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Synthesis of 1-Amino-2-methylindoline by Raschig Process: Parallel Reactions, Modeling, and Optimization

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ABSTRACT: The reaction between chloramine and 2-methylindoline was studied at pH 12.89, $T = 40°C$, and for different initial concentrations of reactants. The interaction includes two concurrent bimolecular mechanisms leading to 1-amino-2-methylindoline and 2-methylindole. The rate laws were determined at the first moments of the reaction by using a differential method. By considering the totality of the reactions that occur in the medium, an appropriate mathematical model was developed. It permits to follow the evolution of the system over time and to calculate the final yields of reaction products. An optimization in terms of the initial contents of 2-methylindoline and chloramine was performed. It indicated that the maximum yield of 1-amino-2-methylindoline does not exceed 56%. The results show the limit of the Raschig process for the synthesis of indolic hydrazines in aqueous medium. © 2002 Wiley Periodicals, Inc. Int J Chem Kinet 34: 575–584, 2002
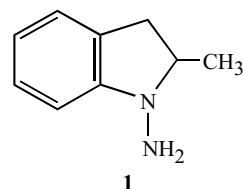
INTRODUCTION

The heterocyclic compounds including an unsymmetrical hydrazino group are used in the pharmaceutical industry as precursors of medicinal drugs [1–5].
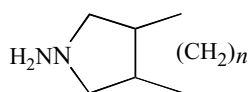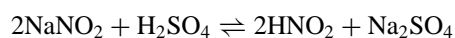

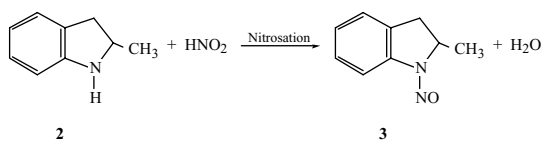In particular, 1-amino-2-methylindoline (**1**, NAMI) is a precursor of an antihypertensive drug whose common international name is *Indapamide*.
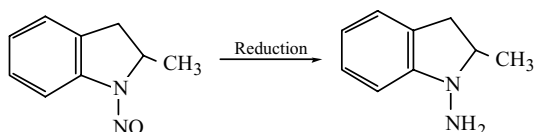

1

At present, it is prepared by the Wright and Willette process [5], which is carried out in two steps:

The nitrosation of 2-methylindoline (**2**, MI) by addition of sodium nitrite to an acid solution of amine:

$$2NaNO_2 + H_2SO_4 \rightleftharpoons 2HNO_2 + Na_2SO_4$$

The reduction of 1-nitroso-2-methylindoline (**3**) by a chemical or catalytic way:

The nitrosation step leads to a high yield (96%, $T = 5°C$, $[H_2SO_4] = 2.5$ M) but, before reduction, **3** must always be purified by distillation or recrystallization. Several methods are proposed to reduce 1-nitroso-2-methylindoline [5–9]. Nevertheless, it must be handled with a lot of caution because of its highly carcinogenic properties [10,11], which cause problems of industrial exploitation. To avoid the nitrosated intermediates, we have undertaken a study on the amination of **2** in aqueous medium by the Raschig process [12,13]. This most environmentally sound route can be schematized by the following two reactions:

$$NaOCl + NH_3 \rightarrow NH_2Cl + NaOH$$

$$RR'NH + NH_2Cl + OH^- \rightarrow RR'NNH_2 + Cl^- + H_2O$$
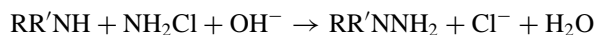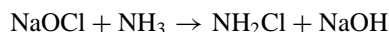
However, it presents the disadvantage of leading to several by-products. This behavior is due to the oxidation and amination properties of NH_2Cl, which appear simultaneously. In particular, the reaction between **1** and chloramine is one of the principal side reactions observed during the synthesis of 1-amino-2-methylindoline by the Raschig process [14]. This reaction limits the yield and leads to products, which are difficult to separate during the continuous extraction of 1-amino-2-methylindoline [15].

The first elementary step involves the neutral and ionic forms of **1** and leads transiently to an aminonitrene:
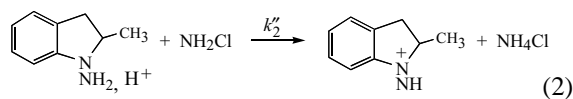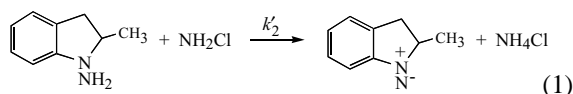
Kinetic law is expressed by

$$-d[NAMI]/dt = k_2'[NAMI][NH_2Cl]$$
$$+ k_2''[NAMIH^+][NH_2Cl]$$

where k_2' and k_2'' are the rate constants of the above reactions. The interaction exhibits a specific acid catalysis and the global rate constant is linear as a function of a_{H^+} ($K_a^{NAMIH^+} = 8.51 \times 10^{-5}$ [15]):

$$k_2 = k_2' + k_2'' a_{H^+} / K_a^{NAMIH^+}$$

At $T = 25°C$ and for $a_{H^+} \approx [H^+]$

$$k_2' = 3.17 \times 10^{-3}\, M^{-1}\, s^{-1} \quad k_2'' = 10.6 \times 10^3\, M^{-1}\, s^{-1}$$

The activation parameters were determined at pH 12.89 where the ionic process (NH_2Cl–$NAMIH^+$) is negligible. The values are the following:

$$\Delta H_2^{\circ\#} = 57.2\, kJ\, mol^{-1}$$
$$\Delta S_2^{\circ\#} = -100.7\, J\, mol^{-1}\, K^{-1}$$
$$k_2 = 92.8 \times 10^6 \exp(-59.7/RT)\, M^{-1}\, s^{-1}$$
$$(E_2\ \text{in kJ mol}^{-1})$$

