

**SYNTHESIS OF 2-AMINO-6-SUBSTITUTED
5,6-DIHYDRO-4*H*-1,3-THIAZIN-4-ONES
FROM α,β -UNSATURATED ACYL ISOTHIOCYANATES**

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Reactions of α,β -unsaturated acyl isothiocyanates with primary and secondary amines were studied. Thioureas formed from the weakly basic secondary amines easily underwent cyclization in hot benzene to yield 2,6-disubstituted 5,6-dihydro-4*H*-1,3-thiazin-4-ones. Their structure was proved by IR, ¹H-NMR and mass spectral methods.

The synthesis of a 1,3-thiazine system from α,β -unsaturated carboxylic acids and thioureas has been published in several papers¹⁻⁶. Our preceding papers^{7,8} dealt with reactions of α,β -unsaturated acyl isothiocyanates with alkali metal hydrosulfides under formation of 6-substituted 2-thioxo-4-oxoperhydro-1,3-thiazines.

This paper concerns the reactions of the above-mentioned isothiocyanates with amines; the thioureas formed in this way were supposed to cyclize under formation of derivatives of 1,3-thiazine. As found, primary and basic secondary amines gave thioureas, which did not cyclize when heated in organic solvents. We did not succeed even in an alkaline medium, in which the formation of an ambident ion and thereby an enhancement of nucleophilicity of sulfur were anticipated (Scheme 1).

Less basic aromatic secondary amines easily reacted with α,β -unsaturated acyl isothiocyanates and furnished 2-amino-6-substituted 5,6-dihydro-4*H*-1,3-thiazin-4-ones. To study this reaction 4-substituted-3-phenylpropenyl isothiocyanates and 3-(2-furyl)propenyl isothiocyanate were reacted with diphenylamine, phenylmethylamine or phenylcyclohexylamine. Diphenylamine and phenylcyclohexylamine afforded with those isothiocyanates in benzene either under reflux, or at room temperature directly the respective thiazines. The more basic phenylmethylamine required for cyclization a several hour's heating in benzene. The substituted thioureas thus formed could be isolated (Scheme 2, Table I).

The structure of the synthesized products was inferred on the basis of spectral ¹H-NMR and mass) evidence (Table II). The infrared spectra showed intense absorption bands of carbonyl groups $\nu(\text{C}=\text{O})$ in the 1660 cm^{-1} region and broad

thioamide bands $\nu(\text{N}=\text{C}=\text{S})$ in the $1480-1508\text{ cm}^{-1}$ range. The $^1\text{H-NMR}$ spectra displayed instead of *trans*-ethylenic protons two multiplets of $-\text{CH}_2-\text{CH}-$ protons of an ABX system at $4.47-4.72$ ppm (δ scale, CH) and $2.78-2.95$ (CH_2). Mass spectra of *XXIII*, *XXVIII* and *XXX* revealed little intense peaks of molecular ions, the m/z values of which were in line with molecular weights of the proposed structures. The principal fragmentation pathways of molecular radical ions are given in Scheme 3.

EXPERIMENTAL

3-Phenylpropenoyl isothiocyanate⁹ (*I*), 3-(2-furyl)propenoyl isothiocyanate¹⁰ (*II*), 3-(4-methylphenyl)propenoyl isothiocyanate¹¹ (*XVII*), 3-(4-methoxyphenyl)propenoyl isothiocyanate¹¹

TABLE I
Survey of the Synthesized 2,6-Disubstituted 5,6-Dihydro-4*H*-1,3-thiazin-4-ones

