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Ring Chain Transformations. XII [1]

Synthesis of N-(3-Aminothioacryloyl)lactam Imines and their Transformation to 4-(ω-Amino-alkyl)thiazoles or N-(Thien-2-yl)lactam Imines

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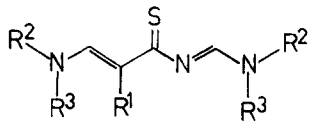
3-Aminothioacryloyl-formamidines **1** [2] are easily available from substituted thioacetamides **2** and formamide acetals and could be used as versatile building blocks for heterocyclic products [3, 4]. In order to apply the concept of ring chain transformation [5] to this class of compounds we tried to synthesize analogues of **1** where one or both terminal amino groups were attached to the neighbouring carbon atom by alkyl bridges.



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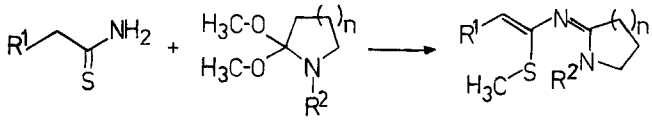


2 **3** **4**

4	6	n	R^1	R^2	R^3R^4
a	**a**	1	4-Cl-Ph	Me	$(CH_2)_5$
	b	1	Ph	Me	$(CH_2)_5$
	c	1	Ph	Me	$(CH_2)_4O$
d	**d**	1	4-Br-Ph	Me	$(CH_2)_5$
	e	1	4-Cl-Ph	Me	$(CH_2)_4$
	f	1	Ph	Me	$(CH_2)_4$
	g	1	4-Cl-Ph	Me	H 4-Cl-Ph
	h	2	4-Cl-Ph	Me	$(CH_2)_5$
	i	2	4-Cl-Ph	Me	$(CH_2)_4O$
l	**j**	2	4-Cl-Ph	Me	$(CH_2)_4$
	k	2	CN	Me	$(CH_2)_4O$
l		2	4-Cl-Ph	Et	–
	m	2	Ph	Et	Me Me
	n	3	4-Cl-Ph	Me	$(CH_2)_5$
	o	3	Ph	Me	$(CH_2)_5$
p		3	4-Br-Ph	Me	–

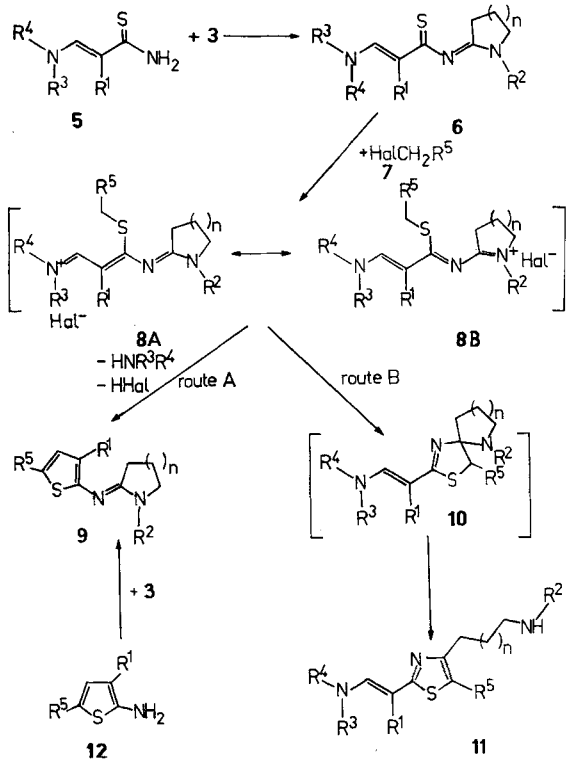
Reaction of substituted thioacetamides **2** with excess lactam acetals **3** results in the expected lactam imine formation but additional S-methylation occurs, resulting in bridged methylthio-azabutadiene sytems **4** (see Table 3) [6].