According to pH, the aminonitrene undergoes a dehydrogenation or a dimerization leading to 1-amino-2-methylindole (**4**) or azo(2-methyl)indoline (**5**), respectively [16]:
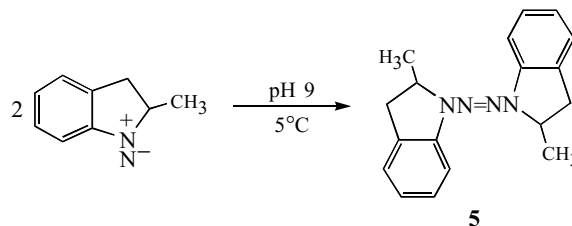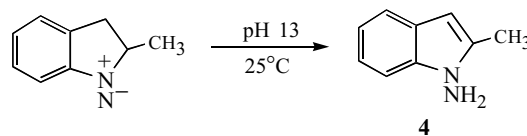
Another side reaction consists of an alkaline degradation of chloramine (pH >11). This reaction has been studied by several authors [17–20].

The first step corresponds to the formation of an hydroxylamine intermediate, which immediately reacts with a second molecule of chloramine to give hydroxylhydrazine:

$$NH_2Cl + OH^- \xrightarrow{k'_3} NH_2OH + Cl^- \quad (slow)$$

(3)

$$NH_2OH + NH_2Cl \xrightarrow{k''_3} NH_2NHOH + HCl \quad (fast)$$

(4)
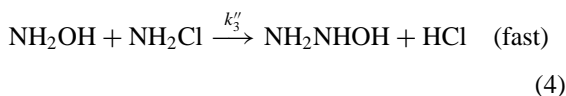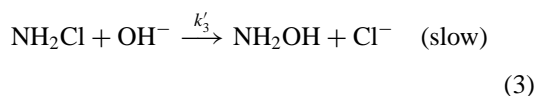
Upon contact with oxygen, the reaction leads to NO^-, N_2O, $N_2O_2^{2-}$, and $ONOO^-$ [20]:

$$NH_2OH + NH_2Cl \rightarrow \frac{1}{2}N_2O + NH_4Cl + \frac{1}{2}H_2O$$

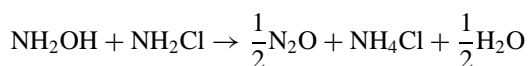In any case, the reaction follows a second-order law $(-d[NH_2OH]/dt = 0)$ and the rate constant with respect to NH_2Cl is found from the relation

$$-d[NH_2Cl]/dt = k_3[NH_2Cl][OH^-]$$

where $k_3 = 2k'_3 = 6.2 \times 10^{-5} \ M^{-1} \ s^{-1}$. A complementary study on the temperature effect confirms the proposed activation energy ($E_3 = 86.9$ kJ mol^{-1}) [20,21].

In order to define the optimum conditions of the synthesis of **1**, we had to establish a mathematical model able to describe the totality of the experimental results. It is first necessary to determine the parameters governing the kinetics of the interaction between 2-methylindoline and chloramine. The overall interactions are then included in a kinetic model in order to represent the evolution of the system according to the reactant concentrations, pH, and temperature. It is the object of this paper.

EXPERIMENTAL

Reagents

Water was passed through an ion-exchange resin, then twice distilled, deoxygenated, and stored under nitrogen.

All reagents and salts used were reagent grade products from Aldrich and Prolabo RP.

Chloramine was prepared immediately before use by reacting an aqueous NH₃–NH₄Cl solution with sodium hypochlorite as previously described [22,23].

Procedure and Analysis

Chloramine shows a UV absorption in water at $\lambda = 243$ nm ($\varepsilon = 458$ M^{-1} cm^{-1}). It was analyzed in the reaction medium by HPLC at its maximum wavelength. The instrument used was a HP 1100 chromatograph equipped with a diode array detector. The column was a 250×4.6 mm ODS column (dp $= 5$ μm). The mobile phase was H₂O/MeOH (75:25% v/v) with a flow rate of 1 ml min^{-1}.

The MI solution, adjusted to the desired pH by addition of sodium hydroxide, was introduced into the reactor. While the thermal equilibrium is reached, an aqueous solution of chloramine was prepared and then rapidly treated according to a procedure published elsewhere [14,24]. 2-Methylindoline exhibits two absorption bands in water at $\lambda_1 = 238$ nm ($\varepsilon_1 = 6940$ M^{-1} cm^{-1}) and $\lambda_2 = 288$ nm ($\varepsilon_2 = 2302$ M^{-1} cm^{-1}) [15]. Taking into account the impossibility of simultaneous determination of MI and chloramine by UV, the reaction mixture was analyzed by GC and HPLC. The analytical conditions and the apparatus were previously described [15,16].

RESULTS AND DISCUSSION

Study of MI-NH₂Cl Interaction

Kinetic Evidence of Competitive Reactions. The experiments were carried out in alkaline medium (pH 12.89) where the formation of **5** is neutralized. The reactant concentrations were kept lower than 20×10^{-3} M so as to maintain a homogeneous mixture. A temperature of 40°C allowed to reduce the reaction time and consequently limits the alkaline-hydrolyzed percentage of chloramine. The solutions were prepared in deoxygenated water in order to avoid the oxidation of MI and NAMI by dissolved oxygen. A nitrogen cover was also maintained.

