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NOVEL 1,2,4-DITHIAZINEAZETIDINONES FROM THE 6-THIOAMIDES AND 6-THIONCARBAMATES OF PENICILLIN SULFOXIDES

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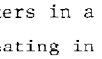
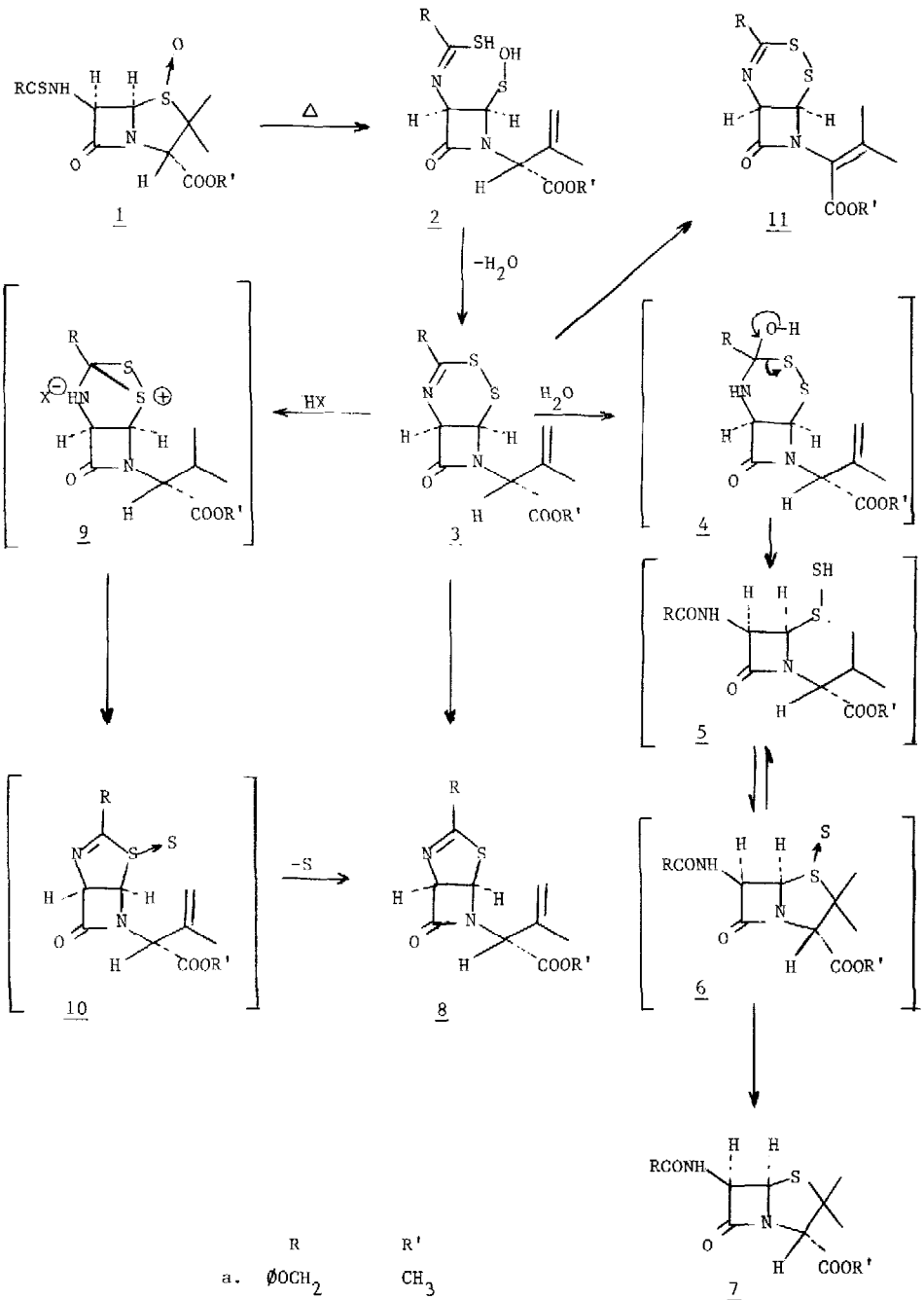
Penicillin sulfoxides on thermolysis generate the reactive azetidinone sulfenic acids [3,4]. These compounds in the presence of various catalysts are transformed into desacetoxycephalosporin. In addition, the sulfenic acids undergo intermolecular trapping reactions with olefins or acetylenes [5], with azo compounds [6], with arylsulfinic acids [7], with silylated amides [4b] and imides [8], and with mercaptans [9] or thioamides [10]. Many of these products were utilised for the preparation of cephalosporins and modified penicillins, the azetidinone-4-disulfides [9] being particularly well suited for this purpose (see for example Ref. 11 and other publications by the same authors).

Trimethyl phosphite converts the sulfenic acids to the thiazolineazetidinones, 8 [12], and with added acetic anhydride the azetidinone-4-thiolacetates [13] are formed.

