Regiospecific Synthesis, Structure and Electron Ionization Mass Spectra of 1,3-Thiazolidin-4-ones Containing the Acridine Skeleton

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The synthesis of regioisomeric 3-alkyl(aryl)-2-(acridin-9'-yl)imino-1,3-thiazolidin-4-ones (**8b**–**i**) and 2-alkyl(aryl)imino-3-(acridin-9'-yl)-1,3-thiazolidin-4-ones (**11a**–**i**) was performed by the reaction of 3-(acridin-9-yl)-1-alkyl(aryl)thioureas **5a**–**i** with methyl bromoacetate and bromoacetyl bromide, respectively, *via* the corresponding isothiourea hydrobromides with excellent regioselectivity. The structure, NMR spectra and mass spectrometric behavior of the resulting compounds are discussed.

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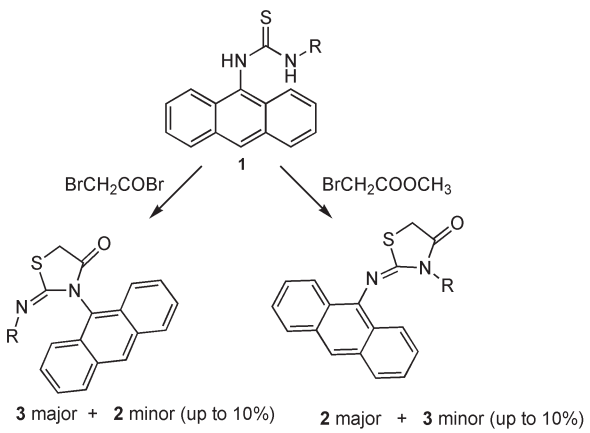
Introduction.

Although the discovery of acridine as well as the clinical use of the first drug involving this skeleton is a part of history, the interest in these compounds continues to exist still today [1,2]. Mostly investigated characteristics of acridine derivatives are their biological activity [3], intercalating effects [4] and chemiluminiscence including fluorescence [5,6]. All effects are directly dependent on a moiety that is attached to the acridine skeleton.

For some time our group has been interested to study the synthesis, structure, fluorescence and biological activity of acridine derivatives [7,8,9]. We found it interesting to prove the possible biological synergetic effect by combining the acridine skeleton with other biologically active moieties. Due to our experiences in *S,N*-heterocyclic chemistry we decided to choose thiazoline and thiazolidine entities for this purpose.

Thiazolidines themselves are a vast group of heterocycles that accounts for a broad spectrum of biological activity [10–13]. Reviews on their synthesis, reactions and biological activities have been published [14,15]. Thiazolidinones, which are mostly prepared by treatment of 1,3-disubstituted thioureas with haloalkanoic acid derivatives, represent an interesting subunit of these compounds. Whereas the symmetrical thioureas give rise to a single product, unsymmetrical thioureas afford two regioisomeric 2-imino-1,3-thiazolidin-4-ones (*cf.* Scheme 1). However, in most cases only one isomer predominates [14]. When one of the thiourea substituents was a heterocyclic moiety, the cyclised products contained this residue always in the 2-imino position of thiazolidin-4-ones [12,13,16].

Scheme 1



In our previous work we found out that 1-substituted 3-(acridin-9-yl)thioureas reacted with methyl bromoacetate to give 3-substituted 2-(acridin-9'-yl)imino-1,3-thiazolidin-4-ones and 2-(substituted imino)-5-methoxycarbonylspiro[9',10'-dihydroacridine-9',4-(1,3-thiazolidines)] whereas the bromoacetonitrile afforded only the spiro compound [17]. In recent papers we were trying to synthesize both regioisomers of 2-imino-1,3-thiazolidin-4-ones, using 3-(anthracen-9-yl)-1-alkylthioureas **1** as starting compounds [18,19]. The reaction between **1** and methyl bromoacetate yielded mainly 2-(anthracen-9'-yl)imino-3-alkyl-1,3-thiazolidin-4-ones **2** together with some of the regioisomeric 3-(anthracen-9'-yl)-2-alkylimino-1,3-thiazolidin-4-ones **3** (Scheme 1). Treatment of **1** with bromoacetyl bromide again yielded **2** and **3**, but with a reversed product distribution ratio. As shown, the selected electrophiles can lead to reversed regioisomers. Therefore we were interested to learn how the acridine skeleton influences the reaction course and biological activity of respective regioisomers.

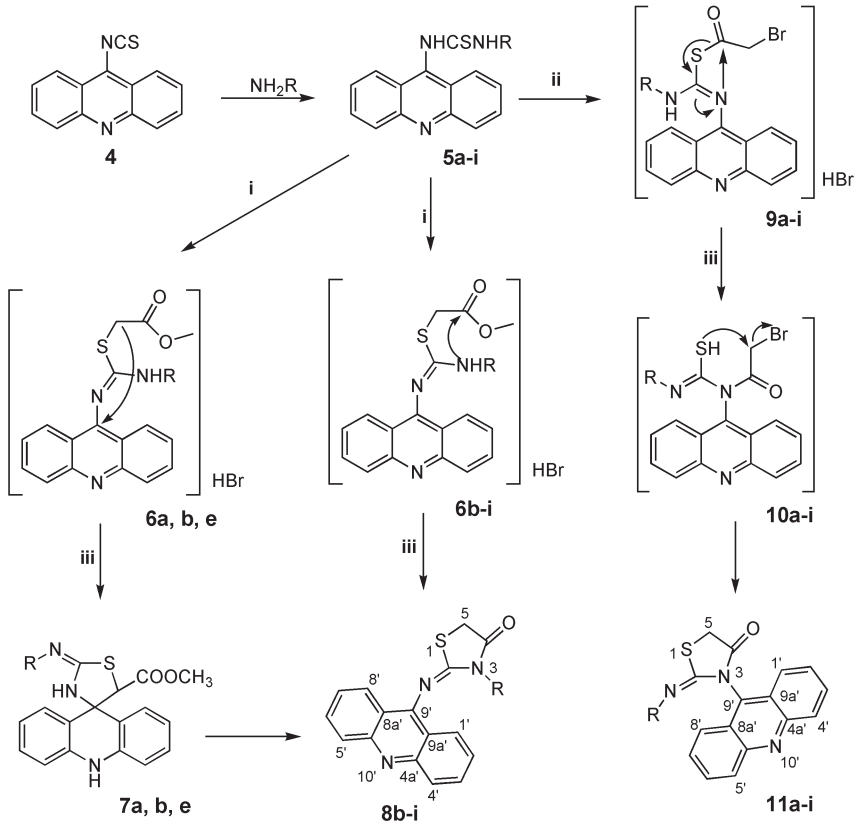
Results and Discussion.

As a starting compound, 9-isothiocyanatoacridine **4** was used. Treatment of **4** with aliphatic and aromatic primary amines yielded substituted 3-(acridin-9'-yl)-1-alkyl(aryl)thioureas **5a**–**i** that were then let to react with methyl bromoacetate to give *S*-methoxycarbonylmethyl isothiourea hydrobromides **6a**–**i** (Scheme 2 and Table 1). Subsequent cyclization under basic conditions (triethylamine in dry benzene) afforded 2-*tert*-butylimino-5-(methoxycarbonyl)spiro[9',10'-dihydroacridine-9',4-(1,3-thiazolidine)] **7a** (Tables 2 and 3) and 2-(acridin-9'-

yl)imino-3-alkyl(aryl)-1,3-thiazolidin-4-ones **8b**–**i** (Tables 2–6). However, *S*-bromoacetyl isothiourea hydrobromides **9a**–**i**, (Table 1) obtained from **5a**–**i** by treating with bromoacetyl bromide, yielded the reversed regioisomers, 2-alkylimino-3-(acridin-9'-yl)-1,3-thiazolidin-4-ones **11a**–**i** (Scheme 2, Tables 2–6).

observing the growth of the CH_2S signal at 3.78 ppm). A similar transformation occurred for the spiro derivative (**7e**) containing the *s*-Bu group in $CDCl_3$ in the presence of catalytic amount of $(Et)_3N$. However, transformation of the spiro derivative with *t*-Bu group (**7a**) failed showing that indeed there had to be some steric factor preventing the

Scheme 2



R: **a** = *tert*-butyl, **b** = isopropyl, **c** = propyl, **d** = allyl, **e** = *sec*-butyl, **f** = butyl, **g** = cyclohexyl, **h** = benzyl, **i** = phenyl
i = $BrCH_2COOCH_3$, CH_2Cl_2; **ii** = $BrCH_2COBr$, CH_2Cl_2; **iii** = $(C_2H_5)_3N$, benzene

In accord with mechanism for reactions of anthracene analogues of **5a**–**i** with bromoacetyl reagents thoroughly discussed in our previous papers [18,19] it was presumed that the reaction of the thioureas **5a**–**i** with methyl bromoacetate was initiated by an attack of sulfur on the α-carbon atom of the ester to afford slowly the alkylation products **6a**–**i**, (Scheme 2) which cyclized in the presence of triethylamine to pure regioisomers **8c**–**i**. However, isothiourea **6a** bearing bulky *tert*-butyl substituent gave rise to a spiro derivative **7a** only and isopropyl isothiourea hydrobromide **6b** gave in the same conditions a mixture of both spiro and condensation derivatives **7b** and **8b**, respectively. On stirring of the reaction mixture at room temperature, the spiro isomer **7b** transformed stepwise to the pure condensation product **8b** (the reaction was followed by ^1H NMR in deuteriochloroform at 12, 24, 48 and 96 h, by

formation of **8a**. The process could be formally explained by the cleavage of the C9'-C5 bond of the spiro ring and a subsequent cyclization of the open form intermediate obtained with a simultaneous release of methanol. Very different was the reaction of the thioureas **5a**–**i** with bromoacetyl bromide leading to sole reversed regioisomers **11a**–**i**. The starting compounds afforded insoluble intermediates **9a**–**i** immediately after mixing with the reagent as proved by TLC (Scheme 2). The high rate of **9a**–**i** formation in contradition to slow formation of intermediates **6a**–**i** indicated that other than the Br-CH_2 reaction centre, namely the bromocarbonyl carbon had been attacked by the sulfur nucleophile. Indeed, a strong kinetic evidence for a primary *S*-acylation in reactions of thioureas with acetyl or benzoyl chlorides was described by Pratt and Kaválek [20–22]. The structural proof of **9a**–**i** was hampered by their fast transformation

