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9-Isothiocyanatoacridines: Convenient Synthons for New Functionalized 9-Acridinyl Derivatives

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Abstract

The specific physicochemical and spectral properties (dipole moments, NMR and fluorescence spectra) of 2- and 4-substituted 9-isothiocyanatoacridines were studied and compared with the series of *m*, *p*-substituted phenyl and benzoyl isothiocyanates. The high reactivity of heterocumulene bonds in the NCS group and that of 9 and 10 position in the acridine skeleton were utilized for the synthesis of new types of compounds, e.g. spiro dihydroacridine 9(10*H*),4'-thiazolines. Iminothiocarbonates or dithiocarbamates are the intermediates of these unusual addition-cyclization reactions. A new reagent, 1-azonium-4-azabicyclo[2.2.2]octane hydrogen-sulfide [DABCOH]$^{(+)}$SH$^{(-)}$, was developed for the preparation of hitherto inaccesible 9-acridinyl dithiocarbamates as well as 3-(9'-acridinyl)-5-substituted tetrahydro-1,3,5-thiadiazine-2-thiones. The reaction of iminothiocarbonates with bromoacetyl bromide represents a general method for the synthesis of 3-substituted 1,3-thiazolidine-2,4-diones from various type of isothiocyanates. The reaction of 9-hydrazinoacridine with 1-isothiocyanato-1-ethoxy-propane affords, instead of the expected 1,2,4-thiazoline derivative, the *N*-acridinium-9-yl-*N*'-propylidenehydrazine thiocyanate. The structures of the synthesized compounds were confirmed with IR, NMR, MAS spectra and X-ray analysis.

Keywords: Isothiocyanates, 9-acridinyl derivatives, spectra, kinetics, fluorescence

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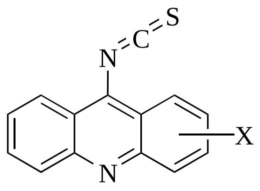
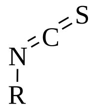
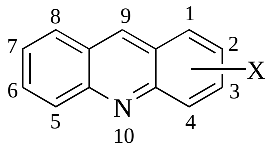
Introduction

Two remarkable facts inspired us to study the 9-isothiocyanatoacridines: the high reactivity of the N = C = S group and the biologically atractive acridine skeleton.







X = H, 2-OCH_3, 2-CH_3, 2-Cl, 2-NO_2, 4-CH_3, 4-OCH_3

The results, which we obtained during 30 years of experience with more than 200 isothiocyanates (ITC), allowed us to characterize the following main types of reactions of the -NCS group [1a,b]: a) biologically important Ad_N reactions with -SH, -NH_2, -OH groups, b) cyclo-condensation reactions of bifunctionalized ITC forming heterocyclic compounds with rings of various size, and c) cycloadditions with controlled selectivity (regio, chemo or periselectivity). In the case of acridine derivatives, the next important properties can be pointed out [2a]: antimicrobial activity [2b], intercalating effect resulting in cytostatic activity [2c] and fluorescence [2d].

Results and Discussion

To obtain a new view on structure and reactivity of 9-isothiocyanatoacridines, the dipole moments and spectral properties were studied and compared with those of a series of *meta*- and *para*-substituted phenyl and benzoyl isothiocyanates [3a-d]. The experimental values of dipole moments, as well as values determined by vectorial addition of group dipole moments, give evidence that the charge distribution in the molecule of 9-isothiocyanatoacridine is delocalized.

Table 1. *SCS (ppm) of the -Cl, -NH_2 and -NCS substituents on ipso carbon in phenyl and acridinyl derivatives*

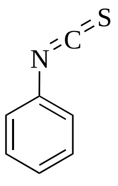
Compound	^{a}Cl	^{b}NH_2	^{a}NCS
Benzene (C = 128.5)	+5.9	+19.2	+2.4
Acridine (C-9 = 135.9)	+5.1	+13.8	–3.7

^{a}$CDCl_3$; ^{b}$(CD_3)_2SO$; SCS = $\delta\,(^{13}C_{ipso} - X) - \delta\,(^{13}C_{ipso} - H)$

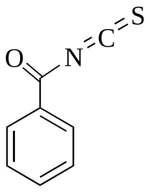
Table 2. *The values of IR absorption bands and ^{13}C-NMR resonance signals of the NCS group of acridinyl, phenyl and benzoyl isothiocyanates [5,6]*

*Parameter	Bz-N = C = S	Acr-N = C = S	Ph-N = C = S
ν_{as} (NCS)	1930–1987	2045–2075	2103–2137
^{13}C (NCS)	145.4–150.8	140.2–142.9	133.9–140.4

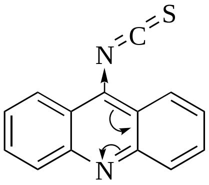
*Measured in $CHCl_3$ ($CDCl_3$)



μ = 11.4*

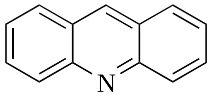


μ = 10.9*



μ = 2.8*

pK$_a$ 4.1



μ = 6.9*

pK$_a$ 5.58

*·10^{-30} Cm

We can assume, that in the proximity of the -NCS group the -I effect operates , while in the acridine nucleus the -M effect of the heteroatom is evident (see also the pKa values) [4]. This fact is also manifested when comparing the ipso substituent chemical shifts (SCS) increments of the -NCS, -NH_2, -Cl substituents for C-9 carbon in ^{13}C-NMR spectra of 9-acridinyl derivatives and their phenyl analogs [5].