In contrast, the sulphur atom of 3-aminothioacrylamides **5** remains unaffected in reaction with lactam acetals **3** while a C–N-bond connection takes place giving the anticipated bridged N-(3-aminothioacryloyl) lactam imines **6** (see Table 3). Products **6** are usually obtained in good yields. An additional exchange of the starting aminomethylidene group R^2R^3NCH in **5** like is found with formamide acetals [2] was not observed in reactions with lactam acetals **3**. It further is worth mentioning that 3-aminothioacrylamides **5** with a N-monosubstituted amino group (R^3 = H) also give corresponding N-(3-aminothioacryloyl)lactam imines **6** without suffering a sub-

Table 1 MNDO-Calculations of semicyclic 2-aza-3-(4-chlorobenzyl)pentamethinium structures **8** (R = aryl = 4-ClC_6H_4, n = 1, 2, and 3)

n	Index[a)]	Atom C_1	Atom C_5
1	q_{Netto}	0.393	0.273
	V	3.759	3.860
	q^{Mullik}	3.544	3.722
2	q^{Netto}	0.404	0.267
	V	3.752	3.863
	q^{Mullik}	3.531	3.728
3	q_{Netto}	0.411	0.295
	V	3.749	3.845
	q^{Mullik}	3.526	3.701

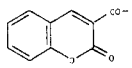
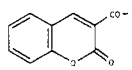
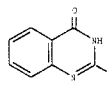
q_{Netto}: net atomic charge, V: Valence; $q^{Mulliken}$: Mulliken atomic charge; calculated by using MOPAC



sequent cyclization to pyrimidine-4-thiones, which was observed with non-bridged N-(3-aminothioacryloyl)formamidines **1** (R^3 = H) [3].

The N-(3-aminothioacryloyl)lactam imines **6** consist of both, a 3-aminothioacrylamide moiety and a N-thioacyllactam imine unit. The two separated substructures are known to react with acidic methylhalides **7** giving 2-aminothiophenes by normal cyclization [7] or 4-aminoalkyl-1,3-thiazoles by ring chain transformation [8] respectively. Consequently the combined structures **6** should be able to undergo both reactions, too. I.e. after primary S-methylation (formation of **8**) and deprotonation of the S–CH_2 group intramolecular attack can either occur at the methine carbon (formation of bridged 5-amidinothiophenes **9**, route A) or at the amidine carbon atom giving a spiro intermediate **10** which opens the saturated ring furnishing 4-(ω-aminoalkyl)-2-(aminovinyl)-thiazoles **11** (ring chain transformation, route B).

Practical investigations revealed that the direction of the reaction of N-(3-aminothioacryloyl)lactam imines **6** with substituted methylhalides **7** depends on different factors, such as the substituents R^1 and R^5 and the size of the lactam imine ring. Six-membered starting compounds **6** (n = 2) have a higher tendency to from 4-(ω-aminoalkyl)thiazoles **11** as compared to five and seven-membered **6** (n = 1 or 3 respectively). The formation of thiophenes **9** is preferred, if R^5 are strongly electron withdrawing (nitro in case of n = 2 or aroyl), nitro and dinitro-