Table 1
Physical and Spectral Data for the Intermediate Isothiourea Hydrobromides **6a–i**, **9a–i**

No.	Yield (%)	mp (°C)	ir (cm^{-1}) (NH), (C=O), (C=N)	^{1}H NMR (δ, ppm) in deuteriochloroform – DMSO-d_6 (2:1)
6a	71	120-123	3430, 1737, 1610	9.15-7.35 (m, 8H, H-arom), 3.78 (s, 3H, OCH_3), 3.46 (s, 2H, CH_2CO), 1.65 (s, 9H, 3×CH_3)
6b	85	213-215	3430, 1740, 1630	8.5-7.33 (m, 8H, H-arom), 4.03 (m, 1H, CH), 3.75 (s, 2H, CH_2CO), 3.53 (s, 3H, OCH_3), 1.26 (d, 6H, 2×CH_3, J 6 Hz)
6c	61	149-151	3440, 1773, 1627	8.67-7.35 (m, 8H, H-arom), 3.83 (s, 2H, CH_2CO), 3.68 (s, 3H, OCH_3), 3.5 (m, 2H, CH_2N), 1.75 (m, 2H, CH_2), 0.98 (t, 3H, CH_3, J 7.2 Hz)
6d	78	181-183	3425, 1734, 1640	9.28-7.5 (m, 8H, H-arom), 6.05 (m, 1H, CH), 5.46 (m,2H,CH_2), 4.70 (d, 2H, CH_2), 4.05 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2CO)
6e	87	217-219	3445, 1738, 1632	8.86-7.38 (m, 8H, H-arom), 3.96 (sept, 1H, CH), 3.69 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2CO), 1.6 (m, 2H, CH_2), 1.31 (d, 3H, CH_3, J 6 Hz), 0.71 (t, 3H, CH_3, J 7.1 Hz)
6f	80	168-170	3433, 1740, 1630	9.28-7.42 (m, 8H, H-arom), 4.06 (m, 1H, NH), 3.74 (s, 2H, CH_2CO), 3.69 (s, 3H, OCH_3), 3.5 (q, 2H, CH_2N), 1.53 (m, 4H, 2×CH_2), 0.95 (m, 3H, CH_3)
6g	82	179-181	3467, 1740, 1620	8.89-7.36 (m, 8H, H-arom), 3.91 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2CO), 2.48-0.86 (m, 10H, H-cyclohexyl)
6h	69	170-172	3410, 1748, 1640	8.92-7.35 (m, 8H, H-arom), 7.31-6.86 (m, 5H, H-phenyl), 4.86 (s, 2H, CH_2), 3.75 (s, 2H, CH_2CO), 3.55 (s, 3H, OCH_3)
6i	59	172-174	3395, 1750, 1635	8.4-6.78 (m, 8H, H-arom and H-phenyl), 3.96 (s, 2H, CH_2CO), 3.63(s, 3H, OCH_3)
9a	79	275-278	3458, 1773, 1630	8.99-7.4 (m, 8H, H-arom), 4.46 (s, 2H, CH_2CO), 1.61 (s, 9H, 3×CH_3)
9b	97	196-198	3440, 1770, 1610	8.95-7.83 (m, 8H, H-arom), 4.62 (s, 2H, CH_2CO), 3.55 (m, 1H, CH), 0.94 (d, 6H, 2×CH_3, J 7.2 Hz)
9c	92	238-240	3410, 1785, 1634	9.13-7.78 (m, 8H, H-arom), 4.73 (s, 2H, CH_2CO), 3.49 (t, 1H, NH, J 6 Hz), 3.23 (m, 2H, CH_2N), 1.32 (sext, 2H, CH_2), 0.68 (t, 3H, CH_3, J 7 Hz)
9d	98	168-170	3450, 1733, 1645	9.18-7.85 (m, 8H, H-arom), 5.6 (m, 1H, CH), 4.93 (m, 2H, CH_2), 4.63 (s, 2H, CH_2CO), 3.86 (m, 2H, CH_2)
9e	90	232-235	3425, 1780, 1635	9.03-7.79 (m, 8H, H-arom), 4.57 (s, 2H, CH_2CO), 3.2 (m, 1H, CH), 3.61 (br s, 1H, NH), 1.6 (m, 2H, CH_2), 0.86 (d, 3H, CH_3, J 6 Hz), 0.56 (t, 3H, CH_3, J 7 Hz)
9f	94	226-228	3433, 1765, 1627	8.95-7.83 (m, 8H, H-arom), 4.66 (s, 2H, CH_2CO), 3.19 (t, 2H, CH_2, J 6 Hz), 1.18 (m, 4H, 2×CH_2), 0.67 (t, 3H, CH_3, J 5 Hz)
9g	89	248-252	3430, 1770, 1607	8.86-7.78 (m, 8H, H-arom), 4.61 (s, 2H, CH_2CO), 3.16 (m, 1H, CH), 1.75-0.45 (m, 10H, 5×CH_2)
9h	95	165-169	3451, 1775, 1623	8.93-7.75 (m, 8H, H-arom), 7.35-6.72 (m, 5H, H-phenyl), 4.61 (s, 2H, CH_2CO), 4.39 (s, 2H, CH_2)
9i	78	192-194	3427, 1772, 1638	9.42-7.5 (m, 8H, H-arom), 7.48-6.35 (m, 5H, H-phenyl), 4.53 (s, 2H, CH_2CO)

Table 2
Physical and ^{1}H NMR Spectral Data for the thiazolidines **7a**, **8b–i**, **11a–i**

No	Yield (%)	mp (°C)	ir (cm^{-1}) (CH_2), (C=O), (C=N)	^{1}H NMR (δ, ppm) in deuteriochloroform
7a [a]	19	191-193	2977, 1716, 1652	7.49 (d, 1H, H-1', J 7.8 Hz), 7.30 (d, 1H, H-8', J 7.8 Hz), 7.22 (td, 1H, H-6', J 7.9, 7.3 and 1.4 Hz), 7.19 (td, 1H, H-3', J 7.9, 7.3 and 1.5 Hz), 6.98 (td, 1H, H-7', J 7.8, 7.3 and 1.1 Hz), 6.94 (td, 1H, H-2', J 7.8, 7.3 and 1.1 Hz), 6.87 (dd, 1H, H-5', J 7.9 and 1.1 Hz), 6.82 (dd, 1H, H-4', J 7.9 and 1.1 Hz), 6.44 (s, 1H, NH), 4.5 (br s, 1H, thiazolidine NH), 4.09 (s, 1H, CHS), 3.14 (s, 3H, OCH_3), 1.58 (s, 9H, 3×CH_3)
8b	62	165-167	2975, 1710, 1646	8.22 (ddd, 2H, H-4',5', J 8.8, 1.1 and 0.7 Hz), 7.89 (ddd, 2H, H-1',8', J 8.6, 1.4 and 0.7 Hz), 7.78 (ddd, 2H, H-3',6', J 8.8, 6.6 and 1.4 Hz), 7.48 (ddd, 2H, H-2',7', J 8.6, 6.6 and 1.1 Hz), 5.12 (sept, NCH, J 6.9 Hz), 3.78 (s, 2H, CH_2S), 1.77 (d, 6H, 2×CH_3, J 6.9 Hz)
8c	67	175-178	2967, 1717, 1645	8.22 (d, 2H, H-4',5', J 8.8 Hz), 7.89 (d, 2H, H-1',8', J 8.6 Hz), 7.78 (ddd, 2H, H-3',6', J 8.8, 6.6 and 1.4 Hz), 7.48 (ddd, 2H, H-2',7', J 8.6, 6.6 and 1.1 Hz), 4.10 (m, 2H, CH_2N), 3.84 (s, 2H, CH_2S), 2.01 (m, 2H, CH_3CH_2), 1.14 (t, 3H, CH_3, J 7.5 Hz)
8d	73	153-154	2975, 1728, 1640	8.22 (d, 2H, H-4',5', J 8.8 Hz), 7.89 (d, 2H, H-1',8', J 8.6 Hz), 7.78 (ddd, 2H, H-3',6', J 8.8, 6.5 and 1.4 Hz), 7.48 (ddd, 2H, H-2',7', J 8.6, 6.5 and 1.1 Hz), 6.14 (m, 1H, –CH=, J 17.1, 10.2 and 2×5.8 Hz), 5.52 (m, 1H, H_{trans} of $=CH_2$, J 17.1, 2×1.5 and 1.1 Hz), 5.45 (m, 1H, H_{cis} of $=CH_2$, J 10.2, 2×1.2 and 1.1 Hz), 4.74 (m, 2H, NCH_2, J 5.8, 1.5 and 1.2 Hz), 3.87 (s, 2H, CH_2S)
8e	28	155-158	2973, 1720, 1658	8.21 (d, 2H, H-4',5', J 8.8 Hz), 7.87 (d, 2H, H-1',8', J 8.6 Hz), 7.77 (m, 2H, H-3',6'), 7.48 (m, 2H, H-2',7'), 4.87 (m, 1H, NCH, J 9.3, 3×6.9 and 6.3 Hz), 3.80 (s, 2H, CH_2S), 2.45 (m, 1H, CH_2, J 9.3, 3×7.3 and -13.7 Hz), 2.01 (m, 1H, CH_2, J 3×7.6, 6.3 and -13.7 Hz), 1.75 (d, 3H, CH_3, J 6.9 Hz), 1.14 (t, 3H, CH_3, J 7.6 and 7.3 Hz)
8f	54	122-124	2964, 1723, 1647	8.22 (d, 2H, H-4',5', J 8.8 Hz), 7.89 (d, 2H, H-1',8', J 8.6 Hz), 7.77 (ddd, 2H, H-3',6', J 8.8, 6.5 and 1.4 Hz), 7.48 (ddd, 2H, H-2',7', J 8.6, 6.5 and 1.1 Hz), 4.13 (m, 2H, CH_2N), 3.83 (s, 2H, CH_2S), 1.96 (m, 2H, $CH_3CH_2CH_2$), 1.55 (m, 2H, CH_3CH_2), 1.07 (t, 3H, CH_3, J 7.4 Hz)

