# Stereochemistry, Tautomerism, and Reactions of Acridinyl Thiosemicarbazides in the Synthesis of 1,3-Thiazolidines*

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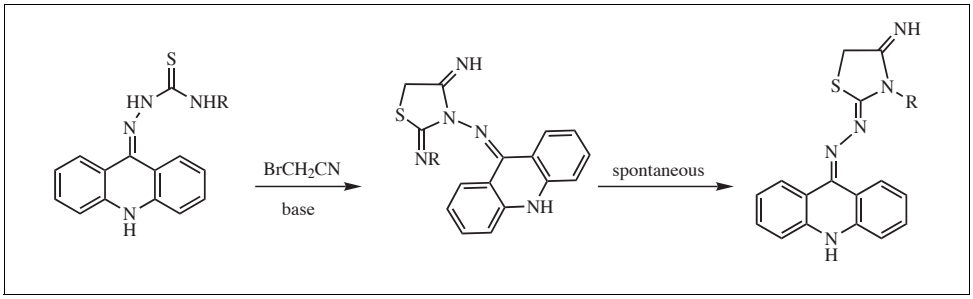
Received August 30, 2005




Acridin-9-yl hydrazine upon treatment with various isothiocyanates (RNCS, R = methyl, allyl, phenyl, *p*-methoxy phenyl, and *p*-nitro phenyl) yielded the corresponding thiosemicarbazides with acridine substituted on the carbazide-type side. The alkyl-substituted compounds were present in solution as equilibria consisting of the major H-10, H-12 tautomer (either *E* or *Z* or both about the $C_{13}$–$N_{14}$ bond) and the minor H-10, SH tautomer (either *E* or *Z* or both). The major species for the aromatic-substituted compounds was the H-10, H-12 *E* tautomer, with the evident minor species being the H-10, H-12 *Z* tautomer. The thiosemicarbazides were each quantitatively converted into the analogous semicarbazides upon treatment with mesitylnitrile oxide wherein all structures were present in solution as the H-10 tautomers with *Z* conformation about the $C_{13}$–$N_{14}$ bond. Methylation of the compounds with methyl iodide yielded S-methylated compounds wherein the *Z* configuration dominated in each case over the *E* configuration along the $N_{12}$–$C_{13}$ double bond. Treatment of the thiosemicarbazides with methyl bromoacetate resulted in the formation of 1',3'-thiazolidin-4'-ones wherein the *Z* configuration predominated in each case over the *E* configuration along the $N_{12}$–$C_{13}$ double bond. With bromoacetonitrile as the bifunctional electrophile, the initial 1',3'-thiazolidin-4'-imines that formed spontaneously underwent Dimroth-type rearrangement to the regiosiomeric 1',3'-thiazolidin-4'-imines.

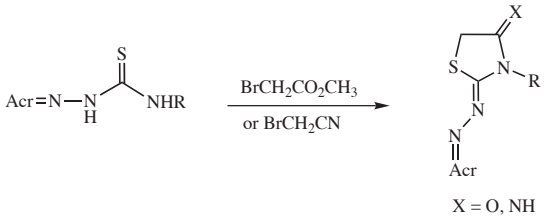
*J. Heterocyclic Chem.*, **43**, 645 (2006).

## Introduction.

In this work, as part of an examination of thiosemicarbazides containing the acridine moiety (an extension of our long-standing studies with acridine- [1–7] and anthracene-substituted [8,9] thioureas for the purposes of obtaining new and novel type structures concomitant with potential biological applications), we focused on acridines substituted at the β-carbazide-type nitrogen {Acr–NH–NH–C(=S)–NH–R, prepared from acridin-9-yl hydrazine and isothiocyanates} to complement our companion report [10] which focused on acridines substituted at the urea-type nitrogen {Acr–NH–C(=S)–NR–$NH_2$, prepared from acridin-9-yl isothiocyanate and methyl/phenyl hydrazine}. Surprisingly, only limited synthetic exploitation of 9-hydrazinylacridine [11–14] has been made. (See also the accompanying articles [10,15] for informative introductions and background information on this type of work; overviews of the syntheses of thiosemicarbazides have been described [16,17] and aliphatic thiosemicarbazides in particular have been systematically studied [18].) In contrast to the complementary work [10,19] where a slew of interesting structures were realized though the primary targets of thiazolidines were not forthcoming due to spiro formation *et alia*, this work progressed closer to plan and we were able to produce sets of 1,3-thiazolidin-4-ones and 4-imino-1,3-thiazolidines with relative ease. The usefulness of thiazolidines has been well reviewed [20–22] and described [8,9] and the reaction mechanism of acridine- [23] and anthracene-substituted [8,9] thioureas with methyl bromoacetate to yield 1,3-thiazolidin-4-ones rationalized.

The thiosemicarbazides prepared from 9-hydrazinylacridine were subsequently transformed to semicarbazides

with mesitylnitrile oxide to broaden the range of compounds examined as part of our long-term additional bioactivity and fluorescence studies and moreover, semicarbazides are more conveniently prepared from their thio analogues; methylated with methyl iodide; and reacted with the bifunctional electrophiles methyl bromoacetate and bromoacetonitrile resulting in thiazolidines:




One of the features of this work was that for the majority of the products, a coplanar 9,10-dihydroacridin-9-ylidenehydrazono structure was present with extended conjugation. This is due to the propensity of the N-10 acridine nitrogen to deprive N-11 of its proton, resulting in the formation of a 9,10-dihydroacridin-9-ylidene structure attached through a C=N double bond to the thiosemicarbazide moiety. Such extended coplanarity is of interest in light of the fact that the biological activity of acridines is often ascribed to their intercalation into the stacked base pairs of the DNA precisely due to their planarity [24–26].

Results and Discussion.

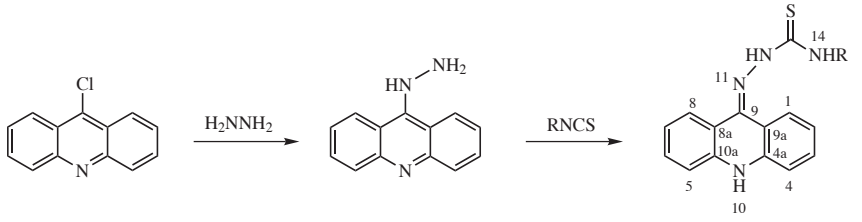
For an outline of the general structural protocol, see the preceding article [10]. To limit repetitious descriptions, structural determinations are not described in detail and structures are essentially only presented but based on thorough analysis with only pivotal points pertaining to unexpected or peculiar structures being described explicitly. The $^{1}H$, $^{13}C$, and $^{15}N$ chemical shifts of the compounds are compiled in Tables 1 and 2 whilst the homonuclear couplings extracted by spin simulation [27] are presented only for selected cases given the close similarity of the couplings in the acridine moiety (see also ref [10]) but are inclusive of examples where couplings were present in other segments.

Thiosemicarbazides **1a–e**.

Acridin-9-yl hydrazine [11], obtained from 9-chloroacridine [28] and hydrazine hydrate, upon treatment with isothiocyanates (RNCS: R = methyl, **a**; allyl, **b**; phenyl, **c**; *p*-methoxyphenyl, **d**; *p*-nitrophenyl, **e**) yielded the corresponding thiosemicarbazides **1a–e** (Scheme 1). Reaction proceeded only *via* the β nitrogen to provide the 1,4-disubstituted thiosemicarbazides **1a–e**; 2,4-disubstituted thiosemicarbazides resulting from attack by the α nitrogen were not observed despite the use of benzene, diethyl ether, and methanol as reaction media. The acridin-9-yl thiosemicarbazides **1a–e** can exist in a number of tautomeric and isomeric forms and, indeed, in solution thiosemicarbazides **1a–d** were present as more than one species resulting in the NMR spectra being quite complex. For each of the four compounds **1a–d**, two significant species in solution, major and minor, were discerned and for all eight of these structures the H-10 (9,10-dihydroacridin-9-ylidene) tautomer as indicated in Scheme 1 was deemed to be present. This was unequivocally proven by the non-equivalency of the side rings of the acridine moiety (as expected for such a structure though chemical exchange between respective signals of the acridine skeleton could be observed); the shielding of C-4a and C-10a to values less than 142 ppm [1,29,30] {for the H-11 (acridine) tautomer, values in the range 147–151 ppm would be expected [31,32]}; as well as NOE enhancements of the H-4 and H-5 protons upon irradiation of H-10 signal.

For the alkyl-substituted derivatives **1a** and **1b**, C-13 of the major species (89% and 91%, respectively) resonated

Scheme 1




9-chloroacridine

acridin-9-yl hydrazine

**1a**: R = methyl
**1b**: R = allyl
**1c**: R = phenyl
**1d**: R = *p*-methoxyphenyl
**1e**: R = *p*-nitrophenyl

The preparation of thiosemicarbazides **1a–e**. The numbering of the R substituents begins at the N-bound carbon with 1".

