REACTION OF α,β-UNSATURATED ACYL ISOTHIOCYANATES WITH ALKALI METAL HYDROSULPHIDES

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Received July 1st, 1975

Nucleophilic addition reactions of α,β-unsaturated acyl isothiocyanates and cinnamoyl isothiocyanates with alkali metal hydrosulphides have been studied. On the basis of the results obtained, a method for the preparation of compounds of 1,3-thiazine and 1,3-selenothiazine type has been worked out. The structure of the prepared products was confirmed by IR, UV and ^{1}H-NMR spectra. In the case of 6-phenyl-2-thioxo-4-oxoperhydro-1,3-thiazine, the observed fragmentation in the mass spectrum was interpreted in detail and the values of ^{1}H-NMR parameters for an ABX system of protons of the heterocyclic nucleus were computed.

Highly reactive α,β-unsaturated acyl isothiocyanates can be useful intermediates in organic synthesis because their multiple bonds can participate in some cyclization reactions. In a previous paper[1] we studied reactions of cinnamoyl isothiocyanates with crotonic enamines which afforded tetrasubstituted pyrimidine-4-thiones. In the present study we investigate additions of alkali metal hydrosulphides to aliphatic, aromatic and heterocyclic α,β-unsaturated acyl isothiocyanates in order to synthesise compounds of 1,3-thiazine type.

Several derivatives of 2-thioxo-4-oxo-1,3-thiazine, which exhibit a marked effect on central nervous system[2], are described. Gresham and collaborators[3,4] prepared these compounds by reaction of lactones of fatty β-hydroxy acids with ammonium dithiocarbamate followed by cyclisation of the addition product. Analogously were prepared[5,6] also N-substituted 2-thioxo-4-oxoperhydro-1,3-thiazines (*I*).

Garraway prepared 3-alkyl-3,4-dihydro-2-thioxo-4-oxo-1,3-thiazines[7] (*II*) and 3-alkyl-2-thioxo-4-oxoperhydro-1,3-thiazines[8] (*I*) by addition of N-alkyl dithiocarbamic acids to propiolic and acrylic acid, respectively. Some 2-thioxo-4-oxoperhydro-1,3-thiazines (*I*) exhibit antiradiation activity and were synthesised by reaction of N-substituted dithiocarbamides with substituted acrylic acids[9,10]. McDonald and McKinnon studied the reaction of cinnamoyl isothiocyanate with P_2S_5 which they anticipated to afford 3-thioxo-1,2,4-dithiazole[11]. They found, however, on the basis of ^{1}H-NMR spectra that the product was 6-phenyl-2-thioxo-4-oxoperhydro-1,3-thiazine (*III*).

We assumed that in the reaction of α,β-unsaturated acyl isothiocyanates with alkali metal hydrosulphides the adduct can be intramolecularly stabilised by cyclisation because of high nucleophilicity of sulphur and an electron deficit on the

β-carbon of the ethylenic group. The reaction was carried out by the addition of a substituted cinnamoyl, crotonyl and furylacryloyl isothiocyanate to an aqueous solution of alkali metal hydrosulphide. In the first reaction step an unstable alkali metal salt of dithiocarbamic acid is formed and this is intramolecularly cyclised to the corresponding 6-substituted 2-thioxo-4-oxoperhydro-1,3-thiazine (Equation (*A*), Table I).

The IR, UV and ^{1}H-NMR spectra of the products are in accord with their assumed structure (Table II). The infrared spectrum exhibits strong bands ν(NH) at 3345 cm^{-1} and ν(C=O) at 1720 cm^{-1}. Three absorption bands due to ν(—NH—C=S) are found at 1065, 1240–1260 and 1432 cm^{-1}. In accord with literature data for analogous compounds[5], the UV spectra of the synthesised compounds exhibit two absorption maxima of high intensity at 260 and 312 nm (Table II). Heterocyclic protons —CH_2—CH—in 1,3-thiazines afford a ^{1}H-NMR spectrum with an ABX spin system. All compounds display a broad signal corresponding to the amide

TABLE I

Yields, Physical Constants and Elemental Analyses of 6-Substituted 2-Thioxo-4-oxoperhydro--1,3-thiazines *IV*–*X*

