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SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. PART 4. PREPARATION OF CIS-3-ACYLAMINO-4-MERCAPTOAZETIDIN-2-ONES BY ACID HYDROLYSIS OF THIAZOLINOAZETIDINONES

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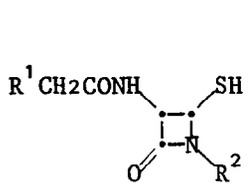
cis-3-Acylamino-4-mercaptoazetidinones 1 possess a common structure both to penicillins and cephalosporins and are potential intermediates for syntheses of β-lactam antibiotics.[1] Precedent total syntheses of 1 have included rather tedious processes for regeneration of free mercapto group on treatment with transition metals and then with hydrogen sulfide.[2] Related syntheses of several β-lactam compounds which can be considered to involve transient formation of mercaptans 1 or the corresponding mercaptids and simultaneous trapping of them by alkylation,[3,4] by acylation,[5] or by intramolecular cyclization giving thiazolinoazetidinones 2[6] also have been reported.

There have been known several examples of the ring opening of thiazolinoazetidinones 2. The oxidative ring opening accompanied by intramolecular alkylation[7] and the alkylative ring opening with α-halocarbonyl compounds in the presence of a weak base[8] might have proceeded through transient formation of the mercaptans. A method for preparation of 1 by ring opening of 2 with silver perchlorate and subsequent treatment of the resulting silver mercaptids with hydrogen sulfide has been reported from this laboratory.[9] During the synthetic study of 3-hydroxycephems,[9] we have found a simple and general procedure for the preparation of cis-3-acylamino-4-mercaptoazetidin-2-ones 1 by acid hydrolysis of the corresponding thiazolinoazetidinones 2. In this communication, we wish to report the procedure more in detail and several attempts to utilize 1 for syntheses of β-lactam antibiotics.

As shown in TABLE 1, hydrolysis of 2a proceeded most smoothly in strong acid conditions (run 1,2) to give 1a [mp 44-46°; $[\alpha]_D^{23}$ -74.2 ± 4.2° (C = 0.271, $CHCl_3$); nmr ($CDCl_3$, δ, ppm) 5.5 (m, 2H, C_3, C_4), 5.29 (s, 2H, PNB), 5.17 (broad s, 1H, $\prec^{H}_{H}$), 5.03 (broad s, 1H, $\prec^{H}_{H}$), 4.87 (s, 1H, $>NCH-$), 4.57 (s, 2H, V), 2.12 (d, 1H, J = 8.5 cps, SH), 1.93 (s, 3H, CH_3); ir ($CHCl_3$) 3415, 1776, 1748, 1693, 1517 cm^{-1}] in high yield, which was identified with an authentic sample of 1a prepared from the corresponding silver mercaptide.[9] Hydrolysis with 2N-hydrochloric acid (run 3) proceeded less satisfactorily giving a 1:1 mixture of 1a and a less polar by-product, to which the thiazole structure 3a was assigned based on an nmr signal characteristic to the thiazole proton ($CDCl_3$, δ 7.90[2e]) and ir absorption bands ($CHCl_3$, 3405, 1749, 1675, and 1526 cm^{-1}). Lattrell[2e] has observed formation of thiazole 3 in an attempted



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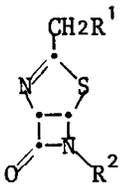

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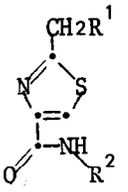

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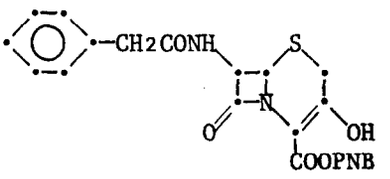

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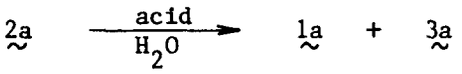
TABLE 1. Hydrolysis[a] of 2a under various acid conditions