Table 1

$^{13}C$ and $^{15}N$ NMR Chemical Shifts[a] ($\delta$ in ppm) for Compounds **1–6** in DMSO-$d_6$ at 25 °C

| | C-1 | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C-9 | C-9a | N-10 | C-10a | N-11 | C-13/ C-2' | N-14/ N-3' | others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a**, major | 127.35 | 119.38 | 131.11 | 116.50 | 141.00 | 115.06 | 130.10 | 120.74 | 125.41 | 119.02 | 141.42 | 114.22 | – | 138.41 | – | 178.05 | – | 31.04 (C-1") |
| **1a**, minor | | | 130.40 | 116.70 | 140.30 | 115.20 | 129.70 | | | 118.70 | 143.00 | | – | 138.40 | – | 157.30 | – | – |
| **1b**, major | 127.55 | 119.58 | 131.35 | 116.70 | 141.14 | 115.27 | 130.35 | 120.95 | 125.54 | 119.08 | 142.08 | 114.35 | – | 138.58 | – | 177.56 | – | 46.10 (C-1"), 135.41 (C-2"), 115.53 (C-3") |
| **1b**, minor | | | | | | | | | | | | | – | – | – | – | – | – |
| **1c**, major | 130.43 | 121.06 | 133.90 | 116.59 | 140.39 | 117.95 | 132.84 | 123.53 | 122.06 | 112.87 | 138.77 | 112.03 | – | 138.17 | – | 176.82 | – | 140.88, (C-1"), 120.53 (C-2"/6"), 128.44 (C-3"/5"), 121.79 (C-4") |
| **1c**, minor | 127.73 | 119.68 | 131.52 | 116.80 | 141.13 | 115.34 | 130.58 | 121.06 | 125.84 | 118.83 | 143.26 | 114.40 | – | 138.57 | – | 175.61 | – | 139.48 (C-1"), 125.24 (C-2"/6"), 128.12 (C-3"/5"), 125.01 (C-4") |
| **1d**, major | 130.39 | 120.85 | 133.59 | 116.26 | 140.20 | 117.69 | 132.53 | 123.26 | 121.81 | 112.82 | 137.80 | 112.00 | – | 137.98 | – | 176.93 | – | 133.93 (C-1"), 122.37 (C-2"/6"), 113.44 (C-3"/5"), 154.46 (C-4"), 55.13 (OMe) |
| **1d**, minor | 127.49 | 119.48 | 131.29 | 116.61 | 141.00 | 115.11 | 130.33 | 120.85 | 125.71 | 118.76 | 142.65 | 114.22 | – | 138.59 | – | 175.97 | – | 133.93 (C-1"), 127.03 (C-2"/6"), 113.14 (C-3"/5"), 156.65 (C-4"), 55.15 (OMe) |
| **1e**[b] | 130.2[c] | 122.0[c] | 133.2[c] | 117.0[c] | 139.0[c] | 117.0[c] | 133.2[c] | 122.0[c] | 122.0[c] | 111.9[c] | 139.9[c] | 111.9[c] | – | 139.0[c] | – | 175.89 | – | 146.84 (C-1"), 118.13 (C-2"/6"), 124.28 (C-3"/5"), 140.64 (C-4") |
| **2a** | 127.67 | 119.26 | 130.77 | 116.16 | 141.32 | 114.94 | 129.56 | 120.75 | 125.25 | 120.13 | 138.52 | 114.64 | – | 138.42 | – | 158.13 | – | 26.41 (C-1") |
| **2b** | 127.62 | 119.17 | 130.68 | 116.07 | 141.22 | 114.87 | 129.48 | 120.67 | 125.08 | 120.02 | 138.54 | 114.54 | – | 138.45 | – | 157.29 | – | 41.57 (C-1"), 136.68 (C-2"), 114.49 (C-3") |
| **2c** | 127.84 | 119.44 | 131.05 | 116.32 | 141.35 | 115.10 | 129.88 | 121.00 | 125.34 | 119.82 | 140.12 | 114.51 | – | 138.57 | – | 154.79 | – | 139.32 (C-1"), 119.52 (C-2"/6"), 128.71 (C-3"/5"), 122.46 (C-4") |
| **2d** | 127.74 | 119.24 | 130.82 | 116.17 | 141.25 | 114.94 | 129.65 | 120.79 | 125.29 | 119.82 | 139.62 | 114.51 | – | 138.47 | – | 154.90 | – | 132.31 (C-1"), 121.36 (C-2"/6"), 113.72 (C-3"/5"), 154.81 (C-4"), 55.17 (OMe) |
| **2e** | 127.90 | 119.36 | 131.09 | 116.31 | 141.21 | 115.09 | 129.97 | 120.85 | 125.44 | 119.48 | 141.41 | 114.35 | – | 138.46 | – | 154.13 | – | 146.14 (C-1"), 118.47 (C-2"/6"), 124.88 (C-3"/5"), 141.27 (C-4") |
| **3a**, major | 131.79 | 118.51 | 130.00 | 115.14 | 140.41 | 114.82 | 129.23 | 120.23 | 124.96 | 121.45 | 141.62 | 117.34 | – | 138.44 | – | 162.24 | – | 30.79 (C-1"), 12.07 (SMe) |
| **3a**, minor | 131.98 | 118.22 | 130.20 | 115.04 | 140.49 | 114.75 | 129.40 | 120.20 | 125.69 | 121.04 | 143.28 | 117.03 | – | 138.63 | – | 160.42 | – | 29.54 (C-1"), 12.64 (SMe) |
| **3b**, major | 131.76 | 118.45 | 130.06 | 115.13 | 140.34 | 114.85 | 129.27 | 120.24 | 124.95 | 121.35 | 141.85 | 117.13 | – | 138.42 | – | 161.26 | – | 45.87 (C-1"), 135.84 (C-2"), 115.27 (C-3"), 12.20 (SMe) |
| **3b**, minor | 131.98 | 118.30 | 130.31 | 115.13 | 140.40 | 114.49 | 129.50 | 120.31 | 125.70 | 120.80 | 141.40 | 116.80 | – | 138.64 | – | 159.30 | – | 45.13 (C-1"), 136.24 (C-2"), 115.30 (C-3"), 12.80 (SMe) |
| **3c**, major | 129.53 | 121.71 | 134.76 | 117.47 | 140.48 | 117.47 | 134.03 | 122.77 | 123.77 | 116.30 | 137.88 | 112.14 | – | 138.01 | – | 160.94 | – | 148.56 (C-1"), 124.85 (C-2"/6"), 128.89 (C-3"/5"), 121.15 (C-4"), 13.56 (SMe) |
| **3c**, minor | 129.40 | 121.30 | 134.10 | 117.50 | 140.3[c] | 117.50 | 133.36 | 123.03 | 124.80 | 116.30 | 139.79 | 111.23 | – | 138.1[c] | – | 160.13 | – | 146.95 (C-1"), 125.89 (C-2"/6"), 128.76 (C-3"/5"), 121.15 (C-4"), 14.80 (SMe) |
| **4a** | 131.66 | 119.35 | 131.11 | 115.88 | 140.33 | 115.40 | 130.51 | 120.72 | 125.02 | 119.46 | 147.28 | 115.58 | – | 138.27 | – | 160.65 | – | 172.00 (C-4'), 31.90 (C-5'), 29.45 (C-1") |
| **4b** | 131.75 | 119.18 | 131.14 | 115.85 | 140.29 | 115.42 | 130.52 | 120.73 | 124.99 | 119.44 | 147.44 | 115.48 | – | 138.27 | – | 159.39 | – | 171.69 (C-4'), 31.85 (C-5'), 44.93 (C-1"), 131.69 (C-2"), 117.05 (C-3") |
| **4c** | 131.83 | 118.84 | 130.96 | 115.69 | 140.17 | 115.42 | 130.54 | 120.71 | 124.99 | 119.27 | 147.66 | 115.42 | – | 138.20 | – | 160.12 | – | 171.57 (C-4'), 32.25 (C-5'), 135.46 (C-1"), 128.17 (C-2"/6"), 128.95 (C-3"/5"), 128.50 (C-4") |
| **4d** | 131.94 | 118.86 | 130.98 | 115.68 | 140.18 | 115.40 | 130.51 | 120.69 | 124.99 | 119.30 | 147.57 | 115.31 | –270.9 | 138.20 | –87.5[d] | 160.27 | –219.7 | 171.68 (C-4'), 32.13 (C-5'), 127.99 (C-1"), 129.28 (C-2"/6"), 114.12 (C-3"/5"), 159.07 (C-4"), 55.41 (OMe) |

