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Synthesis of the *N*-Allylthioamide Derivatives of Cyclic Oxo- and Dioxo- Acids and Their Cyclization to the Derivatives of 4,5-Dihydrothiazole

by A. Wesołowska[1], T.S. Jagodziński[1*], J.G. Sośnicki[1] and P.E. Hansen[2]

[1]*Department of Organic Chemistry, Technical University of Szczecin, 71-065 Szczecin, Aleja Piastów 42, Poland*
[2]*Department of Life Sciences and Chemistry, Roskilde University, P.O.Box 260, DK-4000 Roskilde, Denmark*

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The title *N*-allylthioamides (**1a–f**) were synthesized in the reaction of allyl isothiocyanate with enamines (**1a–c**) and 1,3-diketones (**1d**–**f**), respectively, carried out in an acetonitrile solution in the presence of DBU. When treated with the bromine–dioxane complex or with iodine, they underwent cyclization to the corresponding derivatives of 4,5-dihydrothiazole (**2a–g**). NMR spetroscopy made it possible to elucidate the tautomeric structures of the thioamides and thiazolines.

Key words: 4,5-dihydrothizole, *N*-allylthioamides

The thioamide derivatives of unsaturated carboxylic acids as well as *N*-alkenylthioamides are often used in the synthesis of heterocyclic compounds [1–10]. A nucleophilic attack of the sulfur or nitrogen atom on the electrophilic center generated from the olefinic bond can be responsible for this intramolecular heterocyclization, although an electrophilic mechanism initiated, for instance, by increased electrophilicity of the thiocarbonyl function owing to its *S*-methylation has to be also considered. In the presence of Lewis acids *N*-allylthioamides cyclize to form, depending on the substituents at the olefinic center, the appropriate 4,5-dihydrothiazoles or 1,3-thiazines [1]. A higher regioselectivity was observed when *p*-toluenesulfonic acid or phenylselenyl bromide were used as the heterocyclizing agents [2]. Only 4,5-dihydrothiazoles were obtained in the cyclizations promoted by a halogen [3].

A similar intramolecular heterocyclization induced by electrophilic agents is also known in the case of the thioamide derivatives of γ,δ-unsaturated carboxylic acids. 2-Iminothiolactones [4] and γ-lactams [5–7] were obtained in this way with high chemo- and regioselectivity. The research carried out by Takahata and co-workers on the asymmetric 1,2-allyl [6] and 1,3-homoallyl [7] induction in the synthesis of γ-lactams led them further to the synthesis of chiral amino acids [8]. An analogous synthetic procedure was used later to investigate the stereochemical aspects of the

*Author for correspondence.

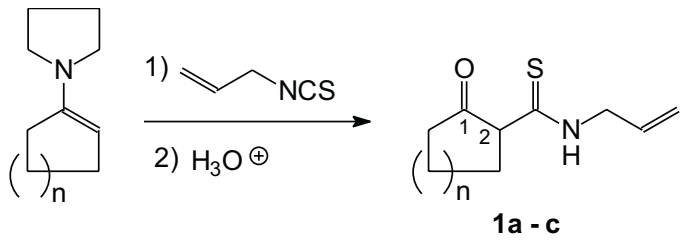
iodine-promoted heterocyclization of β-substituted δ,ε-unsaturated thioamides, which effected in the formation of 4,6-*cis*-disubstituted δ-lactams [9].

A simple Friedel-Crafts synthesis of the *N*-allylthioamides derived from aromatic and heteroaromatic carboxylic acids and their cyclization to the appropriate derivatives of 4,5-dihydrothiazole have been published earlier [10]. The present research is concerned with the synthesis of the *N*-allylthioamides derived from cyclic oxo and dioxo carboxylic acids and with their subsequent cyclization. In addition to the synthetic results, a NMR study of the tautomeric equilibria in the thioamides and 4,5-dihydrothiazoles is also presented. The investigation of such equilibria by tracing the deuterium isotope effects in the ^{13}C-NMR spectra was the subject of our earlier publication [11].

RESULTS AND DISCUSSION

The *N*-allylthioamides derived from oxo acids (**1a–1c**) were obtained in the reaction of allyl isothiocyanate with the appropriate enamine according to the method developed earlier for other thioamides [12], whereas those derived from dioxo acids were prepared allyl isothiocyanate and the appropriate 1,3-diketone in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Best results were obtained when the reaction was run at room temperature with 1 ml of DBU used per 1 g of the ketone. Both reactions were regioselective and gave satisfactory yields of the products. The analytical samples were prepared by column chromatography on silica gel.

