KINETICS OF REACTIONS OF 9-ISOTHIOCYANATOACRIDINE WITH AROMATIC AND ALIPHATIC AMINES AND FLUORESCENCE PROPERTIES OF THE 1-ACRIDIN-9-YL-3-ALKYL(ARYL)THIOUREAS OBTAINED

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Received July 15, 1994
Accepted September 5, 1994

Dedicated to Professor Milan Kratochvil on the occasion of his 70th birthday.

Kinetics of nucleophilic addition reaction of 9-isothiocyanatoacridine with seventeen aliphatic and aromatic amines in organic solvents has been studied by the VIS spectroscopic method. 9-Isothiocyanatoacridine reacted by about two orders of magnitude faster than phenyl isothiocyanate. The reaction rates of aliphatic amines were markedly affected by steric effects. Excepting 1-acridin-9-yl-3-butylthiourea (*IIIo*), the products obtained exhibited weaker fluorescence than the starting 9-isothiocyanatoacridine.

Thanks to their high reactivity, isothiocyanates represent very useful reagents in nucleophilic additions as well as cycloadditions[1]. From the biochemical point of view, of great importance are reactions of the NCS group with the OH, NH and SH groups present in essential biomolecules[2,3] (enzymes, peptides, DNA, RNA). Various authors[4–6] have studied the mechanism of reactions of aromatic and aliphatic isothiocyanates and acyl isothiocyanates, both in aqueous and anhydrous media. In this respect, 9-isothiocyanatoacridines proved to be very interesting because their high fluorescence and specific biological properties of the acridine skeleton made them potential fluorogenic reagents and important intermediates in the synthesis of biologically active organic compounds[7–9]. In our preceding studies[10,11] we investigated the reactions of 9-isothio-

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cyanatoacridine with various amino acids in aqueous buffered solutions leading to fluorescent *N*-9-(acridinylthiocarbamoyl)amino acids. We have found that the reactivity of 9-isothiocyanatoacridines lies between that of aryl and acyl isothiocyanates. So far, only reactions of isothiocyanates with aliphatic amines have been studied because aromatic amines absorb strongly in the UV region and the overlap of the absorption bands of both compounds hindered application of UV-spectroscopic methods. However, the strong absorption of 9-isothiocyanatoacridines in the visible region of the spectrum enabled us to study the reactivity of the NCS group also with aromatic amines of the aniline type.

The present communication affords quantitative data on the reactivity of 9-isothiocyanatoacridine with a series of aliphatic and aromatic primary amines in order to study structure–reactivity relationships. At the same time we were interested in the fluorescence and physicochemical properties of the obtained 1-acridin-9-yl-3-alkyl(aryl)-thioureas from the viewpoint of possible biological effects.

EXPERIMENTAL

Spectral Measurements

Proton NMR spectra (δ, ppm) were measured on a Tesla BS 587A (80 MHz) instrument at room temperature in $(CD_3)_2SO$ with tetramethylsilane as internal standard. Infrared spectra (ν, cm^{-1}) were obtained with an IR-75 (Zeiss, Germany) double-beam spectrometer using KBr technique. UV-VIS spectra were recorded on a UV-3000 Shimadzu spectrophotometer, concentration $1.99 \cdot 10^{-5}$ mol l^{-1} (*IIIb* – *IIIn*) and $0.99 \cdot 10^{-4}$ mol l^{-1} (*IIIa*, *IIIo* – *IIIr*). Fluorescence spectra were measured at 25 °C on an RF 5000 Shimadzu spectrofluorimeter in dimethylformamide (excitation wavelength 395 nm), the thiourea concentration being $4 \cdot 10^{-6}$ mol l^{-1} (except for *IIIo* whose concentration was $2 \cdot 10^{-6}$ mol l^{-1}). The fluorescence spectrum of compound *I* was measured in dimethylformamide at concentration $1 \cdot 10^{-6}$ mol l^{-1}.

Kinetic Measurements

Kinetic measurements were performed at 420 nm on UV-VIS SuperScan 3 (Varian, Australia) and Specord M 42 (Zeiss, Germany) spectrophotometers at 25 °C. The concentration of isothiocyanate *I* was $0.66 \cdot 10^{-4}$ mol l^{-1}, concentration of the amines *IIa* – *IIr* $0.33 \cdot 10^{-2}$ mol l^{-1}; this ensured a pseudo-first order reaction. Apparent rate constants k' (s^{-1}) were obtained from the slope of the linear dependence log [log (A_∞/A_t)] against time t. The rate constant k (l mol^{-1} s^{-1}) was calculated by dividing k' with the amine concentration.