Compound Substituent	M.p., °C[a] (yield, %)	Formula (mol.w.)	Calculated/Found		
			% C	% H	% N
IV	132–133	$C_5H_7NOS_2$	37·26	4,34	8·69
CH_3	(58·8)	(161·2)	37·43	4·55	8·82
V	140–141[b]	$C_{10}H_9NOS_2$	53·80	4·03	6·27
C_6H_5	(66·7)	(223·2)	54·03	4·27	6·22
VI	157–158	$C_{11}H_{11}NOS_2$	55·69	4·64	5·90
4-$CH_3C_6H_4$	(61·4)	(237·2)	55·93	4·71	5·76
VII	171–172	$C_{11}H_{11}NO_2S_2$	52·17	4·34	5·53
4-$CH_3OC_6H_4$	(64·3)	(253·2)	51·84	4·57	5·50
VIII	162–164[b]	$C_{10}H_8ClNOS_2$	46·61	3·10	5·43
4-ClC_6H_4	(58·3)	(257·7)	46·83	3·24	5·42
IX	156–158	$C_{10}H_8BrNOS_2$	39·75	2·65	4·63
4-BrC_6H_4	(59·7)	(302·1)	39·37	2·65	4·45
X	119–120[b]	$C_8H_7NO_2S_2$	45·07	3·28	6·57
C_4H_3O	(60·6)	(213·2)	44·78	3·30	6·45

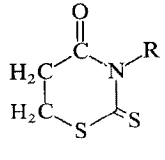
[a] From chloroform–light petroleum; [b] from tetrachloromethane.

TABLE II

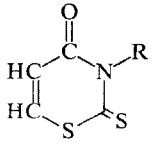
Spectral Data for 6-Substituted 2-Thioxo-4-oxoperhydro-1,3-thiazines *IV*–*X*

Compound	ν(NH—C=S)		ν(C=O)	ν(NH)	λ_{1max} (log ε_1)
IV	1 062	1 239	1 719	3 347	259
	1 262	1 432			(4·07)
V	1 062	1 241	1 725	3 045	261
	1 267	1 432			(4·11)
VI	1 062	1 249	1 720	3 348	261
	1 259	1 432			(4·16)
VII	1 062	1 249	1 720	3 348	258
	1 259	1 432			(4·13)
VIII	1 062	1 242	1 725	3 345	260
	1 264	1 432			(4·13)
IX	1 062	1 239	1 722	3 347	260
	1 263	1 432			(4·54)
X	1 062	1 248	1 724	3 348	257
	1 271	1 432			(4·11)

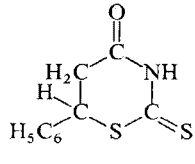
proton at $\delta \sim 9{\cdot}60$ and a signal due to aromatic protons at $\delta \sim 7{\cdot}30$. The integrated intensities are in accord with the given analysis of the ^{1}H-NMR spectra. The calculation for an ABX system[12,13] for 6-phenyl-2-thioxo-4-oxoperhydro-1,3-thiazine



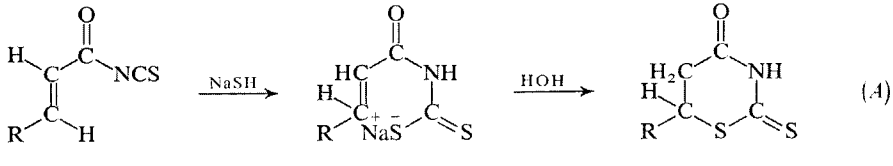
I



II



III



IV–*X* (*A*)

R = CH_3; C_6H_5; 4-$CH_3C_6H_4$; 4-$CH_3OC_6H_4$; 4-ClC_6H_4; 4-BrC_6H_4, C_4H_3O;

TABLE II
(*Continued*)

λ_{2max} (log ε_2)	δNH	δArH	δCH	δCH_2	δCH_3
310 (4·09)	9·62	—	3·57	2·87	1·35
312 (4·21)	9·80	7·48	4·77	3·20	—
312 (4·28)	9·68	7·13	4·68	3·19	2·30
313 (4·20)	9·55	7·00	4·68	3·13	3·86
312 (4·21)	9·68	7·28	4·75	3·13	—
312 (4·22)	9·59	7·30	4·79	3·17	—
313 (4·17)	9·80	—	4·68	3·23	—

gave the following parameters: $\nu_A = 260{\cdot}9$ Hz, $\nu_B = 254{\cdot}1$ Hz, $\nu_X = 381{\cdot}5$ Hz; $J_{AB} = +16{\cdot}5$ Hz, $J_{AX} = -10{\cdot}7$ Hz, $J_{BX} = +5{\cdot}3$ Hz. The structure of this derivative

