

MECHANISM OF THE OXIDATIVE CONDENSATION
OF ACRIDINES WITH NUCLEOPHILES
I. KINETICS OF THE CONDENSATION OF ACRIDINES
WITH METHYL-SUBSTITUTED HETEROCYCLIC ALKIODIDES

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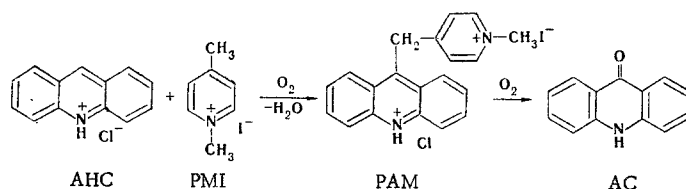
UDC 547.835.9.07:541.127

The kinetics of the reaction of acridine hydrochloride with the alkiodides of 2- and 4-picolines, 2- and 4-methylquinolines, 2-methylbenzothiazole, and 1,2-dimethylbenzimidazole in the presence of air oxygen were investigated. It is shown that the reaction is second-order overall and first order in each of the components at a constant oxygen concentration. The reaction rate constants were calculated, and a mechanism is proposed for the reaction.

In [1, 2] we described the reaction of acridine and its salts with heterocycles containing an active methyl group. The reaction proceeds in the presence of an oxidizing agent (sulfur or air oxygen) and gives 9-acridinylheterylmethanes.

This reaction can formally be regarded as nucleophilic substitution of the hydride ion. It is known that substitution of the hydride ion is realized in strongly alkaline media (the Chichibabin reaction) [3] or in the presence of an oxidizing agent (including oxidation by the substrate itself) [4].

In order to ascertain the mechanism of the reaction described above, we investigated the kinetics of the condensation of acridine hydrochloride with a series of alkiodides of methyl-substituted heterocycles in the presence of air oxygen in dimethylformamide (DMF). The reaction of acridine hydrochloride (AHC) with 4-picoline methiodide (PMI) was studied in greater detail. It was established that the pyridylacridinylmethane (PAM) formed as a result of the reaction is oxidized further to acridone (AC) under the reaction conditions.



The reaction is complicated by slower parallel processes involving the oxidation of the starting AHC to acridone and self-condensation of the alkiodides to the corresponding monomethyldinecyanines; these reactions play an appreciable role in the presence of a large excess of a given reagent. Side reactions can be disregarded when the component ratio is equimolar.

Oxidation proceeds through air oxygen dissolved in the DMF. Air was bubbled through the reaction mixture at a flow rate of $15 \text{ cm}^3/\text{min}$.

The rate constants at $110\text{--}130^\circ\text{C}$ were measured. The course of the reaction was monitored by spectrophotometry.

The kinetic curves, which were treated by the integral method, satisfied a second-order equation (Fig. 1). We determined the partial order with respect to AHC and PMI at the start of the reaction [5].

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TABLE 1. Rate Constants for the Condensation of AHC with Methyl-Substituted Heterocyclic Alkiodides*

Methyl substituted heterocycle	Reaction temp., °C	$k \cdot 10^3$, liter/mole·sec
4-Picoline methiodide	110	0,345±0,01
	120	0,50 ±0,006
	130	0,77 ±0,01
2-Picoline methiodide	110	0,098±0,004
	120	0,132±0,007
	130	0,176±0,005
4-Picoline ethiodide	120	0,51 ±0,01
4-Picoline isopropiodide	120	0,47 ±0,01
Lepidine methiodide	120	0,51 ±0,02
Quinaldine methiodide	120	0,25 ±0,02
2-Methylbenzothiazole methiodide	120	0,183±0,003
1,2-Dimethylbenzimidazole methiodide	120	0,031±0,003
Acridine - base + 4-picoline methiodide	120	0,062±0,003

* c_0 of acridine = c_0 of methyl-substituted heterocycle = 0,184 mole/liter.

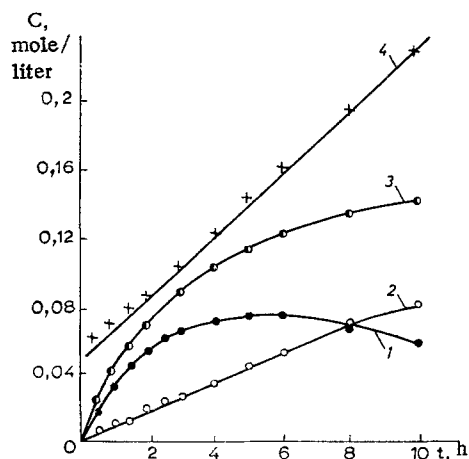


Fig. 1. Kinetic curves of the buildup of: 1) PAM; 2) AC; 3) overall curve; 4) dependence of $1/(c_0-x)$ on t ($c_0^{\text{AHC}} = c_0^{\text{PMI}} = 0,184$ mole/liter).

$$\omega_0 = k[\text{AHC}]^{n_1} [\text{PMI}]^{n_2}$$

The values determined in this manner were, respectively, $n_1 = 1.2$ and $n_2 = 0.74$ (Figs. 2 and 3).

In the presence of a 10-40-fold excess of PMI, the kinetic curves of the consumption of AHC follow a first-order equation.

Carrying out of the reaction in a large excess of one of the components is impossible, inasmuch as the rates of the side reactions become comparable to the rate of the primary reaction, and they cannot be taken into account.