Recently, Tanida and co-workers in a study of deuterium incorporation found that 1 (R = ϕCH_2, R^1 = CH_2-  -NO_2) on heating in D_2O-toluene gave 8 (59%) and recovered 1 with no deuterium incorporation, and suggested the intermediacy of the dithiazine, 3, which they were not able to isolate [14]. We have found that the thioamides and thiocarbamates, 1, [15] on thermolysis are converted in essentially quantitative yields to the novel 1,2,4-dithiazineazetidinones (the 3-substituted-4,5-dithia-2,7-diazabicyclo[4,2,0]oct-2-ene-8-one-7-isopropenyl acetates), 3.

The pure compounds, 1, are thermolysed at 120° in a suitable solvent such as toluene or dioxane (1% w/v solution) under reflux in a nitrogen atmosphere for 2 to 4 hrs (the time for complete reaction depending on 1). Concentration gave 3. In the case of 1a, particularly with aged samples, the addition of dimethylaniline (½ to 1 mole eq.) was necessary to obtain clean reactions. (Freshly prepared pure 1a did not require dimethylaniline.) In all these reactions there was no indication in the nmr spectra of any formation of the possible α,β-isomers, 11, (although these are formed on treatment of 3 with triethylamine); and, in the case of 3c there was no sign of the possible decarboxylated product.

The thermolysis reactions required carefully controlled conditions, the nature of the products depending on a number of factors including the nature of the "R" group, the temperature and time of heating, the purity of 1, and of the solvent, and the nature of the



	R	R'
a.	ϕOCH_2	CH_3
b.	ϕO	CH_3
c.	ϕO	H
d.	CH_3S	CH_3

impurities. Thus, compound 1a, when heated in the presence of methyl 6-phenoxyacetamido-penicillinate sulfoxide (a possible contaminant), or 2-mercaptobenzothiazole (a compound used to prepare azetidinone-4-disulfides[9]), or monopyridinium dichloromethylphosphonate (a catalyst used to convert penicillin sulfoxides to desacetoxycephalosporins), gave 8a as the main product. Extended reaction times (16 hrs) and higher temperatures also favoured the formation of 8, this extrusion of sulfur probably proceeding as indicated through dithiiranium, 9, and thiazoline thiosulfoxide, 10, intermediates.

The presently available physical data on these compounds will not distinguish between 3 and 10. However structure 3 appears to most easily explain the various reactions that have been explored.

The stability of 3 and their further reactions were dependent on the nature of the "R" group. Thus 3b and 3c were quite stable and were isolated as solids which could be recrystallised without decomposition. Compound 3a, formed under the appropriate conditions in high yield and purity (from the pmr spectrum), is quite unstable and rapidly changes on exposure to light, moisture and air. In fact pmr samples in unpurified $CDCl_3$ show changes in their spectra after about half an hour. Solutions of 3a (1% w/v) in moist dioxane (or toluene), exposed to light (12 hr exposed to a 500 watt incandescent light at ambient temperature) gave about 40% of 8 and 20% of 7 with other unidentified products. The identity of 8 and 7 was confirmed by isolation by column chromatography and direct comparison (pmr and ir spectra and tlc) with authentic samples. A mechanism for the formation of 8 and 7 is indicated in the scheme, in which the thiosulfoxides 6 and 10 undergo spontaneous loss of sulfur, a reaction with precedence [16].

Table 1 summarises the pmr spectral data on compounds 3. These are reactive compounds and useful intermediates for the preparation of β-lactam compounds. They have been converted in high yields to cephalosporins [17].

Table I

pmr spectral characteristics of the 1,2,4-dithiazeneazetidinones, 3.

Compound	pmr solvent	PMR SIGNALS (δ)					
		$-\!\!\!\!\diagup\!\!\!\!\diagdown CH_3$	-COOR'	CHCOOR'	$-\!\!\!\!\diagup\!\!\!\!\diagdown \overset{CH_2}{CH_3}$	β-lactam H's (J c/s)	R
3a	$CDCl_3$	1.90(s)	3.80(s)	4.95(s)	5.10(s), 5.20(d)	5.73(d) with wings	4.85(s)CH_2; 6.92 to 7.50(m) C_6H_5
3b	$CDCl_3$	1.97(s)	3.80(s)	4.99(s)	5.10(s), 5.22(d)	5.45(d) and 5.69(d) (5 c/s)	7.15 to 7.50(m) C_6H_5
3c	$DMSOd_6$	1.89(s)	Cf R.	4.85(s)	5.20(br s)	5.52(d) and 5.87(d) (5 c/s)	7.15 to 7.68(m) C_6H_5 and COOH
3d	$CDCl_3$	1.91(s)	3.80(s)	4.93(s)	5.10(s), 5.20(d)	5.62(d) and 5.82(d) (5 c/s)	2.47(s) $-SCH_3$

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