Table 1 (continued)

| | C-1 | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C-9 | C-9a | N-10 | C-10a | N-11 | C-13/ C-2' | N-14/ N-3' | others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5d** | 125.82 | 121.00 | 131.72 | 115.94 | 138.06 | 117.13 | 132.19 | 120.14 | 126.51 | 114.61 | 159.06 | 117.68 | –266.0 | 139.46 | – | *166.9* | – | *157.75* (C-4'), 29.66 (C-5'), 142.22 (C-1"), 121.35 (C-2"/6"), 114.07 (C-3"/5"), 155.59 (C-4"), 54.99 (OMe) |
| **6a** | 131.59 | 119.07 | 130.76 | 115.67 | 140.32 | 115.21 | 130.09 | 120.52 | 125.90 | 119.90 | 145.73 | 116.01 | –272.2 | 138.30 | –98.9 | 163.0[d] | –254.0 | 163.52[e] (C-4'), 30.71 (C-5'), 30.08 (C-1") |
| **6b** | 131.75 | 119.15 | 131.12 | 115.85 | 140.30 | 115.42 | 130.49 | 120.71 | 125.00 | 119.42 | 147.42 | 115.50 | – | 138.28 | – | *159.39* | – | *171.67* (C-4'), 31.85 (C-5'), 44.93 (C-1"), 131.71 (C-2"), 117.07 (C-3") |
| **6c** | 131.84 | 118.58 | 130.62 | 115.44 | 140.13 | 115.23 | 130.16 | 120.51 | 124.87 | 119.62 | 146.35 | 115.44 | –272.0 | 138.21 | –95.0 | *162.79* | –236.4 | *162.66* (C-4'), 31.12 (C-5'), 136.96 (C-1"), 128.81 (C-2"/6"), 128.91[c] (C-3"/5"), 127.89[c] (C-4"), –155.9 (N-15) |
| **6d** | 131.95 | 118.60 | 130.65 | 115.45 | 140.16 | 115.23 | 130.14 | 120.50 | 124.88 | 119.66 | 146.30 | 115.69 | –272.1 | 138.21 | –95.0 | 162.80 | –237.2 | 162.80 (C-4'), 31.08 (C-5'), 129.32 (C-1"), 129.88 (C-2"/6"), 114.20 (C-3"/5"), 158.73 (C-4"), 55.37 (OMe) |

*N.b.* Assignments within a row can be interchanged if italicized. [a] Values are given to only one decimal place for very broad signals or those measured indirectly; $^{13}C$ referenced internally to TMS (0 ppm); $^{15}N$ referenced externally to $CH_3NO_2$ (0 ppm). [b] Spectra recorded at 80 °C. [c] Broad signal. [d] Or N-12. [e] C-3'and C-4' assigned on the basis of Roslund *et al.* [35].

at *ca*. 178 ppm, typical for a C=S carbon and thus the major species in both cases is either the *E* or the *Z* isomer of the H-10, H-12 tautomer (as indicated in Scheme 2). Whether the equilibrium between these two geometric isomers for the major species of **1a** and **1b** is highly biased or the interconversion is very fast was not discerned. For the minor species of **1a** and **1b**, C-13 resonated at *ca*. 157 ppm and this can only be accounted for by an SH tautomer. This tautomer may exist as either a *Z* isomer (preferred based on similar work [33]) and/or an *E* isomer, but the preference nor the existence of an equilibrium was not ascertained. The driving force for favoring such tautomerisation could be attributed to the energy gain arising from the extended conjugated system, based on the strong tendency of an acridine moiety with a $C_9$–NH–R segment to adopt a 9,10-dihydro arrangement. Intriguingly, extraordinary deshielding (9.6–9.8 ppm) was noted for the H-1 proton for the minor species of **1a** and **1b**, and indeed for many other similar structures in this work, suggestive of the presence of a grouping with a strong magnetic anisotropy. In this instance the strong magnetic anisotropy was provided by the two conjugated imino bonds.

Scheme 2




Solution-state tautomers and isomers contributing to the equilibria of thiosemicarbazides **1a–e**. Compounds **1a** and **1b** were found to be an equilibrium of the major H-10, H-12 tautomer (either *E* or *Z* or both) and the minor H-10, SH tautomer (either *E* or *Z* or both). The major species for compounds **1c–e** was the H-10, H-12 *E* tautomer with the evident minor species for **1c** and **1d** being the H-10, H-12 *Z* tautomer.

For phenyl and 4-methoxyphenyl thiosemicarbazides **1c** and **1d**, C-13 of both the major and minor isomers (78:22

Table 2
$^1$H NMR Chemical Shifts[a] ($\delta$ in ppm) and Multiplicities[b] for Compounds **1–6** in DMSO-$d_6$ at 25 °C

| | H-1[c] | H-2[d] | H-3[d] | H-4[c] | H-5[c] | H-6[d] | H-7[d] | H-8[c] | H-10 | H-12 | H-14 | others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a**, major | 8.28 | 7.07 | 7.47 | 7.25 | 7.15 | 7.41 | 7.05 | 8.42 | 10.48, s | 10.03, s | 8.35, q | 3.09 (3H, d, H-1"), |
| **1a**, minor | 9.61 | – | – | – | – | – | – | 8.20 | 10.23, s | – | 6.75, q | 2.99 (3H, d, H-1") |
| **1b**, major | 8.29 | 7.08 | 7.48 | 7.26 | 7.16 | 7.42 | 7.06 | 8.41 | 10.53, s | 10.11, s | 8.48, t | 4.28 (2H, d, H-1"), 5.97 (ddt, H-2"), 5.12 (m, H-3"*c*), 5.20 (m, H-3"*t*) |
| **1b**, minor | 9.83 | 7.22 | 7.67 | 7.45 | 7.45 | 7.67 | 7.38 | 8.08 | – | – | – | 4.05 (2H, d, H-1"), 5.95 (ddt, H-2"), 5.10 (m, H-3"*c*), 5.24 (m, H-3"*t*) |
| **1c**, major | 9.80 | 7.23 | 7.73 | 7.48 | 7.53 | 7.72 | 7.44 | 8.16 | 11.99, s | 13.44, s | 9.36, s | 7.74 (2H, m, H-2"/6"), 7.34 (2H, m, H-3"/5"), 7.01 (m, H-4") |
| **1c**, minor | 8.37 | 7.13 | 7.52 | 7.30 | 7.19 | 7.46 | 7.09 | 8.53 | 10.64, s | 10.51, s | 9.91, s | 7.69 (2H, m, H-2"/6"), 7.39 (2H, m, H-3"/5"), 7.22 (m, H-4") |
| **1d**, major | 9.77 | 7.22 | 7.72 | 7.45 | 7.50 | 7.72 | 7.43 | 8.14 | 11.90, s | 13.45, s | 9.22, s | 7.59 (2H, m, H-2"/6"), 6.94 (2H, m, H-3"/5"), 3.77 (3H, s, OMe) |
| **1d**, minor | 8.37 | 7.11 | 7.51 | 7.29 | 7.18 | 7.42 | 7.07 | 8.54 | 10.61, s | 10.37, s | 9.82, s | 7.50 (2H, m, H-2"/6"), 6.95 (2H, m, H-3"/5"), 3.78 (3H, s, OMe) |
| **1e**[e] | 9.70, br s | 7.39, br s | 7.75, m | 7.56, m | 7.56, m | 7.75, m | 7.39, br s | 8.20, br s | 12.05, br s | 13.20, br s | 9.80, s | 7.97 (2H, m, H-2"/6"), 8.16 (2H, m, H-3"/5") |
| **2a** | 8.26 | 7.00 | 7.40 | 7.17 | 7.08 | 7.33 | 7.01 | 8.26 | 10.17, s | 8.92, s | 7.03, q | 2.76 (3H, d, H-1") |
| **2b** | 8.23 | 6.99 | 7.39 | 7.16 | 7.06 | 7.32 | 6.99 | 8.26 | 10.17, s | 8.99, s | 7.22, dd | 3.83 (2H, d, H-1"), 5.90 (ddt, H-2"), 5.06 (dd, H-3"*t*), 5.17 (dd, H-3"*c*) |
| **2c** | 8.32 | 7.03 | 7.43 | 7.20 | 7.10 | 7.36 | 7.03 | 8.30 | 10.28, s | 9.42, s | 8.97, s | 7.63 (2H, m, H-2"/6"), 7.29 (2H, m, H-3"/5"), 7.01 (m, H-4") |
| **2d** | 8.34 | 7.04 | 7.43 | 7.21 | 7.11 | 7.36 | 7.02 | 8.34 | 10.25, s | 9.32, s | 8.85, s | 7.55 (2H, m, H-2"/6"), 6.89 (2H, m, H-3"/5"), 3.73 (3H, s, OMe) |
| **2e** | 8.36 | 7.07 | 7.46 | 7.23 | 7.13 | 7.39 | 7.07 | 8.36 | 10.37, s | 9.82, s | 9.62, s | 7.97 (2H, m, H-2"/6"), 8.22 (2H, m, H-3"/5") |
| **3a**, major | 9.62 | 6.88 | 7.30 | 7.06 | 7.01 | 7.27 | 6.92 | 8.14 | 10.02, s | – | 6.40, q | 2.34 (3H, s, $SCH_3$), 2.96 (3H, d, J = 3.6 Hz, H-1") |
| **3a**, minor | 9.58 | – | – | – | – | – | – | 8.38 | 10.11, s | – | – | 2.49 (3H, s, $SCH_3$), 2.90 (3H, d, J = 4.2 Hz, H-1") |
| **3b**, major | 9.48 | 6.83 | 7.30 | 7.05 | 7.01 | 7.27 | 6.92 | 8.13 | 10.03, s | – | 6.57, t | 2.37 (3H, s, $SCH_3$), 4.02 (2H, b s, H-1"), 5.98 (ddt, H-2"), 5.15 (dq, H-3"*c*), 5.27 (dq, H-3"*t*) |
| **3b**, minor | 9.53 | – | – | – | – | – | – | 8.36 | 10.17, s | – | – | 2.45 (3H, s, $SCH_3$), 3.89 (2H, d, H-1"), 6.02 (ddt, H-2"), 5.15 (dq, H-3"*c*), 5.27 (dq, H-3"*t*) |
| **3c**, major | 9.38 | 7.42 | 7.86 | 7.27 | 7.24 | 7.89 | 7.44 | 8.38 | 9.95, s | – | 12.82, s | 2.58 (3H, s, $SCH_3$), 7.70 (2H, m, H-2"/6"), 7.38 (2H, m, H-3"/5"), 7.13 (m, H-4") |
| **3c**, minor | 9.19 | 7.56 | 7.75 | 7.02 | 7.04 | 7.76 | 7.58 | 8.38 | 9.12, s | 10.03, s | 12.26, s | 2.68 (3H, s, $SCH_3$), 7.68 (2H, m, H-2"/6"), 7.40 (2H, m, H-3"/5"), 7.15 (m, H-4") |
| **4a** | 9.35 | 7.03 | 7.46 | 7.23 | 7.19 | 7.44 | 7.07 | 8.26 | 10.63, s | – | – | 3.93 (2H, s, H-5'); 3.30 (3H, s, H-1") |
| **4b** | 9.26 | 6.97 | 7.45 | 7.22 | 7.18 | 7.44 | 7.07 | 8.25 | 10.63, s | – | – | 4.00 (2H, s, H-5'), 4.44 (2H, dt, $J_{H2"}$ = 5.4, $J_{H3"Z}$ = 1.7, $J_{H3"E}$ = 1.5 Hz, H-1"), 5.94 (1H, ddt, $J_{H3"Z}$ = 17.3, $J_{H3"E}$ = 10.3, $J_{H1"}$ = 5.4, H-2"), 5.30 (1H, dq, $J_{H3"Z,H3"E}$ = 17.3, $J_{H3"E}$ = –1.4, $J_{H1"}$ = 1.7, H-3"Z), 5.26 (1H, dq, $J_{H3"Z}$ = –1.4, $J_{H2"}$ = 10.3, $J_{H1"}$ = 1.5, H-3"*E*) |
| **4c** | 8.68 | 6.57 | 7.33 | 7.13 | 7.16 | 7.43 | 7.07 | 8.27 | 10.59, s | – | – | 4.12 (2H, s, H-5'), 7.49 (m, $^3J_{H3"}$ = 7.9, $J_{H6"}$ = 2.2, $J_{H4"}$ = 1.2, $^5J_{H3"}$ = 0.5 Hz, H-2"/H-6"), 7.61 (m, $J_{H2"}$ = 7.9, $J_{H3"}$ = 1.6, $J_{H4"}$ = 7.5, $^5J_{H2"}$ = 0.5 Hz, H-3"/H-5"), 7.53 (m, $J_{H3"}$ = 7.5, $J_{H2"}$ = 1.2 Hz, H-4") |
| **4d** | 8.75 | 6.61 | 7.43 | 7.16 | 7.15 | 7.35 | 7.07 | 8.28 | 10.58, s | – | – | 4.09 (2H, s, H-5'), 7.40 (m, $^3J_{H3"}$ = 8.8, $J_{H6"}$ = 2.5, $^5J_{H5"}$ = 0.3 Hz, H-2"/H-6"), 7.14 (m, $^3J_{H2"}$ = 8.8, $J_{H5"}$ = 3.0, $^5J_{H6"}$ = 0.3 Hz, H-3"/H-5"), 3.85 (3H, s, OMe) |
| **5a** | 8.44 | 7.16 | 7.59 | 7.34 | 7.36 | 7.53 | 6.99 | 7.98 | 11.19 | – | – | 4.14, 4.26 (2H, ABqt, $J_{gem}$ = –15.9, –16.0 Hz, H-5') |
| **5b** | 8.23 | 7.26 | 7.74 | 7.54 | – | – | – | – | 11.25 | – | – | – |
| **5c** | 8.55 | – | – | – | – | – | – | 8.09 | – | – | – | 4.18, 4.31 (2H, ABqt, $J_{gem}$ = –16.18 Hz, H-5') |

