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NOVEL TRENDS IN THE CHEMISTRY OF ACRIDINES. NEW FLUORESCENT BIOREAGENTS AND SYNTHONS ON THE BASIS OF 9-ISOTHIOCYANATOACRIDINES

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9-Isothiocyanatoacridines containing a reactive NCS group, together with a biologically active acridine skeleton, were used for the synthesis of new acridine heterocycles. Their reactivity with aliphatic and aromatic amines as well as 15 amino acids was quantified by kinetic measurements. Sodium O-alkyl-N-(9-acridinyl)-iminothiocarbonates obtained by addition of sodium alkoxides to the title compounds gave three types of products with organic halogen reagents. The reaction of above iminothiocarbonates with alkyl halides led to the fluorescent S-alkyl derivatives, whereas bromoacetyl bromide and alkyl bromoacetates afforded the 3-(9-acridinyl)-1,3-thiazolidine-2,4-diones and a new heterocycle, spiro[dihydroacridine-9(10H),4'-thiazoline], respectively.

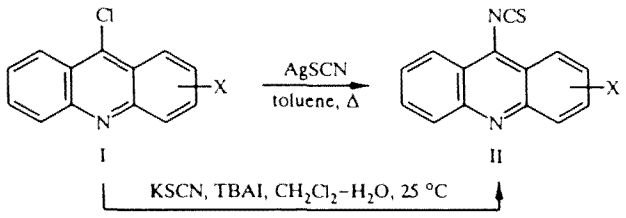
INTRODUCTION

As is generally known, acridine derivatives possess extensive biological activity and special physicochemical properties [1-3]. Among the most important properties of acridines, their ability to intercalate into DNA stands out. In this sense, 9-amino-substituted acridine compounds have been shown to bind to DNA by intercalation and possess antitumour activities [4]. Moreover, the high fluorescence of this class of acridines allows their utilization as fluorescent labeling agents for biomolecules [5]. In the present communication, we focus on the study of synthesis, reactivity, fluorescence, and some reactions of 9-isothiocyanatoacridines (ITCA) which represent the proper combination of a reactive NCS group with a biologically active acridine skeleton.

RESULTS AND DISCUSSION

The title compounds were prepared from the corresponding 9-chloroacridines by heating with silver thiocyanate in dry toluene or by an application of phase-transfer catalysis methods [5] (Scheme 1).

Scheme 1



X = H, 2-MeO, 2-Me, 2-Cl, 2-NO_2, 4-MeO, 4-Me

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TABLE 1. Rate Constants of the Reaction of 2- and 4-Substituted 9-Isothiocyanatoacridines II with Glycine RNH_2 (R = $HOOC-CH_2$) in Clarc—Lubs Buffer (pH 11.1) and DMFA (7:3)

X	2-NO_2	2-Cl	H	4-CH_3O	2-CH_3	2-CH_3O	4-CH_3
k^a	9,4	2,9	1,7	1,6	1,4	1,3	1,2

*[$l \cdot mol^{-1} \cdot s^{-1}$]

TABLE 2. Rate Constants of 9-Isothiocyanatoacridine II (X = H) with 4-R-Substituted Anilines in Acetonitrile

R	4-CH_3O	4-C_2H_5O	4-CH_3	H	4-Cl	4-Br	4-CH_3CO	4-CN
k^a	1,151	0,926	0,605	0,577	0,307	0,284	0,052	0,044

*[$l \cdot mol^{-1} \cdot s^{-1}$]

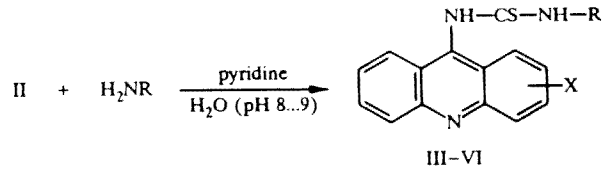
TABLE 3. Selected Rate Constants of Reactions of 9-Isothiocyanatoacridine (II, R = H) with Amino Acids in Clarc—Lubs Buffer (pH 9.8) and Acetonitrile (7:3)

Aa	Leu	Gly	Ile	Val	Met	Arg	Ser
k [$l \cdot mol^{-1} \cdot s^{-1}$]	3,1	2,7	2,6	2,0	1,4	0,9	0,7
k/k_x[a]	19,4	21,9	18,3	12,9	16,1	13,0	8,4

[a] k_x — rate constants for analogous reactions of Ph—NCS

In order to obtain information about the reactivity of ITCAs, the kinetics of their reactions with aliphatic and aromatic amines, as well as 15 amino acids, was studied [6-8].