Table 2 (continued)

No	Yield (%)	mp (°C)	ir (cm^{-1}) (CH_2), (C=O), (C=N)	^{1}H NMR (δ, ppm) in deuteriochloroform
8g	56	186-188	2968, 1715, 1645	8.22 (d, 2H, H-4',5', J 8.8 Hz), 7.88 (m, 2H, H-1',8', J 8.6, 1.4 and 0.8 Hz), 7.78 (m, 2H, H-3',6', J 8.8, 6.5 and 1.4 Hz), 7.49 (m, 2H, H-2',7', J 8.6, 6.5 and 1.1 Hz), 4.70 (m, 1H, CHN, J 2×12.3 and 2×3.4 Hz), 3.78 (s, 2H, CH_2S), 2.70 (m, 2H, J 12.3, 11.7, 3.8 and -13.3 Hz), 2.0–1.2 (m, 8H)
8h	22	135-137	2973, 1733, 1653	8.19 (d, 2H, H-4',5', J 8.8 Hz), 7.74 (ddd, 2H, H-3',6', J 8.8, 6.5 and 1.4 Hz), 7.66–7.63 (m, 4H, H-1',8' and *o*-C_6H_5), 7.46–7.41 (m, 3H, *m*- and *p*-C_6H_5), 7.38 (ddd, 2H, H-2',7', J 8.6, 6.5 and 1.1 Hz), 5.28 (s, 2H, NCH_2), 3.88 (s, 2H, CH_2S)
8i	18	130-133	2963, 1715, 1642	8.20 (d, 2H, H-4',5', J 8.8 Hz), 7.88 (d, 2H, H-1',8', J 8.6 Hz), 7.76 (ddd, 2H, H-3',6', J 8.8, 6.6 and 1.4 Hz), 7.64 (m, 2H, *m*-C_6H_5, J 8.0, 7.5 and 2.1 Hz), 7.61 (m, 2H, *o*-C_6H_5, J 8.0, 2.7 and 1.1 Hz), 7.53 (m, 1H, *p*-C_6H_5, J 2×7.5 and 2×1.1 Hz), 7.49 (ddd, 2H, H-2',7', J 8.6, 6.6 and 1.1 Hz), 4.03 (s, 2H, CH_2S)
11a	64	194-196	2985, 1722, 1638	8.30 (d, 2H, H-4',5', J 8.8 Hz), 7.79 (ddd, 2H, H-3',6', J 8.8, 6.6 and 1.3 Hz), 7.77 (d, 2H, H-1',8', J 8.7 Hz), 7.57 (ddd, 2H, H-2',7', J 8.7, 6.6 and 1.1 Hz), 4.28 (s, 2H, CH_2S), 1.05 (s, 9H, 3×CH_3)
11b	92	182-185	2990, 1725, 1640	8.31 (d, 2H, H-4',5', J 8.8 Hz), 7.79 (ddd, 2H, H-3',6', J 8.8, 6.5, 1.3 Hz), 7.78 (d, 2H, H-1',8', J 8.7 Hz), 7.57 (ddd, 2H, H-2',7', J 8.7, 6.5 and 1.1 Hz), 4.25 (s, 2H, CH_2S), 3.47 (sept, 1H, CHN, J 6×6.2 Hz), 0.91 (d, 6H, 2×CH_3, J 6.2 Hz)
11c	48	172-174	2965, 1720, 1634	8.31 (d, 2H, H-4',5', J 8.9 Hz), 7.82–7.78 (m, 4H, H-3',6' and H-1',8'), 7.58 (ddd, 2H, H-2',7', J 8.7, 6.5 and 1.1 Hz), 4.28 (s, 2H, CH_2S), 3.19 (t, 2H, CH_2N, J 2×6.8 Hz), 1.37 (m, 2H, CH_2, J 3×7.4 and 2×6.8 Hz), 0.70 (t, 3H, CH_3, J 2×7.4 Hz)
11d	47	158-160	2982, 1730, 1640	8.32 (d, 2H, H-4',5', J 8.9 Hz), 7.83–7.79 (m, 4H, H-3',6' and H-1',8'), 7.60 (m, 2H, H-2',7', J 8.7, 6.5 and 1.1 Hz), 5.69 (m, 1H, CH, J 17.1, 10.3 and 2×5.0 Hz), 4.92 (m, 1H, H_{cis} of CH_2, J 10.3 and 3×1.7 Hz), 4.88 (m, 1H, H_{trans} of CH_2, J 17.1, 2×1.9 and 1.7 Hz), 4.31 (s, 2H, CH_2S), 3.90 (dt, 2H, CH_2N, J 5.0, 1.9 and 1.7 Hz)
11e	71	224-228	2975, 1728, 1648	8.31 (d, 2H, H-4',5', J 8.9 Hz), 7.82–7.77 (m, 4H, H-3',6' and H-1',8'), 7.58 (m, 2H, H-2',7'), 4.26 (s, 2H, CH_2S), 3.19 (m, 1H, CHN, J 8.2, 3×6.2 and 4.6 Hz), 1.28 (m, 1H, CH_2, J 3×7.4, 4.6 and -13.5 Hz), 1.13 (m, 1H, CH_2, J 8.2, 3×7.4 and -13.5 Hz), 0.91 (d, 3H, CH_3, J 6.2 Hz), 0.63 (t, 3H, CH_3, J 2×7.4 Hz)
11f	63	144-147	2978, 1725, 1643	8.31 (d, 2H, H-4',5', J 8.9 Hz), 7.82–7.77 (m, 4H, H-3',6' and H-1',8'), 7.59 (ddd, 2H, H-2',7', J 8.7, 6.5 and 1.1 Hz), 4.28 (s, 2H, CH_2S), 3.22 (t, 2H, CH_2N, J 7.2 and 6.6 Hz), 1.33 (m, 2H, CH_2), 1.12 (m, 2H, CH_2), 0.77 (t, 3H, CH_3, J 7.4 Hz)
11g	30	172-176	2993, 1722, 1645	8.30 (d, 2H, H-4',5', J 8.8 Hz), 7.82–7.76 (m, 4H, H-3',6' and H-1',8'), 7.57 (ddd, 2H, H-2',7', J 8.7, 6.5 and 0.9 Hz), 4.27 (s, 2H, CH_2S), 3.13 (m, 1H, CHN, J 2×9.8 and 2×3.6 Hz), 1.57–0.93 (m, 10H, 5×CH_2)
11h	57	201-203	2980, 1725, 1645	8.32 (d, 2H, H-4',5', J 9.0 Hz), 7.83–7.79 (m, 4H, H-3',6' and H-1',8'), 7.59 (m, 2H, H-2',7'), 7.15–7.12 (m, 3H, *m*- and *p*-C_6H_5), 6.94 (m, 2H, *o*-C_6H_5), 4.48 (s, 2H, CH_2N), 4.31 (s, 2H, CH_2S)
11i	78	195-197	2987, 1727, 1637	8.34 (d, 2H, H-4',5', J 8.8 Hz), 7.91 (d, 2H, H-1',8', J 8.7 Hz), 7.83 (m, 2H, H-3',6', J 8.8, 6.5 and 1.3 Hz), 7.66 (m, 2H, H-2',7', J 8.7, 6.5 and 1.1 Hz), 7.26 (m, 2H, *m*-C_6H_5, J 8.1, 7.5 and 1.6 Hz), 7.08 (m, 1H, *p*-C_6H_5, J 2×7.5 and 2×1.1 Hz), 6.81 (m, 2H, *o*-C_6H_5, J 8.1, 2.2 and 1.1 Hz), 4.30 (s, 2H, CH_2S)

[a] Here none of the hydrogens (nor carbons) in the acridine moiety (*e.g.* H-1' and H-8') are chemically equivalent; within the H-1'/H-8' pair, the proton with larger chemical shift was arbitrarily labelled as H-1'. The numbering of the other atoms in the acridine skeleton follows this choice.

/decomposition in the solution while recording the NMR spectra. This way, a clear confirmation of the structure of **9** by ^{13}C NMR that sensitively reflects the sulfur atom directly bound to methylene carbon was impossible; however, proton chemical shifts of **9a–i** in the region 4.53–4.73 ppm satisfactorily corresponded to those of a CH_2 group directly bound to a bromine atom (an additive increment of a bromine is +1.97 ppm; that of a sulfur +1.23 ppm). Anthracenyl analogues of **9a–i** decomposed during crystallization in methanol back to the starting anthracenyl thioureas [18,19] and no product possessing an S-CH_2-$COOCH_3$ moiety that should be formed in hot methanol from an intermediate having an S-CH_2-CO-Br grouping was found. These facts support *S*-acylation as a primary step in the reaction of **5a–i** with bromoacetyl bromide. The cyclization of the *S*-acylated isothiourea hydrobromides **9a–i** to the reversed regioisomers **11a–i** occurred in the presence of triethylamine, after rearrangement of the bromoacetyl group onto the nitrogen atom bearing acridine skeleton *via* intermediates **10a–i**. The migration of the *S*-acyl group to nitrogen in isothioureas is well known and has been studied in depth kinetically [20,21,22]. Regrouping is accelerated by base towards the preferred neutral imino but not the amino nitrogen [20] bearing the acridinyl group, which is the more stable imino tautomeric form of isothiourea as had been proved by an *ab initio* calculation for *S*-bromoacetyl-*N*-phenyl-*N´*-*n*-propylisothiourea [19]. Final attack of the sulfur atom on the α-carbon atom of the $COCH_2Br$ group afforded the thiazolidinone regioisomers **11a–i** (Scheme 2). Isolation of only one regioisomer, **11**, in this work unlike anthracenyl analogues [18,19] where a minor portion (up to 10%) of analogues of