Chemicals

9-Isothiocyanatoacridine was prepared[11] by reaction of 9-chloroacridine with AgSCN. Amines (Fluka) were purified by crystallization or distillation. Acetonitrile was dried over phophorus pentoxide and distilled. Dioxane was distilled and dried over sodium. Ethyl acetate was purified by heating with potassium carbonate followed by distillation.

Preparation of 1-Acridin-9-yl-3-alkyl(aryl)thioureas *IIIa – IIIr*

Method A (ref.[12]). The appropriate amine (*IIa – IIc, IIf – IIh, IIl*; 2.7 mmol) was added to a solution of 9-isothiocyanatoacridine (*I*; 0.5 g, 2.2 mmol) in anhydrous ethanol (100 ml) and the reaction mixture was refluxed for about 1 h. After cooling (and in some cases partial evaporation of the solvent), the reaction mixture was filtered and the material on filter was washed with ethanol.

Method B. Amine *IId, IIe, IIi – IIk* or *IIm – IIr* (2.7 mmol) was added dropwise to a stirred solution of 9-isothiocyanatoacridine (*I*; 0.5 g, 2.2 mmol) in chloroform (10 ml). The reaction mixture was stirred at room temperature until a precipitate deposited. This was collected on filter, washed with light petroleum and dried.

1-Acridin-9-yl-3-phenylthiourea (IIIa) was prepared from 9-isothiocyanatoacridine and aniline as described by Sinsheimer and coworkers[12].

1-Acridin-9-yl-3-(2-methoxyphenyl)thiourea (IIIb), m.p. 180 – 184 °C; yield 46%. For $C_{21}H_{17}N_3OS$ (359.5) calculated: 70.17% C, 4.77% H, 11.69% N; found: 70.43% C, 4.68% H, 11.46% N. IR spectrum: 3 395 (NH); 1 630, 1 506 (C=N, C=C); 1 550, 1 410, 1 105 (NHCS); 1 250 (CH_3O). ^{1}H NMR spectrum: 9.59 s, 1 H (NH); 6.61 – 8.35 m, 12 H (ArH); 3.81 s, 3 H (CH_3O).

1-Acridin-9-yl-3-(3-methoxyphenyl)thiourea (IIIc), m.p. 182 – 184 °C; yield 52%. For $C_{21}H_{17}N_3OS$ (359.5) calculated: 70.17% C, 4.77% H, 11.69% N; found: 70.12% C, 4.59% H, 11.49% N. IR spectrum: 3 234 (NH); 1 631, 1 525 (C=N, C=C); 1 566, 1 400, 1 115 (NHCS); 1 220 (CH_3O). ^{1}H NMR spectrum: 10.75 s, 1 H (NH); 6.44 – 8.35 m, 12 H (ArH); 3.56 s, 3 H (CH_3O).

1-Acridin-9-yl-3-(4-methoxyphenyl)thiourea (IIId), m.p. 179 – 180 °C; yield 58%. For $C_{21}H_{17}N_3OS$ (359.5) calculated: 70.17% C, 4.77% H, 11.69% N; found: 70.31% C, 4.61% H, 11.46% N. IR spectrum: 3 230 (NH); 1 631, 1 513 (C=N, C=C); 1 569, 1 400, 1 100 (NHCS); 1 270 (CH_3O). ^{1}H NMR spectrum: 10.67 s, 1 H (NH); 6.61 – 8.32 m, 12 H (ArH); 3.65 s, 3 H (CH_3O).

1-Acridin-9-yl-3-(4-tolyl)thiourea (IIIe), m.p. 184 – 186 °C; yield 49%. For $C_{21}H_{17}N_3S$ (343.5) calculated: 73.44% C, 4.99% H, 12.24% N; found: 73.24% C, 4.75% H, 12.01% N. IR spectrum: 3 183 (NH); 1 630, 1 514 (C=N, C=C); 1 564, 1 400, 1 110 (NHCS); 1 270 (CH_3O). ^{1}H NMR spectrum: 10.71 s, 1 H (NH); 6.81 – 8.31 m, 12 H (ArH); 2.18 s, 3 H (CH_3).