Scheme 2



III–VI

III X = H, R = *i*-Pr, *n*-Bu, *t*-Bu, Bz, *c*-Hex; IV X = H; R = Ph, 2-CH_3O-Ph, 3-CH_3O-Ph, 4-CH_3O-Ph, 4-CH_3-Ph, 4-Cl-Ph, 4-C_2H_5O-Ph, 4-Br-Ph, 4-NO_2-Ph, 4-CH_3CO-Ph, 4-$(CH_3)_2N$-Ph, V X = H; RNH = Gly, Phe, Ala, Val, Leu, Ile, Trp, Ser, Met, Glu, Arg, His, Thr, Asn, Asp; VI X = H, 2-CH_3O, 2-CH_3, 2-Cl, 2-NO_2, 4-CH_3O, 4-CH_3; RNH = Gly

The reactions are typical Ad_N ones accelerated by electron-withdrawing substituents on the acridine skeleton and increasing basicity of anilines (Tables 1, 2).

From a comparison of reaction rates of butylamine, isopropylamine, and *tert*-butylamine with IIa (63:19:1, respectively), it follows that steric hindrance plays an important role.

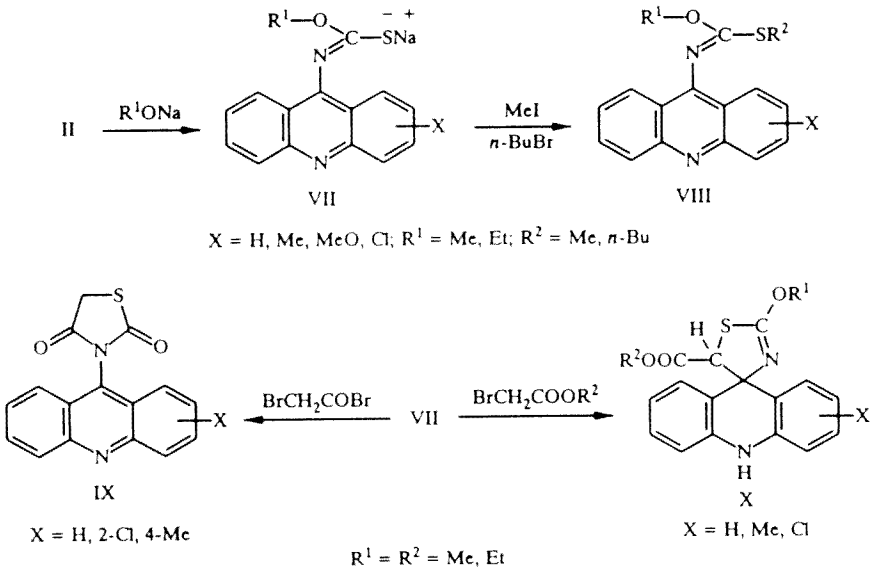
The rate constants of II (X = H) with amino acids showed the reaction to proceed 6-22 times faster than the analogous one of phenylisothiocyanate with amino acids (Table 3).

The amino acid derivatives V show high relative fluorescence, which is suitable for the fluorometric determination of nanomolar amounts of N-(9-acridinylaminothiocarbonyl) amino acids [7].

In order to obtain new fluorogens, a simple method for preparation of O-methyl-S-alkyl-N-(9-acridinyl)imino-thiocarbonates VIII via addition of sodium alkoxide to 9-isothiocyanatoacridines II and subsequent alkylation of formed sodium salts VII with alkyl halides has been elaborated [9] (Scheme 3). The compounds VIII were obtained in very good yields and exhibited an intensive green fluorescence in UV light.

Using the bromoacetic acid derivatives (bromoacetyl bromide, esters of bromoacetic acid) instead of alkylhalides, the reaction afforded new interesting compounds, namely N-(9-acridinyl)-1,3-thiazolidine-2,4-diones IX [10] and 2′,5′-disubstituted spiro[dihydroacridine-9(10H),4′-thiazolines] X [11]. The reaction with bromoacetyl bromide was carried out also with other types of isothiocyanates and proved to be the general way for the synthesis of various N-substituted-1,3-thiazolidines-2,4-diones [10].

Scheme 3



More attractive was the second reaction with alkyl bromoacetates, which resulted in a new spiro derivative of acridine type X [11]. As follows from x-ray crystallography [12], the condensed benzene rings of the dihydroacridine skeleton adopt an arch shape, whereas the central and thiazoline rings have the boat and envelope conformation, respectively. Results of NMR measurements are in agreement with proposed structures of the synthesized compounds.

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