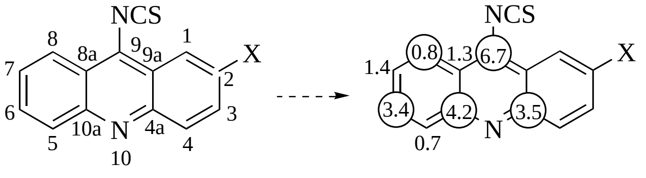
The polarity of the -NCS group is also reflected very convincingly by comparison of the IR absorption bands and the ^{13}C-NMR resonance signals of 9-acridinyl, phenyl and benzoyl isothiocyanates. From the obtained values is evident, that the electrophility of carbon atom of the -NCS group increases in the order phenyl < acridine < benzoyl isothiocyanates (Table 2) [5,6].

This conclusion is comparable with the reactivity of 9-ITC-acridine towards *n*-butylamine [7a,b]. From the values given in Table 3, it follows, that ITC-acridine reacts two orders of magnitude faster than phenyl ITC and two order of magnitude slower than benzoyl ITC. The ratio of the rate constants of acridinyl and phenyl ITC with 15 amino acids shows that the reaction proceeds from 6 to 22 times faster in the case of acridines which could be of interest from a biological point of view [7c].

Table 3. *Comparison of rate constants of phenyl, 9-acridinyl and benzoyl isothiocyanates [7] with* n*-butylamine in acetonitrile at 25 °C*

Rate constants	Ph-NCS	Acr-NCS	Ph-CONCS
k ($l\cdot mol^{-1}\cdot s^{-1}$)	0.055	16.97	2893

^{13}C-NMR study of 2-substituted 9-isothiocyanatoacridines enabled us to conclude, that the substituent effect is also transferred to unsubstituted benzene ring [8]. For the atoms separated by an even number of bonds from substituent (C-9, C-4a, C-10a, C-6), the maximum differences of ^{13}C chemical shifts in a measured series are from 3 to 5 times greater (3.3–6.7 ppm) than those for carbon atoms separated by an odd number of bonds (0.5–1.5 ppm for C-4, C8a, C-5 and C-7).



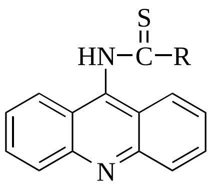
X = H, 2-OCH$_3$, 2-CH$_3$, 2-Cl, 2-NO$_2$

Numbers in circle correspond to SCS values (in ppm).

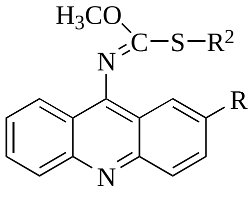
To elucidate the fluorescence properties of 48 9-acridinyl derivatives, in addition to 2- and 4-substituted 9-isothiocyanatoacridines [5], the fluorescence spectra of 9-acridinylthioureas **1a-d** [9] and 9-acridinyl iminothiocarbonates **2a-d** [9b] were also measured (Fig. 1, Table 4).

All compounds under investigation exhibited an intense green-yellow fluorescence band in UV light. The substitution on the acridine skeleton has a negative influence on the intensity of the fluorescence of acridine isothiocyanates with the exception of the 2-methoxy derivative, which is 2.2 times more intense than the unsubstituted derivative. In a large series of the investigated compounds, the thiourea with amino acid residues other than proline **1a,b** exhibit higher fluorescence than the equivalent isothiocyanates This is in contrast to aromatic thioureas **1c,d** which have lower fluorescence.