Under these conditions, the reactants were stable and in their neutral state (at 25°C, $K_a^{MIH^+} = 6.76 \times 10^{-6}$ [15], $K_a^{NH_3Cl^+} = 3.41 \times 10^{-2}$ [25,26]). Figure 1 presents a series of chromatograms recorded at $t = 1$, 18, and 29 min for a mixture of initial concentrations of 10×10^{-3} M in NH₂Cl and 10.5×10^{-3} M in MI.

We observe the decrease of **2** ($t_R = 1.52$ min) and correlatively the appearance of three signals at $t_R = 1.86$, 2.88, and 2.13 min. GC–MS analyzes show that the two first signals correspond to 1-amino-2-methylindoline (**1**) ($t_R = 1.86$ min) and its oxidation product ($t_R = 2.88$ min), 1-amino-2-methylindole (**4**). The third ($t_R = 2.13$ min) results from an oxidation of 2-methylindoline by chloramine. A structural
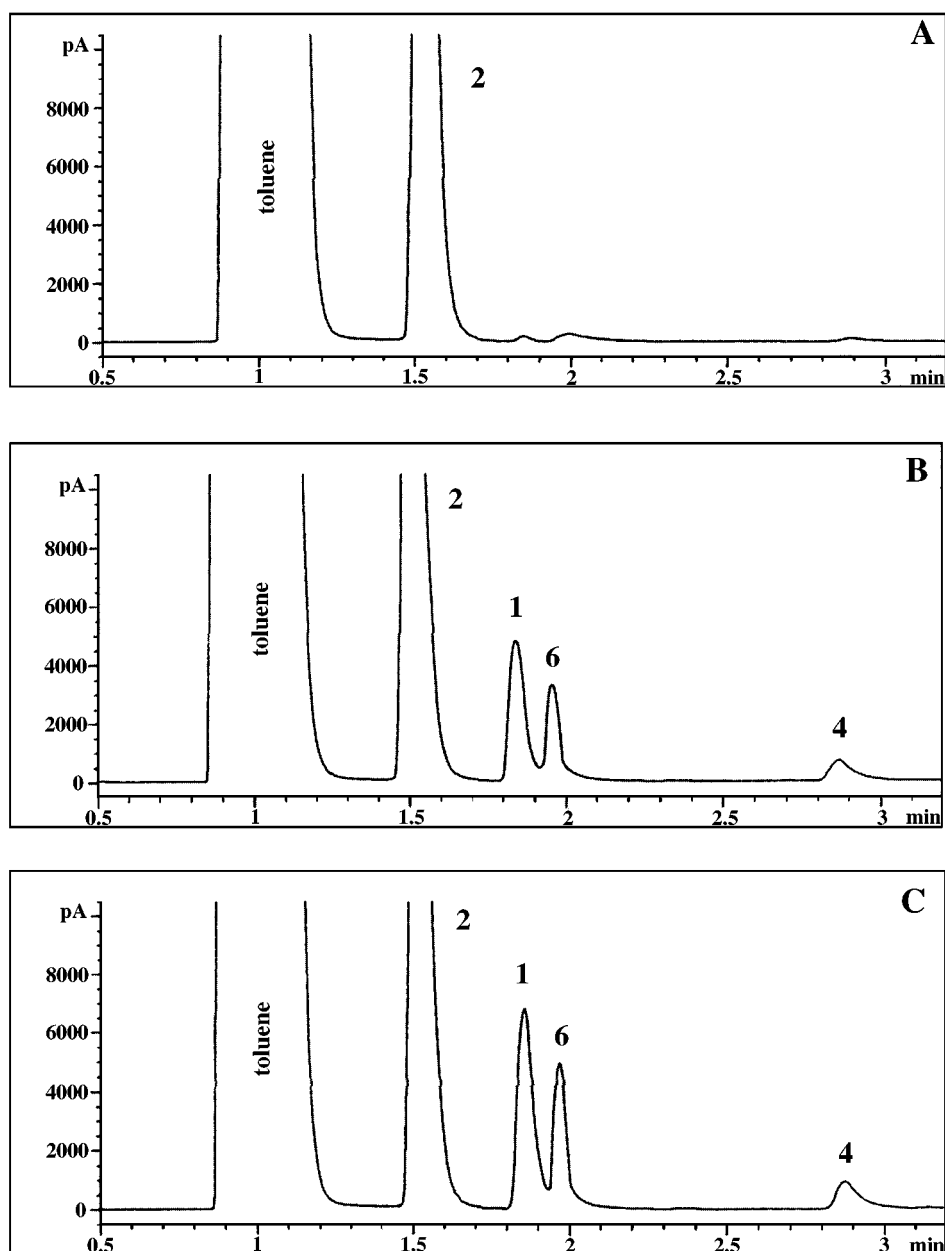
Figure 1   Kinetics of the formation of NAMI. GC analyses recorded as a function of time, A: $t = 1$ min, B: $t = 18$ min, C: $t = 29$ min, (pH 12.89, $[NH_2Cl]_0 = 10 \times 10^{-3}$ M, $[MI]_0 = 10.5 \times 10^{-3}$ M, $T = 40°C$).

characterization leads to 2-methylindole (**6**).

6
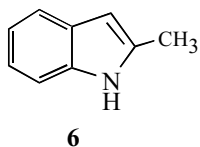
Table I indicates the variation of the concentrations of **1, 2, 4**, and **6** according to time. In particular, we note that I_1/I_2 ratio is constant and close to 1.3

(Table II):

$$I_1 = \int_0^t d([NAMI] + [4]) \quad I_2 = \int_0^t d[6]$$

where I_1 and I_2 are the instantaneous material balance of the reaction products.