1-Acridin-9-yl-3-(4-ethoxyphenyl)thiourea (IIIf), m.p. 182 – 185 °C; yield 67%. For $C_{22}H_{19}N_3OS$ (373.4) calculated: 70.78% C, 5.13% H, 11.26% N; found: 70.54% C, 5.04% H, 11.18% N. IR spectrum: 3 169 (NH); 1 625, 1 508 (C=N, C=C); 1 563, 1 395, 1 110 (NHCS); 1 230 (C_2H_5O). ^{1}H NMR spectrum: 10.68 s, 1 H (NH); 6.62 – 8.33 m, 12 H (ArH); 1.24 t, 3 H, *J* = 7.1 Hz (CH_3); 3.91 q (CH_2).

1-Acridin-9-yl-3-(4-chlorophenyl)thiourea (IIIg), m.p. 185 – 188 °C; yield 50%. For $C_{20}H_{14}ClN_3S$ (363.9) calculated: 66.04% C, 3.88% H, 11.55% N; found: 66.23% C, 3.91% H, 11.38% N. IR spectrum: 3 175 (NH); 1 626, 1 485 (C=N, C=C); 1 562, 1 390, 1 100 (NHCS). ^{1}H NMR spectrum: 10.81 s, 1 H (NH); 7.10 – 8.29 m, 12 H (ArH).

1-Acridin-9-yl-3-(4-bromophenyl)thiourea (IIIh), m.p. 190 – 192 °C; yield 51%. For $C_{20}H_{14}BrN_3S$ (408.3) calculated: 58.85% C, 3.46% H, 10.29% N; found: 58.63% C, 3.27% H, 10.41% N. IR spectrum: 3 175 (NH); 1 627, 1 484 (C=N, C=C); 1 562, 1 385, 1 100 (NHCS). ^{1}H NMR spectrum: 10.81 s, 1 H (NH); 6.96 – 8.28 m, 12 H (ArH).

1-Acridin-9-yl-3-(4-nitrophenyl)thiourea (IIIi), m.p. 166 – 169 °C; yield 46%. For $C_{20}H_{14}N_4O_2S$ (374.4) calculated: 64.18% C, 3.77% H, 14.97% N; found: 64.09% C, 3.81% H, 14.75% N. IR spectrum: 1 625, 1 520 sh (C=N, C=C); 1 560, 1 385, 1 030 (NHCS); 1 550 sh, 1 361 (NO_2). ^{1}H NMR spectrum: 11.02 s, 1 H (NH); 7.23 – 8.35 m, 12 H (ArH).

1-Acridin-9-yl-3-(4-acetophenyl)thiourea (IIIj), m.p. 168 – 170 °C; yield 32%. For $C_{22}H_{17}N_3OS$ (371.5) calculated: 71.14% C, 4.61% H, 11.31% N; found: 71.08% C, 4.80% H, 11.14% N. IR spectrum: 3 226 (NH); 1 624, 1 488 (C=N, C=C); 1 545, 1 380, 1 100 (NHCS); 1 669 (CO). ^{1}H NMR spectrum: 10.93 s, 1 H (NH); 7.08 – 8.35 m, 12 H (ArH); 2.46 s, 3 H (CH_3).

1-Acridin-9-yl-3-(4-cyanophenyl)thiourea (IIIk), m.p. 164 – 166 °C; yield 34%. For $C_{21}H_{14}N_4S$ (354.4) calculated: 71.19% C, 3.98% H, 15.81% N; found: 71.26% C, 3.74% H, 15.90% N. IR spectrum: 3 213 (NH); 1 636, 1 610, 1 520 (C=N, C=C); 1 567, 1 420, 1 100 (NHCS); 2 235 (CN). ^{1}H NMR spectrum: 10.93 s, 1 H (NH); 7.13 – 8.35 m, 12 H (ArH).

1-Acridin-9-yl-3-(4-dimethylaminophenyl)thiourea (IIIl), m.p. 180 – 184 °C; yield 81%. For $C_{22}H_{20}N_4S$ (372.5) calculated: 70.97% C, 5.41% H, 15.05% N; found: 70.76% C, 5.52% H, 15.18% N. IR spectrum: 3 225 (NH); 1 622, 1 509 (C=N, C=C); 1 556, 1 400, 1 100 (NHCS). ^{1}H NMR spectrum: 10.59 s, 1 H (NH); 6.37 – 8.33 m, 12 H (ArH); 2.77 s, 6 H ($(CH_3)_2N$).

