

**α -(3-Phoxymethyl-7-oxo-4-thia-2,6-diazabicyclo[3.2.0]hept-2-ene-6-yl)-
 α -isopropenylacetates, Useful Intermediate from
Penicillin to Cephalosporin**

Hiroshi TANIDA, Ryonosuke MUNYUKI, and Tadahiko TSUSHIMA

Shionogi Research Laboratory, Shionogi and Co., Ltd., Fukushima-ku, Osaka 553

(Received July 24, 1975)

Synopsis. Reaction of α -[2-(Benzothiazol-2-yl)-dithio-3-phenoxyacetamido-4-oxoazetidin-1-yl]- α -isopropenylacetates with phosphorus pentasulfide afforded the title compound. The first step in this reaction is suggested as an intramolecular nucleophilic attack of the thioamide function, initially resulted from the 3-acetamido groups, towards the disulfide-sulfur at the 2 position.

Warming of a penicillanic acid sulfoxide ester (**1**) with 2-mercaptobenzothiazol gave in an excellent yield the disulfide (**3**).^{1,2} It has been evidenced that the formation of **3** is a result of intermolecular thiol trapping of the sulfenic acid intermediate (**2**) existing in a thermal equilibrium with **1**.^{3,4} Since cleavage of the disulfide linkage and recyclization into new series of penicillin and cephalosporin is possible under mild conditions, the disulfide derived from 2-mercaptobenzothiazol may be a useful intermediate more than those from other thiols.² We have suggested that the side chain at C-6 might participate in reactions with the sulfenic acid (Formula **5**→**6**). Based on this hypothesis, we undertook an experiment to transform **3** into the thioamide **7**, because the thioamide function is known as a good nucleophile,⁶ perhaps, better than the acetamide.

The reaction of **3** ($R = \text{PhOCH}_2$), derived from Penicillin V, with diphosphorus pentasulfide was tried. When a benzene solution of **3** containing 1.1 mol equiva-

lents of phosphorus pentasulfide was refluxed for 30 min, there was found to form mainly the thiazoline-azetidinone **8** (the title compound) by liberating 2-mercaptobenzothiazol. The structure of **8** was established by comparing with an authentic sample prepared by the reported method.⁷

Reaction of **1** with trimethyl phosphite in refluxing benzene is known to give **8**.⁷ This reaction has been considered as an initial formation of the sulfenic acid followed by reduction by the trivalent phosphorus reagent into a thiol which attacks at the amide-carbon as a nucleophile to give the cyclized **8**. Reduction of the disulfide **3** into a thiol by the pentavalent phosphorus reagent, diphosphorus pentasulfide, is improvable. Alternatively, it seems us doubtless that the thioamide-sulfur in **7**, initially formed by an action of diphosphorus pentasulfide on **3**, reacts as a nucleophile toward the sulfide-sulfur to give **6** ($X = S$) which does not unfortunately survive under the reaction conditions but, as a result of several steps of thermal rearrangements as shown in the last formulas, affords the stable **8** by eliminating sulfur.

Finally, it should be pointed out that the present reaction is a simple procedure to obtain **8**, which is known as an important intermediate for the conversion of penicillin derivatives into cephalosporin derivatives.^{2,4}

Experimental

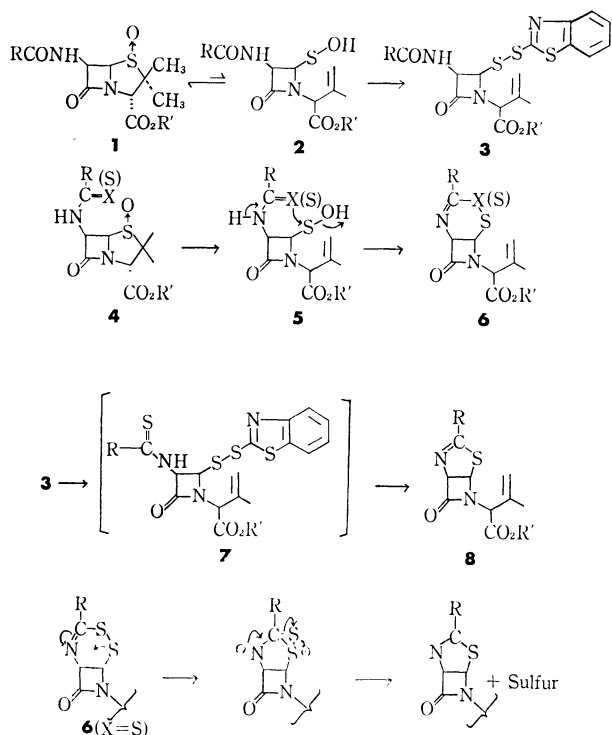
Reaction of 3 ($R = \text{PhOCH}_2$) with P_2S_5 . a) *With the Methyl Ester ($R' = \text{CH}_3$):* A solution of 329 mg (0.62 mmol) of **3** in 5 ml of benzene suspended with 35 mg (0.16 mmol) of P_2S_5 was refluxed for 30 min. The reaction mixture was filtered, evaporated under a reduced pressure and extracted with carbon tetrachloride.

After evaporation of the solvent, the residue (377 mg) was separated by thin-layer chromatography (benzene-ethyl acetate=4:1). The main fraction was the thiazolin derivative **8** (the title methyl ester) in 37.5% yield: IR (CHCl_3) 1780 and 1745 cm^{-1} ($\text{C}=\text{O}$), NMR (CDCl_3) δ 1.76 (s, 3, allylic CH_3), 3.77 (s, 3, COOCH_3), 4.93 (s, 2, PhOCH_2), 4.83 (s, 1, $-\text{CHCOOCH}_3$), 5.10 (broad, m, 1, vinyl H), 4.50 (d, 1, vinyl H, $J = 9.0$ Hz), and 5.97 (m, 2, azetidinone H); CD ($c = 0.1467$, in dioxane) 270 $m\mu$ ($[\theta] -1040$), 245 (+13300), and 209.5 (−29300).

b) *With the 2,2,2-Trichloroethyl Ester ($R' = -\text{CH}_2\text{CCl}_3$):* The corresponding **8** ($R' = -\text{CH}_2\text{CCl}_3$), mp 139–141 °C, was similarly obtained by the above procedure.

References

- 1) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, **1973**, 3001.
- 2) T. Kamiya, *Yuki Gosei Kagaku Kyokai Shi*, **33**, 24 (1975).



- 3) a) D. H. R. Barton and P. G. Sammes, *Proc. Roy. Soc., Ser. B*, **179**, 345 (1971); b) D. H. R. Barton, *Pure Appl. Chem.*, **33**, 1 (1973).
- 4) R. D. G. Cooper and D. O. Spry, "Cephalosporins and Penicillins Chemistry and Biology," ed. by E. H. Flynn, Academic Press, New York, N. Y., and London (1972), Chapter V.
- 5) H. Tanida, R. Muneyuki, and T. Tsushima, *Tetrahedron Lett.*, **1975**, 3063.
- 6) S. Winstein and R. Boschan, *J. Amer. Chem. Soc.*, **72**, 4669 (1950).
- 7) R. D. G. Cooper and F. L. José, *ibid.*, **92**, 2575 (1970).
-