

## CONFIGURATION AND CONFORMATION STUDY OF *S*-ALLYL *O*-METHYL *N*-(2- AND 4-SUBSTITUTED ACRIDIN-9-YL)THIOCARBONIMIDATES IN RELATION TO THEIR [3,3] SIGMATROPIC REARRANGEMENT

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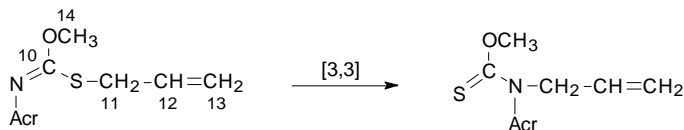
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Configuration and conformations of *S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates were studied by means of NMR spectroscopy, dipole moments and quantum chemical calculations. The *E* configuration was proved for the unsubstituted and 2-chloro derivatives from the NOE-difference spectra. Experimental values of dipole moments were related to those obtained from vector addition. Quantum chemical calculations pointed to the chair conformation of these compounds in transition state for above-mentioned rearrangement.

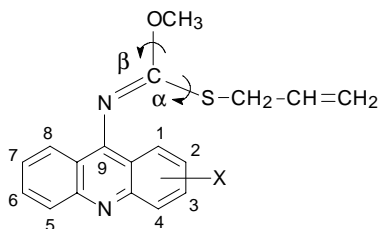
**Key words:** Acridines; Thiocarbonimidates; NOE NMR spectroscopy; Dipole moments; PM3 and HF/3-21G calculations.

In our preceding papers<sup>1</sup>, we studied geometrical structure and dipole moments of a series of 2- and 4-substituted 9-isothiocyanatoacridines as the starting compounds for the synthesis of various acridin-9-yl derivatives. We have prepared *S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates<sup>2</sup> possessing a distinct fluorescence<sup>3</sup> which may be used as markers for biomolecules. Multiple C=N bond combined with allyl group in the position 9 of acridine creates a system capable in principle to undergo a [3,3] sigmatropic rearrangement (*S*→*N* allyl rearrangement<sup>4</sup>, Scheme 1). To obtain further information on these rearrangement studied<sup>5</sup> in our laboratory, we were



SCHEME 1

interested in the preferred conformations which can arise by rotation around the single bonds in the thiocarbonimidate grouping at both possible configurations of the imino group on the acridine skeleton. Here we report the determination of dipole moments of six *S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates **1a–1f** in combination with high-resolution NMR measurements and quantum chemical PM3 calculations as a tool to ascertain their polarity and geometrical structure. To get a look on transition state structure in [3,3] sigmatropic rearrangement of these compounds we have also carried out *ab initio* calculation for *S*-allyl *O*-methyl *N*-(pyridin-4-yl)thiocarbonimidate as a model compound.



1	X
a	H
b	2-OCH <sub>3</sub>
c	2-CH <sub>3</sub>
d	2-Cl
e	4-OCH <sub>3</sub>
f	4-CH <sub>3</sub>

## EXPERIMENTAL

*S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates **1a–1f** were synthesized according to ref.<sup>2</sup>

<sup>1</sup>H (399.65 MHz) and <sup>13</sup>C (100.00 MHz) NMR spectra and <sup>1</sup>H NOE-difference spectra of **1a** and **1d** were recorded on a JEOL Lambda-400 NMR spectrometer in deuteriochloroform at laboratory temperature and calibrated with an internal standard tetramethylsilane (0.00 ppm). To assign <sup>1</sup>H and <sup>13</sup>C chemical shifts, the phase-sensitive double-quantum H,H-COSY and TOSCY spectra, H,C-COSY spectra with *f*<sub>1</sub> decoupling and selective INEPT spectra were measured.

