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PHOTOCHEMICAL REACTIONS OF 3-ACYL-2-THIOTETRAHYDRO-1,3-THIAZINES; A NEW SYNTHESIS OF CEPHAM ANALOGUES

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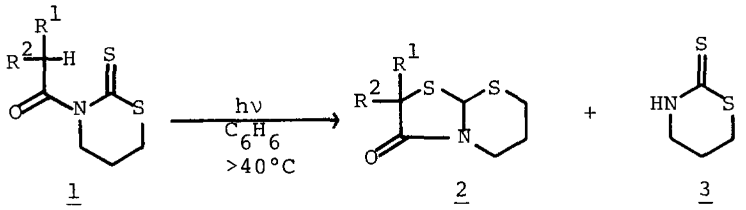
summary: Photolysis of 3-acyl-2-thiotetrahydro-1,3-thiazines followed by acetylation gave bicyclic β-lactams accompanied by Type II cleavage products. High temperature photolysis of them gave 2,9-dithia-6-azabicyclo[4,3,0]nonan-7-ones involving α-cleavage reactions of thioxo-β-lactams which were produced by ring opening reactions of thiazine rings of β-lactams.

The synthesis of β-lactams has been of continuing interest for many years because of the medical importance of penicillin and cephalosporine antibiotics. Previously we reported the photochemical synthesis of β-lactams involving Type II reactions of α-oxoamides,1) intramolecular [2+2] photocycloaddition of N-thiobenzoylmethacrylamides,2) and Type II reactions of monothioimides.3) Now we wish to report the photochemical reactions of 3-acyl-2-thiotetrahydro-1,3-thiazines. It has been reported that N-acyl-2-thionothiazolidines afforded only Type II cleavage products.4)

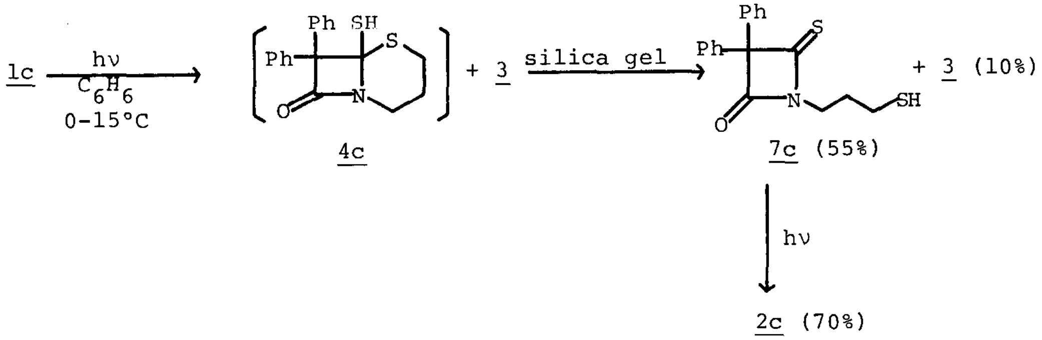
When 3-acetyl-2-thiotetrahydro-1,3-thiazine (1a) was irradiated in benzene with a 1000W high pressure mercury lamp under argon above 40 °C. Type II cleavage product, 2-thiotetrahydro-1,3-thiazine (3) was obtained in 48% yield. Photolysis of N-isobutyroyl derivative (1b) gave a similar result. In the cases of 1c-e, 2,9-dithia-6-azabicyclo[4,3,0]nonan-7-ones (2c-e) were obtained as main products as shown in table 1. When thiazine (1c) was irradiated at low temperature (0-15°C), the ir spectrum of the photoreaction mixture indicated the presence of bicyclic β-lactam (4c) (1760 cm^{-1}). However, the β-lactam (4c) could not be isolated. Instead of 4c, thioxo-β-lactam (7c) was obtained in 55% by silica gel column chromatography of the mixture. (Scheme 1)

The mechanism for the formation of 2 is reasonably explained in terms of a thiacarbene (8) formed by α-cleavage reaction of 4 as shown in Scheme 2. When 7c was irradiated in benzene, 2c was obtained in 70% yield as a sole