Complementary trials carried out under the same conditions of pH and temperature but at different

Table I Study of NH_2Cl–MI Interaction; Variation of the Concentrations of **1, 2, 4**, and **6** with Respect to Time

Time (min)	[MI] ($\times 10^3$ M)	[NAMI] ($\times 10^3$ M)	[4] ($\times 10^3$ M)	[6] ($\times 10^3$ M)
0	10.46	0.00	0.00	0.00
1	10.11	0.05	0.05	0.10
17	8.48	1.02	0.19	0.82
29	7.53	1.41	0.21	1.18
41	6.84	1.74	0.31	1.54
65	5.60	2.13	0.40	1.94
97	5.08	2.50	0.55	2.40
136	4.53	2.66	0.66	2.69
196	4.30	2.82	0.81	2.90

$[NH_2Cl]_0 = 10 \times 10^{-3}$ M, $[MI]_0 = 10.5 \times 10^{-3}$ M, pH 12.89, $T = 40°C$.

concentrations of MI and NH_2Cl lead to results that are identical. In all cases, the plots $I_1 = f(I_2)$ are lines with a slope about 1.30 ($r^2 = 0.994$) (Fig. 2). These results confirm the existence of a competitive process to the formation of 1-amino-2-methylindoline.

Thus, by deriving with respect to time, we obtain

$$d([\mathbf{1}] + [\mathbf{4}])/dt = p\, d[\mathbf{6}]/dt$$

where p is the I_1/I_2 ratio. The oxidation of 2-methylindoline could not be avoided, and the rate laws of appearance of **1** and **4** are written as

$$d[\mathbf{1}]/dt = \nu_1 k_1 [MI]^\alpha [NH_2Cl]^\beta$$
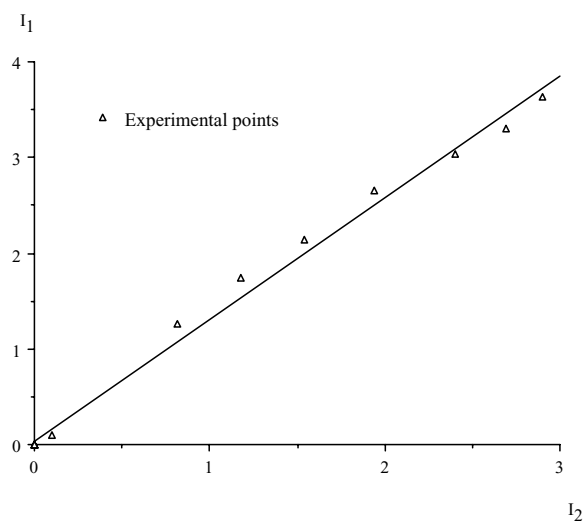$$- \nu_2 k_2 [NAMI][NH_2Cl]$$
$$d[\mathbf{4}]/dt = \nu_2 k_2 [NAMI][NH_2Cl]$$

Knowing that $\nu_2 = 1$ [14], we deduce

$$d[\mathbf{6}]/dt = \nu_1 [MI]^\alpha [NH_2Cl]^\beta k_1/p$$

Table II Study of NH_2Cl–MI Interaction; Kinetic Evidence of a Competitive Mechanism

$[NH_2Cl]_0 = 0.01$ M, $[MI]_0 = 0.0105$ M		$[NH_2Cl]_0 = 0.005$ M, $[MI]_0 = 0.0148$ M	
Time (min)	([1] + [4])/[6]	Time (min)	([1] + [4])/[6]
17	1.48	15	1.49
29	1.37	28	1.40
41	1.33	49	1.37
65	1.30	65	1.30
97	1.27	77	1.31
136	1.23	106	1.30
196	1.25	171	1.24

pH 12.89, $T = 40°C$.

Figure 2 Study of MI–NH_2Cl interaction. Kinetic evidence of a competitive mechanism ($T = 40°C$, pH 12.89): (a) $[NH_2Cl]_0 = 10 \times 10^{-3}$ M, $[MI]_0 = 10.5 \times 10^{-3}$ M; (b) $[NH_2Cl]_0 = 5 \times 10^{-3}$ M, $[MI]_0 = 14.8 \times 10^{-3}$ M.

The system is then reduced to the reactions (5) and (6) ($k_{11} = k_1/p$) the mechanistic details of which were previously published ($\nu_1 = 1$) [16].

$$(5)$$

$$(6)$$
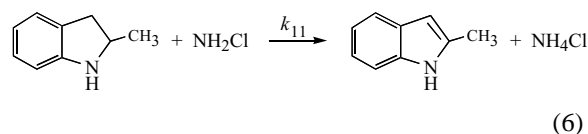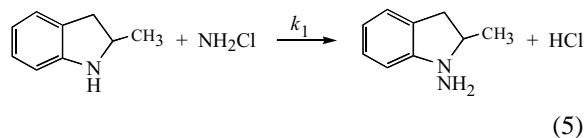
Partial Orders and Rate Constants. Taking into account the oxidation of **1** by chloramine, the rate laws were determined at the first instants of the reaction by using a differential method. The identity between initial and current partial orders was controlled by numeric resolution of the kinetic model. The initial rates of formation of **1** and **6** are written as

$$V_1^0 = (d[NAMI]/dt)_{t=0} = k_1 [MI]_0^{\alpha_0} [NH_2Cl]_0^{\beta_0} \quad (7)$$

$$V_{11}^0 = (d[\mathbf{6}]/dt)_{t=0} = k_{11} [MI]_0^{\alpha'_0} [NH_2Cl]_0^{\beta'_0} \quad (8)$$

where α_0, β_0, α'_0, β'_0 and V_1^0, V_{11}^0 are respectively the initial partial orders and the initial rates of reactions (5) and (6). The slopes of the curves $[NAMI] = f(t)$ and $[\mathbf{6}] = f(t)$ determined at different

initial concentrations of reactants permit the access to the kinetic parameters. Each curve was adjusted by the least-squares method and then extrapolated at $t = 0$. To evaluate β_0, three series of experiments were realized at constant concentration of MI (15×10^{-3} M) and for NH_2Cl contents ranging between 5×10^{-3} and 15×10^{-3} M. α_0 was determined according to the same procedure but while varying the titre of **2** between 7×10^{-3} and 15×10^{-3} M ($[NH_2Cl]_0 = 5 \times 10^{-3}$ M, $T = 40°C$, pH 12.89).