Scheme 1



1a - c

n = 1 (**1a**), 2 (**1b**), 3 (**1c**)

Scheme 2

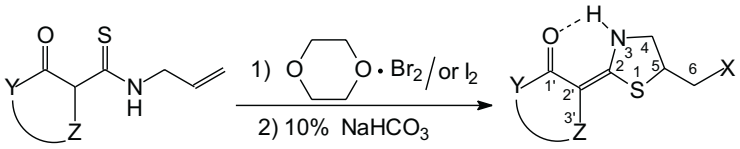
1d - i

1	X	R
d	$-CH_2CMe_2CH_2-$	$-CH_2CH=CH_2$
e	$-(CH_2)_3-$	$-CH_2CH=CH_2$
f		$-CH_2CH=CH_2$
g	$-(CH_2)_2-$	$-CH_3$
h		$-CH_3$
i		$-C_6H_5$

By treatment with iodine or with bromine–dioxane complex [13] in anhydrous tetrahydrofuran the *N*-allylthioamides prepared (**1a–g**) were subsequently converted into the corresponding 5-iodomethyl- (**2e**) and 5-bromomethyl-4,5-dihydrothiazoles (**2a–d, f, g**), respectively. The bromine–dioxane complex, a softer electrophile than the molecular bromine itself, was here applied as a reagent of particular convenience in carrying out the reaction that required a precise dosage of bromine. A 10% aqueous solution of sodium hydrogen carbonate was used to convert the hydrohalides of **2a–g** into the corresponding free bases, which for analytical purposes were purified by column chromatography on silica gel. The stereochemical course of the heterocyclization process of unsaturated thioamides was investigated and described by us earlier [14].

As shown in Scheme 4, both the *N*-allylthioamides **1** and the 4,5-dihydrothiazole derivatives **2** may exist in tautomeric forms: The ^{13}C-NMR investigation of tautomerism of a number of variously *N*-substituted thioamides derived from cyclic oxo and dioxo carboxylic acids by the method of the deuterium isotope effect was described in detail [11,15]. Furthermore, X-ray studies revealed that those derived from cyclic 1,3-dioxo acids occurred in the solid state as the ”cross-conjugated” π-electron systems [16].

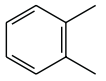
Scheme 3



1 a - f

X = Br, I
Z = CH_2 or C=O

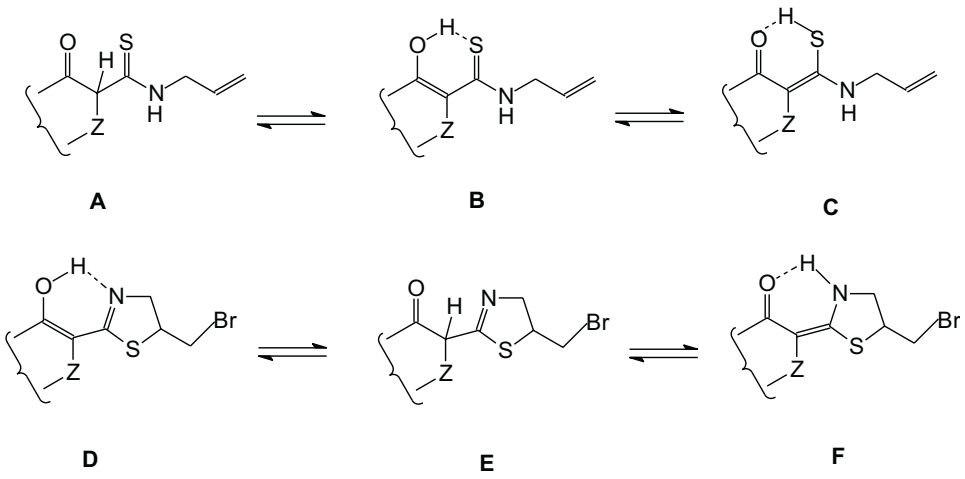
2 a - g

2	X	Y	Z
a	Br	$-(CH_2)_2-$	$-CH_2-$
b	Br	$-(CH_2)_3-$	$-CH_2-$
c	Br	$-(CH_2)_4-$	$-CH_2-$
d	Br	$-CH_2CMe_2CH_2-$	C=O
e	I	$-CH_2CMe_2CH_2-$	C=O
f	Br	$-(CH_2)_3-$	C=O
g	Br		C=O