Compound	R^1/R^2	Formula (m.w.)	M.p., °C (solvent)	Yield %	Calculated/Found		
					% C	% H	% N
<i>XXIII</i>	C_6H_5	$\text{C}_{22}\text{H}_{18}\text{N}_2\text{OS}$	187—188	75	73.72	5.06	7.81
	C_6H_5	(358.5)	(ethanol)		73.90	5.27	7.75
<i>XXIV</i>	$\text{CH}_3\text{C}_6\text{H}_4$	$\text{C}_{23}\text{H}_{20}\text{N}_2\text{OS}$	175—176	81	74.16	5.41	7.52
	C_6H_5	(372.5)	(ethanol)		74.32	5.64	7.59
<i>XXV</i>	$\text{CH}_3\text{OC}_6\text{H}_4$	$\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$	159—161	82	71.11	5.19	7.21
	C_6H_5	(388.5)	(ethanol)		71.37	5.43	7.33
<i>XXVI</i>	BrC_6H_4	$\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{OS}$	180—182	73	60.42	3.92	6.41
	C_6H_5	(437.4)	(ethanol)		60.69	4.01	6.48
<i>XXVII</i>	$\text{O}_2\text{NC}_6\text{H}_4$	$\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$	175—177	69	65.49	4.25	10.41
	C_6H_5	(403.5)	(ethanol)		65.79	4.39	10.58
<i>XXVIII</i>	$\text{C}_4\text{H}_3\text{O}$	$\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$	157—159	69	68.94	4.62	8.04
	C_6H_5	(348.4)	(ethanol)		69.16	4.82	8.23
<i>XXIX</i>	C_6H_5	$\text{C}_{22}\text{H}_{24}\text{N}_2\text{OS}$	184—186	72	72.49	6.64	7.68
	C_6H_{11}	(364.5)	(ethanol)		72.64	6.73	7.81
<i>XXX</i>	$\text{C}_4\text{H}_3\text{O}$	$\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$	161—163	56	67.76	6.25	7.90
	C_6H_{11}	(354.5)	(ethanol-water)		67.89	6.18	7.72
<i>XXXI</i>	C_6H_5	$\text{C}_{17}\text{H}_{16}\text{N}_2\text{OS}$	140—142	84	68.89	5.44	9.45
	CH_3	(296.4)	(tetrachloromethane)		69.05	5.56	9.51
<i>XXXII</i>	$\text{C}_4\text{H}_3\text{O}$	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$	132—134	80	62.91	4.93	9.78
	CH_3	(286.4)	(ethanol-water)		62.98	5.08	9.84

(*XXVIII*), 3-(4-bromophenyl)propenoyl isothiocyanate¹¹ (*XIX*), 3-(4-nitrophenyl)propenoyl isothiocyanate¹¹ (*XX*), N-methyl-N'-3-phenylpropenoylthiourea¹² (*III*), N-methyl-N'-3-(2-furyl)propenoylthiourea¹² (*IV*), N,N-diethyl-N'-3-phenylpropenoylthiourea¹³ (*VII*), N,N-diethyl-N'-3-(2-furyl)propenoylthiourea¹³ (*VIII*), N-phenyl-N'-3-phenylpropenoylthiourea⁹ (*IX*), N-phenyl-N'-3-(2-furyl)propenoylthiourea¹² (*X*), N-benzyl-N'-3-phenylpropenoylthiourea¹² (*XI*), N-benzyl-N'-3-(2-furyl)propenoylthiourea¹² (*XII*), 1-(N-3-phenylpropenoyl)thiocarbamoyl-piperidine¹³ (*XIII*), 1-(N-3-(2-furyl)propenoyl)thiocarbamoylpiperidine¹³ (*XIV*), 1-(N-3-phenylpropenoyl)thiocarbamoylmorpholine¹³ (*XV*), 1-(N-3-(2-furyl)propenoyl)thiocarbamoylmorpholine¹³ (*XVI*), were prepared according to the cited references.

N,N-Disubstituted N'-Acylthioureas *V*, *VI*, *XXI*, *XXII*

A stirred and cooled solution of acyl isothiocyanate (16 mm) in benzene (20 ml) was saturated with gaseous dimethylamine, or alternatively phenylmethylamine (16 mm) was added. The

TABLE II
Spectral Properties of 2,6-Disubstituted 5,6-Dihydro-4*H*-1,3-thiazin-4-ones