Table 3

^{13}C NMR Spectra of Thiazolidines **7a**, **8b**, **d**, **e**, **i** and **11a**, **b**, **e**, **i**

No.	^{13}C NMR (δ, ppm) in deuteriochloroform
7a [a]	170.3 (C=O), 157.0 (C=N), 138.9 (C-4a'), 137.7 (C-10a'), 128.4 (C-3'), 128.1 (C-6'), 127.6 (C-1'), 126.1 (C-8'), 123.7 (C-8a'), 121.4 (C-9a'), 120.7 (C-7'), 120.5 (C-2'), 114.0 (C-5'), 113.2 (C-4'), 83.3 (C-9'), 63.9 (CHS), 53.7 ($C(CH_3)_3$), 52.2 (OCH_3), 29.0 ($C(CH_3)_3$)
8b	171.6 (C=O), 156.7 (C=N), 150.7 (C-9'), 149.8 (C-4a', C-10a'), 130.5, 129.9, 125.3, 123.8 (C-1' to C-8'), 117.8 (C-8a', C-9a'), 48.6 (CHN), 33.3 (CH_2S), 19.3 (CH_3)
8d	171.2 (C=O), 156.4 (C=N), 150.3 (C-9'), 149.7 (C-4a', C-10a'), 135.4 (NCH_2CH=), 130.6, 130.0, 125.3, 123.9 (C-1' to C-8'), 117.9 (C-8a', C-9a'), 115.5 (CH=CH_2), 45.6 (CH_2N), 33.5 (CH_2S)
8e	171.7 (C=O), 156.8 (C=N), 150.5 (C-9'), 149.6 (C-4a', C-10a'), 130.4 (C-3', C-6'), 129.8 (C-4', C-5'), 125.1 (C-2', C-7'), 123.6, 123.5 (C-1', C-8'), 117.7, 117.6 (C-8a', C-9a'), 54.4 (CHN), 33.0 (CH_2S), 25.6 (CH_2), 17.4 (CH_3), 11.5 (CH_3)
8i	171.0 (C=O), 157.2 (C=N), 150.2 (C-9'), 149.4 (C-4a', C-10a'), 134.4 (*i*-C_6H_5), 130.4 (C-3', C-6'), 129.8 (*m*-C_6H_5), 129.7 (C-4', C-5'), 129.6 (*p*-C_6H_5), 128.0 (*o*-C_6H_5), 125.1 (C-2', C-7'), 123.6 (C-1', C-8'), 117.5 (C-8a', C-9a'), 33.5 (CH_2S)
11a	170.2 (C=O), 149.9 (C-4a', C-10a'), 143.5 (C=N), 139.1 (C-9'), 130.5, 127.1, 123.7, 123.1 (C-1' to C-8'), 123.5 (C-8a', C-9a′), 55.0 (C-N), 34.5 (CH_2S), 29.3 (CH_3)
11b	171.0 (C=O), 150.0 (C-4a', C-10a'), 148.1 (C=N), 138.2 (C-9'), 130.4, 130.4 127.2, 122.9 (C-1' to C-8'), 123.6 (C-8a', C-9a'), 54.2 (CHN), 33.2 (CH_2S), 23.3 (CH_3)
11e	171.0 (C=O), 150.0 (C-4a', C-10a'), 148.5 (C=N), 138.3 (C-9'), 130.4, 127.3, 127.3, 122.8 (C-1' to C-8'), 123.6 (C-8a', C-9a'), 60.4 (CHN), 33.3 (CH_2S), 30.7 (CH_2), 21.1 (CH_3), 11.0 (CH_3)
11i	170.8 (C=O), 153.4 (C=N), 149.8 (C-4a', C-10a'), 147.3 (*i*-C_6H_5), 137.0 (C-9'), 130.5 (C-4', C-5'), 130.4 (C-3', C-6'), 129.2 (*m*-C_6H_5), 127.6 (C-2', C-7'), 125.0 (*p*-C_6H_5), 123.2 (C-8a', C-9a'), 122.3 (C-1', C-8'), 120.7 (*o*-C_6H_5), 33.4 (CH_2S)

[a] See footnote in Table 2.

Table 4

Mass Spectrometric Fragments (R.A. usually ≥ 3%) of Compounds **8b–i** and **11a–i** at 70 eV

	R	*m/z* (R.A. %)
11a	*t*-Bu	349(34.5), 334(12.0), 295(6.3), 294(19.2), 293(100), 292(6.1), 248(5.3), 246(3.2), 224(7.6), 221(19.6), 220(9.9), 219(19.3), 218(5.0), 206(6.3), 205(6.3), 195(5.7), 194(11.1), 192(8.1), 191(5.2), 179(4.0),178(7.3), 177(5.3), 164(3.4), 151(4.8), 130(3.9), 57(20.1), 41(9.8), 29(7.4)
8b	iPr	335(100), 294(7.0), 293(33.5), 292(3.4), 248(3.5), 246(3.9), 236(1.8), 224(3.0), 220(19.4), 219(31.1), 218(4.4), 194(3.9), 192(6.9), 191(4.8), 179(1.8), 178(5.5), 177(3.9), 151(3.4)
11b	iPr	335(4.3), 320(2.6), 293(2.6), 248(1.8), 224(9.6), 221(4.0), 220(4.9), 219(10.5), 206(6.1), 205(6.4), 194(3.8), 192(4.8), 180(14.7), 179(100), 178(5.3), 177(3.9), 151(3.4), 43(4.2)
8c	Pr	335(100), 294(2.9), 293(9.2), 292(7.3), 248(11.7), 246(7.6), 236(4.1), 224(4.0), 223(5.0), 220(13.6), 219(27.2), 218(6.1), 205(5.2), 205(5.9), 192(11.9), 191(5.4), 179(3.1), 178(7.7), 177(5.9), 151(5.2)
11c	Pr	335(28.6), 306(7.2), 293(5.9), 248(7.9), 236(3.5), 224(27.7), 223(5.3), 220(7.5), 219(13.9), 218(4.8), 206(13.6), 205(16.1), 204(4.9), 192(8.1), 191(4.5), 180(15.4), 179(100), 178(10.1), 177(7.0), 164(3.3), 151(6.5), 139(3.4), 46(3.8), 43(7.6), 41(4.2)
8d	Allyl	333(100), 332(9.0), 259(3.2), 258(7.0), 246(2.7), 237(5.6), 236(6.0), 221(3.2), 220(4.4), 219(14.7), 218(13.6), 217(23.1), 216(7.1), 205(6.6), 204(4.1), 193(3.9), 192(7.3), 191(13.1), 179(3.6), 178(6.7), 177(5.0), 166(4.0), 151(4.3), 98(3.4), 41(5.9)
11d	Allyl	333(31.2), 291(3.2), 259(2.7), 248(1.9), 236(3.0), 224(17.5), 220(11.5), 219(5.6), 218(8.5), 217(5.8), 206(9.3), 205(13.5), 204(4.9), 193(3.7), 192(8.9), 191(9.6), 180(15.0), 179(100), 178(8.3), 177(6.1), 164(4.0), 151(5.4), 46(3.4), 41(13.0)
8e	*s*-Bu	349(100), 294(23.9), 293(66.4), 292(12.5), 265(3.9), 251(4.5), 249(3.7), 248(17.7), 246(7.5), 236(3.2), 224(3.8), 223(3.9), 221(5.0), 220(8.8), 219(42.2), 218(7.9), 205(3.2), 204(3.4), 194(2.4), 192(11.8), 191(7.0), 179(3.0), 178(9.4), 177(6.1), 164(3.4), 151(6.2), 46(3.0), 41(8.3)
11e	*s*-Bu	349(3.1), 320(10.8), 293(4.1), 292(4.0), 248(2.4), 236(4.2), 224(7.8), 221(5.6), 220(7.3), 219(16.3), 218(5.0), 206(7.7), 205(10.2), 204(5.9), 194(4.3), 193(2.5), 191(4.7), 180(15.0), 179(100), 178(9.6), 177(6.2), 151(5.9), 57(5.0), 46(3.4), 42(3.3), 41(7.6)
8f	Bu	349(100), 348(1.0), 347(1.5), 307(2.6), 294(4.0), 293(8.2), 292(6.0), 248(8.7), 246(5.5), 236(4.5), 223(3.2), 221(3.3), 220(16.1), 219(16.6), 218(4.0), 205(4.3), 204(4.2), 192(7.5), 191(3.0), 179(2.6), 178(4.9), 177(3.2)
11f	Bu	349(29.8), 307(5.3), 306(7.3), 293(6.2), 248(6.3), 236(4.6), 225(4.6), 224(23.2), 223(4.6), 220(8.6), 219(15.1), 218(4.5), 206(12.2), 205(15.8), 204(5.2), 194(3.8), 193(13.3), 192(8.8), 191(4.3), 180(15.8), 179(100), 178(10.9), 177(7.2), 164(3.1), 157(3.8), 152(3.8), 151(6.4), 57(7.7), 41(5.8)
8g	Cyclohexyl	375(36.4), 303(6.6), 302(6.4), 301(24.7), 295(4.0), 294(17.7), 293(27.0), 292(3.1), 251(6.4), 248(3.7), 236(1.4), 221(4.9), 220(35.4), 219(100), 218(4.9), 194(3.2), 193(3.6), 192(11.4), 191(5.6), 179(2.7), 178(4.1), 177(3.1), 106(3.0), 74(2.6), 55(6.3), 47(4.2), 41(6.9)
11g	Cyclohexyl	375(2.7), 293(4.8), 248(1.9), 224(3.8), 221(3.7), 220(4.1), 219(8.1), 206(3.4), 205(5.1), 204(3.1), 194(3.8), 193(3.9), 192(3.6), 180(14.7), 179(100), 178(4.3), 177(2.7), 55(7.0), 41(5.9)
8h	Bzl	383(100), 309(5.4), 308(3.6), 282(3.5), 267(6.2), 266(2.8), 236(3.0), 220(1.6), 219(7.4), 205(4.2), 192(4.0), 191(5.4), 179(2.8), 178(3.4), 177(2.9), 151(2.3), 148(6.5), 91(57.3), 64(6.3)