9	11	n	R^1	R^2	R^3R^4	R^5
a		1	4-Cl-Ph	Me		4-Br-Ph-CO
b		1	4-Cl-Ph	Me		4-NO_2-Ph-CO
c		1	Ph	Me		NO_2
d		1	4-Cl-Ph	Me		
e		1	Ph	Me		$(CN)_2C{=}C$ (Ph)
f		1	4-Cl-Ph	Me		4-NO_2-Ph
g		1	4-Cl-Ph	Me		5-nitro-fur-2-yl
h		2	4-Cl-Ph	Me		NO_2
i		2	CN	Me		4-Br-Ph-CO
j		2	4-Cl-Ph	Me		4-NO_2-Ph
k		3	Ph	Me		4-Br-Ph-CO
l		3	4-Cl-Ph	Me		
m		3	4-Cl-Ph	Me		2,4(NO_2)$_2$-Ph
	n	1	Ph	Me	$(CH_2)_5$	
	o	1	Ph	Me	$(CH_2)_5$	1-(4-NO_2-Ph)-1,2,4-triazol-3-yl
	p	2	4-Cl-Ph	Me	$(CH_2)_5$	4-Br-Ph-CO
	q	2	4-Cl-Ph	Me	$(CH_2)_4$	5-Ph-1,3,4-oxadiazol-2-yl
	r	2	4-Cl-Ph	Me	$(CH_2)_4O$	4-Br-Ph-CO
	s	2	4-Cl-Ph	Me	$(CH_2)_5$	4-NO_2-Ph
	t	2	Ph	Et	CH_3 CH_3	4-Br-Ph-CO
	u	3	4-Cl-Ph	Me	$(CH_2)_5$	2-benzimidazole

phenyl in case of n = 1, 3) while the reaction favours aminoalkylthiazole formation (**11**) if halomethylheteroaromatics **7** (R^5 electron withdrawing heteroaromatic ring) are used.

Sometime mixtures were formed. For example in the reaction mixture of compound **11s** the corresponding thiophene **9j** was detected by TLC. Substance **9j** was synthesized independently by reaction of a 2-aminothiophene **12** with the corresponding lactam acetal **3** (n = 1, R^2 = Me).

An interpretation of the influence of the ring size on the direction of cyclization (route A or B) could be given by the empirical rule that a double bond is preferred endocyclic in six-ring system and exocycling in five or seven-membered ring systems

Table 2 Characterization of N-(1-Methylthiovinyl) lactam-2-imines (**4**) and N-(3-Aminothioacryloyl) lactam imines (**6**)