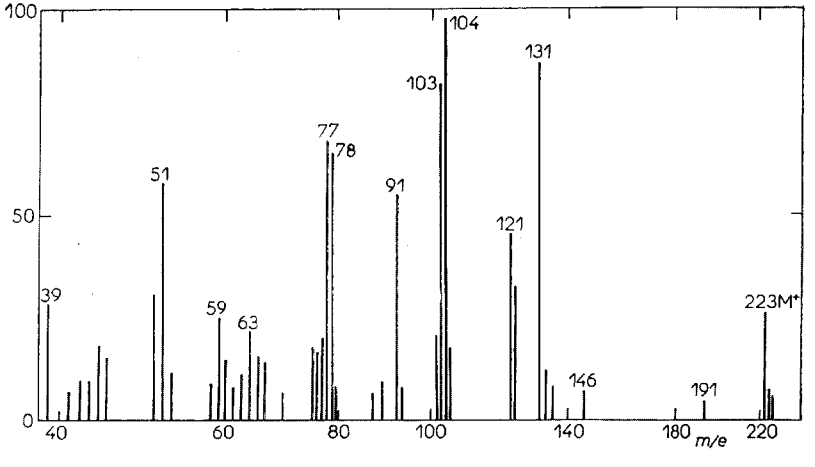
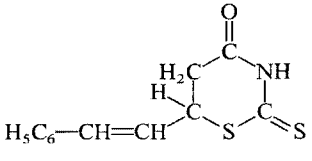


FIG. 1
Mass Spectrum of 6-Phenyl-2-thioxo-4-oxoperhydro-1,3-thiazine

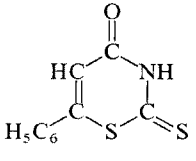
was proved also by its mass spectrum (Fig. 1); the fragmentation of the molecular ion is shown in Scheme 1.

The attempt to synthesise an eight-membered ring by the addition of an alkali metal hydrosulphide to β-styrylacryloyl isothiocyanate (*XI*) was unsuccessful. Also in this case the cyclisation took place at the β-carbon of the conjugated system under formation of 6-styryl-2-thioxo-4-oxoperhydro-1,3-thiazine (*XII*). Cyclisation of β-phenylpropionyl isothiocyanate (*XIII*) which was obtained only as a crude product, afforded 6-phenyl-2-thioxo-4-oxo-3,4-dihydro-1,3-thiazine (*XIV*).

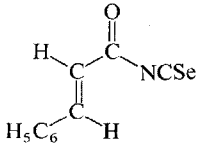
Since selenium is chemically similar to sulphur, we tried to prepare some analogous selenium derivatives by this method. Reaction of potassium selenocyanate with cinnamoyl chloride in acetone afforded the unstable cinnamoyl isoselenocyanate (*XV*) which, upon evaporation of the acetone, was treated with 50% aqueous-methanolic sodium hydrosulphide solution. We assume that the product of the cyclisation is 6-phenyl-2-thioxo-4-oxoperhydro-1,3-selenoazine (*XVI*) (Equation (*B*)) because of greater nucleophilicity of selenium in the formed ambidental anion. The structure of the products *XII*, *XIV* and *XVI* was proved by their elemental analyses as well as IR, UV and ^{1}H-NMR spectra.