### *S*-Allyl *O*-Methyl *N*-(Acridin-9-yl)thiocarbonimidate (**1a**)

<sup>1</sup>H NMR spectrum: 3.52 ddd, 2 H (H-11); 4.27 s, 3 H (CH<sub>3</sub>O); 5.08 ddt, 1 H (H-13 *cis*); 5.15 ddt, 1 H (H-13 *trans*); 5.75 ddt, 1 H (H-12); 7.45 ddd, 2 H (H-2, H-7); 7.74 ddd, 2 H (H-3, H-6); 7.95 ddd, 2 H (H-1, H-8); 8.18 ddd, 2 H (H-4, H-5). *J*(H,H) coupling constants (Hz): <sup>3</sup>*J*(1,2) and <sup>3</sup>*J*(7,8) = 8.66; <sup>3</sup>*J*(2,3) and <sup>3</sup>*J*(6,7) = 6.59; <sup>3</sup>*J*(3,4) and <sup>3</sup>*J*(5,6) = 8.78; <sup>4</sup>*J*(1,3) and <sup>4</sup>*J*(6,8) = 1.46; <sup>4</sup>*J*(2,4) and <sup>4</sup>*J*(5,7) = 1.16; <sup>5</sup>*J*(1,4) and <sup>5</sup>*J*(5,8) = 0.73; <sup>3</sup>*J*(11,12) = 6.98; <sup>3</sup>*J*(12,13 *cis*) = 10.00; <sup>3</sup>*J*(12,13 *trans*) = 16.92; <sup>4</sup>*J*(11,13 *cis*) = 0.98; <sup>4</sup>*J*(11,13 *trans*) = 1.34; <sup>2</sup>*J*(13 *cis*, 13 *trans*) = 1.28. <sup>13</sup>C NMR spectrum: 33.78 (CH<sub>2</sub>); 56.90 (CH<sub>3</sub>O); 118.21 (C-8a, C-9a); 118.28 (=CH<sub>2</sub>); 123.98 (C-1, C-8); 124.58 (C-2, C-7); 129.56 (C-4, C-5); 130.17 (C-3, C-6); 132.92 (-CH=); 149.52 (C-4a, C-10a); 149.58 (C-9); 159.74 (C=N).

### *S*-Allyl *O*-Methyl *N*-(2-Chloroacridin-9-yl)thiocarbonimidate (**1d**)

<sup>1</sup>H NMR spectrum: 3.53 ddd, 2 H (H-11); 4.27 s, 3 H (CH<sub>3</sub>O); 5.11 ddt, 1 H (H-13 *cis*); 5.17 ddt, 1 H (H-13 *trans*); 5.76 ddt, 1 H (H-12); 7.46 ddd, 1 H (H-7); 7.64 dd, 1 H (H-3); 7.74 ddd, 1 H (H-6); 7.89 dd, 1 H (H-1); 7.91 ddd, 1 H (H-8); 8.11 dd, 1 H (H-4); 8.15 ddd, 1 H (H-5). *J*(H,H) coupling

constants (Hz):  ${}^3J(3,4) = 9.24$ ;  ${}^3J(5,6) = 8.78$ ;  ${}^3J(6,7) = 6.59$ ;  ${}^3J(7,8) = 8.69$ ;  ${}^4J(1,3) = 2.38$ ;  ${}^4J(5,7) = 1.09$ ;  ${}^4J(6,8) = 1.43$ ;  ${}^5J(1,4) = 0.55$ ;  ${}^5J(5,8) = 0.76$ ;  ${}^3J(11,12) = 6.89$ ;  ${}^3J(12,13 \text{ cis}) = 10.00$ ;  ${}^3J(12,13 \text{ trans}) = 16.96$ ;  ${}^4J(11,13 \text{ cis}) = 0.93$ ;  ${}^4J(11,13 \text{ trans}) = 1.36$ ;  ${}^2J(13 \text{ cis}, 13 \text{ trans}) = 1.28$ .  ${}^{13}\text{C}$  NMR spectrum: 33.85 ( $\text{CH}_2$ ); 57.04 ( $\text{CH}_3\text{O}$ ); 118.42 (C-8a); 118.46 ( $=\text{CH}_2$ ); 118.56 (C-9a); 122.48 (C-1); 123.95 (C-8); 125.20 (C-7); 129.61 (C-5); 130.33 (C-2); 130.47 (C-6); 131.29 (C-4); 131.31 (C-3); 132.75 ( $-\text{CH}=\text{}$ ); 147.71 (C-4a); 148.91 (C-9); 149.54 (C-10a); 160.33 (C=N).

### S-Allyl O-Methyl N-(4-Methoxyacridin-9-yl)thiocarbonimidate (**1e**)

Yellow oil; yield 80%. For  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$  (338.43) calculated: 67.43% C, 5.36% H, 8.28% N; found: 67.52% C, 5.19% H, 8.24% N.  ${}^1\text{H}$  NMR spectrum: 3.49 d, 2 H (H-11); 4.12 s, 3 H (4-OCH<sub>3</sub>); 4.24 s, 3 H (OCH<sub>3</sub>); 4.95–5.30 m, 2 H (H-13); 5.45–6.05 m, 1 H (H-12); 6.99 dd, 1 H (H-3); 7.30–7.68 m, 3 H (H-1, H-2, H-7); 7.74 ddd, 1 H (H-6); 7.94 dd, 1 H (H-8); 8.35 dd, 1 H (H-5).