At constant concentration of one of the reagents and for two different initial contents of the other (c_i and c_j), the relations (7) and (8) lead to the following equations:

$$\left(V_1^0\right)_{c_i}/\left(V_1^0\right)_{c_j} = \left([MI]_0^{\alpha_0}\right)_{c_i}/\left([MI]_0^{\alpha_0}\right)_{c_j}$$

$$\left(V_1^0\right)_{c_i}/\left(V_1^0\right)_{c_j} = \left([NH_2Cl]_0^{\beta_0}\right)_{c_i}/\left([NH_2Cl]_0^{\beta_0}\right)_{c_j}$$

$$\left(V_{11}^0\right)_{c_i}/\left(V_{11}^0\right)_{c_j} = \left([MI]_0^{\alpha_0'}\right)_{c_i}/\left([MI]_0^{\alpha_0'}\right)_{c_j}$$

$$\left(V_{11}^0\right)_{c_i}/\left(V_{11}^0\right)_{c_j} = \left([NH_2Cl]_0^{\beta_0'}\right)_{c_i}/\left([NH_2Cl]_0^{\beta_0'}\right)_{c_j}$$

We deduce

$$\alpha_0 = \left\{Log\left(V_1^0\right)_{c_i}\big/\left(V_1^0\right)_{c_j}\right\}\big/$$
$$\left\{Log([MI]_0)_{c_i}\big/([MI]_0)_{c_j}\right\}$$

$$\beta_0 = \left\{Log\left(V_1^0\right)_{c_i}\big/\left(V_1^0\right)_{c_j}\right\}\big/$$
$$\left\{Log([NH_2Cl]_0)_{c_i}\big/([NH_2Cl]_0)_{c_j}\right\}$$

$$\alpha_0' = \left\{Log\left(V_{11}^0\right)_{c_i}\big/\left(V_{11}^0\right)_{c_j}\right\}\big/$$
$$\left\{Log([MI]_0)_{c_i}\big/([MI]_0)_{c_j}\right\}$$

$$\beta_0' = \left\{Log\left(V_{11}^0\right)_{c_i}\big/\left(V_{11}^0\right)_{c_j}\right\}\big/$$
$$\left\{Log([NH_2Cl]_0)_{c_i}\big/([NH_2Cl]_0)_{c_j}\right\}$$

$$k_1 = V_1^0\big/\left([MI]_0^{\alpha_0}[NH_2Cl]_0^{\beta_0}\right)$$

$$k_{11} = V_{11}^0\big/\left([MI]_0^{\alpha_0'}[NH_2Cl]_0^{\beta_0'}\right)$$

The overall results are consigned in Table III. In the above concentration range, the partial orders are situated between 0.95 and 1.10, which confirm that the two competitive reactions are bimolecular. At pH 12.89 and $T = 40°C$, the rate constants are $k_1 = 12.7 \times 10^{-3}$ M^{-1} s^{-1} and $k_{11} = 9.83 \times 10^{-3}$ M^{-1} s^{-1}. In addition, we verified that the rate of disappearance of **2** is equal to the sum of the appearance rates of **1** and **6**:

$$-(d[MI]/dt)_{t=0} = (k_1 + k_{11})[MI]_0[NH_2Cl]_0$$

Table III Kinetics of NH_2Cl–MI Interaction; Determination of the Rate Constants of the Formation of **1** and **6**

$[NH_2Cl]_0$ ($\times 10^3$ M)	$[MI]_0$ ($\times 10^3$ M)	k_1 ($\times 10^3$ M^{-1} s^{-1})	k_{11} ($\times 10^3$ M^{-1} s^{-1})
10.0	10.5	12.6	9.95
5.00	14.8	12.2	9.84
8.22	14.8	12.7	9.80
14.6	14.8	12.9	9.91
5.03	7.32	13.1	9.73
5.09	11.4	12.7	9.87
4.98	15.1	12.5	9.74

$T = 40°C$, pH 12.89.

Modeling of NH_2Cl–MI Interaction

To determine the instantaneous concentrations of different species, it is necessary to take into account the overall reactions that intervene in the medium. The system of differential equations was defined from the rate laws of the interactions (1)–(6). Let us indicate respectively by x, a, u, y, z, and g the instantaneous contents of NH_2Cl, **2**, **1**, **6**, **4**, and NH_2OH. At constant values of pH and temperature, the differential system is written ($b = [OH^-]$) as

$$dx/dt = -(k_1 + k_{11})xa - k_2ux - k_3bx \quad (9)$$

$$da/dt = -(k_1 + k_{11})xa \quad (10)$$

$$du/dt = k_1xa - k_2ux \quad (11)$$

$$dy/dt = k_{11}xa \quad (12)$$

$$dz/dt = k_2ux \quad (13)$$

with the initial conditions $t = 0$, $x = x_0$, $a = a_0$, $b = b_0$, and $u = y = z = g = 0$.

