Thermal Reaction of 4-Benzothiazolylidithioazetidinone
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-benzothiazolylidithioazetidinone (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; thyl radical; thermal rearrangement

Our recent article\textsuperscript{2)} has described that the photolysis of 4-benzothiazolylidithioazetidinone\textsuperscript{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\textsubscript{3}-modified cephalosporins, together with a small amount of 3-methyl-2-cephem (3) and 2-mercaptobenzothiazole (4).

![Chemical Structure](chart1.png)

**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 thyl 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 disappearance 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\textsuperscript{4–6)} (5a; mp 150–
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%).

\[ \text{Chart 2} \]

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-methyleenecephem (2)8 and other azetidinone derivatives.

Formation of a symmetrical disulfide of azetidinone (8)9,41 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. Isopropenylisopropylidene 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 work9 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 thyl radical (A) and a benzothiazolyl thiyl radical (B) under the employed conditions.10 The thyl 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 C₄=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 thyl 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-chlorosuccinimide6 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 CDCl₃ 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 F₂₅₄) and a mixed solvent (C₂H₅OH:EtOAc=3:1).

**Pyrolysis of 1-(1-Methoxycarbonyl-2-methyl-2-propenyl)-3-phenylacetamido-4-[benzothiazol-2-yl]thiazo-azetidin-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; C₂H₅OH:EtOAc=10:1) to separate bisbenzothiazolyldisulfide (7) (mp 178°, colorless crystals, 7.8%), 2-mercaptobenzothiazole (4) (mp 180°, 8) Under analogous pyrolytic conditions, 3-methyleenecephem (2) was stable.


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-methylenecephem (2) and other azetidinone derivatives were not 
detected by NMR spectra and TLC.

Pyrolysis of Bis[1-(1-methoxycarbonyl-2-methyl-2-propenyl)-3-phenylacetamidoacetidin-2-one-4-yl]di-
sulfide (8) —— 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\textsubscript{6}H\textsubscript{4}: 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.