Table 2 (continued)

| | H-1[c] | H-2[d] | H-3[d] | H-4[c] | H-5[c] | H-6[d] | H-7[d] | H-8[c] | H-10 | H-12 | H-14 | others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5d** | 8.52 | 7.18 | 7.60 | 7.35 | 7.37 | 7.58 | 7.09 | 8.05 | 11.21 | – | – | 3.67 (3H, s, OMe), 4.12, 4.25 (2H, ABqt, $J_{gem}$ = –15.4, –15.9 Hz, H-5'), 6.44 (2H, b m, H-3"/5"), 6.77 (2H, m, H-2"/6") |
| **6a** | 9.44 | 7.00 | 7.42 | 7.19 | 7.14 | 7.40 | 7.02 | 8.22 | 10.44, s | – | – | 3.95 (2H, s, H-5'); 3.35 (3H, s, H-1") |
| **6b** | 9.26 | 6.97 | 7.45 | 7.22 | 7.18 | 7.44 | 7.07 | 8.25 | 10.61, s | – | – | 4.00 (2H, s, H-5'), 4.44 (2H, d, $J$ = 4.8 Hz, H-1"), 5.94 (1H, ddt, $J$ = 17.2, 10.8, 4.8 Hz, H-2"), 5.30 (1H, dd, $J$ = 17.2, 1.2 Hz, H-3"), 5.26 (1H, dd, $J$ = 10.8, 1.2 Hz, H-3"c) |
| **6c** | 8.72 | 6.51 | 7.29 | 7.09 | 7.11 | 7.39 | 7.02 | 8.22 | 10.20, s | – | – | 4.13 (2H, s, H-5'), 7.44 (2H, m, H-2"/6"), 7.60 (2H, m, H-3"/5"), 7.50 (m, H-4") |
| **6d** | 8.77 | 6.55 | 7.30 | 7.09 | 7.11 | 7.38 | 7.02 | 8.21 | 10.39, s | – | – | 3.85 (3H, s, OME), 4.11 (2H, s, H-5'), 7.34 (2H, m, H-2"/6"), 7.13 (2H, m, H-3"/5") |

[a] $^1$H referenced internally to TMS (0 ppm). [b] Multiplicities are real observations in all cases; legend: b, broad; d, doublet; m, multiplet; s, singlet; t, triplet. [c] dd in each case. [d] ddd in each case. [e] Spectra recorded at 80 °C.

a large difference, of the order of 1.6 ppm, between the chemical shifts of H-1 (9.80 and 9.77 ppm for **1c** and **1d**, respectively) and H-8 (8.16 and 8.14 ppm, respectively) in addition to a deshielded H-10 signal (11.99 and 11.90 ppm, respectively) and a strongly deshielded H-12 signal (13.44 and 13.45 ppm, respectively). It is of particular note that these chemical shifts for H-10 and H-12 were not observed for any other derivatives in this study. By contrast, the signals of the two minor species were much more typical of the expected values for H-1 (both resonated at 8.37 ppm), H-8 (8.53 and 8.54 ppm, respectively), H-10 (10.64 and 10.61 ppm, respectively), and H-12 (10.51 and 10.37 ppm, respectively). To account for the deshieldings observed for the major species, and the very presence of two species *per se*, restricted rotation about the $C_{13}$–$N_{14}$ thioamide bond is postulated. For the major species of **1c** and **1d**, the phenyl ring must be spatially closer to H-12 and the acridine moiety to effect deshielding and thus it is the *E* isomer represented in Scheme 2 whilst the minor species is the *Z* isomer in both cases. Further differences between the major and minor species of **1c** and **1d** can also be seen in the chemical shifts of C-9 and the *ortho* carbons C-2' and 6'. Greater shielding of C-2'(6') and C-9 for **1c**(**d**) major of between 4.5–4.9 ppm in comparison to **1c**(**d**) minor indicates that a steric component is present in addition to any magnetic anisotropy.

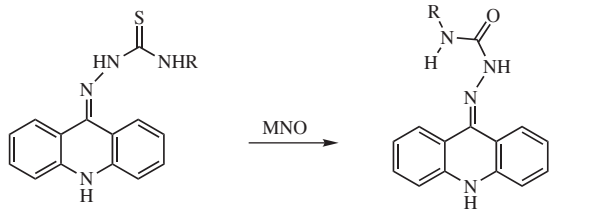
A similar analysis of the solution-state species for the nitro derivative **1e** was precluded by its very poor solubility and little can be said other than that the major species in solution was also the H-10, H-12 *E* tautomer.

Semicarbazides **2a–e**.