The above system can be resolved by the numerical method of Runge–Kutta according to a fourth-order procedure step. However, in order to simplify the mathematical treatment, an algebric solution was developed. It makes it possible to describe the evolution of the system over time from one implicit equation and analytical relations. Moreover, it allows access to the final yields without applying a step-by-step procedure.

Thus, by eliminating t from Eqs. (9) and (10), we deduce:

$$dx/da = 1 + \{k_2/(k_1 + k_{11})\}(u/a)$$
$$+ \{k_3b_0/(k_1 + k_{11})\}(1/a) \quad (14)$$

where $k_2/(k_1 + k_{11})$ is a function of pH and temperature. To integrate Eq. (14), it is necessary to express

$u = f(a)$. From the Eqs. (10) and (11) we obtain

$$\mathrm{d}u/\mathrm{d}a = -k_1/(k_1 + k_{11}) + \{k_2/(k_1 + k_{11})\}(u/a) \tag{15}$$

Let us designate by r_1 and r_2 the following reports:

$$r_1 = k_1/(k_1 + k_{11}) \quad r_2 = k_2/(k_1 + k_{11})$$

The Eq. (15) becomes

$$\mathrm{d}u/\mathrm{d}a = -r_1 + r_2(u/a)$$

By introducing an auxiliary variable $u = \varphi(t)a$, we obtain a differential equation where u and a are separated:

$$-\mathrm{d}(\mathrm{Log}\, a) = \mathrm{d}\varphi/\{r_1 - \varphi(r_2 - 1)\}$$

Its integration ($t = 0$, $a = a_0$) leads to

$$\mathrm{Log}\, a/a_0$$
$$= \{\mathrm{Log}[r_1 - \varphi(r_2 - 1)] - \mathrm{Log}\, r_1\}/(r_2 - 1)$$

which is also written in the form

$$u = a\{1 - (a/a_0)^{r_2-1}\}r_1/(r_2 - 1) \tag{16}$$

after reconsidering of the initial variable $u = \varphi(t)a$. The substitution of u in Eq. (14) leads to a differential equation, which is a function of x and a:

$$\mathrm{d}x/\mathrm{d}t = 1 + r_3\, b_0/a + r_1 r_2\{1 - (a/a_0)^{r_2-1}\}/(r_2 - 1)$$

where $r_3 = k_3/(k_1 + k_{11})$.

Its integration leads to the final expression (at $t = 0$, $x = x_0$, $a = a_0$)

$$x_0 - x = (a_0 - a) + r_1 r_2(a_0 - a)/(r_2 - 1)$$
$$- \{1 - (a/a_0)^{r_2}\}r_1/(r_2 - 1)$$
$$- b_0\, \mathrm{Log}(a/a_0)^{r_3} = 0 \tag{17}$$

For a given value of $x \in [0, x_0]$, the concentration of MI is the root of the implicit equation

$$(x_0 - x) - (a_0 - a)\{1 + r_1 r_2/(r_2 - 1)\}$$
$$+ \{1 - (a/a_0)^{r_2}\}r_1/(r_2 - 1)$$
$$- b_0\, \mathrm{Log}(a/a_0)^{r_3} = 0$$

In particular, at the end of the reaction ($x = 0$), the final content of **2** can be found via the relation (18):

$$x_0 - (a_0 - a_\infty)\{1 + r_1 r_2/(r_2 - 1)\}$$
$$+ \{1 - (a_\infty/a_0)^{r_2}\}r_1/(r_2 - 1)$$
$$- b_0\, \mathrm{Log}(a_\infty/a_0)^{r_3} = 0 \tag{18}$$

It then becomes possible to access the instantaneous concentration and the yield of **1**:

$$u = a\{1 - (a/a_0)^{r_2-1}\}r_1/(r_2 - 1)$$
$$\rho_{\mathbf{1}} = u(a_0, a_\infty, r_1, r_2)/x_0$$

By eliminating t from Eqs. (10) and (12), we obtain an expression of $y = f(a)$:

$$\mathrm{d}y/\mathrm{d}a = -k_{11}/(k_1 + k_{11}) = r_1 - 1$$

which, after integration ($t = 0$, $a = a_0$, $y = 0$), allows to express the variation of y according to a:

$$y = (1 - r_1)(a_0 - a) \tag{19}$$

At $t = \infty$, it becomes easy to calculate the yield in 2-methylindole:

$$\rho_{\mathbf{6}} = y(a_0, a_\infty, r_1)/x_0$$

In a similar way, we established a relation between z and a:

$$\mathrm{d}z/\mathrm{d}a = -r_2(u/a) \tag{20}$$

From Eqs. (16) and (20), we deduce

$$\int_0^z \mathrm{d}z = r_1 r_2/(1 - r_2) \int_{a_0}^a \left[1 - \left(\frac{a}{a_0}\right)^{r_2-1}\right] \mathrm{d}a$$

which leads to z and $\rho_{\mathbf{4}}$:

$$z = r_1 a_0 - a\{r_2 - (a/a_0)^{r_2-1}\}r_1/(r_2 - 1)$$
$$\rho_{\mathbf{4}} = z(a_0, a_\infty, r_1, r_2)/x_0$$

z can also be calculated from the relations (16), (19), and the material balance relative to 2-methylindoline:

$$a_0 - a = u + y + z$$

The concentration of hydroxylamine is determined by integration of the ratio dg/da:

$$dg/da = -\{k_3/(k_1 + k_{11})\}b_0/a = -r_3 b_0/a$$

$$g = r_3 b_0 \log a_0/a$$

$$\rho_{NH_2OH} = g(a_0, a_\infty, r_3, b_0)/x_0$$

The instantaneous contents a, x, u, y, z, and g are expressed in terms of time by numeric resolution of the following integral obtained from the relations (10) and (17):

$$t = 1/(k_1 + k_{11}) \int_{a_0}^{a} \frac{da}{a[s(a) - x_0]}$$

where $s(a)$ is the second term of the equality (17).