The ^{1}H- and ^{13}C-NMR spectra clearly indicate that the thioamides **1a** and **1b** exist in solution as mixtures of the keto (K) and enol (E) forms (Scheme 4, structures A and B, respectively). The K/E ratio was estimated as 56:44 in the case of **1a** and at 80:20 in for **1b**, while there was no trace of the enol form in **1c** (*cf.* Table 1). In view of those figures one may conclude that the K/E ratio depends on the ring size and that the proportion of the keto form is increasing with ring size. Only one tautomer, namely the enol form (Scheme 4, structure B), was observed in the thioamides derived from cyclic dioxo acids. For **1f**, also a 1,3-dioxoderivative, only the enolic form is observed. In this case an enol - thioenol tautomerism takes place (Scheme 4, **B** and **C**). This tautomerism is clearly demonstrated from the observation of large deuterium isotope effects of both signs [15]. This kind of tautomeric equilibrium was also observed in the corresponding methyl (**1h**) and phenyl derivative **1i** [15]. The tautomeric equilibrium is similar although not identical in these compounds (see below). No ketone form was observed in $CDCl_3$ solution. The equilibrium is clearly shifted towards the enol form

judging from the XH chemical shift as well as the C=S chemical shift. This is also in line with the X-ray structure showing only the most stable tautomer, the enol form **B** [16].

Scheme 4



The magnitude of the deuterium isotope effects for **1f** at the C-1 (positive) and the C=S carbon (negative) and the temperature dependence of the isotope effects at the C=S carbon (less negative at lower temperature) shows that the equilibrium is shifted towards the C–OH, (C=S)NH form (B, Scheme 4). A very similar picture is seen for the methyl derivative, **1h** in $CDCl_3$. However, for the phenyl derivative **1i** [15], the isotope effects are much larger suggesting together with the finding of a higher chemical shift of C-1 and lower of C=S that this compound is less on the B-form. This is also supported by the XH chemical shifts of the phenol form (14.4 ppm) compared to those of **1f** and **1h** (15.19 and 15.29 ppm, respectively). The aforementioned equilibrium isotope effects can best be understood by comparison with the β-diketones [17].

A very unusual effect is observed at the C=S, C-1 carbons, the isotope effects are non-additive, showing that even deuteration at the NH position is able to shift the equilibrium slightly and indirectly demonstrating that the NH group most likely is involved in hydrogen bonding with the C=O group at position 3. The non-additivity is

also observed in a very similar way for the methyl derivative. A closer scrutiny of the data for the phenyl derivative likewise reveals non-additivity. The non-additivity is seen for all carbons showing equilibrium isotope effect from deuteration at both the OH and NH groups.

The tautomerism of **1f**, **1h** and the corresponding phenyl derivative **1i** is clearly helped by the annulated benzene ring, as the corresponding non-aromatic compound **1g**, does not show any signs of tautomerism judging from the isotope effects (Table 3). The reason that the some of the five-membered thioamides show tautomerism, whereas the corresponding triketones [17] do not, can be ascribed to the longer S–H bond, thus being better able to form a hydrogen bond in a system with relatively long distance between the heavy atoms ($R_{N..S}$ = 2.441(2) Å) [16].

The thiazoline derivatives **2a–g** can theoretically exist, like the linear thioamides **1a–g**, in three tautomeric forms (Scheme 4, structures D, E, F). However, as evidenced by the ^{1}H- and ^{13}C-NMR spectra as well as by the ^{15}N-NMR spectrum taken for **2e**, they occur only as the tautomers F. ^{13}C-NMR spectroscopy was here particularly useful in identifying the five-membered heterocyclic moiety, whereas the ^{1}H- and ^{15}N-NMR techniques pinpointed the NH form of this heterocyclic compound and provided evidence for a β-dioxo structure of the carboxylic fragment. These structural conclusions are based first and foremost on the ^{1}H-NMR signals, which appear in the 9.05–11.73 ppm region and on the high value of the $^{1}J_{NH}$ coupling constant (95.5 Hz as observed from the ^{15}N-NMR spectrum). A detailed presentation of the NMR data of **2** is given in Table 2.

The discussion on tautomerism based on the present compounds and results and those of references [11] and [15] can be summarized as follows: The thioamides containing a single carbonyl group may exist as both the keto and enol forms, those with two keto functional groups like **1f–1i** as enol forms only. Some of these, the benzannulated ones, **1f**, **1g** and **1i** may furthermore be tautomeric. The thiazolines exist in the keto form.

EXPERIMENTAL

Melting points were determined with a digital Electrothermal apparatus, model IA9300, and are given uncorrected. Infrared spectra were taken in KBr pellets with a Specord M80 instrument. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in a $CDCl_3$ solution and with TMS as internal standard. Assignment were secured by measuring HETCOR and occasionally COLOC spectra. Microanalyses for C, H, S gave results within ± 0.3% of the calculated values.