1-Acridin-9-yl-3-benzylthiourea (IIIm), m.p. 181 – 182 °C; yield 74%. For $C_{21}H_{17}N_3S$ (343.5) calculated: 73.47 C, 4.99% H, 12.24% N; found: 73.25% C, 4.86% H, 12.49% N. IR spectrum: 3 208 (NH); 1 630, 1 523 (C=N, C=C); 1 552, 1 400, 1 110 (NHCS). ^{1}H NMR spectrum: 11.50 s, 1 H (NH); 9.48 t, 1 H, J = 5.9 Hz (NH); 6.89 – 8.25 m, 13 H (ArH); 4.84 d, 2 H, J = 5.9 Hz (CH_2).

1-Acridin-9-yl-3-cyclohexylthiourea (IIIn), m.p. 192 – 194 °C; yield 95%. For $C_{20}H_{21}N_3S$ (335.5) calculated: 71.64% C, 6.31% H, 12.53% N; found: 71.49% C, 6.42% H, 12.41% N. IR spectrum: 3 220 (NH); 1 619, 1 500 (C=N, C=C); 1 575, 1 390, 1 095 (NHCS); 2 930, 2 860 (CH_2). ^{1}H NMR spectrum: 11.58 s, 1 H (NH); 9.18 d, 1 H, J = 8.4 Hz (NH); 7.12 – 8.60 m, 8 H (ArH); 4.25 m, 1 H (CH); 0.75 – 2.20 m, 10 H ($(CH_2)_5$).

1-Acridin-9-yl-3-butylthiourea (IIIo) was prepared from 9-isothiocyanatoacridine and butylamine according to De Leenheer and coworkers[13].

1-Acridin-9-yl-3-tert-butylthiourea (IIIp), m.p. 193 – 195 °C; yield 78%. For $C_{18}H_{19}N_3S$ (309.4) calculated: 69.87% C, 6.19% H, 13.58% N; found: 69.64% C, 6.28% H, 13.73% N. IR spectrum: 3 213 (NH); 1 622, 1 514 (C=N, C=C); 1 586, 1 415, 1 100 (NHCS); 2 988 (*tert*-Bu). ^{1}H NMR spectrum: 8.65 s, 1 H (NH); 6.92 – 8.41 m, 8 H (ArH); 1.30 s, 9 H ($(CH_3)_3$).

1-Acridin-9-yl-3-isopropylthiourea (IIIr), m.p. 197 – 199 °C; yield 77%. For $C_{17}H_{17}N_3S$ (295.4) calculated: 69.15% C, 5.80% H, 14.23% N; found: 69.39% C, 5.68% H, 14.12% N. IR spectrum: 3 222 (NH); 1 631, 1 594, 1 525 (C=N, C=C); 1 561, 1 410, 1 085 (NHCS). ^{1}H NMR spectrum: 11.36 s, 1 H (NH); 8.88 d, 1 H, J = 7.0 Hz (NH); 6.92 – 8.40 m, 8 H (ArH); 4.56 d sept, 1 H, J = 7.0 Hz, 6.5 Hz (CH); 1.21 d, 6 H, J = 6.5 Hz ($(CH_3)_2$).

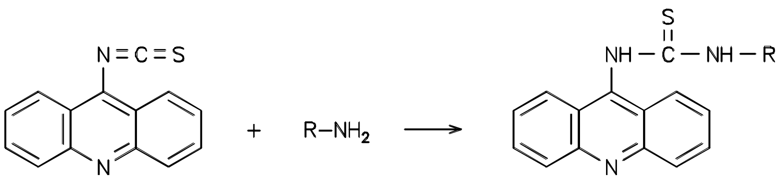
RESULTS AND DISCUSSION

The studied reaction of 9-isothiocyanatoacridine with amines is depicted in Scheme 1. The dependence of the rate constant k' or k on the concentration of isopropylamine in acetonitrile is given in Table I. As seen from the Table, at a 35 to 50-fold excess of the amine the second order rate constants are independent of the amine concentration (average value k = 4.962). We used 50-fold excess of the amine. Because of absorption of the acridine skeleton in the visible region of the spectrum, it was possible to use aliphatic as well as aromatic amines not transparent in the UV region. The reaction gave rise to the corresponding *N,N′*-disubstituted thioureas which were characterized, inter alia, (see Experimental) by UV spectra (comparison with those of authentic thioureas).