	m.p. yield [%] / method	molecular formula[a]	^{1}H-n.m..r. δ (ppm)
4a[b]	92–93 (Ligroin) 93	$C_{14}H_{17}ClN_2S$ (280.82)	2.02 (m, 2H); 2.38 (s, 3H); 2.63 (m, 2H); 3.11 (s, 3H); 3.48 (m, 2H); 5.7 (s, 1H, CH); 7.3 + 7.6 (d, J=8 Hz, 2H)
4d	93–95 (MeOH) 92	$C_{14}H_{17}BrN_2S$ (325.27)	[c]1.92 (m, 2H); 2.51 (s, 3H); 2.59 (m, 2H); 3.03 (s, 3H); 3.42 (m, 2H); 5.6 (s, 1H, CH); 7.4 + 7.6 (d, J=8 Hz, 2H)
4l	67–69 (Ligroin) 61	$C_{16}H_{21}ClN_2S$ (308.87)	1.22 (t, J=7 Hz, 3H); 1.62 (m, 4H); 2.20 (s, 3H); 2.33 (t, J=7 Hz, 2H); 3.21 (t, J=7 Hz, 2H); 3.6 (q, J=7 Hz, 2H); 5.5 (s, 1H); 7.1 + 7.3 (d, J=8 Hz, 2H)
4p[d]	75–77 (Ligroin) 42	$C_{16}H_{21}BrN_2S$ (353.33)	
6a	148–149 (MeOH) 76/A	$C_{19}H_{24}ClN_3S$ (361.97)	[c]1.45 (m, 6H); 1.91 (m, 2H); 2.64 (s, 3H); 3.11 (m, 8H); 7.06 (m, 8H); 8.39 (s, 1H);
6b[e]	140–142 (MeOH) 90/C	$C_{19}H_{25}N_3S$ (327.51)	
6c[f]	138–140 (MeOH) 76/A	$C_{18}H_{23}N_3OS$ (329.46)	
6d	149–152 (MeOH) 35/A	$C_{19}H_{24}BrN_3S$ (406.39)	1.70 (m, 6H); 2.95 (s, 3H); 3.25 (m, 6H); 3.53 (m, 4H); 7.20 + 7.61 (d, 2H, J=8 Hz); 8.51 (s, 1H, CH);
6e	173–175 (MeOH) 66/A	$C_{18}H_{22}ClN_3S$ (347.91)	1.70 (m, 4H); 1.96 (m, 2H); 2.62 (s, 3H); 2.99 (m, 4H); 3.25 (m, 4H); 7.05 (s, 4H); 8.54 (s, 1H, CH);
6f	123–125 (MeOH) 85/C	$C_{18}H_{23}N_3S$ (313.46)	[c]1.69 (m, 6H); 2.64 (s, 3H); 3.06 (m, 8H); 7.11 (s, 5H); 8.60 (s, 1H, CH);
6g[g]	169–171 (MeCN) 69/A 75/C	$C_{20}H_{19}Cl_2N_3S$ (404.37)	1.89 (m, 2H); 2.82 (s, 3H); 3.21 (m, 2H); 3.49 (m, 2H); 7.12–7.32 (m, 8H); 8.51 (d, J=3 Hz, 1H); 13.1 (d, J=12 Hz, 1H);
6h	171–173 (MeOH) 75/A	$C_{20}H_{26}ClN_3S$ (375.96)	[c]1.49 (m, 4H); 1.71 (m, 4H); 2.73 (s, 3H); 3.12 (m, 6H); 7.12 + 7.24 (d, 2H, J=8 Hz); 8.56 (s, 1H, CH);
6i	154–156 (MeOH) 65/B	$C_{19}H_{24}ClN_3OS$ (377.93)	[c]1.70 (m, 4H); 2.71 (s, 3H); 3.12 (m, 8H); 7.16 + 7.20 (d, 2H, J=8 Hz); 8.20 (s, 1H, CH);
6j	135–138 (MeOH) 75/B	$C_{19}H_{24}ClN_3S$ (361.93)	[c]1.71 (m, 8H); 2.74 (s, 3H); 3.12 (m, 8H); 7.18 (m, 4H); 8.71 (s, 1H, CH);
6k	135–138 (AcOEt) 79/C	$C_{14}H_{20}N_4OS$ (292.40)	[c]1.87 (m, 4H); 3.09 (t, 4H, J=7 Hz); 3.18 (s, 3H); 3.49 (m, 4H); 3.81 (m, 8H); 8.70 (s, 1H, CH);
6m	168–169 (MeOH) 59/A	$C_{18}H_{25}N_3S$ (315.48)	0.71 (t, J=7 Hz, 3H); 1.62 (m, 4H); 2.58 (s, 6H); 2.90 (m, 6H); 7.03 (s, 5H); 8.21 (s, 1H, CH);
6n[h]	183–185 (MeOH) 95/C	$C_{21}H_{28}ClN_3S$ (389.99)	
6o[i]	140–142 (EtOH) 98/C	$C_{21}H_{29}N_3S$ (355.59)	

[a] All compounds gave satisfactory micro analysis [b] ^{13}C-n.m.r. δ (ppm): 15.2; 19.3; 27.7; 31.2; 51.4; 107.0; 128.0; 128.1; 129.4; 136.5; 148.9; 163.1 [c] recorded in $CDCl_3$ [d] m.s. 354 (M^+, 9), 339 (44), 171 (58), 68 (100) [e] m.s. 327 (M^+, 22), 294 (86), 196 (100), 141 (68), 55 (58) [f] m.s. 329 (M^+, 9), 141 (100), 55 (34) [g] ^{13}C-n.m.r. δ (ppm): 19.3; 27.3; 30.9; 50.3; 50.4; 65.4; 118.0; 125.4; 126.1; 130.4; 139.4; 149.8; 149.8; 162.2; 208.1 [h] m.s. 389 (M^+, 22),112 (100), 55 (56) [i] m.s. 355 (M^+, 17), 322 (100), 169 (67), 55 (31)