From the above algebraic treatment, we obtained a series of mathematical expressions allowing the complete characterization of the reaction mixture. An optimization of the process is then necessary to define the optimum conditions of synthesis.

Optimization of the Synthesis of 1-Amino-2-methylindoline

The synthesis of **1** must be carried out under strict conditions of concentration and pH. Indeed, in slightly alkaline medium, the quantity of **6** increases rapidly at the expense of 1-amino-2-methylindole. Moreover, the oxidation of **1** by chloramine is accelerated according to a specific acid-catalyzed process [14]. At pH 9, this interaction leads principally to a brown solid **5** [16], which makes the development of a continuous process impossible. These difficulties are enhanced by the instability of **1** and **2**, which increases in acidic medium. A sufficient concentration of sodium hydroxide is thus essential to support the formation of 1-amino-2-methylindoline. An increase of the concentration of chloramine does not improve the yield of **1** because of its implication in the side reactions (1)–(4), and (6). A more concentrated medium in **2** allows the increase in the quantity of 1-amino-2-methylindoline formed by enhancing the reactions (5) and (6) to the detriment of reactions (1)–(4). Finally, the temperature has little influence to favor the yield of **1** [15].

The Figs. 3 and 4 show the variation of the concentrations of NH_2Cl, NH_2OH, **1, 2, 4** and **6** in the following experimental conditions: pH 12.89, $[NH_2Cl]_0 = 10 \times 10^{-3}$ M, $[MI]_0 = 10.5 \times 10^{-3}$ M, and $T = 40°C$. The calculated curves are in good agreement with the experimental points with a maximum error lower than 7%. In particular, we observe that 73% of **2** is consumed
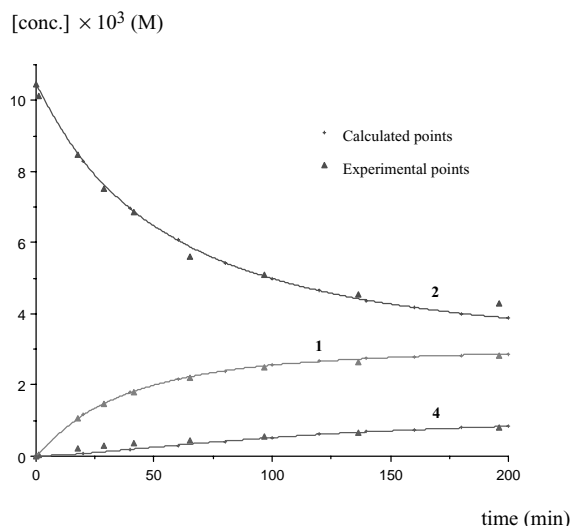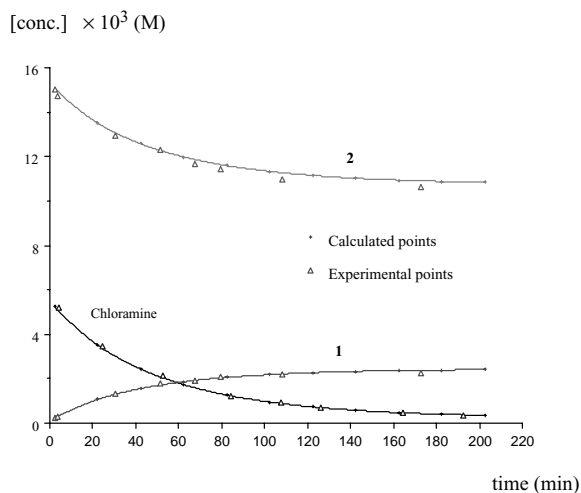
Figure 3 Kinetics of the formation of NAMI. Variation of the concentrations of **1, 2,** and **4** according to time ($[NH_2Cl]_0 = 10 \times 10^{-3}$ M, $[MI]_0 = 10.5 \times 10^{-3}$ M, pH 12.89, $T = 40°C$).

at the end of the reaction whereas NH_2Cl has completely disappeared. The final contents of **6** and **4** are high and reach 106% and 36% of the total quantity of **1** respectively.

The Figs. 5 and 6 present the influence of the concentration of **2**. $[MI]_0/[NH_2Cl]_0$ ratio was fixed at 3 ($T = 40°C$, $[NH_2Cl]_0 = 5 \times 10^{-3}$ M, $[MI]_0 = 14.8 \times 10^{-3}$ M, pH 12.89). We note an increase of 15%
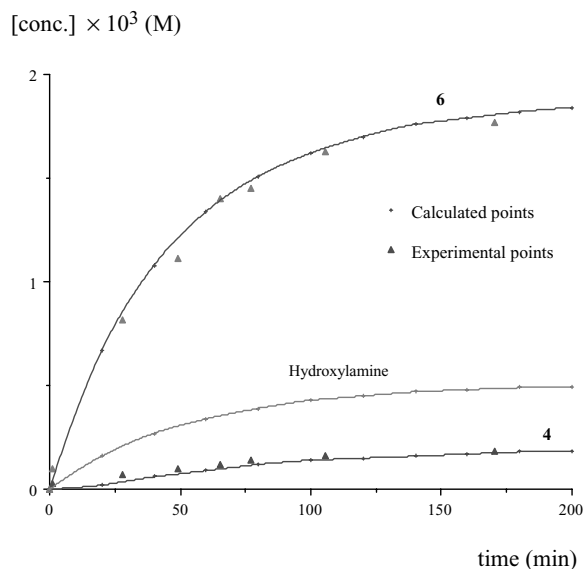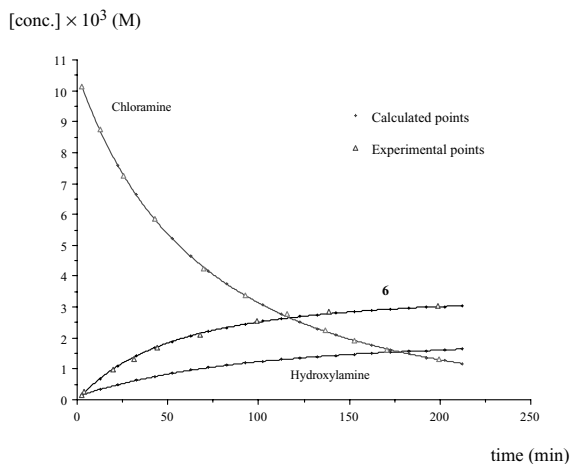
Figure 4 Kinetics of the formation of NAMI. Variation of the concentrations of **6**, NH_2Cl, and NH_2OH as a function of time ($[NH_2Cl]_0 = 10 \times 10^{-3}$ M, $[MI]_0 = 10.5 \times 10^{-3}$ M, pH 12.89, $T = 40°C$).