Table 1: Photolysis of 1 above 40°C

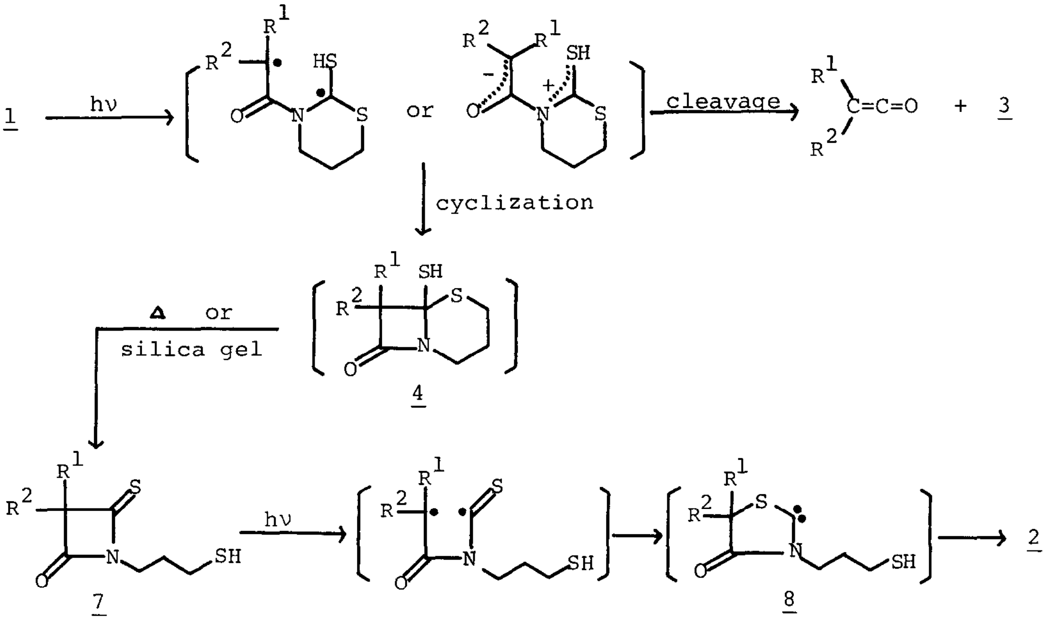


	R^1	R^2	Yield (%) 2	Yield (%) 3
a	H	H	0	48
b	Me	Me	0	59
c	Ph	Ph	51	11
d	MeO	H	31	16
e	EtO	H	56	26



Scheme 1

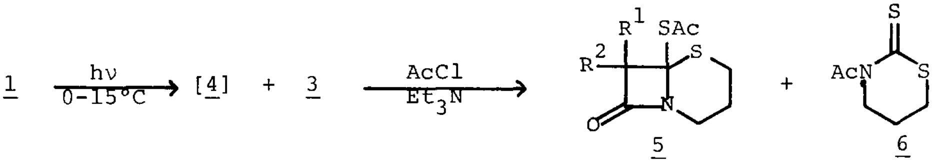
product. It is known that photochemical reactions of azetidin-2,4-diones in methanol undergo ring expansion to produce 5-methoxy-isoxazolid-3-ones via oxacarbenes.5) In the thione photochemictry, α-cleavage reaction is not well documented although a few examples are reported with strained thioketones and dithioesters.6) The photochemical reactions of the thioimide systems undergo hydrogen abstraction reactions3),7) and [2+2] cycloaddition reactions.2),8) However, there is no example of α-cleavage reaction with nitrogen-thiocarbonyl systems.



Scheme 2

It is expected that protection of the mercapto group of 4 make it possible to isolate the β-lactam since 4 was stable at low temperature. When 1c was irradiated at low temperature (0-15°C) and to the reaction mixture acetyl chloride and triethylamine were added, S-acethyl β-lactam (5c) was obtained as expected in 66% yield. In the same manner, cepham analogues (5d, e) were obtained as shown in table 2. The β-lactam (5d) was obtained as a mixture of two stereoisomers (about 10:1), and 5e was a single isomer.9) The stereochemistry of the β-lactams (5d,e) can not be determined. The structures of the photoproducts were determined on the basis of elemental analyses and spectral data.

Table 2: Photolysis of 1 followed by acetylation



	Yield (%)	
	5	6
c	66	10
d	57	15
e	65	23

In conclusion, photolysis of 3-diphenylacetyl-, 3-methoxyacetyl, and 3-ethoxyacetyl-2-thiotetrahydro-1,3-thiazines followed by acetylation gave bicyclic β-lactams. High temperature photolysis of them gave 2,9-dithia-5-azabicyclo[4,3,0]nonan-4-ones via α-cleavage of thioxo-β-lactams. In view of the results of the photoreaction of 1a-e, radical-stabilizing substituents (Ph and OR) seem to enhance the cyclization. However, these substituent effects cannot be explained at present. The present reaction provides not only a useful synthesis of some β-lactams but also the first example of α-cleavage reaction in thioimide systems.

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9) 5e:mp. 83-84°C; i.r.($CHCl_3$): 1765 and 1690 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.22(t, J=6.8Hz, 3H), 1.9(m, 2H), 2.34(s, 3H), 2.5-4.1(m, 4H), 3.72(q, J=6.8Hz, 2H), 4.76(s, 1H). ^{13}C-nmr ($CDCl_3$): δ 15.1(q), 23.4(t), 27.3(t), 30.9(t), 37.3(q), 69.1(t), 77.3(s), 94.1(d), 162.0(s), 193.5(s). E.A.: Calcd. for $C_{10}H_{15}NO_3S_2$; C, 45.95; H, 5.78; N, 5.35. Found; C, 45.99; H, 5.86; N, 5.38%

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