Table 3 Characterization of N-Thienyllactam imines (**9**) and 4-(ω-Aminoalkyl) thiazoles (**11**)

	m.p. yield [%] / method	molecular formula[a]	^{1}H-n.m.r. δ (ppm)
9a[b]	214–216 (MeCN) 73/A (from **6a**)	$C_{22}H_{18}BrClN_2OS$ (473.83)	
9b	224–226 (MeCN/DMF) 97/A (from **6e**)	$C_{22}H_{18}ClN_3O_3S$ (439.92)	2.01 (m, 2H); 2.73 (6, J=7 Hz, 2H); 2.89 (s, 3H); 3.5 (t, J=7 Hz, 2H); 7.4 + 7.8 (d, 2H, J=8 Hz); 7.7 (s, 1H, CH); 8.0 + 8.3 (d, J=8 Hz, 2H);
9c	129–131 (MeOH) 44/A (from **6b**)	$C_{15}H_{15}N_3O_2S$ (301.39)	1.92 (m, 2H); 2.78 (t, J=7 Hz, 2H); 2.91 (s, 3H); 3.4 (t, J=7 Hz, 2H); 7.5 (s, 5H); 8.02 (s, 1H);
9d[c]	198–201 (MeCN) 91/A (from **6a**)	$C_{25}H_{19}ClN_2O_3S$ (462.96)	
9e	246–248 (MeCN) 79/A (from **6c**)	$C_{25}H_{20}N_4S$ (408.52)	[d]2.00 (m, 2H); 2.82 (m, 2H); 3.02 (s, 3H); 3.37 (t, J=6 Hz, 2H); 7.32–7.61 (m, 10H);
9f[e]	203–205 (DMF) 98/B	$C_{21}H_{18}ClN_3O_2S$ (411.91)	
9g	227–229 (AcOEt) 96/A (from **6a**)	$C_{19}H_{16}ClN_3O_3S$ (401.87)	2.12 (m, 2H); 2.91 (m, 2H); 2.92 (s, 3H); 3.37 (m, 2H); 7.1–7.8 (m, 7H);
9h	129–131 (MeOH) 78/A (from **6h**)	$C_{16}H_{16}ClN_3O_2S$ (349.83)	1.76 (m, 4H); 2.55 (t, J=7 Hz, 2H); 3.11 (s, 3H); 3.37 (t, J=7 Hz, 2H); 7.18 (m, 4H); 8.02 (s, 1H, CH);
9i	158–160 (MeOH) 85/A (from **6k**)	$C_{18}H_{16}BrN_3OS$ (402.29)	2.03 (m, 4H); 3.13 (s, 3H); 3.34 (m, 2H); 3.56 (m, 2H); 7.71 (s, 1H); 7.81 (m, 4H);
9j	131–133 (MeOH) 55/B	$C_{22}H_{20}ClN_3O_2S$ (425.93)	1.71 (m, 4H); 2.48 (m, 2H); 3.06 (s, 3H); 3.34 (m, 2H); 7.51 (m, 6H); 7.71 (s, 1H); 8.31 (d, J=8 Hz, 2H);