Experimental measurements necessary for the determination of dipole moments were done in benzene at 20 °C. The values of dipole moments were calculated according to Halverstadt and Kumler<sup>6</sup>. The detailed description of measurements of permittivities, refraction indices and densities is given in our previous paper<sup>1</sup>. Molar refractions  $R_D$  were calculated by an addition of molar refraction of acridine<sup>7</sup> and increments of substituents<sup>8,9</sup>. To calculate dipole moment values by means of vector addition, the following standard data<sup>10,11</sup> for bonding or group moments were used (in  $10^{-30}$  Cm):  $\text{C}_{\text{ar}}-\text{H}$  0.00;  $\text{C}_{\text{ar}}-\text{Cl}$  5.29;  $\text{C}_{\text{ar}}-\text{CH}_3$  1.23;  $\text{C}_{\text{ar}}-\text{SCH}_3$  4.46 ( $\Theta$  77.5°);  $\text{C}_{\text{ar}}-\text{OCH}_3$  4.26 ( $\Theta$  42.0);  $\text{C}-\text{OCH}_3$  3.21 ( $\Theta$  61.0°, ref.<sup>12</sup>);  $\text{C}-\text{S}$  3.00;  $\text{C}-\text{N}$  1.49;  $\text{C}=\text{N}$  4.66;  $\text{C}-\text{H}$  1.33;  $\text{C}_{\text{sp}}{}^2-\text{C}_{\text{sp}}{}^3$  2.33; acridine 6.96, ref.<sup>7</sup>. Valence angles: C9–N–C10 120°; N–C10–O 120°; N–C10–S 120°; C10–S–C11 109°; S–C11–C12 109°; C11–C12–C13 120°.

Quantum chemical PM3 and *ab initio* (HF/3-21G) calculations were performed using standard methods<sup>13–15</sup>.

## RESULTS AND DISCUSSION

The synthetic route<sup>2</sup> to *S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates **1a–1f** may afford two stereoisomers *E* and *Z* (Fig. 1). Under given conditions of the synthesis of **1a–1f**, we have detected and isolated only one of two possible stereoisomers in the overall yields from 57 to 90%. To determine the configuration on the C=N double bond we used the NMR spectra of unsubstituted derivative **1a** and 2-chloro derivative **1d**, the dipole moments measurement of **1a–1f** and quantum chemical PM3 calculations.

The  ${}^1\text{H}$  and  ${}^{13}\text{C}$  chemical shifts of **1a** and **1d** were assigned by 2D correlation method and 1D selective INEPT technique, respectively. The observed H,H coupling constants indicate a long-range interaction in allyl and acridine systems. Different  ${}^3J(\text{H},\text{H})$  values in four-spin system H1 to H4 prove that a bond order of C1–C2 and C3–C4 bonds differs from that of C2–C3. From equivalency of chemical shifts of the corresponding protons on the carbon of both side rings in the acridine skeleton of **1a** can be concluded that the aromate is not fixed with respect to thiocarbonimidate grouping and rotates freely.

An evidence of *E* or *Z* arrangement of compounds **1a** and **1d** was accomplished by the NOE-difference experiment. An irradiation of the methoxy singlet at 4.27 ppm in

**1a** caused a 2.2% intensity enhancement of the signal H-1 and H-8 (relatively to -100% intensity of irradiated signal) without enhancement of any other signal in the spectrum. On the contrary, the irradiation of *S*-allyl CH<sub>2</sub> and CH=CH<sub>2</sub> protons did not give any