Table 4 (continued)

	R	*m/z* (R.A. %)
11h	Bzl	383(5.7), 292(1.4), 224(2.7), 220(2.8), 205(3.3), 192(2.2), 191(2.2), 180(14.7), 179(100), 178(3.4), 177(2.7), 91(65.0), 65(5.9)
8i	Ph	369(100), 296(14.8), 295(11.5), 294(14.5), 236(5.8), 221(12.9), 220(9.6), 204(5.5), 192(7.2), 191(5.4), 179(9.5), 178(9.5), 177(8.5), 164(3.2), 152(4.3), 151(7.6), 150(3.3), 149(9.0), 104(10.8), 77(8.1), 51(5.0), 44(10.1)
11i	Ph	369(100), 368(6.3), 295(5.9), 294(8.2), 251(6.7), 250(34.9), 248(6.2), 224(12.3), 223(4.6), 220(2.6), 206(8.2), 205(24.2), 204(56.2), 192(10.2), 191(3.1), 179(6.0), 178(8.6), 177(6.3), 170(9.6), 154(5.0), 151(6.6), 148(4.2), 104(6.6), 77(8.4), 51(4.0)

Table 5
Accurate Masses for Selected Ions of Compounds **8** and **11**

Compound	Ion composition	Measured	Calculated	Δ/ppm
8b	$C_{19}H_{17}N_3OS^{+\bullet}$	335.1090	335.1092	0.8
	$C_{15}H_8N_2S^+$	248.0408	248.0408	−0.1
	$C_{15}H_8N_3O^+$	246.0663	246.0667	1.8
	$C_{14}H_{10}N_3^+$ (1 part)	220.0878	220.0875	−1.6
	$C_{14}H_8N_2O^+$ (1 part)	220.0648	220.0637	−5.0
	$C_{14}H_9N_3^{+\bullet}$	219.0796	219.0796	0.0
	$C_{14}H_8N_2^{+\bullet}$	204.0693	204.0687	−2.6
	$C_{12}H_7^+$	151.0548	151.0548	−0.4
8c	$C_{19}H_{17}N_3OS^{+\bullet}$	335.1106	335.1092	−4.0
	$C_{14}H_8N_2O^+$	220.0865	220.0874	0.7
	$C_{16}H_{11}N_3OS^{+\bullet}$	293.0632	293.0623	−3.0
	$C_{14}H_8N_2S^{+\bullet}$	236.0407	236.0408	0.3
	$C_{14}H_8OS^+$ (1 part)	224.0285	224.0296	4.8
	$C_{13}H_8N_2S^+$ (1 part)	224.0414	224.0408	−2.4
	$C_{14}H_8N_2^{+\bullet}$ (1 part)	204.0677	204.0687	4.9
	$C_{13}H_8N_2S^+$ (4 parts)	204.0812	204.0813	0.8
	$C_{13}H_8N_2^+$ (1 part)	192.0690	192.0687	−1.7
	$C_{14}H_{10}N^+$ (1 part)	192.0814	192.0813	−0.6
	$C_{13}H_7N_2^+$	191.0613	191.0609	−2.1
8d	$C_{16}H_{11}N^+$	217.0892	217.0891	−0.4
8h	$C_{21}H_{15}N_3^{+\bullet}$	309.1263	309.1266	0.8
	$C_8H_6NS^+$	148.0220	148.0221	0.6
8g	$C_{20}H_{19}N_3^{+\bullet}$	301.1573	301.1579	2.1
11a	$C_{20}H_{19}N_3OS^{+\bullet}$	349.1259	349.1249	−3.0
	$C_{14}H_9N_2O^+$	221.0719	221.0715	−2.0
	$C_{14}H_{10}N_3^+$ (1 part)	220.0874	220.0875	0.3
	$C_{14}H_8N_2O^+$ (2 parts)	220.0640	220.0637	−1.4
	$C_{13}H_7N_2^+$	191.0609	191.0609	0.1
	$C_{13}H_8N^+$	178.0657	178.0657	0.1
11b	$C_{19}H_{17}N_3OS^{+\bullet}$	335.1093	335.1092	−0.2
	$C_{13}H_8N_2S^+$	224.0407	224.0408	0.5
11c	$C_{19}H_{17}N_3OS^{+\bullet}$	335.1104	335.1092	−3.5
	$C_{17}H_{12}N_3OS^+$	306.0718	306.0701	−5.5
	$C_{13}H_8N_2S^+$	224.0411	224.0408	−1.3
	$C_{14}H_{10}N_3^+$ (2 parts)	220.0860	220.0875	6.7
	$C_{14}H_8N_2O^+$ (3 parts)	220.0638	220.0637	−0.8
	$C_{13}H_8N_2^{+\bullet}$ (3 parts)	192.0686	192.0687	0.7
	$C_{14}H_{10}N^+$ (1 part)	192.0814	192.0813	−0.4
	$C_{13}H_9N^{+\bullet}$	179.0741	179.0735	−3.2
	$C_{12}H_6N^+$	164.0500	164.0500	0.0
11d	$C_{19}H_{15}N_3OS^{+\bullet}$	333.0951	333.0936	−4.4
	$C_{17}H_{13}N_3S^{+\bullet}$	291.0834	291.0830	−0.6
11e	$C_{20}H_{19}N_3OS^{+\bullet}$	349.1251	349.1249	−0.8
	$C_{18}H_{14}N_3OS^+$	320.0858	320.0858	0.0
	$C_{16}H_{11}N_3OS^{+\bullet}$	293.0623	293.0623	0.1
11f	$C_{20}H_{19}N_3OS^{+\bullet}$	349.1255	349.1249	−1.9
	$C_{17}H_{13}N_3OS^{+\bullet}$ (3 parts)	307.0778	307.0779	0.3
	$C_{18}H_{17}N_3S^{+\bullet}$ (1 part)	307.1152	307.1143	−3.0
	$C_{17}H_{12}N_3OS^{+\bullet}$	306.0709	307.0701	−2.6
	$C_{15}H_{10}N_2OS^{+\bullet}$	266.0519	266.0514	−2.0
	$C_{14}H_{11}N^+$	193.0881	193.0891	5.6

Table 5 (continued)

Compound	Ion composition	Measured	Calculated	Δ/ppm
11g	$C_{22}H_{21}N_3OS^{+\bullet}$	375.1418	375.1405	−3.3
	$C_{20}H_{19}N_3S^{+\bullet}$	333.1301	333.1300	−0.5
	$C_{14}H_9N_3^{+\bullet}$	219.0796	219.0796	0.1
	$C_4H_7^+$	55.0548	55.0548	−0.2
11h	$C_{23}H_{17}N_3OS^{+\bullet}$	383.1090	383.1092	0.6
11i	$C_{22}H_{15}N_3OS^{+\bullet}$	369.0948	369.0936	−3.3
	$C_{20}H_{13}N_3^{+\bullet}$	295.1093	295.1078	−5.0
	$C_5H_{10}N_2S^+$	250.0559	250.0565	2.2
	$C_{14}H_8N_2^{+\bullet}$	204.0690	204.0687	−1.0
	$C_{13}H_8N^+$	178.0656	178.0657	0.5
	$C_7H_6N^+$	104.0500	104.0500	−0.1

Table 6
CHN Analyses of Selected Intermediate Isothiourea Hydrobromides and the Final Thiazolidinone Products

No.	Formula	Calculated (%)			Found (%)		
		C	H	N	C	H	N
6b	$C_{20}H_{22}N_3O_2SBr$	53.57	4.95	9.37	53.48	4.94	9.14
6c	$C_{20}H_{22}N_3O_2SBr$	53.57	4.95	9.37	53.83	4.91	9.25
6d	$C_{20}H_{20}N_3O_2SBr$	53.82	4.52	9.41	53.05	3.81	8.92
9d	$C_{19}H_{17}N_3OSBr_2$	46.08	3.46	8.48	46.91	3.99	8.15
8b	$C_{19}H_{17}N_3OS$	68.04	5.11	12.53	67.38	5.07	12.45
8c	$C_{19}H_{17}N_3OS$	68.03	5.11	12.53	67.50	4.96	11.91
8d	$C_{19}H_{15}N_3OS$	68.45	4.53	12.60	68.32	4.47	12.62
8e	$C_{20}H_{19}N_3OS$	68.74	5.48	12.02	68.50	5.22	11.93
8f	$C_{20}H_{19}N_3OS$	68.74	5.48	12.02	68.22	5.52	11.98
8g	$C_{22}H_{21}N_3OS$	70.37	5.64	11.19	70.03	5.45	10.99
8h	$C_{23}H_{17}N_3OS$	72.04	4.47	10.96	71.87	4.38	10.72
8i	$C_{22}H_{15}N_3OS$	71.52	4.09	11.37	71.07	3.87	10.79
11a	$C_{20}H_{19}N_3OS$	68.74	5.48	12.02	68.48	5.30	11.90
11b	$C_{19}H_{17}N_3OS$	68.04	5.11	12.53	68.10	5.13	12.52
11c	$C_{19}H_{17}N_3OS$	68.04	5.11	12.53	67.98	5.11	12.49
11d	$C_{19}H_{15}N_3OS$	68.45	4.53	12.60	68.58	4.55	12.86
11e	$C_{20}H_{19}N_3OS$	68.74	5.48	12.02	69.00	5.39	11.97
11f	$C_{20}H_{19}N_3OS$	68.74	5.48	12.02	68.46	5.36	11.61
11g	$C_{22}H_{21}N_3OS$	70.37	5.64	11.19	70.47	5.70	11.13
11h	$C_{23}H_{17}N_3OS$	72.04	4.47	10.96	71.90	4.38	10.99
11i	$C_{22}H_{15}N_3OS$	71.52	4.09	11.37	71.38	3.91	11.39

8 were isolated could be attributed to faster cyclization to **11** where basic acridine instead of anthracene might have played some role in binding of HBr.

Structure Determination.