9k[f]	182–184 (MeOH) 98/A (from **6o**)	$C_{24}H_{23}BrN_2OS$ (467.43)	
9l	214–215 (MeCN) 81/A (from **6n**)	$C_{27}H_{23}ClN_2O_3S$ (491.01)	1.92 (m, 6H); 2.71 (m, 2H); 3.08 (s, 3H); 3.50 (m, 2H); 7.30 (d, J=8 Hz, 2H); 7.53 (s, 1H, CH); 7.73–8.25 (m, 7H);
9m[g]	180–182 (MeCN) 45/A (from **6n**)	$C_{23}H_{21}ClN_4O_4S$ (484.96)	
11n	227–229 (DMF) 89	$C_{28}H_{31}N_5OS$ (485.65)	[h]1.91 (m, 4H); 2.40 (m, 4H); 2.92 (s, 3H); 3.32 (m, 8H); 7.5–8.5 (m, 9H);
11o[i)k)]	107–109 (MeCN) 69	$C_{28}H_{32}ClN_7SO_2$ (566.11)	
11p[j]	203–205 (MeOH) 75	$C_{28}H_{31}BrClN_3OS$ (572.98)	1.50 (m, 6H); 2.02 (m, 4H); 2.73 (s, 3H); 3.05 (m, 8H); 7.3–7.5 (m, 8H); 7.81 (s, 1H);
11q[k)l)]	216–219 (MeOH) 80	$C_{28}H_{31}Cl_2N_5OS$ (556.56)	1.77 (m, 4H); 2.05 (m, 4H); 2.77 (s, 3H); 3.12 (m, 8H); 7.35 (m,4H); 7.48 (m, 2H); 7.93 (m, 3H);
11r	186–189 (MeOH) 82	$C_{28}H_{30}ClN_5OS_2$ (552.16)	1.45 (m, 4H); 2.05 (m, 2H); 2.69 (s, 3H); 3.05 (m, 8H); 3.62 (m, 2H); 7.37 (s, 5H); 7.77 (s, 1H); 7.51 +8.23 (d, J=8 Hz, 2H);
11s	199–201 (MeOH) 71	$C_{27}H_{31}ClN_4O_2S$ (511.08)	1.51 (m, 6H); 1.93 (m, 4H); 2.71 (s, 3H); 3.06 (m, 8H); 7.3–7.5 (m, 8H); 8.24 (s, 1H);
11t	219–220 (MeCN/DMF) 78	$C_{26}H_{31}Br_2N_3OS$ (593.43)	1.19 (t, J=7 Hz, 3H); 1.71 (m, 4H); 2.71 (s, 6H); 2.89 (m, 6H); 7.3–7.6 (m, 9H); 7.82 (s, 1H);
11u	103–107 (MeCN) 83	$C_{29}H_{34}ClN_5S$ (520.1)	[d]1.29 (m, 12H); 2.29 (m+s, 5H); 2.76 (m, 6H); 7.3–7.5 (m, 8H);

