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Thermal Reaction of 4-Benzothiazolyldithioazetidinone Novel Formation of Isothiazolone Derivatives

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In order to compare with the photochemical reaction resulting to the preferential formation of 3-methylenecepham, the thermal reaction of 4-benzothiazolyldithioazetidinone (1) was examined. Pyrolysis of **1** led to the formation of 2-mercaptobenzothiazole (**4**), isothiazolone derivatives (**5a** and **5b**), thiazole derivatives (**6a** and **6b**) and bisbenzothiazolyl disulfide (**7**) in a different manner from the photolysis of **1**. Rearrangements of **1** to **5** and **6** are particularly of interest and their possible mechanisms were discussed.

Keywords——Penicillin derivatives; thiazole derivatives; isothiazole derivatives; disulfide; pyrolysis; thiyl radical; thermal rearrangement

Our recent article[2)] has described that the photolysis of 4-benzothiazolyldithioazetidinone[3)] (1) possessing N-(1-methoxycarbonyl-2-methyl-2-propenyl) side chain produces preferentially 3-methylenecepham (2), which is a versatile intermediate for the synthesis of important class of C_3-modified cephalosporins, together with a small amount of 3-methyl-2-cephem (3) and 2-mercaptobenzothiazole (4).

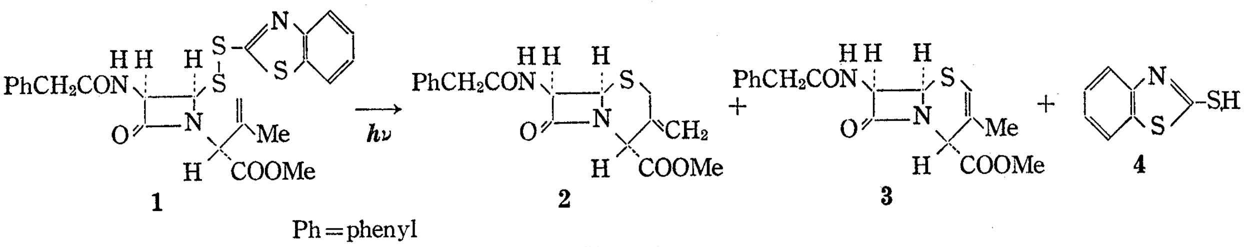

Chart 1

We now wish to report the thermal reaction of **1** which was undertaken in order to compare with the photochemical reaction. The present result is of special interest with respect to that the thermal reaction proceeds in a different manner from the photochemical one dispite involvement of the possible formation of an azetidinone thiyl radical in an initial stage of both the thermal and photochemical reactions. The observed rearrangement leading to isothiazolone derivatives (**5a** and **5b**) is also intriguing from the mechanistic point of view.

Pyrolysis of **1** was carried out without solvent at 140° under nitrogen until disappearence of **1** was complete (monitored by thin-layer chromatography (TLC), about 4 hr). The oily reaction mixture thus obtained was carefully chromatographed on silica gel (solvent: benzene–ethylacetate) to separate six products, *i.e.*, 4-phenylacetamido-isothiazolones[4—6)] (**5a**; mp 150—

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[2)] Y. Maki and M. Sako, *Tetrahedron Lett.*, **1976**, 4291: *idem, J. Am. Chem. Soc.*, **99**, 5091 (1977).

[3)] T. Kamiya, T. Terazi, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, **1973**, 3001.

[4)] R.B. Morin, B.G. Jackson, R.A. Muller, E.R. Lavaganio, W.B. Scanlon, and S.L. Andrew, *J. Am. Chem. Soc.*, **91**, 1401 (1969).

[5)] R.D.G. Cooper and D.O. Spry in "Cephalosporins and Penicillins, Chemistry and Biology," ed. E.H. Flynn, Academic Press, N.Y. 1972, p. 181.

[6)] N.J. Leonard and G.E. Wilson, Jr., *J. Am. Chem. Soc.*, **86**, 5307 (1964).

152°, 16.4% and **5b**; mp 226—228°, 22.2%), 2-benzylthiazole-4-carboxamides[7] (**6a**; mp 62—63°, 48.3% and **6b**; mp 113—115°, 3.0%), 2-mercaptobenzothiazole (**4**; mp 180°, 58.5%) and bisbenzothiazolyl disulfide (**7**; mp 178°, 7.8%).