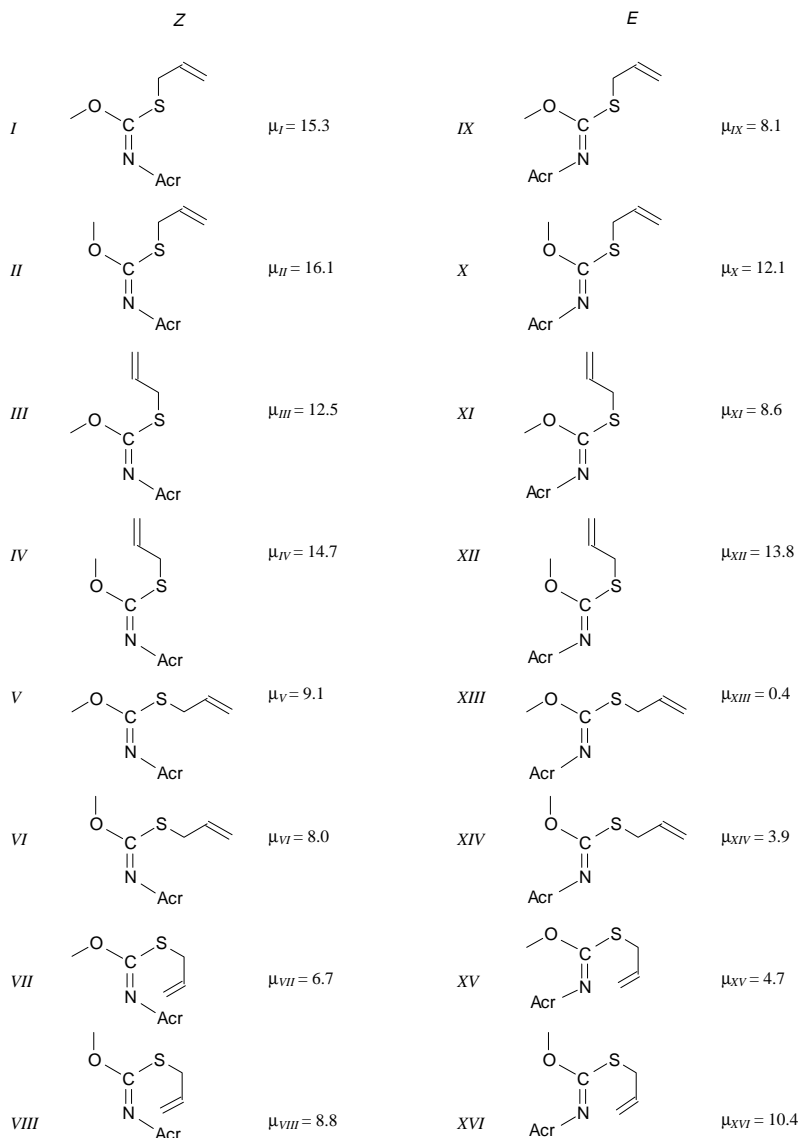


FIG. 1

Conformers of compound **1a** and their theoretical dipole moments ( $\mu$ ) calculated by vector addition method

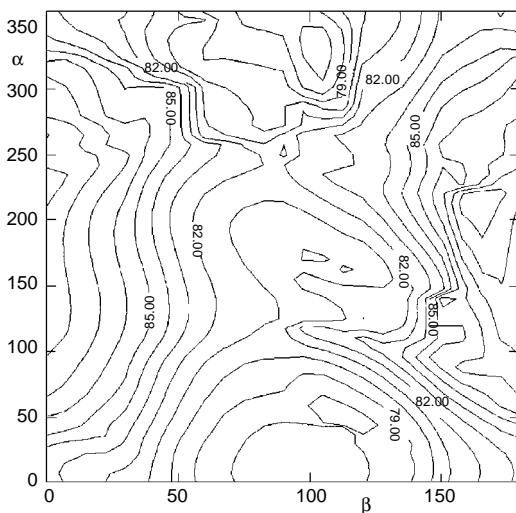
observable enhancement of the intensity of acridine protons. This result confirms *E* configuration of unsubstituted derivative **1a**.

With 2-chloro derivative **1d**, when irradiating the OCH<sub>3</sub> protons, we found the same 0.85% intensity enhancement of both signals of nonequivalent protons H-1 and H-8. This observation supports analogous *E* configuration, as well as a free rotation of acridine with respect to the substituent in 9-position. The second fact cannot be proved for **1d** from chemical shifts analogously as before because all acridine atoms are by virtue of the 2-chloro substitution nonequivalent. The sum of two enhancements (1.70%) is close to **1a** submitting thus an idea of similar interatomic distances between the discussed atoms in the both compounds.

The *E* configuration of **1a** has been approved also by a theoretical approach. Quantum chemical PM3 calculations of the heat of formation for the optimized structures of *E* and *Z* stereoisomers of a **1a** yield for the *E* isomer a value which is by 6.93 kcal/mol lower than that of the *Z* isomer.