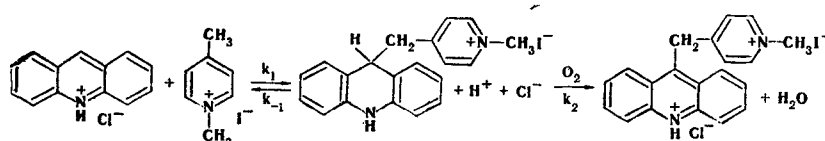
Consequently, it can be assumed that under the conditions of zero order with respect to the oxidizing agent the reaction is second order overall - first order with respect to acridine and first order with respect to the methyl-substituted heterocycle. The certain understatement in the order with respect to PMI is apparently explained by the effect of the disregarded self-condensation side reaction.

The second-order rate constants were calculated graphically. The calculation was made by the method of least squares, and the correlation coefficients were 0.97-0.99 (Table 1).

The reaction rate constant increases on passing from acridine to its hydrochloride by a factor of eight, i.e., the reaction rate depends on the magnitude of $\delta_{(+)}$ on C-9 of acridine. The order of change in the rate constants in the series of heterocycles is in agreement with the lability of the protons of the methyl groups from data on deuterium exchange [6, 7]. The dependence of the rate constant of the investigated reaction on the pK_a values of the protons of the methyl groups attests to the nucleophilic character of the methyl-substituted heterocycle in this reaction.

The results of the kinetic investigations indicate that: a) the reaction is heterolytic, the methyl-substituted heterocycle acts as the nucleophilic partner, and the acridinium compounds act as the electrophilic partner; b) both reagents participate in the rate-limiting step of the process.

Considering the literature data on aromatic nucleophilic substitution [4, 8] and taking into account the characteristic (for acridine) ability to add nucleophiles at the 9 position to give products with the acridan structure [9-11], the following reaction mechanism can be proposed:



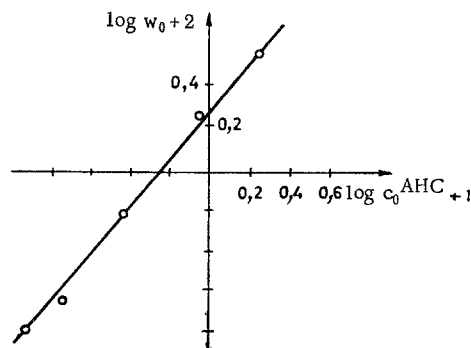


Fig. 2

Fig. 2. Dependence of $\log w_0$ on $\log c_0^{\text{AHC}}$ for $c_0^{\text{PMI}} = 0.184$ mole/liter and $c_0^{\text{AHC}} = 0.184, 0.092, 0.0368, 0.0184,$ and 0.0123 mole/liter.

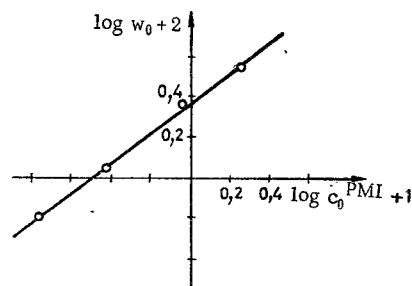


Fig. 3

Fig. 3. Dependence of $\log w_0$ on $\log c_0^{\text{PMI}}$ for $c_0^{\text{AHC}} = 0.184$ mole/liter and $c_0^{\text{PMI}} = 0.184, 0.092, 0.0368,$ and 0.0184 mole/liter.

The expression for the reaction rate is written as follows:

$$w = \frac{k_1 k_2}{k_{-1} + k_2} [\text{AHC}] [\text{PMI}]$$

when $k_{-1} \ll k_2$, $k_{\text{obs}} = k_1$, while when $k_{-1} \gg k_2$, $k_{\text{obs}} = k_2 k_{\text{eq}}$.

The formation of an intermediate was not observed chemically, chromatographically, or by means of UV spectroscopy. The presence in a number of cases of an induction period, the duration of which increases as the reagent concentration decreases and the reaction temperature decreases, speaks in favor of its formation. The equilibrium in the first step is probably shifted almost completely to favor the starting materials, and the addition product therefore cannot be detected.

EXPERIMENTAL

The characteristics of the quaternary salts and their anhydro bases are presented in [2].

Acridine Hydrochloride. Chemically pure grade acridine hydrochloride was converted to the base and crystallized from ethanol three to four times to give a product with mp 110–111°. Hydrogen chloride was passed through a solution of this pure acridine in benzene, and the precipitated hydrochloride was crystallized two to three times from ethanol and dried at 110°.

Methyl-Substituted Heterocyclic Alkiodides. The alkiodides used for this study had purity criteria that were in good agreement with the literature data [12, 13].

Dimethylformamide. The DMF was dried with P_2O_5 and vacuum distilled over P_2O_5 .

Method Used to Make the Kinetic Measurements. Weighed samples of the reagents were dissolved in 10 ml of DMF, and the solutions were placed in a thermostat, the temperature in which was maintained with an accuracy of $\pm 0.3^\circ$. The solutions were held at the reaction temperature for 10 min after which air was bubbled in; the flow rate of the air was monitored by means of a system including a monostat and a manometer and was maintained at $15 \text{ cm}^3/\text{min}$. Under these conditions the reaction proceeds in the kinetic region.

The analysis was performed by selection of samples; PAM was analyzed as the anhydro base. A 0.1-ml sample was diluted with a freshly prepared alcohol solution of NaOH ($c = 10^{-2}$ mole/liter or, in the case of the methylquinolines, $5 \cdot 10^{-4}$ mole/liter), during which the quaternary salts of the diheterylmethanes were converted to the anhydro bases almost instantaneously and quantitatively [2]. The resulting solution was then subjected to spectrophotometry with an SF-4 spectrophotometer. The initial acridine concentration was determined from the optical density at 376–378 nm (shoulder) or 355 nm (maximum). The anhydro base concentration was determined from the absorption in the visible region of the spectrum, while the acridine concentration was determined from the optical density at 400 nm.

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