Table 4. *Relative fluorescence F/F$_0$ of some acridine thioureas **1** and iminothiocarbonates **2**.*



1a-d



2a-d

No	R	F/F$_0$	N$_0$	R^1	R^2	F/F$_0$
1a	Ala	16.1	2a	H	Allyl	1.74
1b	Pro	0.53	2b	H	Me	0.38
1c	NHC$_4$H$_9$	1.36	2c	OCH$_3$	Allyl	3.18
1d	NHC$_6$H$_4$NO$_2$	0.03	2d	OCH$_3$	Me	0.38

1a, b *measured in hepes-acetonitrile (7:3);* ***1c, d*** *and* ***2a-d*** *in acetonitrile referenced to 9-isothiocyanatoacridine (F_0 = 1)*

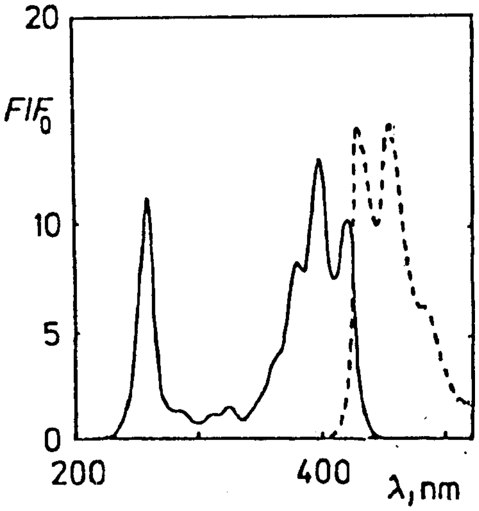
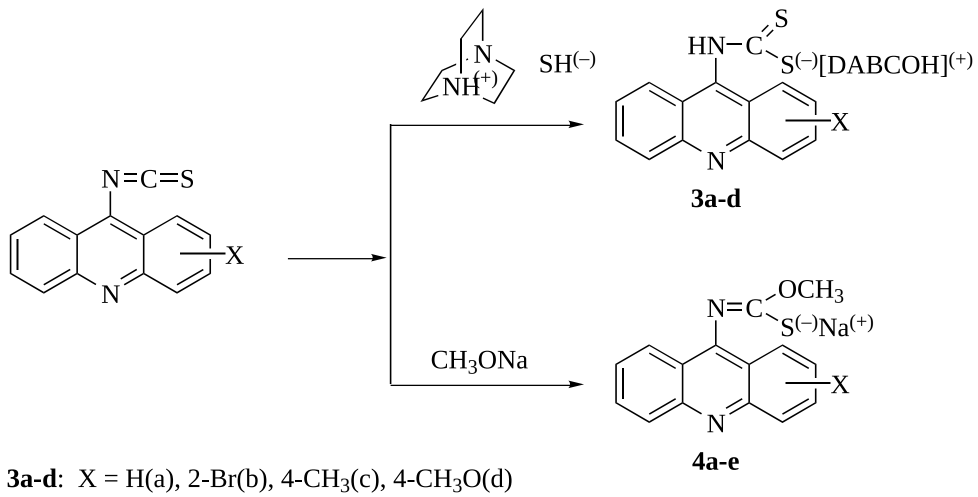
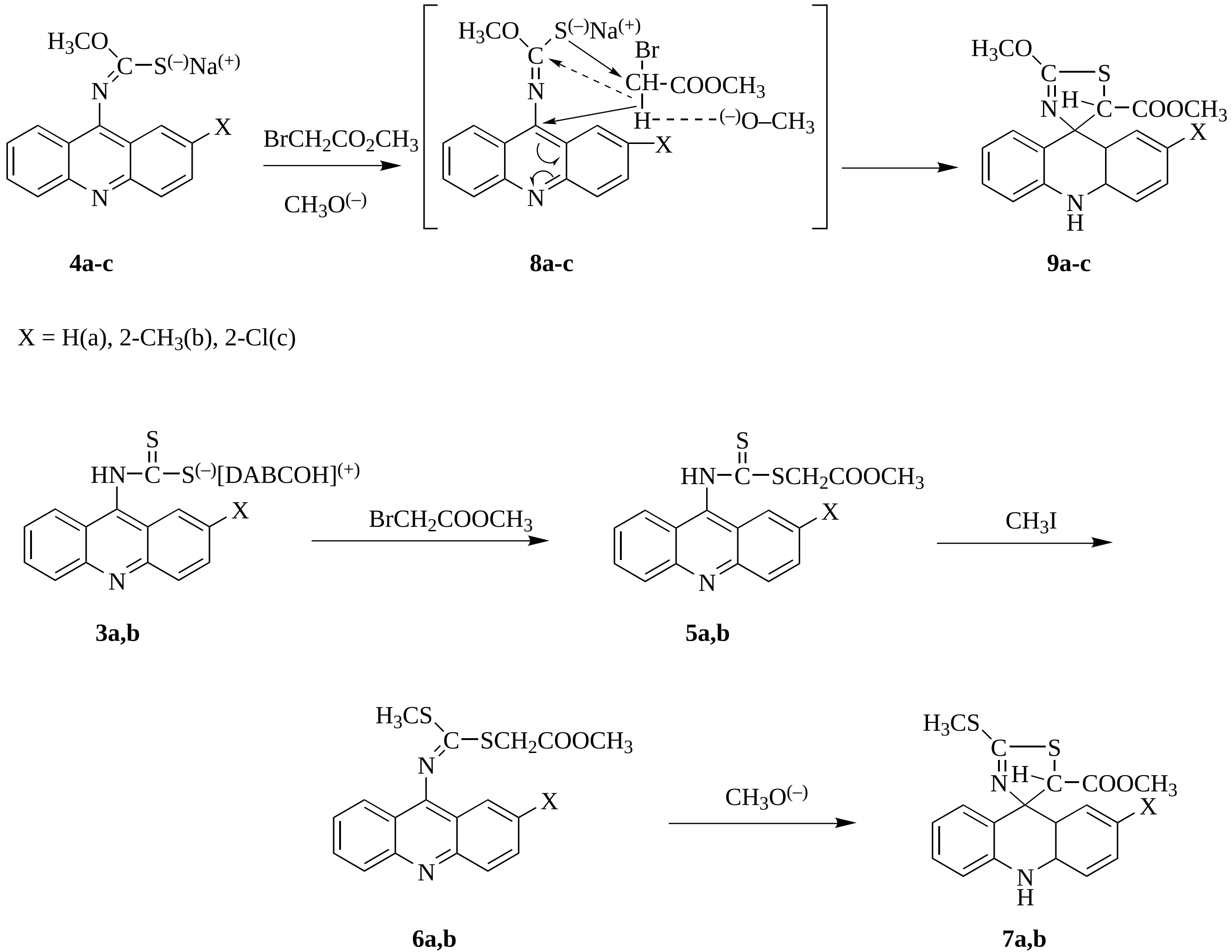