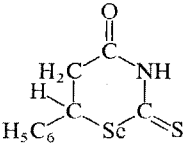
XII



XIV



XV



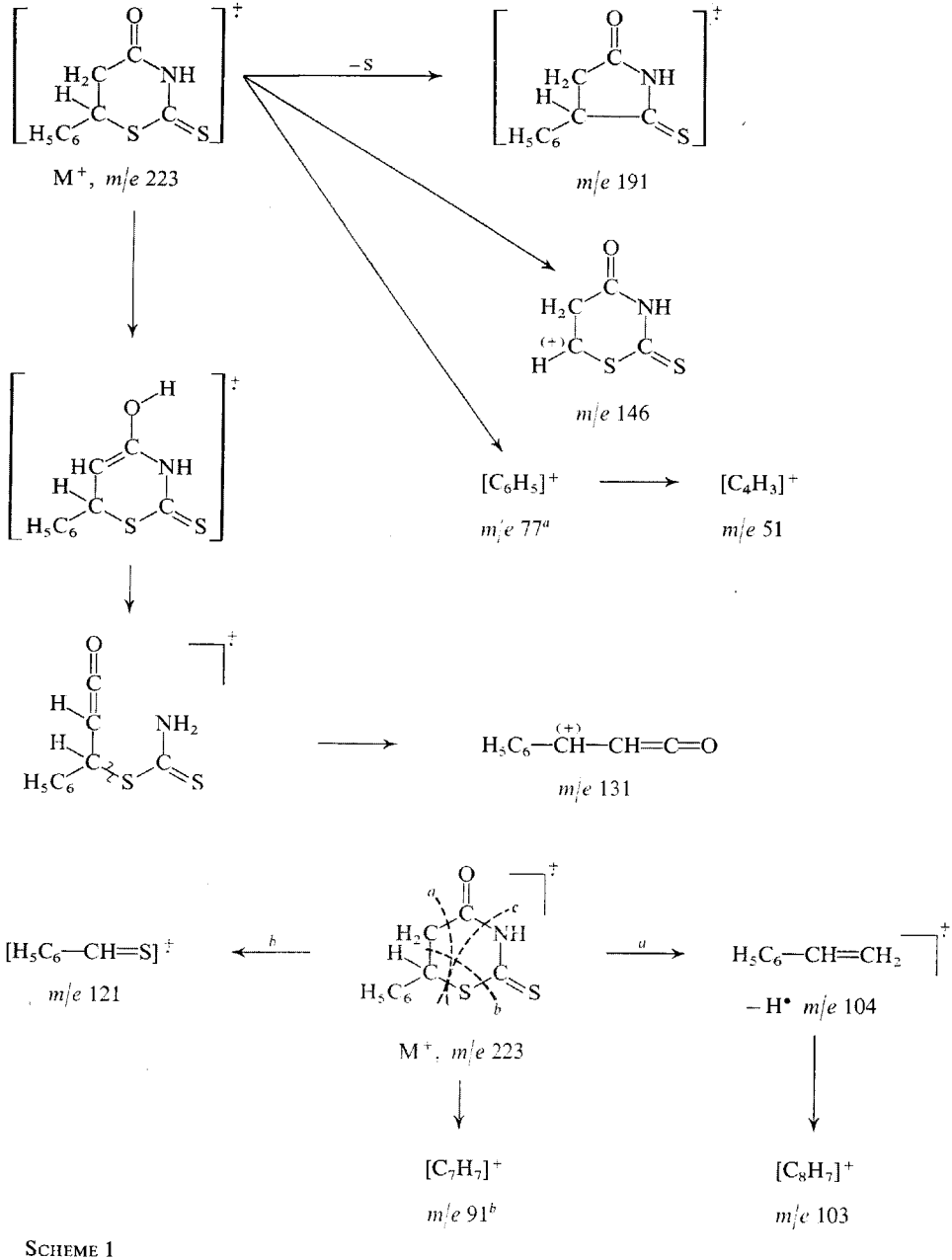
XVI

(*B*)

EXPERIMENTAL

Cinnamoyl isothiocyanates were described in a previous paper[14], crotonyl isothiocyanate[15] and furylacryloyl isothiocyanate[16] were prepared according to the literature.

4-Chlorocinnamoyl isothiocyanate was obtained by reaction of 4-chlorocinnamoyl chloride with $Pb(SCN)_2$ in benzene in 75·4% yield; m.p. 107—108°C (n-hexane). For $C_{10}H_6ClNOS$ (223·7) calculated: 6·26% N, 14·33% S; found: 6·17% N, 14·28% S. IR spectrum ($CHCl_3$): ν(NCS) 1968 cm^{-1}; UV spectrum (cyclohexane): λ_{max} 314 nm (log ε = 4·52); ^{1}H-NMR spectrum ($CDCl_3$, δ): 7·38 m (C_6H_5), 7·05 (AB-q, J_{AB} = 16 Hz, —CH=CH—).



SCHEME 1

a Hydrogen shift to the nucleus affords  —H, *m/e* 78. *b* The peak due to the ion $(C_7H_7)^+$, *m/e* 91, very probably coincides with that of the ion $(CHNS_2)^+$ which has also *m/e* 91 and which can arise by the pathway *c*.

β-Styrylacryloyl isothiocyanate (*XI*) was prepared analogously, yield 72·4%, m.p. 47–49°C (light petroleum). For $C_{12}H_9NOS$ (215·2) calculated: 6·50% N, 14·90% S; found: 6·73% N, 14·86% S. IR spectrum ($CHCl_3$): ν(NCS) 1964 cm^{-1}; UV spectrum (cyclohexane): λ_{max} 340 nm ($\log \varepsilon = 4·78$). β-Phenylpropionyl isothiocyanate (*XIII*) was prepared by treatment of the corresponding chloride with AgSCN in ether. This compound is unstable and its presence in the reaction mixture was proved spectroscopically. IR spectrum ($CHCl_3$): ν(NCS) 1965 cm^{-1}. Cinnamoyl isoselenocyanate (*XV*) is formed in the reaction of potassium selenocyanate with cinnamoyl chloride in acetone. It was obtained only in the crude state as an oil; IR spectrum ($CHCl_3$): ν(NCS) 1963 cm^{-1}.