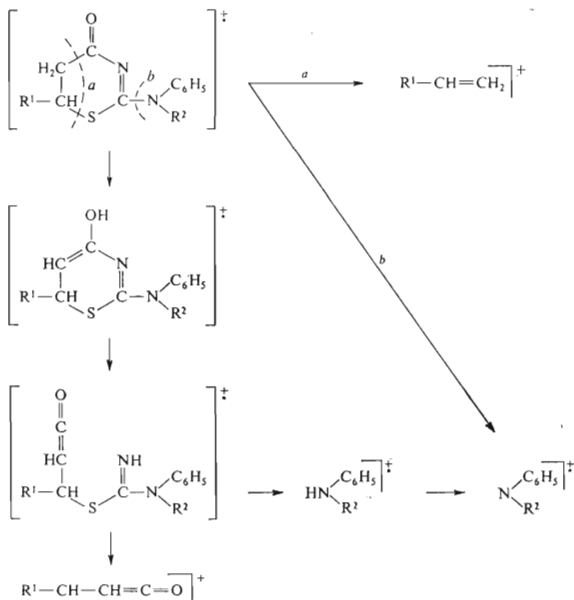
Compound	IR, cm ⁻¹		¹ H-NMR, ppm				Mass spectra <i>m/z</i> , rel. int. (%)
	$\nu(\text{NCS})$	$\nu(\text{C=O})$	$\delta(\text{CH}_3)$	$\delta(\text{CH}_2)$	$\delta(\text{CH})$	$\delta(\text{ArH})$	
<i>XXIII</i>	1 490	1 663	—	2.78	4.52	7.28	358 (19), 169 (91) 168 (59), 131 (99) 104 (31)
<i>XXIV</i>	1 483	1 662	2.28	2.88	4.52	7.23	—
<i>XXV</i>	1 480	1 661	3.75	2.95	4.51	7.31	—
<i>XXVI</i>	1 484	1 665	—	2.90	4.52	7.35	—
<i>XXVII</i>	1 490	1 670	—	2.85	4.67	7.32	—
<i>XXVIII</i>	1 480	1 660	—	2.94	4.72	6.30—7.37	348 (1), 169 (100), 168 (56), 121 (58), 94 (28)
<i>XXIX</i> ^a	1 480	1 655	—	2.87	4.42	7.30	—
<i>XXX</i> ^a	1 485	1 655	—	2.91	4.55	6.23—7.35	354 (9), 175 (45), 174 (51), 121 (96), 94 (60)
<i>XXXI</i>	1 504	1 660	3.55	2.82	4.47	7.27	—
<i>XXXI</i>	1 508	1 658	3.52	2.95	4.58	6.23—7.40	—

^a Contains 2 multiplets $\delta(\text{CH}_2)$ 1.40 and $\delta(\text{CH})$ 5.15 of cyclohexyl.

respective thioureas, which separated immediately were filtered off, washed with light petroleum dried and crystallized from an appropriate solvent.

N,N-Dimethyl-*N'*-3-phenylpropenylthiourea (V): yield 56%, m.p. 115–116°C (ethanol-water). For $C_{12}H_{14}N_2OS$ (234.3) calculated: 61.51% C, 6.02% H, 11.96% N; found: 60.97% C, 6.19% H, 12.13% N. IR spectrum ($CHCl_3$): $\nu(NH)$ 3400 cm^{-1} , $\nu(C=O)$ 1696 cm^{-1} , $\nu(C=C)$ 1632 cm^{-1} , $\nu(NHCS)$ 1560 cm^{-1} , $\gamma(CH=CH)$ 980 cm^{-1} . 1H -NMR spectrum ($CDCl_3$): 10.23 (s, $-NH-$), 7.70 and 6.83 (dd, $-CH=CH-$, $J_{AB} = 16$ Hz), 7.43 (m, C_6H_5), 3.45 and 3.21 (s, CH_3).

