. Chem. Soc.*, **96**, 5008(1975); *Tetrahedron Lett.*, 581(1976) and references cited; (b) J.E. Baldwin, A. Au, M. Christie, S.B. Haber and D. Hessen, *J. Am. Chem. Soc.*, **97**, 5975(1975);(c) A.I. Scott, S.E. Yoo, S. K. Chung and J.A. Lacadie, *Tetrahedron Lett.*, 1137 (1976).

(7) All compounds described herein gave satisfactory microanalytical results and spectral data consistent with their structures.

(8) We did not attempt to optimize the reaction conditions.

(9) Y. Maki and M. Sako, *J. Am. Chem. Soc.*, **97**, 7168(1975).

(10)(a) R.D.G. Cooper, *J. Am. Chem. Soc.*, **92**, 5010(1970); (b) D.H.R. Barton, F. Comer, D.T.C. Greig, G. Lucent, P.G. Sammes and W.G.E. Underwood, *J.C.S.Chem. Commun.*, 1059(1976).

(11)For a recent article on photolysis of disulfides, see Y. Maki and M. Sako, *Tetrahedron Lett.*, 851(1976).

(12)J.K. Kochi " Free Radicals" John-Wiley, New York, N.Y. , 1973, p 711.

(13)A number of examples demonstrating addition of a thiyl radical to a substituted olefine in the anti-Markovnikov's manner have been reported(cf. " Organic Photochemistry" O.L. Chapman, Ed., Macel Dekker, New York, N.Y., Vol 2, 1969, p 181).

(14)T. Sheradsky" The Chemistry of Thiol Group" Part II, S. Patai, Ed., Wiley Interscience, New York, N.Y., 1974, p 702.

(15)Pyrolysis of dithioazetidinones(2) under certain conditions did not give 3-methylenecepham(3). Further details will be reported elsewhere.