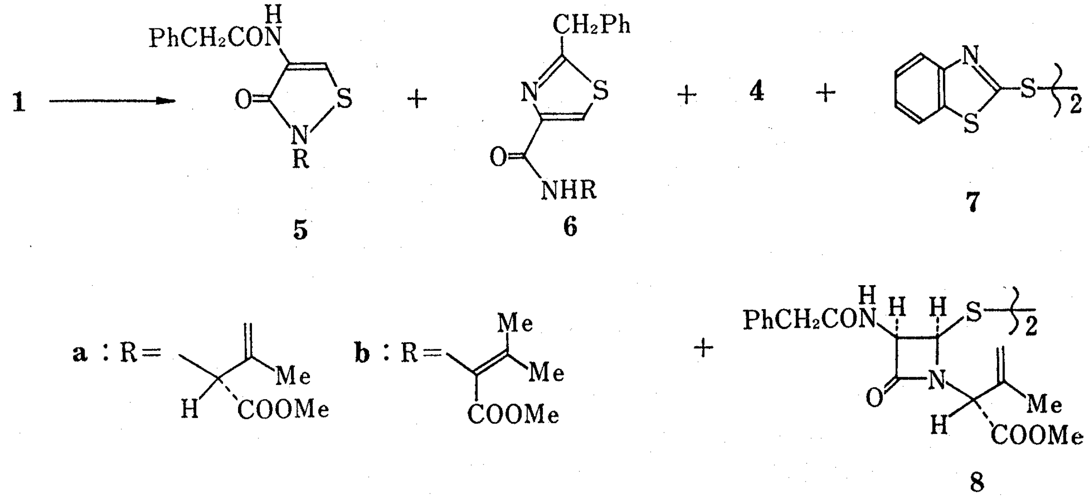

Chart 2

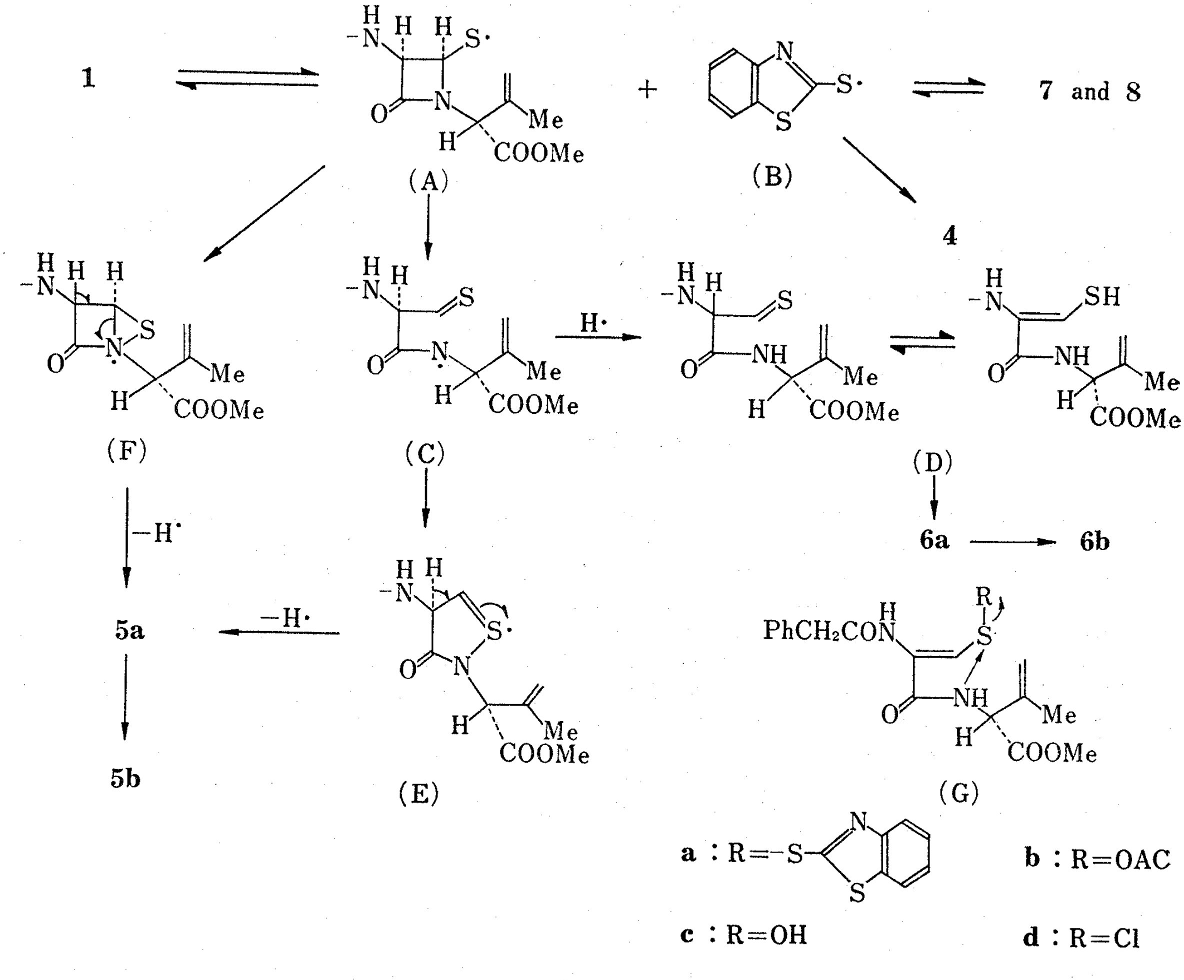

Chart 3

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7) R.D.G. Cooper and F.L. Jose, *J. Am. Chem. Soc.*, **92**, 2574 (1970).

The products (**5a**, **b** and **6a**, **b**) were identical in every respect with authentic samples prepared according to the procedures previously reported.[5,7] The thin-layer chromatography and nuclear magnetic resonance spectrum of the reaction mixture did not show the presence of 3-methylenecepham (**2**)[8] and other azetidinone derivatives.

Formation of a symmetrical disulfide of azetidinone (**8**)[2,4] during the pyrolysis of **1** was observed by virtue of monitoring the reaction by taking TLC. Thermal conversion of the disulfide (**8**) into **5** and **6** was demonstrated by an independent experiment. Isopropenyl-isopropylidene isomerizations (**5a**→**5b**) and (**6a**→**6b**) were observed in the pyrolysis of **5a** and **6a** under the analogous conditions. Accordingly, the isopropylidene derivatives (**5b** and **6b**) appear to be formed as a result of 1,3-hydrogen shift of the initially formed **5a** and **6a**. Although our previous work[9] has demonstrated the photochemical conversion of **5b** to **6b**, no occurrence of analogous conversion was observed under the conditions employed for the present pyrolysis.

On the basis of above facts, we tentatively propose possible reaction sequences for the thermal reactions of **1** as outlined in Chart 3.

