BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48 (11), 3429—3430 (1975)

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

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(Received July 24, 1975)

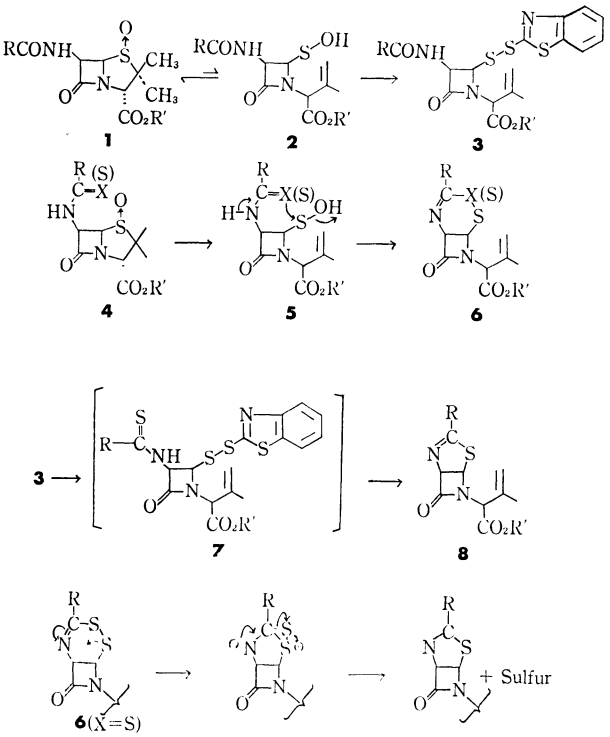
Synopsis. Reaction of α-[2-(Benzothiazol-2-yl)-dithio-3-phenoxyacetamido-4-oxoazetidin-1-yl]-α-isopropenylacetates with phosphorus pentasulfide afforded the title compound. The first step in this reaction is suggested as an intramolecular nucleophilic attack of the thioamide function, initially resulted 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=$PhOCH_2$), derived from Penicillin V, with diphosphorus pentasulfide was tried. When a benzene solution of **3** containing 1.1 mol equivalents 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=$PhOCH_2$–) with P_2S_5. a) With the Methyl Ester (R'=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} (C=O), NMR ($CDCl_3$) δ 1.76 (s, 3, allylic $C\underline{H}_3$), 3.77 (s, 3, $COOC\underline{H}_3$), 4.93 (s, 2, $PhOC\underline{H}_2$), 4.83 (s, 1, $-C\underline{H}COOCH_3$), 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 mμ ([θ]-1040), 245 (+13300), and 209.5 (−29300).

b) With the 2,2,2-Trichloroethyl Ester (R'=$-CH_2CCl_3$): The corresponding **8** (R'=$-CH_2CCl_3$), mp 139—141 °C, was similarly obtained by the above procedure.

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