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SYNTHESES OF SOME DITHIOKETENE ACETAL AZETIDINONE DERIVATIVES

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Abstract — Dithioketene acetal azetidinone derivatives (3)-(8) were prepared by the base induced reaction of 4-acetoxyazetidin-2-one (1) with β-hydroxydithiocinnamic ester and its analogues. The E and Z isomers of the products were separated and their configurations were determined in NOE experiments. Both isomers of compounds (3)-(7) showed moderate synergistical activity with penicillins against some resistant strains of bacteria.

The increasing incidence of resistance of bacteria to penicillins and cephalosporins as the result of the actions of β-lactamases has prompted a search for agents that might overcome this resistance. One approach to this problem is to design an agent that irreversibly inhibits β-lactamase enzymes. Recently, naturally occurring[1] and semisynthetic[2] azetidinone derivatives that inhibit β-lactamase have been reported. The present communication deals with the syntheses of dithioketene acetal azetidinone derivatives[3], some of which act synergistically with penicillins, increasing their activity against resistant strains of bacteria.

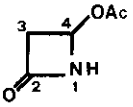
The starting material chosen for the syntheses was the readily available compound 4-acetoxyazetidin-2-one (1), which was first synthesized by K. Clauss et al.[4] The reactivities of (1) with a wide variety of thiols and hydroxy compounds have been demonstrated by them[4] and others. Reaction of (1) with methyl β-hydroxydithiocinnamate (2)[5] in the presence of sodium hydroxide (-5°C. 10 min., in H_2O/THF) gave a mixture of the E and Z isomer of dithioketene acetal in a ratio of 93:7.[6,7] Recrystallization of the mixture from chloroform and ethyl acetate gave pure (3E) in 63 % yield. Silica gel chromatography[8] followed by recrystallization of the residue obtained by concentration of the mother liquor afforded the Z isomer (3Z) in 20 % yield. Both (3E) and (3Z) are rather sensitive to acidic conditions;[8] for example, treatments of (3E) and (3Z) with a catalytic amount of trifluoroacetic acid in DMSO-d_6 respectively gave equilibrated mixtures of E and Z isomers of the

TABLE Dithioketene Acetal Azetidinone Derivatives[a)]

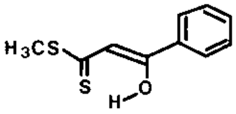
	yield (%)	m.p.[b)] (°C)	NMR(DMSO-d_6) δ			IR($CHCl_3$) cm^{-1}	UV(dioxane)
			C=CH	C_4-H	SCH_3	C=O	λ_{max}nm(log ε)
3E	63	143-146	6.94	5.57	2.48	1785,1630	338(4.23),268(3.97)
3Z	20	124-125	6.94	5.33	2.70	1779,1633	331(4.27),275(3.90),262(3.93)
4E	71	162-163	6.90	5.61	2.44	1785,1625	337(4.21),271(4.03)
4Z	18	165-166	6.91	5.32	2.69	1779,1625	335(4.34),270(4.11)
5E	58	151-152	6.86	5.53	2.47	1785,1623	342(4.30),270(4.15)
5Z	20	169-170	6.90	5.33	2.71	1779,1625	337(4.31),270(4.07)
6E	72	129-130	6.82	5.51	2.44	1785,1612	350(4.39),274(4.10)
6Z	15	130-131	6.84	5.32	2.68	1779,1614	345(4.35),275(3.98)
7E	45	119-120	6.89	5.55	——	1783,1630	338(4.24),277(3.91),261(3.92)
7Z	31	150-151	7.09	5.30	——	1779,1625	337(4.25),279(3.88),262(3.89)
8	63	155-156	7.01	5.60 5.30	——	1780,1630	332(4.21),266(3.95)

a) Satisfactory analytical data were obtained for all compounds.

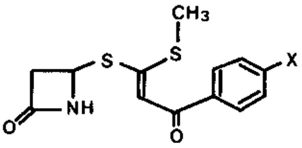
b) All melting points were determined by the capillary method and are uncorrected.