The thiosemicarbazides **1a–e** were each converted, in most cases quantitatively, into the analogous semicarbazides **2a–e** (Scheme 3) upon treatment with mesitylnitrile oxide (MNO). The exchange of S by O was evident by the appearance of an IR absorption band at 1640–1700 $cm^{-1}$ ($\nu_{C=O}$) and a $^{13}$C NMR signal in the range 155–158 ppm for the carbonyl carbon. In contrast to **1a–e**, only one species was observed in solution for each compound. Again though, the non-equivalency of both acridine side rings was evident as was the presence of the H-10 (9,10-dihydroacridinylidene) tautomer. Of note, the chemical shifts of H-12 and H-14 were shielded by more than 1 ppm in comparison to thiosemicarbazides **1** because of the weaker electron withdrawing effect of the carbonyl group. The stereochemistry of **2a–e** was based on semicarbazide **2b** (the overlap of H-1 and H-8 in the other derivatives precluded stereochemical differentiation) where irradiation of H-12 yielded a 20.5% enhancement of the H-1 signal (none for H-8) whilst irradiation of H-14 yielded a 4.8% enhancement of the H-8 signal (none for H-1). This testifies to the hindered rotation about the $C_{13}$–$N_{14}$ bond in

semicarbazides **2a–e** with the *Z* conformation prevalent as indicated in Scheme 3.

Scheme 3




**1a-e**

**2a**: R = methyl
**2b**: R = allyl
**2c**: R = phenyl
**2d**: R = *p*-methoxyphenyl
**2e**: R = *p*-nitrophenyl

The reaction of compounds **1a–e** with mesitylnitrile oxide quantitatively produced the corresponding semicarbazides **2a–e**. All structures were present in solution as the H-10 tautomers with *Z* conformation about the $C_{13}$–$N_{14}$ bond

*S*-Methyl thiosemicarbazides **3a–c**.

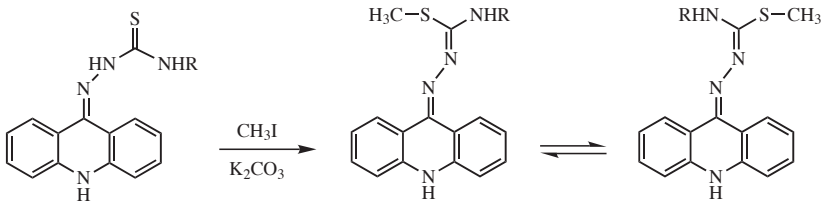
Treatment of thiosemicarbazides **1a–c** with $CH_3I$/ $K_2CO_3$ in acetone afforded the S-methyl derivatives **3a–c** in moderate yields (Scheme 4). For all three compounds, two species were present in solution (**3a**, 83:17; **3b**, 91:9; and **3c**, 60:40). For all six structures, C-13 resonated in the expected range (159–162 ppm), as did the S–$CH_3$ carbons (12–15 ppm), and again the H-10 (9,10-dihydroacridinylidene) tautomer was evident for all six species as was the conjugation of the imino double bonds as evidenced by the strong deshielding of H-1 (0.8–1.5 ppm relative to H-8) in both major and minor species of **3a–c**. The two solution-state species were identified as the *Z* (major) and *E* (minor) geometric isomers about the $N_{12}$=$C_{13}$ double bond based on NOEs for **3a** and **3b** between H-1 and the protons of the R substituents in the case of the major isomer and between H-1 and the S-methyl protons in the minor isomer. The predominance of the *Z* isomer is not surprising in the light of previous studies [33].

The H-14 protons of the major isomers of **3a** and **3b** were strongly shielded (**3a**, 6.40 ppm; **3b**, 6.57 ppm) due to a number of factors, including probably being in the shielding zone of the extended imino double bond conjugation. This is countered in the phenyl derivative **3c** by the anisotropy of the phenyl ring in addition to any conformational shift and H-14 resonates at more typical values (major, 12.82 ppm; minor, 12.26 ppm) in comparison to thiosemicarbazides **1**.

1',3'-Thiazolidin-4'-ones **4a–d**.

Treatment of thiosemicarbazides **1a–d** with methyl bromoacetate provided 1',3'-thiazolidin-4'-ones **4a–d** (Scheme 5). According to literature [8,9], this reaction is a two-step process, nucleophilic displacement of the bromine by the sulfur of the thiosemicarbazide affords the S-carboxyalkylated isothiosemicarbazide which is then followed by nucleophilic attack by one of the nitrogen atoms to the carboxylate carbon eliminating methoxide ion and effecting cyclisation. Since the reactions were conducted in alkaline medium, the second step proceeded successively without isolation of the isothiosemicarbazide intermediates. In principle, three regioisomers resulting from attack by nitrogen atoms N-11, N-12, and N-14 are possible, however, literature reports [20–22] on the formation of thiazolidinone structures resulting from attack of N-12 or N-14 are much more frequent than the formation of six-membered thiadiazine structures resulting from attack of the N-11 nitrogen. The only product isolated in each case was clearly not a thiadiazine as such a structure would have an acridine moiety and not a 9,10-dihydroacridinylidene structure as observed. (The sole formation of only one regioisomer was also evident by TLC.) The NMR data of the thiazolidinone ring was also in accord with previous studies [8,9,23]. Of the two possible regioisomeric thiazolidinone structures, it was clearly the one resulting from attack by N-14 as correlations were observed from the H-3" methyl protons in **4a** and the H-3" allyl methylene

Scheme 4



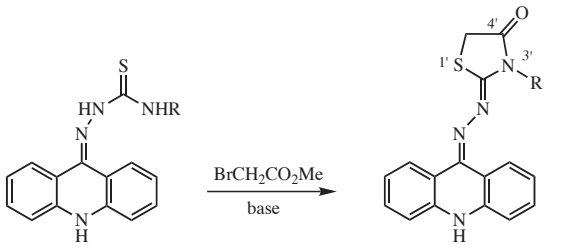

**1a-c** ***Z*** ***E***

**3a**: R = methyl
**3b**: R = allyl
**3c**: R = phenyl

The methylation of **1a–c** yielded the S-methylated compounds **3a–c** wherein the *Z* configuration dominated in each case over the *E* configuration along the $N_{12}$–$C_{13}$ double bond.

protons in **4b** to both C-4' and C-2'. Correlations to C-4' from these protons would be improbable in the regioisomers resulting from attack by N-12. Further evidence in the case of **4d** was a correlation observed between the *ortho* protons of the phenyl ring and a $^{15}N$ NMR signal at −219.7 ppm, a chemical shift consistent with an $sp^3$-hybridized nitrogen. The stereochemistry of the $N_{12}$–$C_{2'}$ bond was determined to be in favor of the sterically less hindered *Z* isomer. This was based on NOE enhancements whereby irradiation of the H-3' methyl (**4a**) or the H-3' methylene protons (**4b**) provided enhancements of the H-1 signals (1.4% and 2.7%, respectively) with no enhancement of the H-8 signals; irradiation of the H-1 proton in 4c resulted in a 3.4% enhancement of the phenyl H-2", H-6" signals whilst irradiation of H-8 did not enhance any of the phenyl signals. Comparison of alkyl **4a** and **4b** *vs*. aryl **4c** and **4d** thiazolidines revealed that the chemical shifts of H-1 and H-2 are shielded in **4c** and **4d** by 0.5–0.6 ppm, attributable to the phenyl ring which is probably perpendicular to the plane of the rest of molecule.

Scheme 5




**1a-d** **Z**

**4a**: R = methyl
**4b**: R = allyl
**4c**: R = phenyl
**4d**: R = p-methoxyphenyl

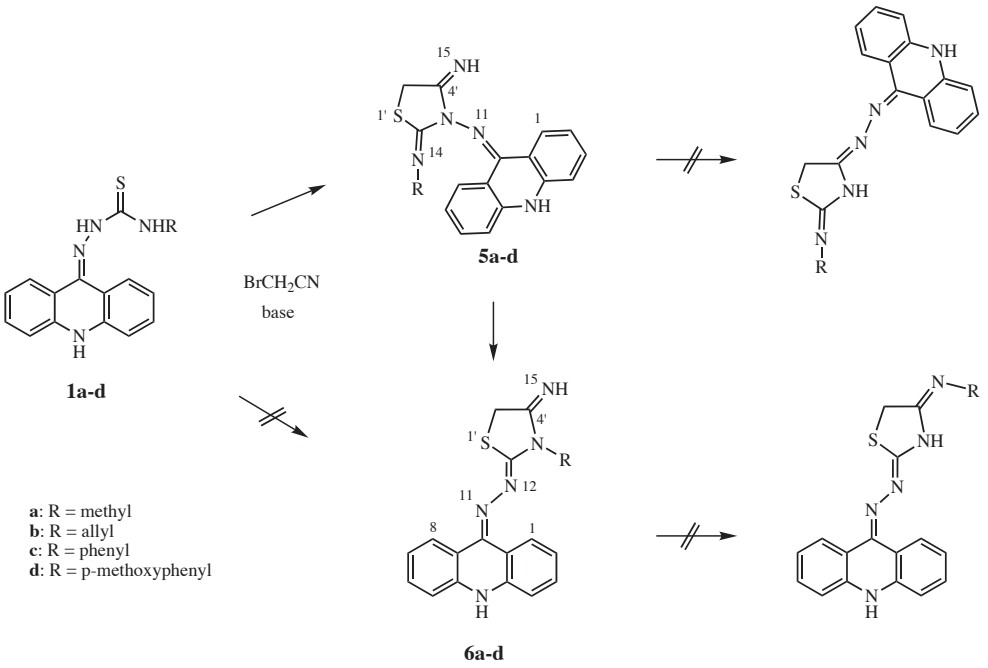
The reaction of thiosemicarbazides **1a–d** with methyl bromoacetate yielded the 1',3'-thiazolidin-4'-ones **4a–d** wherein the *Z* configuration predominated in each case over the *E* configuration along the $N_{12}$–$C_{13}$ double bond.