Because of complexity of the molecule the problem of conformation is more complicated. From NOE spectra follows that methoxy group is near to acridine so assuming planar *E* conformations, IX, XI, XIII and XV might be assessed as more probable than X, XII, XIV and XVI. For modelling non-planar case, isoenergetic maps were plotted for *E* configuration in the dependence on rotation angles around single bonds C10-S ( $\alpha$ ) and C10-O ( $\beta$ ). It follows from Fig. 2, that for  $\beta$  values 80–120° the heat of formation is within narrow range of 78–80 kcal/mol for any value of angle  $\alpha$ . That means a relatively free rotation around C10-S single bond in **1a** in the region of  $\beta$ . The energetically deepest minimum on the isoenergetic map lies at the value of angle  $\alpha$  approximately 330° and  $\beta$  approximately 105°. It is interesting that practically the same values

FIG. 2  
Isoenergetic map (enthalpies of formation in kcal/mol) for unsubstituted compound **1a**.  $\alpha$  and  $\beta$  are angles of rotation around single bonds C10-S and C10-O, respectively (Scheme 1), starting from planar conformation XV ( $\alpha = 0^\circ$ ,  $\beta = 0^\circ$ , see formula **1**)



of  $\alpha$  and  $\beta$  were obtained also for the energetically deepest minima of the other 2- and 4-substituted derivatives **1b**, **1c** and **1f**, what means that the substituents do not change substantially a mutual position of the functional groups on N=C carbon. Low values for rotational barrier (e.g. **1b**: *E* configuration 3.04 kcal/mol; *Z* configuration 7.44 kcal/mol) pointed to possibility of almost free rotation around C9–N bond for *E* configuration.

We also attempt to derive the most probable conformation from comparison of the experimental dipole moments values  $\mu_{\text{exp}}$  (for **1a–1f** shown with other supplementary values in Table I) and dipole moment values for conformers **1a** obtained by vector addition  $\mu_{I-XVI}$  (Fig. 1). From comparison of  $\mu_{\text{exp}} = 13.34 \cdot 10^{-30}$  C m for **1a** and  $\mu_{I-XVI}$  follows that none of expected conformations IX, XI, XIII, XIV and XV fit well with the

TABLE I

Dipole moments  $\mu_{\text{exp}}$  and molar refractions  $R_D$  for *S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates in benzene at 20 °C

X	$\alpha^a$	$\beta^b$	$P_{2\infty}, \text{cm}^3 \text{mol}^{-1}$	$R_D, \text{cm}^3 \text{mol}^{-1}$	$\mu_{\text{exp}} \cdot 10^{30}, \text{C m}$
H	6.17	-0.41	428.76	95.93	13.34
2-CH <sub>3</sub> O	8.76	-0.28	538.49	101.34	15.29
2-CH <sub>3</sub>	9.71	-0.43	549.43	99.58	15.49
2-Cl	8.47	-0.21	649.55	100.77	17.14
4-CH <sub>3</sub> O	3.29	-0.18	253.18	101.34	8.86
4-CH <sub>3</sub>	5.28	-0.18	337.55	99.58	11.26

<sup>a</sup> Slope of relationships  $\epsilon_{12}$  versus weight fractions  $w_2$ . <sup>b</sup> Slope of relationships  $1/d_{12}$  versus weight fractions  $w_2$ .

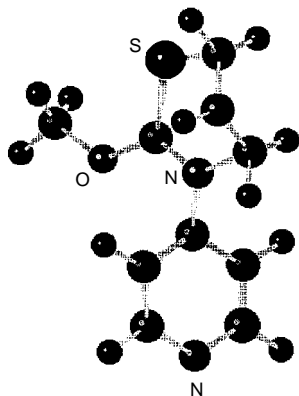


FIG. 3  
*Ab initio* (HF/3-21G) calculated structure of transition state for *S*-allyl *O*-methyl *N*-(pyridin-4-yl)-thiocarbonimide as a model compound

experimental dipole moment values. We assume that the values  $\mu_{\text{exp}}$  result from contribution of several, probably non-planar conformations possessing of different lifetime.

Regarding synthetic aspects of the problem it is interesting to assess which of the above-mentioned configurations or conformations is advantageous for the realization of [3,3] sigmatropic rearrangement described in our preceding paper<sup>5</sup>. Optimized distance between N and C13 for the starting configuration (conformation XV), transition state and product of the [3,3] sigmatropic rearrangement are 376, 169 and 149 ppm, respectively. It is known<sup>16</sup> that these Pd<sup>2+</sup>-catalyzed rearrangements take course *via* chair-like structure intermediate, which is similar to transition state structure in thermal non-catalyzed reaction. In this case only chair and boat conformations are energetically advantageous and to these are structurally near conformations XIV and XV (Fig. 1). As follows from Fig. 3, illustrating *ab initio* (HF/3-21G) calculated structure of transition state for *S*-allyl *O*-methyl *N*-(pyridin-4-yl)thiocarbonimidate, as a model compound, atomic grouping in [3,3] sigmatropic rearrangement creates a chair-like conformation. Qualitatively we have obtained the same results for structure of transition state of *S*-allyl *O*-methyl *N*-(acridin-9-yl)thiocarbonimidate by means of PM3 calculations.

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