***N*-Allylthioamides of cyclic oxo acids (1a–c). General procedure**. The appropriate enamine (0.05 mol) was treated in an Erlenmayer flask under stirring and ice-water cooling (0–3°C) with allyl isothiocyanate (4.96 g, 0.05 mole) added dropwise over 30 min. Stirring was continued at the same temperature for 30 min and the mixture was left thereafter for 24 h at 0–5°C. Upon hydrolysis with 2% hydrochloric acid (4 h) the mixture was extracted with ethyl acetate (2 × 100 ml) and the organic layer was washed with water and dried with anhydrous sodium sulfate. Evaporation of the solvent left the crude product that was purified by passing through a chromatographic column packed with silica gel; a *n*-heptane-ethyl acetate mixture 6:4 for **1a** and benzene for **1b, 1c** was used as the eluent. Recrystallization from a suitable solvent was the final purification step.

Table 1. Yields and physical properties of the *N*-allylthioamides **1a–f.**

Compounds	m.p. [°C] (solvent)	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)	Analyses [%] calculated found			IR ν (cm^{-1})	Yield %
				C	H	S		
1a **(mixture of tautomers; keton (K): enol (E) = 56: 44**	oil	($CDCl_3$, 400 MHz): 1.81–1.89 [m, 4-C<u>H</u>H (K), 4-CH_2 (E)], 2.06–2.18 [m, 4-CH<u>H</u> (K)], 2.29–2.66 [m, 3-CH_2 (K, E), 5-CH_2 (K, E)], 3.21 [dd *J* = 9.3, *J* = 9.7, 2-CH (K)], 4.28–4.33 [m, NCH_2 (K, E)], 5.21–5.33 [m, =CH_2 (K, E)], 5.87–5.97 [m, =CH (K,E)], 6.59 [br s, NH (E)], 8.79 [br s, NH (K)], 13.45 [br s, OH, (E)].	($CDCl_3$, 100 MHz): 17.02 [C-4 (E)], 19.90 [C-4 (K)], 28.75 [C-3 (E)], 30.04 [C-3 (K)], 34.46 [C-5 (E)], 38.87 [C-5 (K)], 45.66, 48.11 (NCH_2 (K, E)], 59.81 [C-2 (K)], 106.15[C-2 (E)], 117.86, 117.89 [(2=CH_2 (K, E)], 131.47, 132.23 [2=CH (K, E)], 176.22 [C-1 (E)], 188.68 [C=S (E)], 197.64 [C=S (K)], 215.78 [C-1 (K)].	58.97 58.78	7.09 7.13	17.49 17.93	3500–3200 br (NH and OH) 1750–1700 br (C=O)	59
1b **(mixture of tautomers; keton (K): enol (E) = 80 : 20**	oil	^{1}H NMR ($CDCl_3$, 400 MHz): 1.66–2.02 [m, 3-C<u>H</u>H (K), 4-C<u>H</u>H (K), 5-CH_2 (K), 2CH_2 (E)], 2.12–2.19 [m, 4-CH<u>H</u> (K)], 2.27 [t *J* = 5.9, CH_2 (E)], 2.37 [t *J* = 5.9, CH_2 (E)], 2.41–2.50 [m, 6-CH_2 (K)], 2.77–2.84 [m, 3-CH<u>H</u> (K)], 3.81 [dd *J* =5.1, *J* = 11.7, 2-CH (K)], 4.26–4.35 [m, NCH_2 (K, E)], 5.22–5.34 [m, =CH_2 (K, E)], 5.89–5.99 (m, =CH (K, E)], 6.81 [br s, NH (E)], 9.62 [br s, NH (K)], 14.65 [br s, OH (E)].	^{13}C NMR ($CDCl_3$; 100 MHz): 21.57, 22.67, 24.68 [3CH_2 (E)], 25.57 [C-5 (K)], 28.65 [C-4 (K)], 30.94 [CH_2 (E)], 38.13 [C-3 (K)], 42.81 [C-6 (K)], 46.51, 48.28 [NCH_2 (E, K)], 62.54 [C-2 (K)], 104.23 [C-2 (E)], 117.91, 118.25 [=CH_2 (K, E)], 131.65, 132.38 [=CH (K, E)], 171.66 [C-1 (E)], 191.24 [C=S (E)], 200.82 (C=S (K)], 212.53 [C-1 (K)].	60.88 61.05	7.66 7.48	16.25 15.99	3420–3120 br (NH and OH) 1705 (C=O)	61

Table 1 (continuation)