Run	Acid-solvent (ml)	Conditions	Yield[b] (%) 1a	3a	2a
1	30% $HClO_4$-CH_2Cl_2-Acetone (0.5-4.0-4.0)	r.t., 1 hr	~100	-	-
2	40% TsOH-CH_2Cl_2-Acetone (0.5-4.0-4.0)	r.t., 1 hr	~100	-	-
3	2N-HCl-THF (0.8-4.0)	r.t., 1.5 hr	~50	~50	-
4	30% H_3PO_4-CH_2Cl_2-Acetone (1.0-4.0-10.0)	r.t., 5.5 hr	~76	~7	~17
5	30% HOAc-CH_2Cl_2-Acetone (1.0-4.0-8.0)	r.t., 6.5 hr	-	-	100

[a] Each run was carried out using 200 mg of 2a. [b] Estimated from nmr.

reverse conversion of 1 into 2 by heating 1 with trimethyl phosphite. Recently, we have noticed that Baldwin and Christie[10] have discussed more precisely the conversion of 2 into 3. With moderate acids (30% phosphoric acid shown in run 4, 30% trifluoroacetic acid and 10% oxalic acid), 2a was converted incompletely into 1a where the formation of thiazole 3a was inevitable. Most of the starting material was recovered on treatment of 2a with 30% acetic acid (run 5).

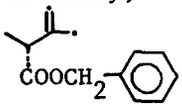
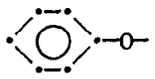
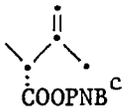
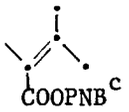
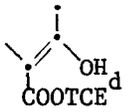
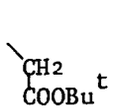
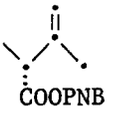
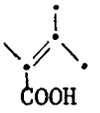
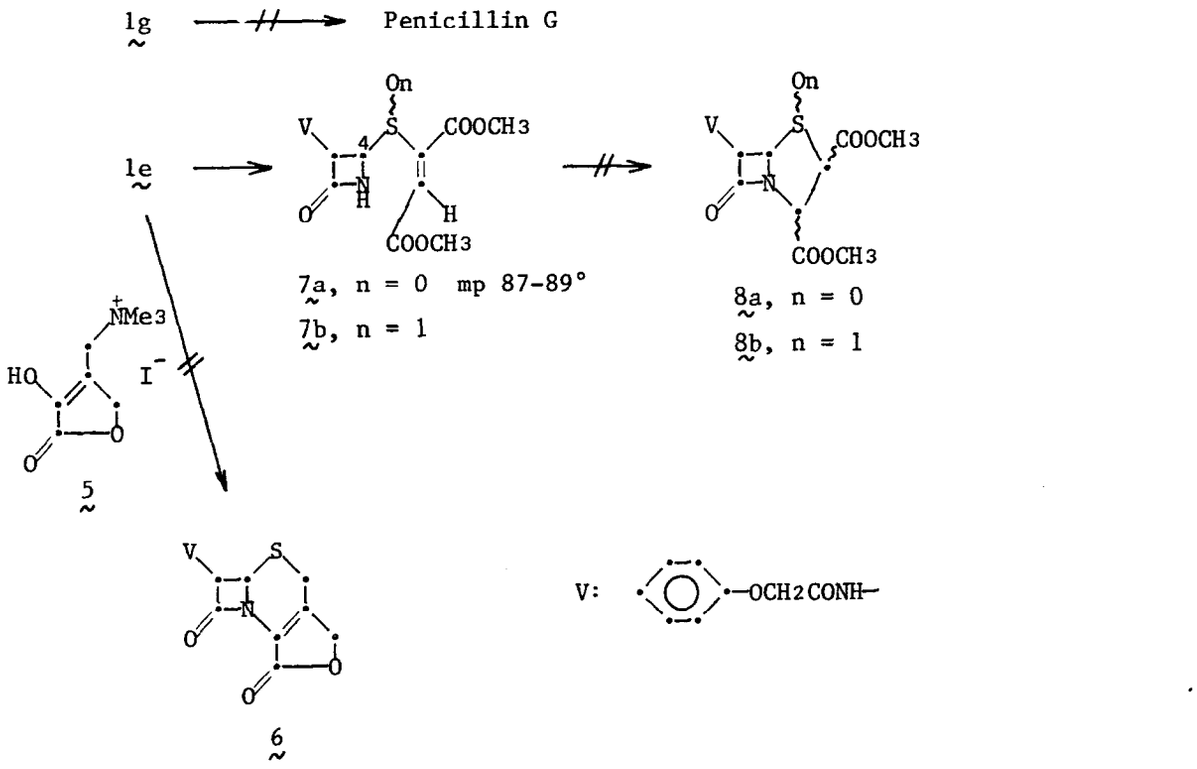
Recently, two other groups[10,11] have observed that acid hydrolysis of 2i (R^1 =  , R^2 = ) and 2e in methanol containing diluted hydrochloric acid and in acetic acid gave the corresponding thiols 1i and 1e in high yield without formation of thiazoles 3i and 3e, respectively. In these cases, the products crystallized out from the reaction solution. Rapid removal of the formed mercaptans 1 might be an essential factor for preventing the formation of thiazoles 3 under the moderate acid conditions.