It is noteworthy given the results of the preceding section that the course of the reaction reflects the likely position of the tautomeric equilibrium of the S-carboxyalkylated isothiosemicarbazide intermediate (N-14 amino, N-12 imino), as postulated previously [8,9]. However, given the very different natures of the nitrogen atoms in question here with N-12 likely to be a much stronger nucleophile in its amino form in comparison to N-14, the result only holds due to the high susceptibility to nucleophilic attack of the carboxy carbon of the ester moiety.

4'-Imino-1',3'-thiazolidines **5a–d** and **6a–d**.

Treatment of thiosemicarbazides **1a–d** with bromoacetonitrile could potentially provide a number of products after treatment with base, *e.g*. an esoteric spiro bicyclic structure [1,15] resulting from attack of the nitrile nitrogen on C-9; a spiro product resulting from attack of the methylene carbon of bromoacetonitrile on C-9; a 1,3,4-thiadiazine structure resulting from attack of N-11 onto the nitrile carbon; and the regioisomeric 1,3-thiazolidin-4-imines resulting from attack by either N-12 or N-14 onto the nitrile carbon. Again, the S-methylenenitrile intermediate generated after addition of bromoacetonitrile was not isolated though cyclisation was observed upon treatment with sodium methoxide. As regards these cyclic products, the spiro structures were easy to eliminate as candidate structures as a spiro carbon was not observed. Because of a likely strong preference for adopting the 9,10-dihydroacridinylidene structure, C-9 in the S-methylenenitrile intermediate is not as susceptible to nucleophilic attack in any case. As with the account presented in the previous section, a 1,3,4-thiadiazine structure was also easily eliminated. That left the two regioisomeric 1,3-thiazolidin-4-imines (**5** and **6**) as the only candidate structures (Scheme 6) as a result of attack by N-12 or N-14, respectively. What was most remarkable was that upon dissolution in DMSO, the samples of the methyl and the *p*-methoxy phenyl provided a spectrum dominated by one set of signals which slowly dissipated with time ($t_{½}$ of the order of hours) to be completely replaced by a new set. (In the case of the allyl derivative, only the final set of signals was observed; in the case of the phenyl derivative, the reaction had progressed to the point where the initial product was only just detectable.) Both sets of signals were consistent 1,3-thiazolidin-4-imines (*vide supra*), thus it was simply a matter of deciding which of the two regioisomers is produced first and then the course of the Dimroth-type rearrangement that it undergoes. The two potential initial products, **5** and **6**, are interconvertable by a Dimroth-type rearrangement (either as a result of attack by hydroxide ion or by deprotonation of the imine to enact ring opening), and additionally there is another Dimroth-only rearrangement available to each structure. The most significant feature of the $^1H$ NMR of the initially observed product was that the methylene protons in the thiazolidine ring were non-equivalent and resonated as an AB quartet, as opposed to the usual observation where they resonate as a singlet due to fast exchange [8,9]. Of the four structures presented in Scheme 6, only one, **5**, could provide such a case. In **5**, steric hindrance limits the coplanarity of the thiazolidine ring and the acridine moiety and this, together with slow inversion at N-3' (née 12) and hindered rotation about the $N_{11}$–$N_{3'}$ bond, means that the introduced chiral axis renders the two protons of the methylene group non-equivalent. Structure **5** was then shown to rearrange to structure **6** instead of its alternate based on the correlations of the methyl (**6a**) or *ortho* (**6c** and **d**) protons to an $sp^3$-hybridized nitrogen or the correlations of the methyl (**6a**) or exocyclic methylene (**6b**) protons to both $sp^2$-hybridized carbon atoms of the thiazolidine ring. (Note, the

Scheme 6




The reaction of **1a–d** with bromoacetonitrile initially yielded the 1',3'-thiazolidin-4'-imines **5a–d** which underwent spontaneous Dimroth rearrangements to regioisomeric 1',3'-thiazolidin-4'-imines **6a–d**. The *Z* configuration predominated in each case over the *E* configuration along the $N_{12}$–$C_{13}$ double bond for the latter set.

imino NH proton was not observed for either structure.) The geometry about the $N_{12}$–$C_{2'}$ bond, however, could not be substantiated in **6**.

It is interesting to note that the course of the reaction (for the initial product **5**) is in opposition to the likely position of the tautomeric equilibrium of the S-alkylated isothiosemicarbazide intermediate (N-14 amino, N-12 imino). This therefore is indicative of the low susceptibility to nucleophilic attack of the nitrile carbon by which the much stronger nucleophilic character of N-12 comes to the fore over N-14 despite the unfavorable equilibrium position.

## EXPERIMENTAL

NMR spectra were acquired using a JEOL Alpha 500 NMR spectrometer operating at 500 MHz for $^1$H, 126 MHz for $^{13}$C, and 51 MHz for $^{15}$N, a JEOL Lambda 400 NMR spectrometer operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C, or a Varian VXR-300 NMR spectrometer operating at 300 MHz for $^1$H and 75 MHz for $^{13}$C. Spectra were recorded at 25 °C unless stated otherwise in DMSO-$d_6$ and both $^1$H and $^{13}$C chemical shifts were referenced internally to TMS ($\delta$ = 0 for both) whilst $^{15}$N spectra were referenced externally to 90% nitromethane in $CD_3NO_2$ ($\delta$ = 0). $^1$H spectra were acquired with single-pulse excitation, 45° flip angle, pulse recycle time of 9.5 s and with spectral widths of 7 kHz consisting of 64 k data points (digital resolution 0.11 Hz pt$^{-1}$), zero-filled to 128 k prior to Fourier transformation. Spin analysis was performed using Perch [27] iteration software for the extraction of $^1$H chemical shifts and $J_{H,H}$ coupling constants. Since the reliable extraction of small couplings approaching the linewidth is heavily dependent on whether they are to a degree resolvable on at least one spin for Perch to reliably extract them, only those couplings reliably extracted by Perch are reported whilst couplings buried in the linewidth on both interacting spins are not reported (*i.e.*, not extracted) even if their likely presence is probable or is evident from homodecoupling experiments or COSY experiments. The signs of the couplings were assumed based on the number of intervening bonds, *i.e.* if n is even, $^nJ$ was entered as a negative value; if n is odd, $^nJ$ was entered as a positive value. NOE difference measurements were acquired using saturation times of 6 s and with reduced resolution (3.9 Hz pt$^{-1}$); 1 Hz of exponential weighting was usually applied prior to Fourier transformation. (NOE difference measurements also provided concomitantly saturation transfer information.) DQF-COSY and NOESY spectra were acquired in phase-sensitive mode with spectral widths and resolution appropriately optimized from the 1-D spectra, and processed with zero-filling (× 2, × 4) and exponential weighting (1 Hz) applied in both dimensions prior to Fourier transformation. $^{13}$C spectra were acquired with single-pulse excitation, 45° flip angle, pulse recycle time of 3.5 s and with spectral widths of 30 kHz consisting of 64 k data points (digital resolution 0.46 Hz pt$^{-1}$), and with 1 Hz exponential weighting applied prior to Fourier transformation. DEPT 135° spectra were acquired with similar spectral windows and with a pulse delay time of 3 s. CHDEC (CHSHFT with f1 homonuclear decoupling), HSQC PMG [34], and HMBC BIRD experiments were acquired in phase-sensitive mode and magnitude mode (for

the latter experiment) with spectral widths and resolution appropriately optimized from the 1-D spectra and processed with zero-filling (× 2, × 4), a 2π/3-shifted sinebell function (for HMBC spectra), and exponential weighting (5 Hz, 25 Hz) applied in both dimensions prior to Fourier transformation. Both HSQC and HMBC spectra utilized a $^1J_{HC}$ coupling of 145 Hz, whilst the HMBC correlations were optimized for a long-range $^nJ_{HC}$ coupling of *ca*. 8 Hz. The length of the purge pulse (typically 0.7 ms) and BIRD relaxation delay (typically 400 ms) were optimized on the incoming FID. Experiments were performed with vendor-supplied pulse sequences except in the case of the sign determination of long-range couplings [35]. With minor isomers, only clearly visible signals are reported, signals that were overlapped, broad, or too weak to be certain are excluded. $^{15}$N were generally acquired indirectly from the f1 dimension of FGHSQC or FGHMBC experiments where both HSQC and HMBC spectra utilized a $^1J_{HN}$ coupling of 90 Hz whilst the HMBC correlations were optimized for a long-range $^nJ_{HN}$ coupling of *ca*. 8 Hz with similar processing as *per* above. The f1 windows and resolution were set according to judgment based on previous experience and affordability. In particular cases, when sample amounts were substantial or when strongly warranted, refocused-INEPT experiments were run for the direct observation of $^{15}$N nuclei where the final two delays were set to either 1/(4*J*) or 3/(4*J*).