N,N-Dimethyl-*N'*-3-(2-furyl)propenylthiourea (VI): yield 44%, m.p. 138–140°C (ethanol-water). For $C_{10}H_{12}N_2O_2S$ (224.1) calculated: 53.59% C, 5.39% H, 12.50% N; found: 53.41% C,



$R^1 = C_6H_5-, C_4H_3O-; R^2 = C_6H_5-, C_6H_{11}-$

SCHEME 3

5.43% H, 12.56% N. IR spectrum (CHCl₃): $\nu(\text{NH})$ 3402 cm⁻¹, $\nu(\text{C}=\text{O})$ 1696 cm⁻¹, $\nu(\text{C}=\text{C})$ 1632 cm⁻¹, $\nu(\text{NHCS})$ 1566 cm⁻¹, $\gamma(\text{CH}=\text{CH})$ 972 cm⁻¹. ¹H-NMR spectrum (CDCl₃): 10.10 (s, —NH—), 7.42 and 6.61 (dd, —CH=CH—, $J_{\text{AB}} = 16$ Hz), 3.42 and 3.18 (ss, CH₃).

N-Phenyl-*N*-methyl-*N'*-3-phenylpropenoylthiourea (XXI): yield 91%, m.p. 129—130°C (methanol-water). For C₁₇H₁₆N₂OS (296.4) calculated: 69.56% C, 5.43% H, 9.45% N; found: 69.53% C, 5.32% H, 9.56% N. IR spectrum (CHCl₃): $\nu(\text{NH})$ 3400 cm⁻¹, $\nu(\text{C}=\text{O})$ 1678 cm⁻¹, $\nu(\text{C}=\text{C})$ 1632 cm⁻¹, $\nu(\text{NHCS})$ 1503 cm⁻¹, $\gamma(\text{CH}=\text{CH})$ 980 cm⁻¹. ¹H-NMR spectrum (CDCl₃): 8.44 (ss, —NH—), 7.53 and 7.00 (dd, —CH=CH—, $J_{\text{AB}} = 16$ Hz), 7.36 (m, C₆)₅, 3.71 (s, CH₃).

N-Phenyl-*N*-methyl-*N'*-3-(2-furyl)propenoylthiourea (XXII): yield 75%, m.p. 118—120°C (methanol-water). For C₁₅H₁₄N₂O₂S (286.4) calculated: 62.91% C, 4.93% H, 9.78% N; found: 62.81% C, 5.08% H, 9.88% N. IR spectrum (CHCl₃): $\nu(\text{NH})$ 3400 cm⁻¹, $\nu(\text{C}=\text{O})$ 1673 cm⁻¹, $\nu(\text{C}=\text{C})$ 1629 cm⁻¹, $\nu(\text{NHCS})$ 1496 cm⁻¹, $\gamma(\text{CH}=\text{CH})$ 969 cm⁻¹. ¹H-NMR spectrum (CDCl₃): 8.13 (s, —NH—), 7.31 (m, C₆H₅ and doublet of proton —CH=CH—), 6.75 (d, —CH=CH—, $J_{\text{AB}} = 16$ Hz), 3.69 (s, CH₃).

2,6-Disubstituted 5,6-Dihydro-4*H*-1,3-thiazin-4-ones XXIII—XXXII

a) Acyl isothiocyanate (5 mmol) dissolved in benzene (10 ml) was dropwise added to a stirred solution of diphenylamine or phenylcyclohexylamine (5 mmol) in benzene (10 ml). After a 1 h-reflux the solution was cooled and the separated precipitate suction-filtered, washed with light petroleum, dried and crystallized from a suitable solvent (Table I, derivatives XXIII—XXX).

b) *N,N*-Disubstituted thiourea XXI, XXII (5 mmol) in benzene (20 ml) was refluxed for 3 h. The precipitate which separated from the cooled solution was suction-filtered, washed with light petroleum, dried and crystallized from a suitable solvent (Table I, derivatives XXXI, XXXII).

Spectral Measurements

The IR spectra of chloroform solutions were measured with a UR-20 (Zeiss, Jena) spectrophotometer, the ¹H-NMR spectra of deuteriochloroform solutions were recorded with a Tesla BS 487 A apparatus operating at 80 Hz (tetramethylsilane internal reference) and the mass spectra were taken with an AEI MS 902 S (Manchester) instrument using a direct inlet system at 70 eV and 140°C (XXIII, XXVIII) and 120°C (XXX) ionization chamber temperature, respectively.

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