Figure 1. *Excitation (–) and emission (---) spectra of compound* ***1a*** *at excitation wavelength λ_{ex} 398 nm and emission wavelength λ_{em} 456 nm.*



3a-d: X = H(a), 2-Br(b), 4-CH$_3$(c), 4-CH$_3$O(d)
4a-e: X = H(a), 2-CH$_3$(b), 2-CH$_3$O(c), 2-Cl(d), 4-CH$_3$(e)

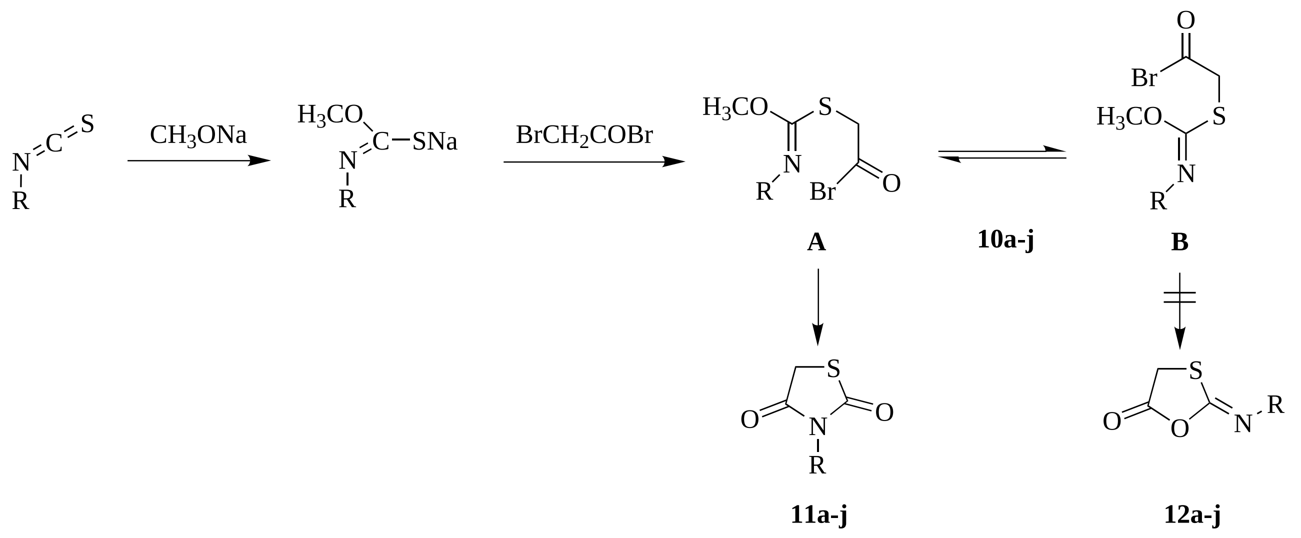
Scheme 1



X = H(a), 2-CH$_3$(b), 2-Cl(c)

X = H(a), 2-CH$_3$(b)

Scheme 2



Scheme 3

11	R
a	9-acridinyl
b	2-chloro-9-acridinyl
c	4-methyl-9-acridinyl
d	methyl
e	phenyl
f	4-methoxyphenyl
g	4-bromophenyl
h	4-chlorophenyl
i	1-naphthyl
j	1-naphthylmethyl

In the case of iminothiocarbonates **2a,d** the intensity of fluorescence in comparison with isothiocyanates, namely for allyl derivatives in combination with a methoxy group, is increased. Unfortunately we did not find direct dependence between the fluorescence intensity and structural parameters of the compounds under study but the series are not representative enough to be generalized.