IR spectra were recorded on a Specord M80 spectrophotometer (Zeiss, Jena) in $CHCl_3$ or KBr discs. Elemental analysis was performed using a Perkin–Elmer CHN 2400 analyser. EI mass spectra were acquired on a VG Analytical 7070E instrument using 70 eV for ionisation. ESI-MS analysis was performed using a Perkin–Elmer Sciex API-365 triple quadrupole mass spectrometer equipped with a pneumatically-assisted ion spray interface with the needle voltage set at +5,000 V (–4400 V), the orifice plate voltage at +35 V (–35 V) and the ring voltage at +220 V (–200 V) for positive (negative) ion measurements. The nebuliser gas (purified air) flow was set at position 9 and that for the curtain gas ($N_2$) at position 12. The heated nitrogen gas temperature was set at 300 °C and the gas flow rate at 7 L min$^{-1}$. Masses were scanned from *m/z* 100 to 3,000 in 0.30 amu steps.

Methyl, allyl, phenyl, 4-methoxyphenyl, and 4-nitrophenyl isothiocyanates, methyl bromoacetate, and bromoacetonitrile were commercial products from Aldrich. Mesitylnitrile oxide was prepared according to ref [36]. Reactions were monitored by thin-layer chromatography (TLC) using Silufol plates (Kavalier) with detection at 254 nm. Preparative column chromatography was performed using Silpearl (Kavalier). Melting points were determined on a Boetius instrument and are uncorrected.

Acridin-9-yl hydrazine [11].

9-Chloroacridine [11] (2 g, 9.4 mmol) in methanol (30 mL) was added to a refluxing solution of hydrazine monohydrate (0.47 g, 0.46 mL, 9.4 mmol) in methanol (30 mL) over 10 min and the refluxing continued for an additional 20 min. Water preheated to 75 °C was then added and the resulting suspension quickly filtered. The refrigerated filtrate provided orange needles of 9-hydrazinoacridine. Yield 77%; mp 169 °C (methanol); Found: C, 74.32; H, 5.08; N, 20.02. $C_{13}H_{11}N$ requires C, 74.62; H, 5.30; N, 20.08%; $\delta_H$(400 MHz; DMSO-$d_6$; $Me_4Si$) 6.26 (2H, br s, $NH_2$), 6.89 (ddd, H-7), 6.89 (ddd, H-2), 6.93 (ddd, H-5), 7.07 (ddd, H-4), 7.19 (ddd, H-6), 7.29 (ddd, H-3), 7.76 (dd. H-8), 8.25 (dd, H-1), 9.70 (s, H-10); $\delta_C$(100 MHz; DMSO-$d_6$; $Me_4Si$) 114.26 (C-5), 115.25 (C-4), 115.52 (C-9a), 118.46 (C-2), 120.26 (C-8), 121.90 (C-8a), 123.69 (C-1), 127.62 (C-6), 128.08 (C-7), 129.45 (C-3), 136.21 (C-9), 138.26 (C-10a), 141.44 (C-4a).

General Procedure for the Preparation of 4-Substituted-1-(9,10-dihydroacridin-9-ylidene)-thiosemicarbazides **1a–e**.

To a solution of substituted isothiocyanate (0.96 mmol) in methanol (5 mL), acridin-9-yl hydrazine (0.2 g, 0.96 mmol) in methanol (5 mL) was added dropwise. The mixture was allowed to stir at room temperature under nitrogen for 24 h until completion of the reaction (monitored by TLC cyclohexane/acetone 3:1). The solvent was then removed under vacuum, ether added, and the resulting precipitate collected by filtration and dried to give product **1**.

4-Methyl-1-(9,10-dihydroacridin-9-ylidene)-thiosemicarbazide (**1a**).

Yield 62%; mp 125–127 °C (methanol); Found: C, 63.66; H, 4.92; N, 19.92. $C_{15}H_{14}N_4S$ requires C, 63.80; H, 5.0; N, 19.84%; $\nu_{max}$(KBr)/cm$^{-1}$: 1100 (C=S); **1a** (major isomer, 90%). **1a** (minor isomer, 10%).

4-Allyl-1-(9,10-dihydroacridin-9-ylidene)-thiosemicarbazide (**1b**).

Yield 77%; mp 134–135 °C (methanol); Found: C, 66.36; H, 5.09; N, 17.91 $C_{17}H_{16}N_4S$ requires C, 66.21; H, 5.23; N, 18.17%; $\nu_{max}$(KBr)/cm$^{-1}$: 1150 (C=S); **1b** (major isomer, 91%). **1b** (minor isomer, 9%).

4-Phenyl-1-(9,10-dihydroacridin-9-ylidene)-thiosemicarbazide (**1c**).

Yield 85%; mp 195–197 °C (methanol); Found: C, 69.95; H, 4.56; N, 16.37 $C_{20}H_{16}N_4S$ requires C, 69.74; H, 4.68; N, 16.27%; $\nu_{max}$(KBr)/cm$^{-1}$:1000–1100 (C=S); **1c** (major isomer, 78%). **1c** (minor isomer, 22%).

4-Methoxyphenyl-1-(9,10-dihydroacridin-9-ylidene)-thiosemicarbazide (**1d**).

Yield 92%; mp 187–188 °C (methanol); Found: C, 67.18; H, 4.97; N, 14.59 $C_{21}H_{18}N_4OS$ requires C, 67.36; H, 4.85; N, 14.96%; $\nu_{max}$(KBr)/cm$^{-1}$: 980 (C=S); **1d** (major isomer, 65%). **1d** (minor isomer, 35%).

4-Nitrophenyl-1-(9,10-dihydroacridin-9-ylidene)-thiosemicarbazide (**1e**).

Yield 94%; mp 230–231 °C (methanol); Found: C, 61.35; H, 4.03; N, 17.66 $C_{20}H_{15}N_5O_2S$ requires C, 61.68; H, 3.88; N, 17.98%.

General Procedure for the Preparation of 4-Substituted-1-(9,10-dihydroacridin-9-ylidene)-semicarbazides **2a–e**.

To a solution of substituted thiosemicarbazide **1** (0.45 mmol) in dry acetonitrile (5 mL), mesitylnitrile oxide (0.072 g, 0.45 mmol) was added. The mixture was allowed to stir for 6 h at room temperature following which the solvent was evaporated under reduced pressure and the solid collected by filtration, dried, and crystallized from methanol to afford **2**.

4-Methyl-1-(9,10-dihydroacridin-9-ylidene)-semicarbazide (**2a**).

Yield 96%; mp 225–227 °C (methanol); Found: C, 67.37; H, 5.18; N, 21.32 $C_{15}H_{14}N_4O$ requires C, 67.65; H, 5.30; N, 21.04%; $\nu_{max}$(KBr)/cm$^{-1}$: 1700 (C=O).

4-Allyl-1-(9,10-dihydroacridin-9-ylidene)-semicarbazide (**2b**).

Yield 92%; mp 122–124 °C (methanol); Found: C, 69.75; H, 5.38; N, 19.26 $C_{17}H_{16}N_4O$ requires C, 69.85; H, 5.52; N, 19.17%; $\nu_{max}$(KBr)/cm$^{-1}$: 1680 (C=O).

4-Phenyl-1-(9,10-dihydroacridin-9-ylidene)-semicarbazide (**2c**).

Yield 95%; mp 229–231 °C (methanol); Found: C, 73.22; H, 4.92; N, 16.76 $C_{20}H_{16}N_4O$ requires C, 73.15; H, 4.91; N, 17.06%; $\nu_{max}$(KBr)/cm$^{-1}$:1680 (C=O).

4-Methoxyphenyl-1-(9,10-dihydroacridin-9-ylidene)-semicarbazide (**2d**).

Yield 52%; mp 223–224 °C (methanol); Found: C, 70.67; H, 4.87; N, 15.48 $C_{21}H_{18}N_4O_2$ requires C, 70.38; H, 5.06; N, 15.63%; $\nu_{max}$(KBr)/cm$^{-1}$: 1640 (C=O).

4-Nitrophenyl-1-(9,10-dihydroacridin-9-ylidene)-semicarbazide (**2e**).

Yield 86%; mp 220 °C (methanol); Found: C, 64.09; H, 4.10; N, 18.49 $C_{20}H_{15}N_5O_3$ requires C, 64.34; H, 4.05; N, 18.76%; $\nu_{max}$(KBr)/cm$^{-1}$: 1640 (C=O).

General Procedure for the Preparation of 4-Substituted *S*-Methyl 1-(9,10-dihydroacridin-9-ylidene)-isothiosemicarbazides **3a–c**.

A suspension containing **1** (0.88 mmol) and anhydrous potassium carbonate (0.122 g, 0.88 mmol) in anhydrous acetone (5 mL) was stirred at room temperature. To this mixture iodomethane (0.126 g, 0.055 mL, 0.89 mmol) was added dropwise and the mixture was allowed to stir for 7 h. After the completion of the reaction, the mixture was poured into water (25 mL) and extracted with chloroform (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and the solvent evaporated off under vacuum to provide the product **3**.

*S*-Methyl 1-(9,10-dihydroacridin-9-ylidene)-4-methyl-isothiosemicarbazide (**3a**).