Conversion of **1** to **7** and **8** seems likely to involve mainly an azetidinone thiyl radical (A) and a benzothiazolyl thiyl radical (B) under the employed conditions.[10] The thiyl radicals (A and B) would be in a state of equilibrium with **1**, **7** and **8**. The key intermediate radical (A) could undergo the further thermal reactions in a sharp contrast to the reactions under the photochemical conditions. Subsequent homolytic cleavage of the C_4–N bond of the azetidinone ring in A could generate an acylamino radical (C) which cyclizes to thiazoles (**6a** and **b**) *via* a thioaldehyde or thiol intermediate (D) produced by hydrogen abstraction.

The acylamino radical (C) could also undergo the cyclization an isothiazolone radical (E) followed by loss of a hydrogen to give isothiazolone derivatives (**5a** and **b**).

An alternative intermediate for the formation of **5a** is a thiaziridine radical (F) which could be formed directly from (A) *via* capture of an electrophilic thiyl radical by an amide nitrogen.

The isothiazolones (**5a** and **b**) have been obtained by the reaction of penicillin sulfoxide ester with acetic anhydride or pyridine.[4,5] Ring-contraction of thiazepines to **5a** upon treatment with N-chlorosuccimide[6] has been also reported. These transformations canberationalized in terms of an open-chain intermediate (G b, c and d).[4-6,11] In the present case, however, the formation of analogous intermediate (Ga) from **1** prior to the homolytic cleavage of the S–S bond seems to be an unfavorable process under the employed conditions.