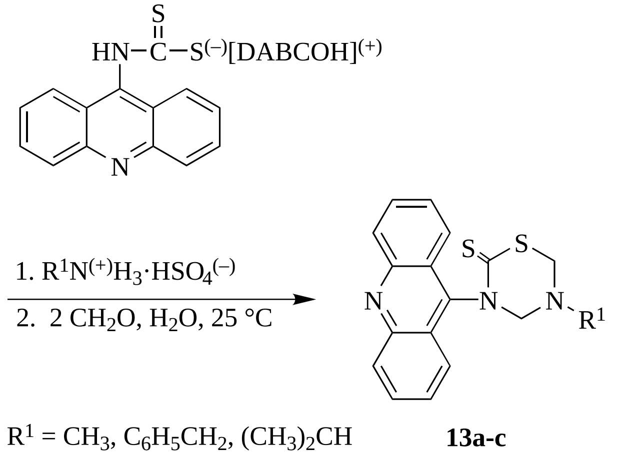
The data obtained, concerning the structure and reactivity of isothiocyanatoacridines, increased our interest in using these derivatives in organic synthesis. Our first attempt to prepare new synthons, i.e. 9-acridinyl dithiocarbamates by hitherto known methods [10] (from amines and carbon disulfide, or isothiocyanates and sodium hydrogen sulfide) was not successful. We ascribe this failure to an amino-imino tautomerism of the starting 9-aminoacridines, or secondly to the instability of the resulting sodium 9-acridinyl dithiocarbamate. However, we found out that the relatively stable dithiocarbamates **3a,b** could be obtained in high yields and in a short time by the reaction of 9-isothiocyanatoacridines with a new reagent, 1-azonium-4-azabicyclo[2.2.2]octane hydrogensulfide $[DABCOH]^{(+)}SH^{(-)}$. This reagent was prepared from 1,4-diazabicyclo[2.2.2]octane and sulfane [11].

As the second type of synthone, we prepared sodium *O*-allyl-(9-acridinyl)-iminothiocarbonates **4a-e** [12] by the addition of an excess of sodium methoxide to isothiocyanatoacridines (Scheme 1).

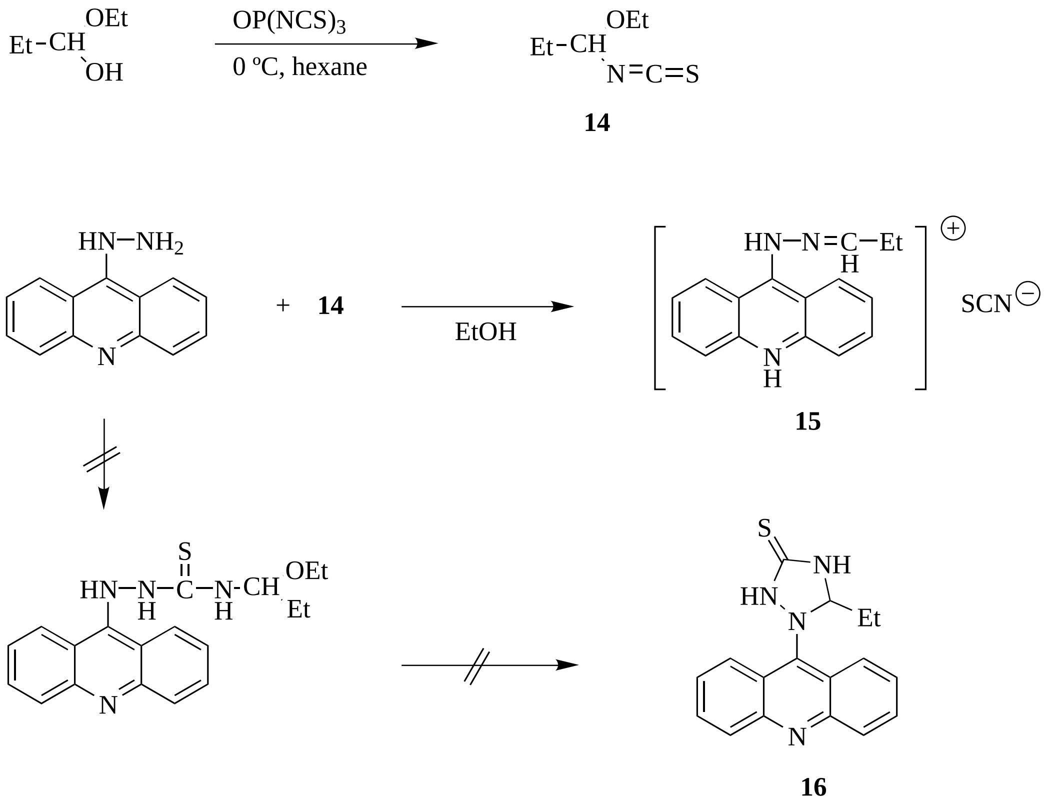
Both intermediates react with methyl bromoacetate with the formation of 2,2',5'-substituted spiro[dihydroacridine 9(10*H*), 4'-thiazolines] according to Scheme 2.