[conc.] $\times 10^3$ (M)

Figure 5 Kinetics of the formation of NAMI. Variation of the concentrations of **1**, **2**, and NH$_2$Cl according to time ([NH$_2$Cl]$_0$ = 5 $\times$ 10^{-3} M, [MI]$_0$ = 14.8 $\times$ 10^{-3} M, pH 12.89, T = 40°C).

in the yield of NAMI whereas ρ_4 undergoes a significant diminution. The yield in 2-methylindole does not exceed 84% of **1**. The overall yields are consigned in Table IV.

The experimental yields show that the final content in NAMI is affected by three interactions: the hydrolysis of NH$_2$Cl, the oxidation of NAMI by chloramine, and the formation of 2-methylindole. In concentrated solution and for a fixed pH, the term Log$(a/a_0)^{r_3}$ relative to the hydrolysis of chloramine becomes negligible. While the oxidation of NAMI can be neutralized by using a great excess of **2**, the concurrent process could

[conc.] $\times 10^3$ (M)

Figure 6 Kinetics of the formation of NAMI. Variation of the concentrations of **4**, **6**, and NH$_2$OH with respect to time (pH 12.89, [NH$_2$Cl]$_0$ = 5 $\times$ 10^{-3} M, [MI]$_0$ = 14.8 $\times$ 10^{-3} M, T = 40°C).

Table IV Modelling of MI–NH$_2$Cl Interaction; Variation of the Yields of **1**, **4**, **6**, and NH$_2$OH According to the [MI]$_0$/[NH$_2$Cl]$_0$ Ratio

Experiment	ρ_1 (%)	ρ_6 (%)	ρ_4 (%)	ρ_{NH_2OH} (%)
a	29.8	31.5	10.7	17.3
b	44.6	37.6	3.8	10.2

T = 40°C, pH 12.89; (a) [NH$_2$Cl]$_0$ = 10 $\times$ 10^{-3} M, [MI]$_0$ = 10.5 $\times$ 10^{-3} M; (b) [NH$_2$Cl]$_0$ = 5 $\times$ 10^{-3} M, [MI]$_0$ = 14.8 $\times$ 10^{-3} M.

also occur. Let us examine how ρ_1/ρ_6 ratio varies when $p = a_0/x_0$ grows ($p \rightarrow \infty$):

$$\rho_1/\rho_6 = r_1 a_\infty \{1 - (a_\infty/a_0)^{r_2-1}\}/$$
$$\{(1 - r_1)(r_2 - 1)(a_0 - a_\infty)\} \quad (21)$$

Taking into account the stoichiometry of MI–NH$_2$Cl interaction, the final content in **2** can be written in the form

$$a_\infty = a_0 - mx_0 \quad (m \leq 1)$$

The substitution of a_∞ by its value in Eq. (21) leads to

$$\rho_1/\rho_6 = r_1(1/h - 1)\{1 - (1 - h)^{r_2-1}\}/$$
$$\{(1 - r_1)(r_2 - 1)\} \quad (22)$$

where $h = m/p(h \rightarrow 0)$.

By applying the development of Mac-Laurin ($h \rightarrow 0$), we prove that

$$(1 - h)^{r_2-1} \approx 1 - (r_2 - 1)h$$

The Eq. (22) depending only on r_1 and ρ_1/ρ_6 is then equal to

$$\rho_1/\rho_6 = r_1/(1 - r_1) = k_1/k_{11}$$

Knowing that $\rho_1 + \rho_6 = 1$, the yields in **1** and **6** cannot exceed:

$$\rho_1 = r_1 = k_1/(k_1 + k_{11})$$
$$\rho_6 = 1 - r_1 = k_{11}/(k_1 + k_{11})$$

At pH 12.89 and T = 40°C, $\rho_1 \leq 56\%$ and $\rho_6 \leq 44\%$.

The preceding results show the limit of the Raschig process for the synthesis of indolic hydrazines. This phenomenon is due to the partial positive character of nitrogen atom, which supports the concurrent reaction leading to 2-methylindole [16]. For example, experiments carried out on the synthesis of 1-amino-2-methylindole by reaction between 2-methylindole and NH$_2$Cl show that the 3-chloro-2-methylindole is the

principal product. To obtain a higher yield of NAMI, it is necessary to operate in a new reaction medium where its formation is favored. A similar study conducted in water–alcohol and water–acetonitrile mixtures is currently in progress.

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