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CATION RADICALS — INTERMEDIATES IN THE VILSMEIER–HAACK REACTION

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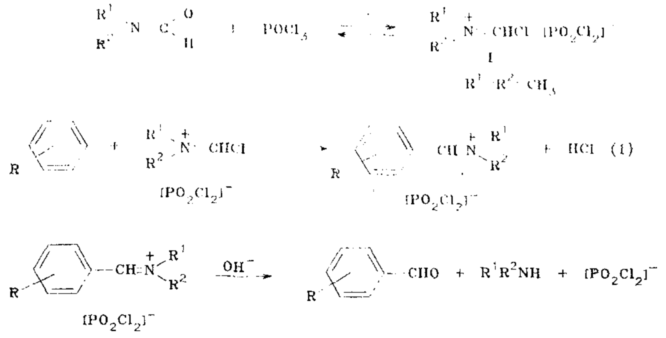
UDC 547.864:541.515

It was observed that cation radicals are intermediate particles in the formylation of N,N'-alkyl- or -aryldihydrophenazines with dimethylformamide in the presence of $POCl_3$. The observed instantaneous cation-radical concentrations in the investigated reactions depend substantially on the concentrations and ratios of the starting reagents and may reach 50-90% based on the substrate undergoing formylation.

The convenient method of obtaining aromatic aldehydes via the Vilsmeier–Haack reaction [1] is finding wide application in organic synthesis [2, 3]. Polycyclic hydrocarbons, aromatic nitrogen-, sulfur-, and oxygen-containing compounds, and a number of other organic substrates can undergo formylation by means of substituted formamides and $POCl_3$, $SOCl_2$, or $COCl_2$ [4]. Despite the extensive utilization of such processes, their mechanism has not yet been elucidated definitively. It is usually assumed [2, 5] that the active electrophilic particle in Vilsmeier–Haack formylation is the cation of iminium salt $R_1R_2\overset{+}{N}{=}CHCl$, X^- (R_1, R_2 = Alk, Ar; X = PO_2Cl_2, Cl, SO_2Cl), which is formed in the reaction of substituted formamides with oxy halides.



We have previously shown [6] that the reaction of some substituted aromatic amines, dihydrophenazines, and phenothiazine with a number of classical electrophilic reagents (HNO_3, Br_2, and $NOBF_4$) may include a step involving electron transfer from the substrate to the electrophile with the formation of intermediate cation radicals. It seemed of interest to ascertain the possibility of the realization of this process in reactions involving formylation with the participation of Vilsmeier complex I. Our electrochemical studies of complex I, which showed that it has a potential ($E^{red}_{1/2}$ = 0.15 V relative to Ag/AgCl, CH_3CN + 0.5 M $NaClO_4$, Pt) sufficient for the oxidation of many organic compounds, served as a prerequisite for this. As the subject of our investigation we used 5,10-dimethyl-5,10-dihydrophenazine (II), since, on the one hand, it readily forms the corresponding aldehyde IV in quantitative

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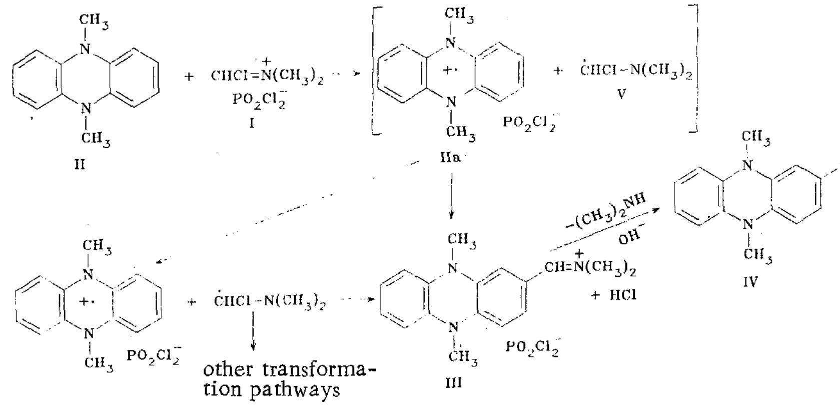
yield [7] under typical formylation conditions, and, on the other, it can form stable cation radical IIa upon oxidation [8], and this makes it possible to identify the occurrence of one-electron acts with its participation.