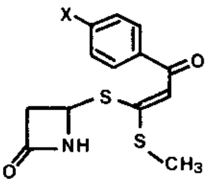
(1)



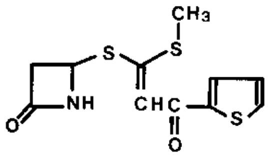
(2)



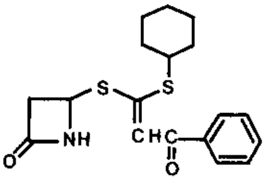
(3E) X = H
(4E) X = CH_3
(5E) X = Cl



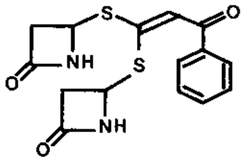
(3Z) X = H
(4Z) X = CH_3
(5Z) X = Cl



(6E) and (6Z)



(7E) and (7Z)



(8)

same ratio (E/Z = 0.52).[10] Several analogues were synthesized in a similar manner from (1) and the corresponding dithioesters[5] and Table summarizes data on their physical and spectroscopic properties. Compound 8 was prepared by the reaction of β-hydroxydithiocinnamic acid[5] with 2 equivalents of (1). The E and Z configurations of the products (3)-(7) were determined from studies on the NMR nuclear Overhauser effect (NOE): irradiation of C_4-H of E isomers increased the intensities of vinyl protons by 17-21 %, whereas irradiation of s-methyl protons (s-methyne proton for 7Z) of Z-isomers increased the intensities of vinyl protons by 16-23 %.

Although compounds reported herein showed only weak activities toward a variety of bacteria, compounds (**3**)-(**7**) synergistically increased the activities of penicillins toward resistant strains of bacteria. For example, treatments of a β-lactamase producing strain of Staphylococcus aureus with (**3E**) and (**3Z**) at a level of 6.25 μg ml^{-1} in combination with penicillin G reduced the minimum inhibitory concentration of penicillin G from >200 to 12.5 μg ml^{-1}. Details of the bioactivities of the compounds in this series will be reported elsewhere.

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3. Quite recently, preparation of secolactams by the reaction of (**1**) with 1,1-dithiomalonic esters, and use of the secolactams for the syntheses of 2-thioalkyl-substituted penems were reported; F. DiNinno, E. V. Linek, and B. G. Christensen, J. Amer. Chem. Soc., 1979, **101**, 2210.
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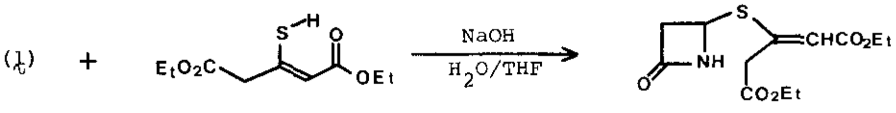
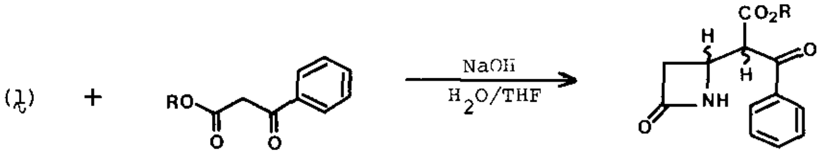
6. The E/Z ratio was determined by comparison of the relative intensities of C_4-H resonances in the NMR spectrum of the mixture of E and Z isomers.
7. An analogous reaction of (**1**) with ethyl 4-ethoxycarbonyl-3-mercaptocrotonate (**i**)[9] afforded a mixture of the E and Z isomer (E/Z = 1.27) of **ii** in 78 % yield. On the other hand, the reaction of (**1**) with alkyl benzoylacetates gave **iii** (R = Et, 45 %, R = t-But.,53 %) as isomeric mixtures. Details of these reactions and the uses of **ii** and **iii** for syntheses of novel antibiotics will be published later.



(**i**) (**ii**)



(**iii**)

8. Partial isomerization of the E isomer to the Z isomer in the silica gel column was observed.

9. F. Duus, *Tetrahedron*, 1972, **28**, 5923.

10. Rotation around the formal double bonds with "push-pull" groups has been recorded in the following literature: M. Neuenschwander, A. Neuenschwander, E. Steinegger, and P. Engel, *Helv. Chim. Acta*, 1979, **62**, 609; J. Sandström and I. Wennerbeck, *Acta Chem. Scand.*, 1970, **24**, 1191; G. Isaksson, J. Sandström, and I. Wennerbeck, *Tetrahedron Lett.*, 1967, 2233.

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