Table II shows relative fluorescence intensities and maxima of the synthesized compounds *IIIa* – *IIIr*. The highest intensity was found for the derivative *IIIo* whose fluorescence emission spectrum is depicted in Fig. 1. No conclusions on the relation between the structure and fluorescence in the studied compounds could be made.

TABLE I
The effect of isopropylamine concentration on the reaction rate of 9-isothiocyanatoacridine in acetonitrile at 25 °C (concentration of isothiocyanate 0.66 . 10^{-4} mol l^{-1}, λ = 420 nm)

Isopropylamine $c \cdot 10^3$ mol l^{-1}	Excess of amine mole %	$k' \cdot 10^2$ s^{-1}	k l mol^{-1} s^{-1}
3.33	50	1.656	4.973
3.00	45	1.475	4.917
2.66	40	1.362	5.120
2.33	35	1.127	4.836
2.00	30	1.075	5.374
1.66	25	0.995	5.993



I *IIa – IIr* *IIIa – IIIr*

II	R
a	phenyl
b	2-methoxyphenyl
c	3-methoxyphenyl
d	4-methoxyphenyl
e	4-tolyl
f	4-ethoxyphenyl
g	4-chlorophenyl
h	4-bromophenyl
i	4-nitrophenyl

II	R
j	4-acetophenyl
k	4-cyanophenyl
l	4-dimethylaminophenyl
m	benzyl
n	cyclohexyl
o	butyl
p	*tert*-butyl
r	isopropyl

SCHEME 1

TABLE II
UV-VIS and fluorescence properties of compounds *IIIa* – *IIIr*

Compound	λ_{max}, nm	λ_{em}, nm	F/F_0[a]	Compound	λ_{max}, nm	λ_{em}, nm	F/F_0[a]
IIIa	429.6 3.94	438, 457	0.04	*IIIj*	413.1 4.15	436, 462	0.04
IIIb	410.3 4.25	433, 460	0.12	*IIIk*	412.0 4.21	437, 460	0.08
IIIc	411.0 4.26	434, 456	0.05	*IIIl*	411.0 4.20	435, 460	0.07
IIId	410.1 4.27	436, 460	0.04	*IIIm*	424.3 3.92	455, 480	0.02
IIIe	409.0 4.21	435, 460	0.06	*IIIn*	423.4 3.92	–	–
IIIf	409.2 4.22	435, 459	0.05	*IIIo*	424.0 3.91	435, 460	1.36
IIIg	411.1 4.28	435, 458	0.09	*IIIp*	425.9 4.09	–	–
IIIh	410.2 4.25	430, 460	0.07	*IIIr*	422.7 4.09	–	–
IIIi	380.0 4.23	436, 458	0.03				

[a] Relative fluorescence, where $F_0 = F$ for $1 \cdot 10^{-3}$ mM solution of 9-isothiocyanatoacridine at the higher wavelength maximum. Excitation wavelength λ_{ex} = 395 nm.

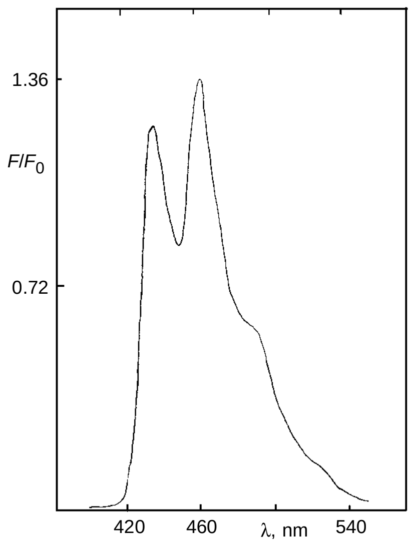


FIG. 1
Fluorescence emission spectrum of 1-acridin-9-yl-3-butylthiourea *IIIo* (dimethylformamide, c 2 . 10^{-6} mol l^{-1}, at excitation wavelength λ_{ex} = 395 nm). Spectra referenced to that of 9-isothiocyanatoacridine measured under the same conditions

Substitution Effects

The rate constants for the reaction of 9-isothiocyanatoacridine with aromatic amines are given in Table III. Their values correlate well with the substituent parameters σ_p and σ_p^- according to the relationship log k = 1.658 – 1.524 σ_p (correlation coefficient r = 0.972) and log k = 1.710 – 1.113 σ_p^- (correlation coefficient r = 0.993), respectively. The negative slope of the given relationships shows that electron-donating substituents on the benzene ring of the aromatic amines accelerate the reaction rate; this is in accord with the mechanism of reaction of phenyl isothiocyanate with amines[14,15]. In the case of aromatic amines there is a correlation between rate constants and pK_a values (log k = –0.072 + 0.388 pK_a; r = 0.994) which does not hold for amino acids[10] and aliphatic amines.