1c **(100% of keto-form)**	64–66 (hexane/benzene)	^{1}H NMR ($CDCl_3$, 400 MHz): 1.27–1.33 (m, 1H, 5-C<u>H</u>H), 1.43–1.71 (m, 2H, 4-C<u>H</u>H, 6-C<u>H</u>H), 1.80–2.00 (m, 4H, 3-C<u>H</u>H, 4-CH<u>H</u>, 5-C<u>H</u>H, 6-CH<u>H</u>), 2.23–2.33 (m, 1H, 3-CH<u>H</u>), 2.60–2.66 (m, 2H, 7-CH_2), 4.03 (dd J = 3.5, J = 11.5, 1H, 2-CH), 4.27–4.31 (m, 2H, NCH_2), 5.20–5.31 (m, 2H, =CH_2), 5.87–5.97 (m, 1H, =CH), 9.07 (br s, 1H, NH).	^{13}C NMR ($CDCl_3$, 100 MHz): 23.35 (C-6), 27.87 (C-5), 28.96 (C-4), 34.97 (C-3), 43.74 (C-7), 48.37 (NCH_2), 65.19 (C-2), 117.99 (=CH_2), 131.59, (=CH), 200.46 (C=S), 213.65, (C-1).	62.52 62.71	8.11 7.92	15.17 14.93	3400–3150 br (NH) 1730–1650 br (C=O)	70
1d	oil	^{1}H NMR ($CDCl_3$, δ 400 MHz): 1.10 (s, 6H, 2CH_3), 2.42, 2.68 (two s, 4-CH_2, 6-CH_2), 4.23 (m, 2H, NCH_2), 5.25 (dd J = 1.2, J = 10.4, =C<u>H</u>H), 5.32 (dd J = 1.1, J = 17.2, CH<u>H</u>), 5.91–6.00 (m, 1H, =CH), 12.44 (br s, 1H NH), 17.10 (s, 1H, OH).	^{13}C NMR ($CDCl_3$; δ 100 MHz): 27.85, (2CH_3), 30.00 (C-5), 46.19, 46.36 [C-4, C-6), 52.36, (NCH_2), 107.64 (C-2), 117.77, (=CH_2), 131.54, (=CH), 188.55 (C-3), 189.89 (C=S), 198.94 (C-1).	60.21 60.24	7.10 7.37	13.40 13.60	3100–2800 br (NH and OH) 1670–1620 br (C=O)	54
1e	oil	^{1}H NMR ($CDCl_3$, 400 MHz): 1.96 (quintet J = 6.6, 2H, 5-CH_2), 2.55 (t J = 6.9, 2H, 3-CH_2), 2.72 (t J = 6.4, 2H, 6-CH_2), 4.22–4.25 (m, 2H, NCH_2), 5.25 (dd J = 1.2, J = 10.4, 1H, =C<u>H</u>H), 5.31 (dd J = 1.10, J = 18.3, 1H, =CH<u>H</u>), 5.90–5.98 (m, 1H, =CH), 12.47 (br s, 1H, NH), 17.12 (s, 1H, OH).	^{13}C NMR ($CDCl_3$, 100 MHz): 18.87 (C-5), 33.05, 38.70 (C-4, C-6), 46.46 (NCH_2), 108.60 (C-2), 117.70 (=CH_2), 131.56 (=CH), 188.82 (C-3), 191.32, (C=S), 199.22 (C-1).	56.79 56.79	6.15 6.30	15.17 15.30	NH and OH hidden 1670–1620 br (C=O)	43

Table 1 (continuation)

1f	112.4–114.3 (heptane)	^{1}H NMR ($CDCl_3$, 400 MHz): 4.31 (t J = 5.5, 2H, NCH_2), 5.27–5.37 (m, 2H, $=CH_2$), 5.91–6.01 (m, 1H, =CH), 7.51–7.58 (m, 4H, C_6H_4), 10.02 (br s, 1H NH), 15.29 (s, 1H, OH).	^{13}C NMR ($CDCl_3$; 100 MHz): 45.46, (NCH_2), 102.94 (C-2), 118.06 ($=CH_2$), 121.7, 122.13, 132.95, 133.43, 133.64, 137.24, (C_6H_4), 131.67 (=CH), 185.02, (C=S), 187.68 (C-1), 192.51, (C-3).	63.59 63.20	4.48 4.90	13.06 13.54	3500–3400 (OH) 3400–3200 (NH) 1700–1670 br (C=O)	36