The structures of the reaction products were confirmed by spectral methods. The ^1H and selected ^{13}C NMR chemical shifts made it possible to recognize both regioisomeric products. Whereas the SCH_2 protons in the ^1H NMR spectrum of 2-(acridin-9'-yl)imino-3-isopropyl-1,3-thiazolidin-4-one (**8b**) resonate at 3.78 ppm and the CHN proton at 5.12 ppm, in the case of 2-isopropylimino-3-(acridin-9'-yl)-1,3-thiazolidin-4-one **(11b**) the SCH_2 group appears as a singlet at 4.25 ppm and the CHN proton as a septet at 3.47 ppm. Moreover, in the ^{13}C NMR spectrum of **8b** the chemical shifts of C-9' and C=N carbon atoms are 150.7 ppm and 156.7 ppm, respectively whereas in that of **11b** C-9' and C=N resonate at 138.2 and 148.1 ppm, respectively (*cf*. Figure 1).

Mass Spectrometry.

Within each series (**8** or **11**), the low-resolution mass spectra of the alkyl-substituted compounds (**a**–**e**) were all similar to one another in terms of the fragmentation pathways followed, presumably giving rise to identical or corresponding ion structures (see Table 4 for a listing of the main or otherwise interesting ions for **8b**–**i** and **11a**–**i**). The fragmentation pathways which resembled closely those of the corresponding anthracenyl derivatives [19] were elucidated using standard methodology consisting of metastable ion analyses (*B*/*E* and B^2/E linked scans) and determination of the elemental compositions of the ions by accurate mass measurements. The elemental compositions of selected ions of compounds **8** and **11** are listed in Table

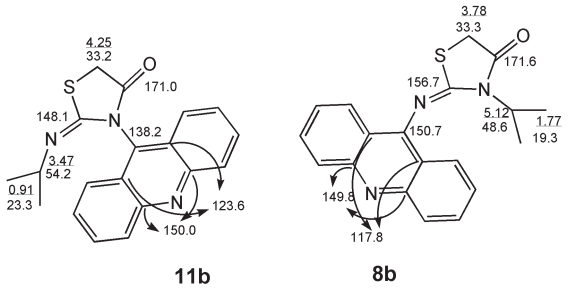


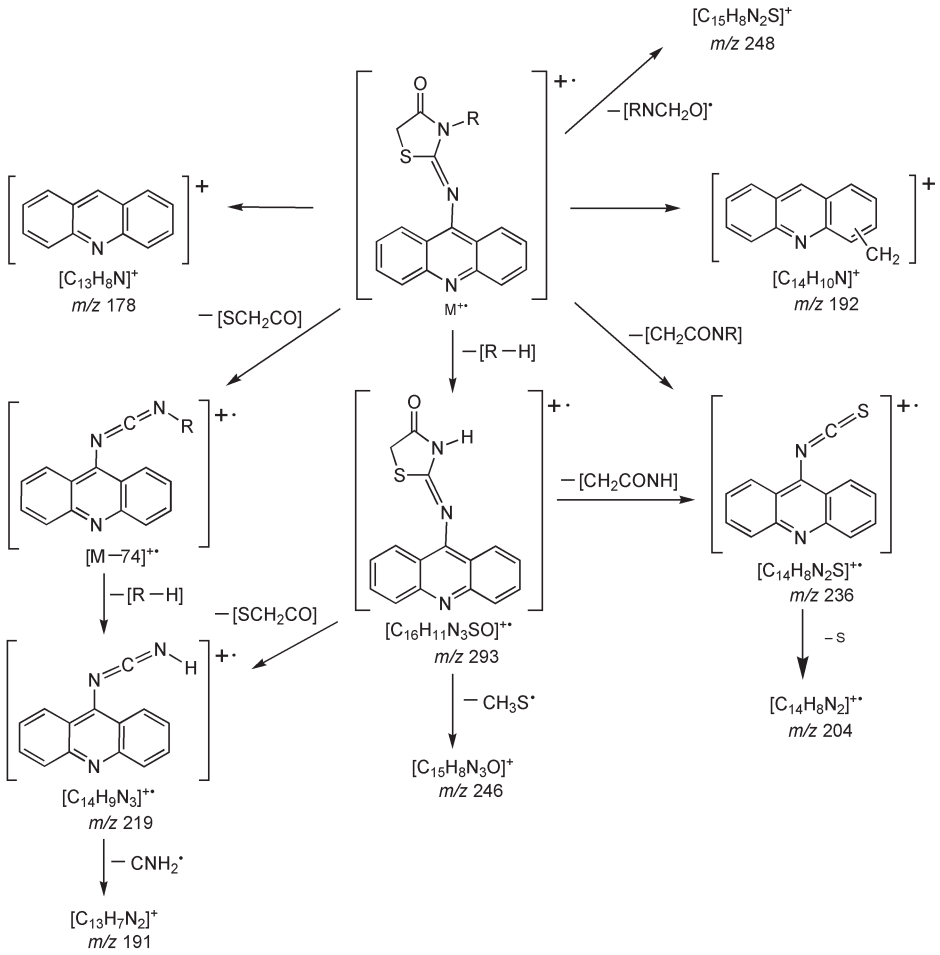
Figure 1. Comparison of selected ^{1}H and ^{13}C NMR chemical shifts of **8b** and **11b**.

5 but they were determined also for all other crucial ions. With respect to the relative abundances (RAs) of the ions from the alkyl-substituted compounds, **a**–**e**, these were considerably uniform across each series with the exception of the *t*-butyl-substituted compound **11a**, which differed notably from its respective series counterparts in this context. No doubt, this is due to the steric bulk of the *t*-butyl group and as a consequence, the RAs of many of the ions of **11a** were perturbed in comparison to the corresponding ion intensities of **8b**–**d** or **11a**–**d**, respectively, although the fragmentation pathways appeared to remain essentially the same in each case.

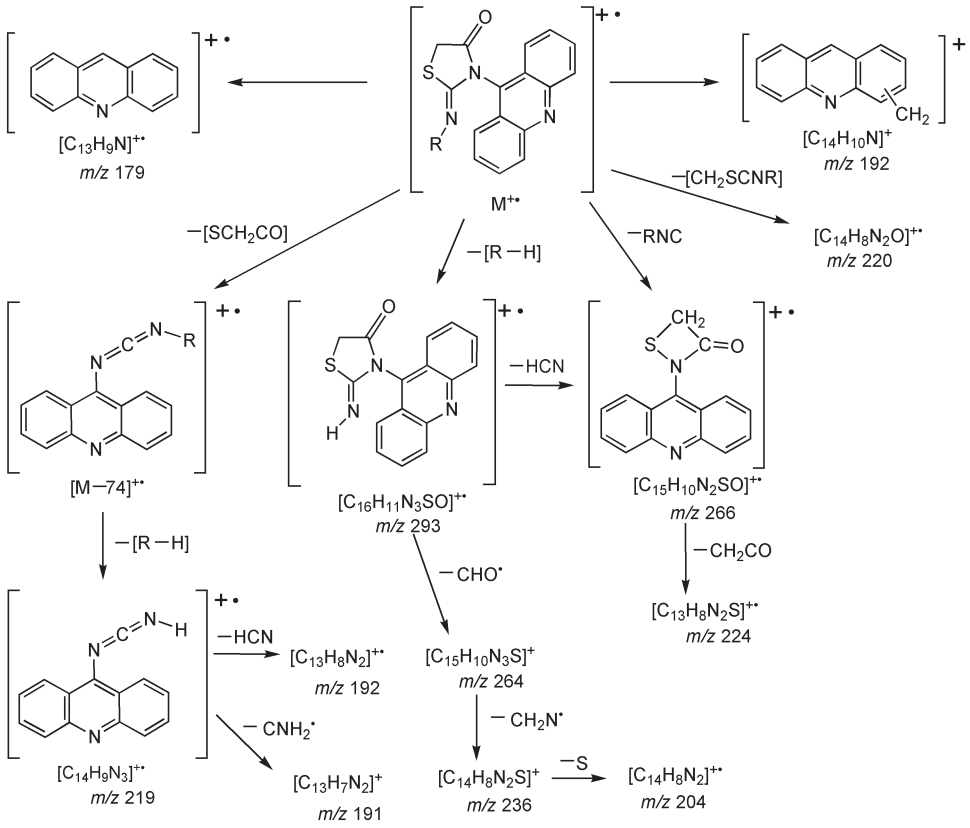
The spectra of compounds **8i** and **11i** (R = phenyl) displayed some unique ion structures as a consequence of the presence of the phenyl group giving rise to additional fragmentation pathways, but otherwise the fragmentation pathways and many of the RAs of the corresponding ions were similar to those of their alkyl-substituted counterparts within each series. Of the cyclohexyl-substituted compounds **8g** and **11g**, only **8g** displayed unique and characteristic differences whilst **11g** behaved similarly to the alkyl-substituted derivatives **11a**–**e**. These substituent-specific differences as well as the differences between the two series are now discussed in more detail.

The notable and more interesting of the fragmentation pathways for **8** and **11** are given in Schemes 3 and 4, respectively, although it should be evident that the ion structures

Scheme 3



Scheme 4



11

shown in are only tentative at best. For the analogous anthracenyl derivatives [19] some regioisomerization occurred in mass spectrometric conditions (gas phase) to both directions. Although this appears to be less so in the case of the acridinyl derivatives, however, there are a few specific ions which do indicate that regioisomerization is also possible from **8**→**11** and from **11**→**8**. Namely, most of them show the ions *m/z* 248, $C_{15}H_8N_2S^+$ and *m/z* 220, $C_{14}H_8N_2O^{+\bullet}$ (Tables 4 and 5) of which the latter can easily be formed directly from the molecular ions of **11** (as shown by metastable studies) through loss of the neutral fragment, $RNCSCH_2$ (Scheme 4). Similarly, the fragment *m/z* 248 can be formed directly from the molecular ions of **8** (as shown again by metastable studies) through loss of $RNCH_2O^{\bullet}$ radical. Since both of these ions are formed from the molecular ions of **8** and **11**, this indicates that most probably some regioisomerization, as postulated above, occurs in the gas phase under mass spectrometric conditions.