In the case of dithiocarbamates the first intermediate was the corresponding methoxycarbonyl ester **5a,b**, which by treatment with methyl iodide affords *S*-methyl-*S*-methoxycarbonyl derivative **6a,b**. This compound was cyclized by subsequent reaction with sodium methoxide to the final spiro derivative **7a,b**.

On the other hand, the reaction with iminothiocarbonate proceeds in the presence of an excess of sodium methoxide. The carbanion, generated from methyl bromoacetate in the



Scheme 4



Scheme 5

second step of the reaction, immediately attacks the acridine C-9 carbon with the formation of the spiro compound. This step is facilitated due to binding of the proton to the hetero nitrogen and thus the 9,10-dihydroacridine product is stabilized [13a]. As deduced from X-ray crystallography, the condensed benzene rings of the dihydroacridine skeleton adopt an arch shape whereas the central and thiazoline ring have a boat and envelope conformation, respectively [13b].

Using bromoacetyl bromide instead of methyl bromoacetate, the sulfur atom of iminothiocarbonates was preferentialy alkylated and not acylated [14] (the acyl carbon atom gives a harder acid) (Scheme 3).

We can demonstrate this intermediate in two rotational conformers **A** and **B** **10a-j** (Scheme 3). Cyclization from **A** affords 1,3-thiazolidine-2,4-diones **11a-j**, whereas the cyclization of **B** results in 2-amino-1,3-oxathiolanes **12a-j**. The spectral data and independent synthesis have unequivocally confirmed that the reaction affords exclusively the corresponding thiazolidine-2,4-diones. We also performed this reaction with other types of isothiocyanates. From the experiments it follows that the reaction represents a general method for the synthesis of 3-substituted 1,3-thiazolidine-2,4-diones from various types of isothiocyanates.

The above mentioned 9-acridinyl dithiocarbamates were used to derivatize interesting pesticides, as tetrahydro-1,3,5-thiadiazine-2-thiones with acridine skeleton (Scheme 4).

The dithiocarbamates reacted in water solution with ammonium sulfate and formaldehyde to 3-(9'-acridinyl)-5-substituted tetrahydro-1,3,5-thiadiazine-2-thiones in excelent yields [11].

No less interesting was the reaction of 9-hydrazinoacridine with 1-ethoxy-1-isothiocyanatopropane. This iso-thiocyanate was prepared by the reaction of phosphoryl isothiocyanate with propanalethyl acetal [15] (Scheme 5).

Instead of expected triazolidine **16**, whose derivatives are formed in the analogous reaction of α-isothiocyanatoethers with phenyl or methyl hydrazine, we obtained *N*-acridinium-9-yl-*N*'-propylidenehydrazine thiocyanate **15**, the structure of which was also corroborated by X-ray analysis [16] (Fig. 2). The NH- group of the ring system forms an interionic hydrogen bond with the N-atom of the thiocyanate ion, while the NH-group of the side chain forms a weak hydrogen bond with the S-atom of a different anion.

All structures of the synthetized compounds were also unambiguously confirmed by IR, UV, NMR and MS spectra as well as by elementary analysis.

The main goal of this contribution is to present a new look at the broad possible use of 9-isothiocyanatoacridines as convenient intermediates for organic synthesis, biologically interesting compounds, and fluorescence microanalytical reagents.

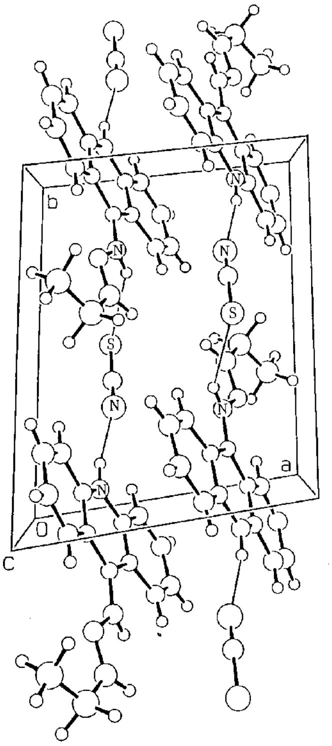


Figure 2. *Molecular packing of* N-*arcidinium-9-yl*-N*'-propylidenehydrazine thiocyanate.*