Yield 76%; mp 190–192 °C (methanol); Found: C, 64.60; H, 5.12; N, 18.54. $C_{16}H_{16}N_4S$ requires C, 64.84; H, 5.44; N, 18.90%; $\nu_{max}$(KBr)/cm$^{-1}$: 1530 (C=N); **3a *Z*** (major isomer, 83%). **3a *E*** (minor isomer, 17%).

*S*-Methyl 1-(9,10-dihydroacridin-9-ylidene)-4-allyl-isothiosemicarbazide (**3b**).

Yield 58%; mp 160–162 °C (methanol); Found: C, 67.39; H, 5.30; N, 17.49 $C_{18}H_{18}N_4S$ requires C, 67.05; H, 5.63; N, 17.38%; $\nu_{max}$(KBr)/cm$^{-1}$: 1530 (C=N); **3b *Z*** (major isomer, 91%). **3b *E*** (minor isomer, 9%).

*S*-Methyl 1-(9,10-dihydroacridin-9-ylidene)-4-phenyl-isothiosemicarbazide (**3c**).

Yield 52%; mp 149–152 °C (diethyl ether); Found: C, 69.99; H, 5.13; N, 15.75 $C_{21}H_{18}N_4S$ requires C, 70.36; H, 5.06; N, 15.63%; $\nu_{max}$(KBr)/cm$^{-1}$:1650 (C=N); **3c** (major isomer, 60%). **3c** (minor isomer, 40%).

General Procedure for the Preparation of 2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-substituted-1',3'-thiazolidin-4'-ones **4a–d**.

To a solution of thiosemicarbazide **1** (0.54 mmol) in methanol (5 mL), methyl bromoacetate (0.082 g, 0.051 mL, 0.54 mmol) was added dropwise and the mixture left to stir for 2 h after which sodium methoxide (0.029 g, 0.54 mmol) was added. The reaction mixture was stirred for another 1 h then poured into cold water (25 mL) and the resulting precipitate of 4 collected by filtration, dried, and crystallized from diethyl ether.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-methyl-1',3'-thiazolidin-4'-one (**4a**).

Yield 82%; mp 288–290 °C (diethyl ether); Found: C, 63.56; H, 4.12; N, 17.17 $C_{17}H_{14}N_4OS$ requires C, 63.33; H, 4.38; N, 17.38%; $\nu_{max}$ (KBr)/cm$^{-1}$: 1560–1600 (C=N), 1730 (C=O); $J_{H,H}$ couplings (Hz) extracted by spin simulation [27]: $J_{H1,H2}$ = 8.4, $J_{H1,H3}$ = 1.5, $J_{H1,H4}$ = 0.5, $J_{H2,H3}$ = 7.0, $J_{H2,H4}$ = 1.3, $J_{H3,H4}$ = 8.3, $J_{H5,H6}$ = 8.2, $J_{H5,H7}$ = 1.2, $J_{H5,H8}$ = 0.5, $J_{H6,H7}$ = 7.0, $J_{H6,H8}$ = 1.5, $J_{H7,H8}$ = 8.2.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-allyl-1',3'-thiazolidin-4'-one (**4b**).

Yield 73%; mp 225–228 °C (diethyl ether); Found: C, 65.32; H, 4.28; N, 16.15 $C_{19}H_{16}N_4OS$ requires C, 65.50; H, 4.63; N, 16.08%; $\nu_{max}$(KBr)/cm$^{-1}$: 1540 (C=N), 1620 (C=O); $J_{H,H}$ couplings (Hz) extracted by spin simulation [27]: $J_{H1,H2}$ = 8.4, $J_{H1,H3}$ = 1.5, $J_{H1,H4}$ = 0.4, $J_{H2,H3}$ = 7.0, $J_{H2,H4}$ = 1.3, $J_{H3,H4}$ = 8.3, $J_{H5,H6}$ = 8.2, $J_{H5,H7}$ = 1.2, $J_{H5,H8}$ = 0.5, $J_{H6,H7}$ = 7.0, $J_{H6,H8}$ = 1.5, $J_{H7,H8}$ = 8.2.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-phenyl-1',3'-thiazolidin-4'-one (**4c**).

Yield 71%; mp 136–138 °C (diethyl ether); Found: C, 68.45; H, 4.20; N, 14.35 $C_{22}H_{16}N_4OS$ requires C, 68.73; H, 4.19; N, 14.57%; $\nu_{max}$ (KBr)/cm$^{-1}$: 1580 (C=N), 1700 (C=O); $J_{H,H}$ couplings (Hz) extracted by spin simulation [27]: $J_{H1,H2}$ = 8.5, $J_{H1,H3}$ = 1.5, $J_{H1,H4}$ = 0.4, $J_{H2,H3}$ = 7.0, $J_{H2,H4}$ = 1.3, $J_{H3,H4}$ = 8.3, $J_{H5,H6}$ = 8.2, $J_{H5,H7}$ = 1.2, $J_{H5,H8}$ = 0.5, $J_{H6,H7}$ = 7.0, $J_{H6,H8}$ = 1.5, $J_{H7,H8}$ = 8.2.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-(4''-methoxyphenyl)-1',3'-thiazolidin 4'-one (**4d**).

Yield 74%; mp 282–284 °C (ethanol); Found: C, 66.27; H, 4.16; N, 13.19 $C_{23}H_{18}N_4O_2S$ requires C, 66.65; H, 4.38; N, 13.52%; $\nu_{max}$(KBr)/cm$^{-1}$: 1600 (C=N), 1700 (C=O); $J_{H,H}$ couplings (Hz) extracted by spin simulation [27]: $J_{H1,H2}$ = 8.5, $J_{H1,H3}$ = 1.5, $J_{H1,H4}$ = 0.5, $J_{H2,H3}$ = 7.0, $J_{H2,H4}$ = 1.2, $J_{H3,H4}$ = 8.2, $J_{H5,H6}$ = 8.2, $J_{H5,H7}$ = 1.2, $J_{H5,H8}$ = 0.4, $J_{H6,H7}$ = 7.0, $J_{H6,H8}$ = 1.5, $J_{H7,H8}$ = 8.2.

General Procedure for the Preparation of 2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-substituted-4'-imino-1',3'-thiazolidines **5a–d** and 4'-(9,10-Dihydroacridin-9-ylidene)-hydrazono-2'-substituted imino-1',3'-thiazolidines **6a–d**.

Bromoacetonitrile (64 mg, 0.53 mmol) was added to a solution of thiosemicarbazide **1** (0.53 mmol) in methanol (5 mL) and the mixture left to stir for 2 h after which sodium methoxide (0.029 g, 0.54 mmol) was added. The reaction mixture was then left to stir for another 30 min before being poured into cold water. The solid precipitate was collected by filtration, washed with ether, dried, and crystallized from diethyl ether to afford **5** (which then subsequently isomerized in DMSO solution to **6**).

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-methyl-4'-imino-1',3'-thiazolidine (**5a**).

Yield 60%; mp 232–235 °C (diethyl ether); Found: C, 63.30; H, 4.62; N, 21.53 $C_{17}H_{15}N_5S$ requires C, 63.53; H, 4.70; N, 21.79%.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-allyl-4'-imino-1',3'-thiazolidine (**5b**).

Yield 29%; mp 261–263 °C (diethyl ether); Found: C, 65.34; H, 4.62; N, 19.89. $C_{19}H_{17}N_5O$ requires C, 65.68; H, 4.93; N, 20.16%; $J_{H,H}$ couplings (Hz) extracted by spin simulation [27]: $J_{H1,H2}$ = 8.4, $J_{H1,H3}$ = 1.2, $J_{H2,H3}$ = 7.2, $J_{H2,H4}$ = 1.2, $J_{H3,H4}$ = 8.0, $J_{H5,H6}$ = 8.0, $J_{H5,H7}$ = 1.2, $J_{H6,H7}$ = 6.8, $J_{H6,H8}$ = 1.0, $J_{H7,H8}$ = 8.2.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-phenyl-4'-imino-1',3'-thiazolidine (**5c**).

Yield 78%; mp 132–134 °C (diethyl ether); Found: C, 68.73; H, 4.28; N, 18.45 $C_{22}H_{17}N_5S$ requires C, 68.91; H, 4.47; N, 18.26%.

2'-(9,10-Dihydroacridin-9-ylidene)hydrazono-3'-(4''-methoxyphenyl)-4'-imino-1',3'-thiazolidine (**5d**).

Yield 75%; mp 250–253 °C (diethyl ether); Found: C, 66.43; H, 4.39; N, 16.59 $C_{23}H_{19}N_5OS$ requires C, 66.81; H, 4.63; N, 16.94%.

Acknowledgements.

Financial support from the Slovak grant agency VEGA, grant no. 1/2471/05 (J. I. and P. K.); the Slovak Ministry of Education, International project SK-FIN (J. I. and P. K.); the Academy of Finland, grant no. 4284 (K. P.); and CIMO (E. B.), is gratefully acknowledged. The authors are also grateful to Jana Baranová for assistance with the synthetic work.

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*) Part 2. For Part 1 see the preceding article (ref [10]). **) Corresponding author.

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