Only the allyl derivatives **8d** and **11d** show the ion $C_{16}H_{11}N^+$ at *m/z* 217 which is formed much easier from the former (% of total ion current 5.7) than from the latter (% of TIC 1.4). This can also be an indication that its formation requires regioisomerization from **11**→**8**.

EI Fragmentation of the 3-Substituted 2-(acridin-9'-yl)imino-1,3-thiazolidin-4-ones (**8**).

The base peak in the mass spectra of the 3-substituted 2-acridinylimino-1,3-thiazolidin-4-ones (**8**) was always the molecular ion except for compound **8g** where the base peak was *m/z* 219, $C_{14}H_9N_2^{+\bullet}$ (≡ $[M–C_6H_{10}–SCH_2CO]^{+\bullet}$) resulting from the facile loss of [cyclohexyl–H], no doubt due to the steric effects of the cyclohexyl group, which is thus reflected in the abundance of this ion. The alkyl-substituted compounds **8b–e** also generally showed a significant $[M–(R–H)]^{+\bullet}$ ion at *m/z* 293, from which fragmentation continued to produce ions of *m/z* 219, $C_{14}H_9N_3^+$, by loss of SCH_2CO (this process can also occur in the reverse order, see Scheme 3) and of *m/z* 246 by loss of $CH_3S^{\bullet}$. From the ion of *m/z* 219 (3–100 %), which was present in all spectra of 8, loss of CNH_2 can result in an ion of *m/z* 191, or the loss of just HCN yield an ion at *m/z* 192, $C_{13}H_8N_2^+$. The compounds of series 8 also generally displayed the ion of *m/z* 192 with the composition $C_{14}H_{10}N^+$ which results from a transfer of a methyl to the acridinyl moiety with the consequent loss of a hydrogen (or, equivalently, by just the transfer of methylene). Also of note, the ions corresponding to the acridinyl moieties (*m/z* 177–

179) were all rather weak for **8b–g**, the acridinyl ion *m/z* 178, $C_{13}H_8N^+$ (3.4–9.5 %) being the most prominent (Scheme 3) opposite to the situation with compounds **11** except **11a** (*t*-Bu) where *m/z* 179 (the molecular ion of acridine) formed always the base peak of the spectra. Also the ions *m/z* 177 and 179 for **8** are formed mainly directly from the molecular ion concomitant with transfer of hydrogen atoms, but their RAs are small (1.8–9.5%) in this series.

All of the compounds in series **8** display an ion of *m/z* 236, $C_{14}H_8N_2S^{+\bullet}$ (RA 1.4–6.0%). This ion results from cleavage of the heterocyclic ring and consequent loss of the CH_2CONR group from the molecular ion, but it can also arise from the ion *m/z* 293 (*cf.* **11** where the situation is quite different, *vide infra*).

EI Fragmentation of the 2-Substituted 3-acridin-9'-yl-2-imino-1,3-thiazolidin-4-ones (**11**).

In comparison with **8**, the molecular ions of **11** were clearly less abundant (RAs for **11a–i**, 3–35%), except for compound **11i** (R = phenyl) for which the molecular ion was also the base peak. This can be rationalized on the basis that the acridinyl moiety cannot abstract hydrogen from phenyl as easily as it can from the alkyl groups in **11a–h** to form the ion of *m/z* = 179, $C_{13}H_9N^{+\bullet}$ (the molecular ion of acridine), the base peak in these latter compounds. In the case of **11a** (R = *t*-butyl), the loss of [*t*-butyl–H] occurs faster (RA of $[M–(t\text{-butyl–H})]^{+\bullet}$ = 100%) than the abstraction of one of its hydrogens by the acridinyl moiety resulting in a low RA (4%) of the *m/z* 179 ion. Interestingly, ions corresponding to the acridinyl moiety and $[Acr\text{-}H]^{+\bullet}$ (*m/z* 178 and 177, respectively) were observed for **11a–d**,**g**, albeit at low RAs (4–7%). Again, the compounds of series **11** also generally displayed a peak of *m/z* 192 with the composition $C_{14}H_{10}N^+$ resulting from the net transfer of methylene to the acridinyl moiety, in addition to the same nominal mass ion $C_{13}H_8N_2^{+\bullet}$. Both series **8** and **11** showed some amount of the ion *m/z* 191 $C_{13}H_7N_2^+$ obtained from the ion *m/z* 219 *via* loss of CH_2N. All compounds **11a–h** showed a significant peak at *m/z* = 224, $C_{13}H_8N_2S^+$, (3–28%) which must result from the very weak ion $[M–RNC]^+$, *m/z* 266, via loss of CH_2CO shown by metastable ions and accurate mass measurements.

The *m/z* 236, $C_{14}H_8N_2S^{+\bullet}$, results in a concerted manner from a very low-abundance product ion of *m/z* 264, $C_{15}H_{10}N_3S^+$, which is itself formed simply by the loss of $CHO^\bullet$ from the ion of *m/z* 293 (Scheme 4). In the case of **11i** (R = phenyl) the enhanced conjugation increased the stability of the molecular ion so much that it was the base peak of the spectrum and the abstraction of hydrogen from phenyl was not favourable, *i.e*. the formation of acridine ion, *m/z* 179 (6%), occurred but not as the base peak like in the case of all of compounds **11** except **11a** (R = *t*-Bu) as stated above. Accordingly the ions *m/z* 178 and 177 were somewhat more abundant (8.6 and 6.3%) for **11i**.

Conclusions.

The reaction paths that are followed and the ensuing kinetics for the formation of the 1,3-thiazolidin-4-ones (**8** or **11**) from *N*-(acridin-9'-yl)-*N*'-alkylthioureas using methyl bromoacetate or bromoacetyl bromide appear to be determined by the position of the tautomeric equilibria and the stereochemistries of the intermediates, aside from the state of protonation. The former is mainly determined by conjugation preferences, but is perhaps assisted by favorable NH–π-orbital interactions [13]. The latter consideration is essentially determined by steric hindrance but is perhaps also assisted by favorable NH–π-orbital interactions. In the case of phenyl *vs* acridinyl (**i**), the factors favoring acridinyl over alkyl remained unexpectedly invariant in comparison to all alkyl (aroyl) *vs* acridinyl cases (**a**–**f**) where the course of the reactions was amenable to rationalization.

Once obtained and their assigned structures validated, the regioisomeric 3-alkyl(aryl)-2-(acridin-9'-yl)imino-1,3-thiazolidin-4-ones (**8**) and 2-alkyl(aryl)imino-3-(acridin-9'-yl)-1,3-thiazolidin-4-ones (**11**) can readily be differentiated, though not necessarily unequivocally, according to their low-resolution mass spectra. The main differences are generally found in the RAs of the molecular ions (generally the base peak in **8** whilst only weak in **11**) and the ion of *m/z* 179 (generally the base peak in **11** whilst only weak in **8**). This latter ion was determined to be $C_{13}H_9N^{+\bullet}$, thus corresponding to the molecular ion of acridine. The compounds of series **11** also generally displayed an ion of *m/z* 224, $C_{13}H_8N_2S^{+\bullet}$, which was very weak or not observed for the compounds of series **8** and is therefore very indicative for series **11**. Other interesting fragmentations unique to each series as well as some substituent-specific fragmentations were also observed.

EXPERIMENTAL

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. IR spectra (cm^{-1}) were measured on a Specord 75 IR spectrophotometer (Zeiss) in potassium bromide discs (thioureas **5c–e** and isothioureas **6a–i** and **9a–i)** and in chloroform (thiazolidines **7a**, **8b–i**, **11a–i**). The reaction course was monitored by tlc Silufol plates (Kavalier®, Czech Republic). Preparative column (flash) chromatography was performed on the Kieselgel Merck Typ 9385, 230-400 mesh. Commercial solvents used in the reactions were dried using standard methods. Reagents bromoacetyl bromide, methyl bromoacetate and triethylamine were purchased from Fluka and primary amines from Sigma – Aldrich. Elemental analyses (Table 6) of the final products (**8** and **11**) and a few intermediate products were performed on a Perkin-Elmer analyser CHN 2400.

NMR spectra.

^{1}H NMR spectra of compounds **7a**, **8b–i** and **11a–i** were recorded on a JEOL Alpha 500 (500.16 MHz for ^{1}H) or a Bruker

AVANCE 500 (500.13 MHz for ^{1}H) NMR spectrometer equipped with a 5-mm inverse broad-band z-gradient probe, in $CDCl_3$ at 25 °C. For **7a**, **8e**, **8i** and **11i**, $^{13}C\{^1H\}$, dqf-COSY, $^1H\{^{13}C\}$-HSQC and $^1H\{^{13}C\}$-HMBC experiments were also performed. All spectra were acquired using standard, vendor-supplied pulse programs. The heteronuclear 2D experiments were optimized on 145 Hz one-bond and 8 Hz long-range $J_{H,C}$ couplings. The ^{1}H NMR spectra of products **7a**, **8b**–**i**, **11a**–**i** were analyzed using PERCH NMR software [23]. NMR spectra for thioureas **5a**–**i** and isothiourea hydrobromides **6a**–**i**, **9a**–**i** were obtained on a Tesla BS 587A (80 MHz for ^{1}H) at room temperature in a mixture of 0.4 mL deuteriochloroform and 0.2 mL hexadeuteriodimethyl sulfoxide. ^{13}C NMR spectra of compounds **8b, d** and **11a, b, e** were obtained on 300 MHz Bruker Avance spectrometer. In all cases tetramethylsilane (TMS) was used as internal standard (δ_{TMS} = 0.00 ppm).

Mass Spectrometry.

Mass spectra were measured on a VG ZabSpec-oa-TOF mass spectrometer (Micromass, Manchester, UK) equipped with Opus data handling software. For low-resolution EI spectra (70 eV) and metastable ion analyses (*B*/*E* and B^2/E linked scans in the first field-free region), the resolution was approximately 3,000 (at 10% peak height), the acceleration voltage was 8 kV, and the ionization current was 200 μA. For accurate mass measurements, the resolution was in the range of 9,000–12,000 (measured at 10% peak height) and a peak-matching technique was applied using perfluorokerosene (PFK) as a source of reference signals. For all experiments, samples were introduced *via* a solids inlet system; the temperature of the ion source was 433 K.