Experimental Section

General

^{1}H- (600 MHz) and ^{13}C- (150 MHz) NMR spectra were recorded in CDCl$_3$ and Me$_2$SO-d$_6$, resp. with a Bruker AMX 600, TESLA BS 587 (80 MHz) and TESLA BS 567 (25 MHz). Absorption spectra of the isothiocyanates were obtained with a UV-3000 Shimadzu spectrophotometer (concentration $1.6{\times}10^{-5}$ mol·l^{-1}) and fluorescence spectra on an RF 5000 Shimadzu spectrofluorimeter (concentration $1.6{\times}10^{-6}$-mol·l^{-1}). Kinetic measurements were performed on UV-VIS SuperScan 3 (Varian) and Specord M 42 (Zeiss) spectrometers. The kinetics of isothiocyanates were followed by the stopped-flow technique (model 1 705, Applied Photophysics). Mass spectra were taken on an SSQ 710 Finnigan spectrometer with direct inlet and determined at an ionizing voltage of 70 eV. IR spectra were recorded on a SPECORD 75 IR (Zeiss). Elemental analyses were performed on a Perkin-Elmer CHN 2400 analyzer. Permittivities of the substances were measured on a Dipolmeter DM 01 (Wissenschaftlich-technische Werksttaten GmbH). Refractive indices were measured on an immersion Abbe refractometer (Zeiss).

Synthesis

*N-(9-acridinyl)methoxycarbonylmethyl dithiocarbamate (**5a**)*

Methyl bromoacetate (0.31 g, 2 mmol) in dichloromethane (10 ml) was added dropwise under N$_2$ to a stirred suspension of 1-azonium-4-azabicyclo[2.2.2]octane *N*-(9-acridinyl)dithiocarbamate (0.77 g, 2 mmol) **3a** in dichloromethane (40 ml), cooled in an ice bath. The mixture was stirred for 2 h at rt. The separated precipitate was filtered off and washed with water (30 ml). The crude product was purified by recrystallization (nitromethane) to give 0.51 g (74%) of **5a** as orange crystals:148–150 °C; IR (KBr): 1730 and 1525 cm^{-1}; ^{1}H-NMR: (Me$_2$SO-d$_6$) δ 3.52 (s, 3H, O-CH$_3$), 3.94 (s, 2H, S-CH$_2$), 7.43–8.29 (m, 8H, AcrH). Anal. Calcd for C$_{17}$H$_{14}$N$_2$O$_2$S$_2$: (342.44), 59.63; H, 4.12; N, 8.18. Found: C, 58.92; H, 3.98; N, 7.86.

*N-(2-methyl-9-acridinyl)methoxycarbonylmethyl dithiocarbamate (**5b**)*

Isolated 0.58 g (81%) from nitromethane: mp 125–128 °C. IR (CHCl$_3$): 1735, and 1570 cm^{-1}); ^{1}H-NMR (CDCl$_3$/Me$_2$SO-d$_6$ (1:2)) δ (ppm) 2.55 (s, 3H, CH$_3$-2), 3.57 (s, 3H, OCH$_3$), 3.92 (s, 2H, S-CH$_2$), 7.43–8.46 (m, 7H, AcrH). Anal. Calcd for C$_{18}$H$_{16}$N$_2$O$_2$S$_2$: (356.46), C, 60.65; H, 4.52; N, 7.86. Found: C, 61.25; H, 4.72; N, 8.16.

*S-methyl-S-methoxycarbonylmethyl-N-(9-acridinyl)-iminodithiocarbonate (**6a**)*

Methyl iodide (0.5 g, 3.5 mmol) was added dropwise under N$_2$ to dithiocarbamate **5a** (0.51 g, 1.5 mmol) in methanol (40 ml). The mixture was stirred for 3 h at 50 °C. The solution was filtered with charcoal, the filtrate was concentrated in vacuo and the residue was triturated with a small amount of ether. The crystals obtained were crystallized from a mixture of methanol/ether to give 0.35 g (65%) of **6a** as yellow crystals: mp 150–152 °C. IR (CHCl$_3$): 1735, 1627, and 1560 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ (ppm) 2.69 (s, 3H, S-CH$_3$), 3.48 (s, 3H, O-CH$_3$), 4.16 (s, 2H, S-CH$_2$), 7.7–9.11 (m, 8H, AcrH), ^{13}C NMR (CDCl$_3$) δ (ppm) 15.75 (*S*-CH$_3$), 34.75 (*S*-CH$_2$CO), 53.26 (O-CH$_3$), 116.31, 120.04, 125.30, 127.13, 136.69, 140.27 and 162.56 (^{13}C-Acr), 167.93 and 170.17 (C = N, C = O). Anal. Calcd for C$_{18}$H$_{16}$N$_2$O$_2$S$_2$: (356.46) C, 60.65; H, 4.52; N, 7.86. Found: C, 60.16; H, 4.32; N, 7.55.