9-Isothiocyanatoacridine reacts two orders of magnitude faster than phenyl isothiocyanate and two orders of magnitude slower than benzoyl isothiocyanate. Thus, e.g., the rate constants for reaction with butylamine at 25 °C are: in acetonitrile $k_{benzoyl}$ = 2 893 l mol^{-1} s^{-1}, k_{Acr} = 16.97 mol^{-1} s^{-1}; in cyclohexane $k_{benzoyl}$ = 848 l mol^{-1} s^{-1}, k_{phenyl} = 0.055 mol^{-1} s^{-1} (ref.[14]).

Reactions of 9-Isothiocyanatoacridine in Various Solvents

The reaction of 9-isothiocyanatoacridine with butylamine, isopropylamine and *tert*-butylamine was studied in three solvents: acetonitrile, ethyl acetate and dioxane. The solvents were chosen so as to dissolve 9-isothiocyanatoacridine as well as all the

TABLE III
Rate constants (k', s^{-1}; k, l mol^{-1} s^{-1}) for reactions of 4-substituted anilines with 9-isothiocyanatoacridine in acetonitrile at 25 °C (λ = 425 nm)

Compound	$k' \cdot 10^3$	k	σ_p (ref.[17])	σ_p^- (ref.[17])	pK_a (ref.[18])[a]
IIIa	0.635	0.577	0.000	0.000	4.600
IIId	1.266	1.151	–0.268	(–0.268)	5.310
IIIe	0.666	0.605	–0.170	(–0.170)	5.050
IIIf	1.019	0.926	–0.250	(–0.250)	5.320
IIIg	0.338	0.307	0.227	0.24	3.982
IIIh	0.312	0.284	0.232	0.26	3.888
IIIj	0.057	0.052	0.516	0.82	2.190
IIIk	0.048	0.044	0.628	0.99	1.740

[a] In water at 25 °C.

amines and not to decompose the reaction products. We have found that the solvent affects the reaction rates (Table IV).

Steric Effects

For the study of steric effects we made use of aliphatic amines with substituents of various types (Table V). As seen from comparison of reaction rates for butylamine, *tert*-butylamine and isopropylamine (63 : 1 : 19, respectively), the steric hindrance plays an important role. The reactivity of cyclohexylamine lies between that of butylamine and isopropylamine. The lower reactivity of benzylamine than of butylamine can be ascribed to the electron acceptor effect of the aromatic nucleus which in part is transferred through the CH_2 group. On the other hand, benzylamine reacts six times faster than aniline. Because of different interpretations of the reaction mechanism by different authors[5,15,16,19], a more detailed study with isothiocyanatoacridine will be the subject of further scrutiny.

TABLE IV
Rate constants (k', s^{-1}; k, l mol^{-1} s^{-1}) for reactions of 9-isothiocyanatoacridine with amines in solvents of various polarity at 25 °C (λ = 420 nm)

Amine	Dioxane (ε = 2.2)		Ethyl acetate (ε = 6.1)		Acetonitrile (ε = 36.2)	
	$k' . 10^3$	k	$k' . 10^3$	k	$k' . 10^3$	k
Isopropylamine	2.33	0.68	7.81	2.37	16.56	5.02
Butylamine	5.51	1.67	83.33	25.25	55.99	16.97
tert-Butylamine	–	–	0.39	0.12	0.30	0.27

TABLE V
Rate constants (k', s^{-1}; k, l mol^{-1} s^{-1}) for reactions of 9-isothiocyanatoacridine with aliphatic amines in acetonitrile at 25 °C

Compound	$k' . 10^3$	k	pK_a (ref.[18])[a]
IIIm	3.87	3.52	9.38
IIIn	12.88	11.71	10.64
IIIo	55.99	16.97	10.66
IIIp	0.30	0.27	10.68
IIIr	16.56	5.02	10.67

[a] In water at 25 °C.

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Translated by M. Tichy.