General Procedure for the Preparation of 3-(Acridin-9-yl)-1-alkyl(aryl)thioureas (**5a**–**i**).

The synthesis of the intermediate 3-(acridin-9-yl)-1-alkyl(aryl)thioureas **5a, b, f**–**i** were described in our previous paper [24]. The same method utilizing the reaction of 9-isothiocyanatoacridine with appropriate amines in chloroform was used also for the synthesis of thioureas **5c**, **d**,and **e** in this work.

3-(Acridin-9-yl)-1-propylthiourea (**5c**).

This compound was obtained in 92% yield. Mp 177–179 ˚C; ir (potassium bromide): 3415 (NH), 1623 (N=C), 1580 (C=C), 1070 (NHCS); ^{1}H NMR (deuteriochloroform – DMSO-d_6 2:1): δ 11.35 (s, 1H, NH), 8.75-6.09 (m, 8H, acridinyl protons), 3.68 (t, 1H, NH, J = 6.9 Hz), 3.35 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 0.93 (t, 3H, CH_3, J = 7.0 Hz).

3-(Acridin-9-yl)-1-allylthiourea (**5d**).

This compound was obtained in 98% yield. Mp 185–186 ˚C; ir (potassium bromide): 3430 (NH), 1620 (N=C), 1545 (C=C), 1108 (NHCS); ^{1}H NMR (deuteriochloroform – DMSO-d_6 2:1): δ 11.23 (s, 1H, NH), 9.10-6.80 (m, 8H, acridinyl protons), 5.88 (m, 1H, –CH=, J = 16.4, 10.4, and 6.0 Hz), 5.32 (dd, 1H, H_{trans} of $=CH_2$, J = 16.5 and 2.4 Hz), 5.02 (dd, 1H, H_{cis} of $=CH_2$, J = 10.4 and 2.4 Hz), 4.33 (m, 1H, NH), 3.81 (t, 2H, J = 6.0 Hz, CH_2).

3-(Acridin-9-yl)-1-(*s*-butyl)thiourea (**5e**).

This compound was obtained in 90% yield. Mp 191–193 ˚C; ir (potassium bromide): 3440 (NH), 1625 (N=C), 1558 (C=C), 1066 (NHCS); ^{1}H NMR (deuteriochloroform – DMSO-d_6 2:1): δ 10.95 (br s, 1H, NH), 8.70-6.10 (m, 8H, acridinyl protons), 3.35 (m, 1H, CH), 1.75 (m, 2H, CH_2), 1.16 (d, 3H, CH_3, J = 6.0 Hz), 0.93 (t, 3H, CH_3, J = 7.0 Hz). The other NH was not detected (very broad signal).

General Procedure for the Preparation of the Intermediate 3-(Acridin-9-yl)-1-alkyl(aryl)-2-methoxycarbonyl-methyl Isothiourea Hydrobromides (**6a**–**i**).

Methyl bromoacetate (0.15 g; 1 mmol) was added to a suspension of thiourea (1 mmol) in dichloromethane (15 mL) at once. Well-stirred reaction mixture turned homogeneous at room temperature within an hour. On standing a part of product precipitated. The reaction course was followed by tlc (eluent: benzene/acetone 5:2). Ether was added to the reaction mixture and the precipitated product was collected by filtration, washed with ether and dried. Physical and spectral data of compounds **6** are shown in Tables 1 and 6.

General Procedure for the Preparation of the Intermediate 3-(Acridin-9-yl)-1-alkyl(aryl)-2-bromoacetyl Isothiourea Hydrobromides (**9a**–**i**).

Bromoacetyl bromide (0.28 g; 1.4 mmol) was added to a well-stirred suspension of thiourea **5a**–**i** (1.4 mmol) in dry dichloromethane (25 mL) in two portions during 10 min. The reaction mixture remained heterogenous. The course of the reaction was followed by tlc (eluent: benzene/acetone 5:2). The precipitate was collected by filtration, washed with ether and dried. Physical and spectral data of compounds **9** are shown in Tables 1 and 6.

General Procedure for the Preparation of 3-Alkyl(aryl)-2-(acridin-9'-yl)imino-1,3-thiazolidin-4-ones (**8b**–**i**).

Triethylamine (0.04 g; 0.4 mmol) was added to *S*-methoxycarbonylmethyl isothiourea hydrobromide **6b**–**i** (0.4 mmol) suspended in dry benzene (12 mL). The reaction mixture became clear after stirring at room temperature for 2 hours. Within the next 2 h the isothiourea completely disappeared, the precipitated triethyl ammonium salt was filtered off and the solution flash-chromatographed over silica gel (10 g, eluent: benzene/acetone 5:2). The solvent was evaporated *in vacuo* and the crude product purified by crystallization from a 2:3 mixture of dichloromethane/*n*-heptane. Physical and spectral data of prepared compounds are shown in Tables 2–6.

2-*tert*-Butylimino-5-(methoxycarbonyl)spiro[9',10'-dihydroacridine-9',4-(1,3-thiazolidine)] (**7a**).

This compound was prepared from **6a** according to the procedure given for the synthesis of **8b**–**i** from **6b**–**i**. Its physical and spectral data are shown in Tables 2 and 3.

General Procedure for the Preparation of 3-(Acridin-9'-yl)-2-alkyl(aryl)imino-1,3-thiazolidin-4-ones (**11a**–**i**).

Two equivalents of triethylamine (0.125 g; 1.24 mmol) were added to the stirred suspension of *S*-bromoacetylisothiourea hydrobromide **9a**–**i** (0.62 mmol) in dry benzene (16 mL). After short stirring at room temperature, the reaction mixture became clear with soft-grained triethylammonium bromide on the bottom of the flask. After the reaction was finished (tlc, eluent: benzene/acetone 5:2), charcoal was added and the ammonium salt was filtered off. The solvent was evaporated off and the product crystallized from a 2:3 mixture of dichloromethane/*n*-hexane. Physical and spectral data of the prepared compounds are shown in Tables 2–6.

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REFERENCES AND NOTES

[1] M. Demeunynck, F. Charmantray and A. Martelli, *Curr. Pharm. Design*, **7**, 1703 (2001).

[2] L. Gude, M. J. Fernandes, K. B. Grant and A. Lorente, *Bioorg. Med. Chem. Lett.*, **12**, 3135 (2002).

[3] K. Michael and Y. Tor, *Chem. Eur. J.*, **4**, 2091 (1998).

[4] A. Kuzuya, K. Machida and M. Komiyama, *Tetrahedron Lett.*, **43**, 8249 (2002).

[5] T. Petzinski, B. Marciniak and G. L. Hug, *J. Photochem. Photobiol. Chem.*, **150**, 2 (2002).

[6] J. Mezsko, A. Sikorski, O. M. Huta, A. Konitz and J. Blazeowski, *Acta Crystallogr. Sect. C*, **58**, 1669 (2002).

[7] P. Kristian, J. Bernát, J. Imrich, I. Danihel, G. Suchár, S. Hočová, T. Bušová, J. Guspanová and A. Linden, *Molecules*, **1**, 181 (1996).

[8] P. Kristian, J. Bernát, J. Imrich, E. Sedlák, J. Alföldi and M. Čornanič, *Heterocycles*, **55**, 279 (2001).

[9] J. Bernát, E. Balentová, P. Kristian, J. Imrich, E. Sedlák, I. Danihel, S. Böhm, N. Prónayová, K. Pihlaja and K. D. Klika, *Collect. Czech. Chem. Commun.*, **69**, 833 (2004).

[10] Z. El-Gendy, R. M. Abdel-Rahman, M. M. Fawzy and M. B. Mahmoud, *J. Indian Chem. Soc.*, **67**, 927 (1990).

[11] H. L. Liu and T. Anthonsen, *Molecules*, **5**, 1055 (2000).

[12] H. Y. Hassan, N. A. El-Koussi and Z. S. Farghaly, *Chem. Pharm. Bull*., **46**, 863 (1998).

[13] H. Y. Hassan, A. A. Ismaiel and H. A. H. El-Sherief, *Eur. J. Med. Chem*., **26**, 743 (1991).

[14] G. R. Newkome and A. Nayak, *Adv. Heterocycl. Chem*., **25**, 83 (1979).

[15] S. P. Singh, S. S. Parmar, K. Raman and V. I. Stenberg, *Chem. Rev*., **81**, 175 (1981).

[16] T. E. Achary, P. N. Dhal and A. Nayak, *J. Indian Chem. Soc.*, **52**, 1204 (1975).

[17] P. Kristian, I. Chomča, J. Bernát and J. Imrich, *Chem. Papers*, **53**, 49 (1999).

[18] K. D. Klika, L. Janovec, J. Imrich, G. Suchár, P. Kristian, R. Sillanpää and K. Pihlaja, *Eur. J. Org. Chem*., 1248 (2002).

[19] K. D. Klika, P. Valtamo, L. Janovec, G. Suchár, P. Kristian, J. Imrich, H. Kivelä, J. Alföldi and K. Pihlaja, *Rapid Commun. Mass Spectrom.*, **18**, 87 (2004).

[20] R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 2823, (1972).

[21] J. Kaválek, J. Jirman and V. Štěrba,, *Collect. Czech. Chem. Commun.*, **50**, 766 (1985).

[22] J. Kaválek, J. Novák and V. Štěrba, *Collect. Czech. Chem. Commun.*, **47**, 2702 (1982).

[23] See for example: R. Laatikainen, M. Niemitz, U. Weber, J. Sundelin, T. Hassinen and J. Vepsäläinen, *J. Magn. Reson., Ser. A*, **120**, 1 (1996). (http://www.perchsolutions.com).

[24] D. Mazagová, P. Kristian, G. Suchár, J. Imrich and M. Antalík, *Collect. Czech. Chem. Commun.*, **59**, 2632 (1994).