6-Substituted 2-Thioxo-4-oxoperhydro-1,3-thiazines *IV–X*

Hydrogen sulphide (0·015 mol) was introduced into an aqueous solution of an alkali hydroxide or ammonia (0·015 mol in 40 ml water) and α,β-unsaturated acyl isothiocyanate (0·01 mol) in acetone (8 ml) was added dropwise under stirring and cooling. The precipitate was filtered and washed with water, dried and crystallised from a suitable solvent. Following compounds were obtained by this procedure:

6-Styryl-2-thioxo-4-oxoperhydro-1,3-thiazine (*XII*), yield 63·1%, m.p. 143–144°C (tetrachloromethane). For $C_{12}H_{11}NOS_2$ (255·4) calculated: 56·44% C, 4·31% H, 5·84% N; found: 56·54% C, 4·62% H, 5·72% N. IR spectrum ($CHCl_3$): ν(NH) 3347 cm^{-1}, ν(C=O) 1721 cm^{-1}, ν(NHCS) 1067, 1242 and 1262, 1432 cm^{-1}; UV spectrum (methanol): λ_{max} 259 nm ($\log \varepsilon_1 = 4·54$), λ_{2max} 313 ($\log \varepsilon_2 = 4·26$). ^{1}H-NMR spectrum ($CDCl_3$, δ): 9·59 (s, NH), 7·32 (m, C_6H_5), 6·37 (dq, —CH=CH—CH—), 4·36 (m, =CH—CH—CH_2), 3·02 (—CH—CH_2). 6-Phenyl-2-thioxo-4-oxo-3,4-dihydro-1,3-thiazine (*XIV*), yield 73·2%, m.p. 173–175°C (tetrachloromethane). For $C_{10}H_7NOS_2$ (221·2) calculated: 54·34% C, 3·17% H, 6·34% N; found: 54·29% C, 3·16% H, 6·33% N. IR spectrum ($CHCl_3$): ν(NH) 3345 cm^{-1}, ν(C=O) 1678 cm^{-1}, ν(NHCS) 1053, 1243 and 1262, 1428 cm^{-1}; UV spectrum (methanol): λ_{1max} 254 nm ($\log \varepsilon_1 = 4·30$), λ_{2max} 310 nm ($\log \varepsilon = 4·23$); ^{1}H-NMR spectrum ($CDCl_3$, δ): 7·46 (m, C_6H_5), 6·70 (s, —CH—). 6-Phenyl-2-thioxo-4-oxoperhydro-1,3-selenoazine (*XVI*), yield 57·2%, m.p. 132–133°C (chloroform–light petroleum). For $C_{10}H_9NOSSe$ (270·1) calculated: 44·46% C, 3·33% H, 5·18% N; found: 44·32% C, 3·43% H, 5·20% N. IR spectrum ($CHCl_3$): ν(NH) 3347 cm^{-1}, ν(C=O) 1722 cm^{-1}, ν(NHCS) 1062, 1240 and 1264, 1430 cm^{-1}; UV spectrum (methanol): λ_{1max} 260 nm ($\log \varepsilon_1 = 4·17$), λ_{2max} 311 nm ($\log \varepsilon_2 = 4·27$); ^{1}H-NMR ($CDCl_3$, δ): 9·85 (s, NH), 7·33 (m, C_6H_5), 4·75 (q, —CH—), 3·28 (t, —CH_2—).

Spectral Measurements

IR absorption spectra of the prepared compounds in chloroform were measured in the region 800–3500 cm^{-1} on a UR-20 (Zeiss) double-beam spectrophotometer, calibrated using a polystyrene foil. UV spectra were taken on a Perkin-Elmer 402 recording spectrophotometer. ^{1}H-NMR spectra were measured in deuteriochloroform on a Tesla BS 487 A (80 MHz) apparatus, using hexamethyldisiloxane as internal standard. Mass spectrum was measured on an MS 902 S (AEI Manchester) spectrometer, using a direct inlet system. The spectrum was taken at 70 eV, ionisation chamber temperature 115°C.

We are indebted to Dr J. Leška of the Mass Spectrum Laboratory of Slovak Technical University, Bratislava for measurement and analysis of the mass spectrum.

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Translated by M. Tichý.