Table 2. Yields and physical properties of the Δ^2-thiazolines **2a–g.**

Com-pounds	m.p. [°C] (solvent)	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)	Analyses [%] calculated found			IR ν (cm^{-1})	Yield %
				C	H	S		
2a	124.3–127.7 (heptane/ethyl acetate)	^{1}H NMR ($CDCl_3$, ^{1}H NMR ($CDCl_3$, 400 MHz): 1.92 (quartet J = 7.5, 2H, 4′-CH_2), 2.34 (t J = 7.8, 2H, 5′-CH_2), 2.47 (m, 2H, 3′-CH_2), 3.48–3.53 (m, 2H, $BrCH_2$), 3.82 (dd J = 6.4, J = 10.7, 1H, 4-C<u>H</u>H), 3.87–3.93 (m, 1H, 5-CH), 4.01 (br d J = 10.7, 1H, 4-CH<u>H</u>), 9.05 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$, 100 MHz): 21.04 [C-4′), 28.24 (C-3′), 32.80 (CH_2Br), 38.82 (C-5′), 46.54 (C-5), 52.56 (C-4), 100.38, (C-2′), 159.79 (C-2), 201.43, (C-1).	41.07 41.27	4.98 5.17	12.20 12.30	3300–3100 br (NH) 1660–1635 br (C=O)	70
2b	126–127 (heptane)	^{1}H NMR ($CDCl_3$, 400 MHz): 1.67–1.74 (m, 4H, $2CH_2$), 2.19–2.37 (m, 4H, $2CH_2$), 3.46–3.52 (m, 2H, $BrCH_2$), 3.84–3.52 (m, 2H, 4-C<u>H</u>H, 5-CH), 4.09 (d J = 9.5, 1H, 4-CH<u>H</u>), 10.76 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$, 100 MHz): 22.9, 23.6 (C-3′, C-5′), 27.7 (t, C-4′), 33.0 ($BrCH_2$), 37.0 (C-6′), 46.4 (C-5), 53.9 (C-4), 99.0, (C-2′), 166.5 (C-2), 192.2 (C-1′).	43.49 43.27	5.11 4.91	11.61 11.60	3300–3000 br (NH) 1605 (C=O)	72

Table 2 (continuation)

2c	152–155 (hexane)	^{1}H NMR ($CDCl_3$, 400 MHz): 1.51–1.79 (m, 6H, $3CH_2$), 2.33 (pseudo t J = 5.0, 2H, CH_2), 2.53 (pseudo t J = 5.6, 2H, CH_2), 3.52 (d J = 7.7, 2H, $BrCH_2$), 3.80–3.92 (m, 2H, 4-C<u>H</u>H, 5-CH), 4.05 (dd, J = 1.3, J = 10.9, 1H, 4-CH<u>H</u>), 10.24 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$, 100 MHz): 24.9, 29.31, 31.7, 32.4, (C-3′, C-4′), C-5′, C-6′), 33.0 ($BrCH_2$), 43.4 (C-7′), 45.8 (C-5), 53.2 (C-4), 103.6, (C-2′), 164.7 (C-2), 198.9 (C-1′).	45.52 45.71	5.56 5.31	11.05 10.89	3300–3100 br (NH) 1660 (C=O)	60
2d	174–173 (nitromethane)	^{1}H NMR ($CDCl_3$, 400 MHz): 1.04, 1.06 (two s, 6H, $2CH_3$), 2.38 (d J = 2.0, 2H, CH_2), 2.41 (s, 2H, CH_2), 3.40 (t J = 10.7, 1H, BrC<u>H</u>H, 3.56 (dd J = 4.2, J = 10.4, 1H, BrCH<u>H</u>), 3.80–3.87 (m, 1H, 5-CH), 3.92 (dd J = 7.8, J = 12.3, 1H, 4-C<u>H</u>H), 4.12 (dt J = 2.0, J = 12.3, 1H, 4-CH<u>H</u>), 11.67 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$, 100 MHz): 28.33, 28.55 ($2CH_3$), 30.91 (C-5′), 33.00 ($BrCH_2$), 45.43 (C-5), 50.50, 51.27 (C-4′, C-6′), 51.90 (C-4), 105.70, (C-2′), 174.15 (C-2), 194.8, 196.53 (C-1′, C-3′).	45.28 45.77	5.07 5.77	10.07 10.17	3300–3100 br (NH) 1650–1600 br (C=O)	73
2e	172.5–175.8 (nitromethane)	^{1}H NMR ($CDCl_3$, 400 MHz): 1.04, 1.06 (two s, 6H, $2CH_3$), 2.37, 2.41 (two s, 4H, $2CH_2$), 3.35 (t, J = 10.5, 1H, I-C<u>H</u>H), 3.43 (dd J = 3.7, J = 10.5, 1H, I-CH<u>H</u>, 3.86–3.93 (m, 2H, 4-C<u>H</u>H, 5-CH), 4.02 (d J = 10.6, 4-CH<u>H</u>), 11.66 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$, δ, 100 MHz): 7.31 (CH_2I), 28.36, 28.57 ($2CH_3$), 30.90 (C-5′), 45.87 (C-5), 50.53, 51.27 (C-4′, C-6′), 53.57 (C-4), 105.62, (C-2′), 174.20 (C-2), 194.84, 196.54 (C-1′, C-3′).	39.48 39.56	4.42 4.52	8.78 8.81	3300–3100 br (NH) 1650–1600 br (C=O)	693