Experimental

All melting points were measured on a Yanagimoto micro-melting point apparatus (a hot-stage type) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer in KBr disk. NMR spectra were obtained on a Hitachi R 20-B (60 MHz) spectrometer using $CDCl_3$ as solvent. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrometer in MeOH solution. Mass spectra were run on a Hitachi RMU-6L. *Rf* values in thin-layer chromatography were obtained by using silica gel plates (Merck TLC plates silica gel 60 F_{254}) and a mixed solvent (C_6H_6: EtOAc=3: 1).

Pyrolysis of 1-(1-Methoxycarbonyl-2-methyl-2-propenyl)-3-phenylacetamido-4-(benzothiazol-2-yl)dithioazetidin-2-one (1)——Disulfide (**1**) (2.0 g) was heated without solvent at 140° under a nitrogen atmosphere for 4 hr. Thin-layer chromatographic analysis of the reaction mixture showed the presence of six-products (**7**: *Rf*=0.91, **4**: *Rf*=0.74, **6a**: *Rf*=0.66, **6b**: *Rf*=0.51, **5a**: *Rf*=0.49 and **5b**: *Rf*=0.37). The oily reaction mixture thus obtained was carefully chromatographed on silica gel (solvent; C_6H_6: EtOAc=10: 1) to separate bisbenzothiazolyldisulfide (**7**) (mp 178°, colorless crystals, 7.8%), 2-mercaptobenzothiazole (**4**) (mp 180°,

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[8] Under analogous pyrolytic conditions, 3-methylenecepham (**2**) was stable.

[9] Y. Maki and M. Sako, *Tetrahedron Lett.*, **1976**, 375.

[10] It is well known that the thermolysis of disulfides generate thiyl radicals (For example, see J.R. Schaeffer, C.T. Goodhue, H.A. Risley, and R.E. Stevens, *J. Org. Chem.*, **32**, 391 (1967); H. Morita and S. Oae, *Heterocycles*, **1976**, 35).

[11] G.A. Koppel and S. Kukolja, *J.C.S. Chem. Commun.*, **1975**, 57.

pale yellow crystals, 58.5%), 2-benzylthiazole-4-carboxamide isopropenyl derivative (**6a**), (mp 62—63°, colorless crystals, 48.3%), 2-benzylthiazole-4-carboxamide isopropylidene derivative (**6b**), (mp 113—115°, colorless crystals, 3.0%), 4-phenylacetamido-isothiazolone isopropenyl derivative (**5a**) (mp 150—152°, colorless crystals, 16.4%) and 4-phenylacetamido-isothiazolone isopropylidene derivative (**5b**), (mp 226—228°, colorless crystals, 22.2%). During this reaction, the formation of disulfide (**8**) was detected by taking TLC ($Rf=0.04$). In this reaction, 3-methylenecepham (**2**) and other azetidinone derivatives were not detected by NMR spectra and TLC.

Pyrolysis of Bis[1-(1-methoxycarbonyl-2-methyl-2-propenyl)-3-phenylacetamidoazetidin-2-one-4-yl]disulfide (8)(3)——Disulfide (**8**) (255.5 mg) was heated without solvent at 150° under a nitrogen atmosphere for 3.5 hr. Thin-layer chromatographic analysis of the reaction mixture showed the presence of four-products, **6a**, **6b**, **5a** and **5b**. The oily reaction mixture thus obtained was carefully chromatographed on silica gel (solvent; C_6H_6: EtOAc=10: 1) to isolate **6a** (18.8%), **6b** (5.2%), **5a** (11.4%) and **5b** (15.5%).

Isomerization of 5a and 6a——Isopropenyl derivative (**5a**) (50 mg) was heated without solvent at 140° under a nitrogen atmosphere for 4.5 hr. Conversion of **5a** into **5b** was monitored by taking NMR spectra and TLC. Other products were not detected by NMR spectra and TLC.

In a similar manner, **6a** was converted into **6b** under the analogous conditions.