*2'-Methylthio-5'-methoxycarbonyl-spiro[dihydroacridine (10H), 4'-tiazoline] (**7a**)*

Sodium methanolate (0.11 g, 2 mmol) was added to a solution of **6a** (0.36 g, 1 mmol) in methanol (30 ml). The mixture was stirred for 0.5 h at rt. Water (50 ml) was added and the solution was neutralized with hydrochloric acid (12%). The pale yellow precipitate was extracted with chloroform (3×15 ml) and dried with $CaCl_2$. The crude product obtained after evaporation of the solvent was recrystallized (chloroform/ether) to give 0.19 g (53%) of **7a** as pale yellow crystals: mp 162–164 °C. IR ($CHCl_3$): 3435, 1830, and 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.75 (s, 3H, -CH_3), 3.18 (s, 3H, O-CH_3), 4.38 (s, 1H, CHCO), 6.52 (bs, 1H, NH), 6.86–7.42 (m, 8H, AcrH). ^{13}C- NMR ($CDCl_3$) δ (ppm) 15.90 (CH_3), 52.25 (CH-5'), 66.51 (CH_3-O), 85.25 (C-9), 113.58, 114.37, 120.49, 121.05, 125.97, 127.69, 128.59 and 128.89 (CH-1, 2, 3, 4, 5, 6, 7, 8), 118.88 and 121.87 (C-8a, 9a), 137.47 and 138.48 (C-4a, 10a), 167.15 a 169.20 (C = N, C = O). Anal. Calcd for $C_{18}H_{16}N_2O_2S_2$: (356.46) C, 60.65; H, 4.52; N, 7.86. Found: C, 59.94; H, 4.34; N, 7.51.

*2'-Methylthio-5'-methoxycarbonyl-spiro[2-methyldihydroacridine 9(10H), 4'thiazoline] (**7b**)*

The product **7b** was prepared according to procedure for **7a** however without isolation of **6b**, i.e. after the methylation of **5b** sodium methanolate (0.11 g, 2 mmol) was added and continued as in **7a** to give 0.2 g (54%) of **7b** as yellow crystals:173–175 °C. IR ($CHCl_3$): 3435, 1740, and 1590 cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.28 and 2.31 (s, 3H, CH_3-2), 2.75 and 2.77 (s, 3H, S-CH_3), 3.18 (s, 3H, O-CH_3), 4.32 and 4.43 (s, 1H, CH-5'), 6.77 (bs, 1H, NH), 6.66–7.40 (m, 7H, AcrH). Anal. Calcd for $C_{19}H_{18}N_2O_2S_2$: (370.48), C, 61.59; H, 4.89; N, 7.56. Found: C, 60.76; H, 4.67; N, 7.23.

N-acridinium-9-yl-N'-propylidenehydrazine thiocyanate (15)

9-Hydrazinoacridine (2.09 g, 10 mmol) in ethanol (10 ml) was added dropwise under N_2 to a stirred and cooled (ice+NaCl) solution of isothiocyanate **14** (1.45 g, 10 mmol) in ethanol (5 ml). The precipitated crude product was recrystallized from ethanol/ether to give 2.16 g (70%) of **C** as deep yellow crystals: mp 188–195 °C. IR ($CHCl_3$): 2985, 2055, 1635, and 1585 cm^{-1}), ^{1}H-NMR (at –38 °C, $CDCl_3$) δ (ppm) 1.30 (t, 3H, J = 7.2 Hz, CH_3), 2.65 (dq, 2H, J = 4.1, 7.2 Hz, CH_2), 6.98 (m, 1H, H-7), 7.00 (m, 1H, H-6), 7.24 (m, 1H, H-2), 7.37 (d, 1H, J = 9.1 Hz, H-5), 7.73 (m, 1H, H-3), 7.83 (d, 1H, J = 8.4 Hz, H-4), 8.36 (d, 1H, J = 8.8 Hz,), 8.59 (t, 1H, J = 4.1 Hz, CH = N), 9.33 (d, 1H, J = 8.9 Hz, H-1), 11.58 (broad, 1H, NH), 12.80 (broad, 1H, NH); ^{13}C-NMR (at –38 °C, $CDCl_3$) δ (ppm) 10.1 (CH_3), 26.8 (CH_2), 110.0 (C-8a), 111.2 (C-9a), 118.0 (CH-5), 118.3 (CH-4), 123.2 (CH-8), 123.7 (CH-2), 124.0 (CH-7), 130.4 (CH-1), 133.6 (CH-6), 134.8 (CH-3), 137.4 (C-10a), 140.0 (C-4a), 149.2 (C-9), 161.1 (CH = N); MS *m/e* 250.2 [M+. - SCN]. Anal. Calcd for $C_{17}H_{16}N_4S$: (308.41), C, 66.21; H, 5.23; N, 18.17. Found: C, 67.01; H, 5.06; N, 18.02.

The details on the synthesis of additional 9-acridinyl derivatives discussed in this paper are given in the original papers **1a–d** [9a], **2a–d** [9b], **3a–d** [11], **4a–e** [12], **9a–c** [13a,b], **11a–j** [14] and **13a–c** [11].

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