Table 2 (continuation)

2f	163.9–165.1 (ethyl acetate)	^{1}H NMR ($CDCl_3$, 400 MHz): 1.95 (quintet J = 6.5, 2H, 5′-CH_2), 2.45–2.58 (m, 4H, 4′-CH_2, 6′-CH_2), 3.40 (t J = 10.6, 1H, BrC<u>H</u>H), 3.57 (dd J = 4.3, J = 10.4, 1H, BrCH<u>H</u>), 3.81–3.88 (m, 1H, 5-CH), 3.94 (dd, J = 7.8, J = 12.4, 1H, 4-C<u>H</u>H), 4.13 (br d, J = 12.4, 1H, 4-CH<u>H</u>), 11.73 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$, 100 MHz): 19.60, (C-5′), 33.14,(CH_2Br), 36.83, 37.55 (C-4′, C-6′), 45.35 (C-5), 51.93 (C-4), 106.81 (C-2′), 174.45 (C-2), 195.27, 197.11 (C-1′, (C-3′).	41.39 41.30	4.16 4.15	11.05 10.83	3200–3100 br (NH) 1650–1600 br (C=O)	78
2g	252.6–253.9 (nitromethane) (decomp.)	^{1}H NMR ($CDCl_3$: DMSO-d_6 = 2:1, 400 MHz): 3.63, (t J = 10.0, 1H, BrC<u>H</u>H), 3.74 (dd J = 5.3, J = 10.1, 1H, BrCH<u>H</u>, 3.97 (dd J = 7.7, J = 12.5, 4-C<u>H</u>H), 4.04 (dd J = 2.8, J = 12.4, 4-CH<u>H</u>), 4.19–4.25 (m, 1H, 5-CH), 7.57–7.65 (m, 4H, ArH), 9.73 (br. s, 1H, NH).	^{13}C NMR ($CDCl_3$:DMSO-d_6 = 1:1, 100 MHz): 34.53, (CH_2Br), 45.59 (C-5), 52.55 (C-4), 100.20 (C-2′), 120.80, 120.90, 132.79, 138.85, 139.14, (ArH), 166.41 (C-2), 188.47, 188.97 (C-1′, C-3′).	48.16 48.46	3.11 3.20	9.89 10.13	3400–3200 br (NH) 1700–1650 br (C=O)	69

For compounds **2e**: ^{15}N NMR (DMSO-d_6, δ, 400 MHz): –253.0 (d, J = 95.5).

Table 3. Deuterium isotope effects on ^{13}C chemical shifts of **1f–1h** and **1i**[a].