TABLE 2 shows representative cis-3-acylamino-4-mercaptoazetidinones 1 obtained by the perchloric acid hydrolysis (run 1) of thiazolinoazetidinones 2a,[6] 2b,[6] 2c,[9] 2d,[12] 2e,[13] 2f,[9] 2g,[14] and 2h.[13] General procedure: 200-300 mg of 2 dissolved in a mixture of 4-5 ml of acetone and 4-5 ml of methylene chloride (or 5 ml of tetrahydrofuran) containing 0.5-1.0 ml of 30% perchloric acid was stirred at room temperature for 10-50 min. Dilution with water and extraction with methylene chloride yielded 1 in an almost quantitative yield. Some products were obtained as stable crystalline material and others as fairly labile foams. All the mercaptans showed reasonable infrared and nmr spectra.

TABLE 2. Spectral Data of 1

	a[9]	b	c	d	e[11]	f	g	h
R^1								
R^2					H			H
	mp 44-46°	foams	foams	semi-solid	mp 137-138°	foams	foams	mp 145-147°
$\nu_{C=O}$ cm^{-1} ($CHCl_3$)	1776	1773	1779	1775	1757	1771	1747[a]	1790
δ_{SH} ppm ($CDCl_3$)	2.12 (d, 8.5cps)	2.12 (d, 9cps)	2.10 (d, 9.5cps)	2.00 (d, 10cps)	3.17[b] (br. s)	2.05 (d, 8cps)	3.2[b] (br. s)	3.1[b] (br. s)

[a] Nujol [b] d_6-DMSO [c] p-nitrobenzyl [d] β,β,β-trichloroethyl



Several attempts to utilize 1 for syntheses of β-lactam antibiotics were carried out in vain. Attempts to cyclize 1g to penicillin G in several conditions (DMSO-H_2O at pH 7.4[15]: THF-H_2O at pH 3.4, 4.0, 5.6 and 8.5) failed; we could not observe formation of any detectable amount of penicillin G on thin-layer chromatography.

Synthesis of 6 by double alkylation of 1e with 5 was attempted under several basic and acid conditions. However, the rate of the alkylation was so slow that decomposition of 1e

proceeded without formation of the desired 6.

Michael addition of dimethyl acetylenedicarboxylate in a concentrated HMPT solution went smoothly with minimal isomerization at the C_4 position giving 7a [nmr ($CDCl_3$, δ, ppm) 7.96 (d, 1H, J = 8 cps, NH), 5.94 (s, 1H, $=<_H$), 5.68 (dd, 1H, J = 5 and 8 cps, C_3), 5.25 (d, 1H, J = 5 cps, C_4), 4.54 (s, 2H, V), 3.83 and 3.63 (two s, 6H, ester Me); ir ($CHCl_3$) 3430, 1790, 1725, 1700 (shoulder) cm^{-1}] in good yield, which was oxidized with m-chloroperbenzoic acid to 7b [nmr ($CDCl_3$, δ, ppm) 6.25 (dd, 1H, J = 5 and 10 cps, C_3), 5.30 (s, 1H, $=<_H$), 5.14 (d, 1H, J = 5, C_4), 4.60 (s, 2H, V), 3.87 (broad s, 6H, ester Me)]. Attempts to cyclize 7a and 7b by intramolecular Michael addition into 8a and 8b,[16] respectively, failed. Difficulty in these cyclizations of 1g and 7 might be interpreted well on the ground of "rules for ring closure," recently developed by Baldwin.[17] In both cases, the cyclization should take the disfavored 5-End-Trig state.

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