[a]All compounds gave satisfactory micro analysis, besides **11t** C + 0.7; H − 0.5 [b]m.s. 472 (M^+, 48), 183 (20), 155 (20), 55 (100) [c]m.s. 462 (M^+, 100), 356 (57), 173 (42), 55 (94) [d]recorded in $CDCl_3$ [e]m. s. 411 (M^+, 100), 184 (20), 85 (17) [f]m.s. 466 (M^+, 44), 250 (56), 181 (51), 68 (100), 55 (95) [g]m.s. 484 (M^+, 24), 153 (100), 68 (57) [h]recorded in TFA-d_4 [i]m.s. 471 (M^+, 17), 216 (25), 198 (66), 44 (100) [j]as hydrobromide [k]as hydrochloride [l]^{13}C-n.m.r.: 25.13 (2 × CH_2); 25.17; 25.22; 29.9; 33.02; 48.65; 51.72; 102.69; 107.71; 123.48; 126.63; 128.39; 128.96; 131.44; 133.50; 136.79; 139.69; 160.12; 162.93; 176.30

[9, 10]. I.e. in 6-membered intermediates **8** resonance structure **8A** predominates thus favouring a nucleophilic attack at the methine C (route A) while in case of 5 and 7-membered systems an amidinium resonance structure **8B** is dominating supporting route B. MNDO-calculations of 2-aza-3-(4-chlorobenzyl)pentamethinium structures **8** (R = aryl = 4-ClC_6H_4, n = 1, 2, and 3) (see Table 1), however, reveal no significant effect of the ring size on the static reactivity indices (net atomic charge q_{netto}, valence V, and Mulliken atomic charge q^{Mullik}). Therefore, the different cyclization behaviour of the azapentamethinium intermediates **8** may be caused by steric effects rather than electronic factors. All compounds **6, 9** and **11** are new. They are usually stable, but some 4-(ω-aminoalkyl)thiazoles partly decompose after repetitive recrystallisation. The structures are confirmed by spectroscopic data (see Tables 2 and 3). Spiro isomers **10** of 4-(ω-aminoalkyl)thiazoles **11** can be ruled out, since typical ^{1}H-nmr signals and m.s.-fragment peaks [5, 8, 11] are observed. As mentioned above and as a further proof for structure **9** these compounds could be synthesized in an alternative way (method B).

Experimental

The melting points were measured with a "Boëtius" hot-stage apparatus and are correceted. The ^{1}H-nmr spectra were measured with a TESLA BS 587 (80 MHz) FT-spectrometer. The ^{13}C-nmr spectra were recorded on a Bruker AM 300. All spectra were taken in DMSO-d_6. Mass spectra were taken with a Hewlett Packard 599 SA spectrometer.

N-(1-Methylthiovinyl)lactam-2-imines (**4**)

The lactam acetal **3** was prepared without isolation by mixing 0.05 mol of the corresponding lactam with 6.3 g (0.05 mol) dimethylsulfate. After 2 h heating at 80 °C the resulting liquid O-alkylation product was purified by extracting impurities three times with diethylether. A solution of 1.2 g (0.052 mol) sodium in 50 ml dry methanol was added with stirring. After the addition of 0.02 mol substituted thioacetamide **2** the mixture was refluxed for 30 minutes. The mixture was cooled to room temperature and was gradually diluted with water to precipitate the product. It was suction filtrated and recrystallized.

N-(3-Aminothioacryloyl)lactam imines (**6**)

Method A
The corresponding lactam was O-alkylated like cited in the forstanding procedure. 1.15 g (0.05 mol) sodium dissolved in 30 ml methanol were added. 0.01 mol of 3-aminothioacrylamide **5** [13] were added with stirring. The mixture was heated on a water bath until all starting material had dissolved (3–4 min, eventually some methanol had to be added). After cooling to room temperature the product crystallized or was precipitated by the addition of some water. It was suction filtrated and recrystallized.

Method B
The corresponding lactam acetal **3** was prepared starting from the corresponding lactim ether in the following way: 0.02 mol of lactim ether [12] were combined with 2.5 g (0.02 mol) dimethylsulfate and heating the resulting mixture at 80 °C for 2 hours. A solution of 1.15 g (0.02 mol) sodium in 40 ml methanol was added. The mixture was heated to boiling while 0,01 mol of 3-aminothioacrylamide **5** were added. The mixture was heated under stirring while the methanol formed continuously distilled off. After cooling to room temperature the mixture was poured into water. The product was extracted with chloroform. After evaporation of the solvent the remaining material was recrystallized.

Method C
0.01 mol-3-aminothioacrylamide **5** and 0.012 mol lactam acetal in 30 ml methanol were refluxed 30 min. After cooling the product crystallized. It was filtrated by suction and recrystallized.

N-Thienyllactam imines (**9**) *and 4-(ω-Aminoalkyl)thiazoles* (**11**)

Method A
A mixture of 0.01 mol N-(3-aminothioacryloyl)lactam imine **6**, 0.01 mol substituted methylhalide **7**, 20 ml acetonitrile and 1 g (0.01 mol) triethylamine was refluxed for 3–4 minutes. After cooling to room temperature the product crystallized or was precipitated by the addition of some water. It was suction filtrated and recrystallized.

N-Thienyllactam imines (**9**)

Method B
A solution of the corresponding lactam acetal was prepared like mentioned in method A. After the addition of 0.025 mol of the 2-aminothiophene **12** (available from **5** and **3**) the mixture was heated to boiling under stirring (about 30 min). The product was isolated like described in method A.

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