		1f[b]			**1h**[b,c]			**1i**[d]		**1g**[d,e]	
	$^{n}\Delta$ C-x(OD)	$^{n}\Delta$ C-x(ND)	$^{n}\Delta$ C-x(OD,ND)[f]	$^{n}\Delta$ C-x(OD)	$^{n}\Delta$C-x(ND)	$^{n}\Delta$ C-x(OD,ND)[f]	$^{n}\Delta$ C-x(OD)	$^{n}\Delta$ C-x(ND)	$^{n}\Delta$ C-x(OD,ND)[f]	$^{n}\Delta$ C-x(OD)	$^{n}\Delta$ C-x(ND)
C-1	0.728 (0.741)	0.022 (0.021)	0.728 (0.741)	0.734	0.018	0.734	0.997 (0.937)	0.082 (0.077)	1.067 (n.m)	0.430 (0.433)	0 (0)
C-2	–0.295 (n.m.)	0.035 (n.m.)	–	–0.34	0	—	–0.619 –0.580	–0.031 –0.027	–0.619 –0.586	–0.165 (0.165)	0.041 (0.036)
C-3	–0.098 (0.096)	0.035 (0.042)	n.m[i] (–0.033)	–0.100	0.030	n.m.	–0.114 (0)	0.040 (0)	0.075 n.m	0.041[h] (0.052)[h]	–0.048[h] (–0.035)[h]
C-4[l]	0 (0)	0 (0)	– –	0	0	–	–0.045 (0)	0 (0)	– –	0.025[m] (0.024)[m]	0 (0)
C-5[k]	–0.068 (–0.067)	0 (0)	– –	–0.068	0	–	–0.138 (–0.123)	0 (0)	– –	0.157 (0.157)	0 (0)
C-6[k]	0 (0)	0 (0)	– –	0	0	–	0 (0)	0 (0)	– –	–	–
C-7[l]	–0.039 (–0.039)	0 (0)	– –	0	0	–	–0.045 (n.m)	0 (n.m)	– –	–	–
C-3[a]	0.349[g] (0.341)	0.019[m] (0.020)	0.328[g] (0.321)	0.345	0	–	–0.230 –0.215	0.062 0.067	–0.164	–	–
C-7[a]	0.156 (0.157)	0 (0)	– –	0.157	0	–	0.726 (n.m)	0.104 (0.074)	0.804 –	–	—
C=S	–0.797 (–0.814)	0.093 (0.084)	0.675 (0.706)	–0.810	0.094	–0.687	–2.056 (–1.851)	–0.067 (–0.067)	–2.056 (–1.851)	–0.109 (–0.110)	0.160 (0.151)

Table 3. (continuation)

C-1′	0 (–0.024)	0.137 (0.136)	– –	0.061	0.146	0.205	0.364 0.318	0.045 0.037	0.397 n.m.	–0.033 (–0.030)	0.146 (0.141)
C-2′	0.020 (0.024)	–0.049 (–0.053)	n.o.[j] n.o.	–	–	–	0.083 (0.092)	0.152 (0.143)	0.240 (0.236)	–	–
C-3′	0 (0)	0.047 (0l048)	– –	–	–	–	0.073[m] (0.067)	0[m] (0)	– –	–	–
C-4′	–	–	–	–	–	–	0.118 (0.118)	0.050 (0.046)	n.m n.m.	–	–

[a]In ppm.
[b]Temperature 240 K. Values in brackets measured at 260 K.
[c]Assignment of isotope effects due to deuteration at the NH position is secured as only these splittings were observed at high temperature.
[d]Temperature 220 K. Values in brackets measured at 250 K.
[e]All isotope effects are additive.
[f]The combined effect of deuteration at both sites.
[g]May be interchanged.
[h]Values may be interchanged.
[i]n.m. – means not measured possibly because of overlap or too low intensity.
[j]n.o. – means not observed.
[k]Values may be interchanged within **1f**, **1h** and **1i**.
[l]Values may be interchanged within **1f**, **1h** and **1i**.
[m]Sign uncertain.

***N*-Allylthioamides of cyclic dioxo acids (1d–i). General procedure.** To a stirred and cooled (ice bath) suspension of the suitable β-diketone (0.07 mol) and of allyl isothiocyanate (9.92 g, 0.1 mol) of DBU (10 mL) was added at 0–2°C in small portions over 45 min. The homogeneous solution was stirred at this temperature for 1 h, then left standing 1–3 days at room temperature, and thereafter poured into 20% acetic acid (50% acetic acid has to be used in the case of indanedione). Enough ethyl acetate was added to dissolve any oil present and the organic layer was washed with water, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with chloroform as the mobile phase and finally recrystallized from a suitable solvent. Only in the reactions starting with indanedione the crude crystals were separated by filtration and next recrystallized as above.

The synthesis of the compounds **1h** and **1i** we described previously [16]. The compound **1g** was obtained according to the procedure described previously [16]; yield 25%,. m.p. = 106–107°C (ethanol).

5-Bromomethyl-4,5-dihydrothiazoles (2a–g). General procedure. The bromine-dioxane complex (2.48 g, 0.01 mol) was added in small portions to the stirred and cooled (ice bath) solution of *N*-allylthioamide (**1a–f,** 0.01 mol) in dry dioxane (15–20 mL). A slightly exothermic effect was observed and deposition of crystals or oils begun soon. After 0.5–1 h dry diethyl ether was added to the mixture and the crystalline material was filtered. Only in the reaction starting with **1b** the addition of diethyl ether caused deposition of an oil. The isolated hydrobromide salt was shaken for a few minutes with a 10% aqueous solution of sodium hydrogen carbonate and the crystals were filtered off. The crude product was dissolved in acetonitrile or acetic acid and filtered through a 10 cm layer of alumina followed by elution with suitable solvent. The solid material left upon evaporation of the solvent was recrystallized from a suitable solvent.

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