We have found that in the reaction of dihydrophenazine II in benzene–dimethylformamide (9:1) (the preparative conditions for the formylation of II [7]) with $POCl_3$ the reaction mixture initially takes on a green coloration, which then gradually changes to red violet. Absorption bands (λ_{max} 375, 453, 462, 618, 660, and 728 nm) that are characteristic for cation radical IIa — the product of one-electron oxidation of dihydrophenazine II [8] — appear in the visible region of the electronic spectra at the start of the reaction, and their intensities increase with time. The intensities of these bands then pass through maxima with a simultaneous increase with time in the intensity of the absorption band at 544 nm, which evidently belongs to intermediate product III of electrophilic substitution in the aromatic ring of dihydrophenazine II (see the scheme). The fact that the hydrolysis of the indicated product with aqueous alkali, as expected in conformity with the concepts developed in [2], leads to 5,10-dimethyl-2-formyl-5,10-dihydrophenazine (IV) (λ_{max} in benzene 359 and 438 nm) [7] may serve as a weighty confirmation of this. The rate of formation of III increases appreciably as the concentrations of dihydrophenazine II and $POCl_3$ in the starting reaction mixture are increased.

Thus it follows from the spectrophotometric investigations that two intermediate particles, viz., cation radical IIa and product III, are formed in the Vilsmeier–Haack formylation of dihydrophenazine II in benzene–dimethylformamide (DMF); it may be assumed that cation radical IIa is the precursor of product III. Vilsmeier complex I evidently acts as a one-electron oxidant of dihydrophenazine under the conditions of the investigated process. The electrochemical redox potentials of dihydrophenazine II [9] and complex I provide evidence for the thermodynamic possibility of the occurrence of this process. It is appropriate to note that $POCl_3$ in the absence of DMF is not reduced electrochemically on a Pt electrode in the region of positive potentials and, as we have established, does not oxidize II in the media used in our research. Dihydrophenazine II undergoes slow oxidation by air oxygen, which is catalyzed by the HCl that is liberated as a result of the hydrolysis of $POCl_3$, only in the case of prolonged standing of solutions of II with $POCl_3$ in air.

Our investigations with the tetrafluoroborate of IIa, which was isolated in the form of an individual salt [8], have shown that cation radical IIa formed in the course of the reaction does not react with DMF, benzene, and $POCl_3$. Consequently, its subsequent conversion to III involves the reaction with the product of electron transfer rather than with the starting components of the reaction mixture. This reaction product is evidently the active $\dot{C}HCl-N(CH_3)_2$ radical (V), which arises as a result of one-electron reduction of complex I by dihydrophenazine II.



(2)

Recombination of radical V with intermediate cation radical IIa should lead to the formation of product III.

On the basis of these investigations and the literature data the mechanism of the investigated reaction can be represented by a scheme that includes a step involving electron transfer from the substrate to the electrophile.

According to the scheme, cation radical IIa and radical V formed in the redox act can recombine both in a "cage" and upon emergence into the solution; in the latter case the probability of recombination will decrease in dilute solutions, since radical V is an unstable particle that is capable of rapid spontaneous transformations. Taking this into account, it may be assumed a priori that the higher the observed concentration of cation radical IIa in solution, the lower the probability of the formation of product III. Unfortunately, under the conditions of the synthesis of aldehyde IV indicated in [7] it is not possible to spectrophotometrically accurately evaluate the degree of conversion of dihydrophenazine II to the corresponding cation radical and to determine its maximum instantaneous concentration, since the reaction mixture separates into layers (polar complex I and cation radical IIa are only slightly soluble in benzene). To eliminate these hindering effects in the measurement of the instantaneous concentration of cation radical IIa in the formylation of the dihydrophenazine we replaced the benzene in the mixture of solvents by dioxane, which has similar polarity but solvates the cation radical and complex I much better. The dioxane—DMF volume ratio was 9:1.

In this medium, as in benzene—DMF, we also observed the formation of cation radical IIa in the course of the formylation of dihydrophenazine II by the Vilsmeier complex; the maximum instantaneous concentration of cation radical IIa when $C_0^{II} = 7.5 \cdot 10^{-4}$ mole/liter and $C_0^{POCl_3} = (0.75\text{–}3.8) \cdot 10^{-3}$ mole/liter reaches $(4.0\text{–}4.15) \cdot 10^{-4}$ mole/liter, which amounts to 53-55% of the starting concentration of the aromatic substrate. As the $POCl_3$ concentration and, consequently, the concentration of Vilsmeier complex I in solution increase, the rate of oxidation of dihydrophenazine II by the complex increases substantially, and the maximum instantaneous concentration of cation radical IIa increases. Thus, when $C_0^{POCl_3} = 7.5 \cdot 10^{-2}$ and $1.15 \cdot 10^{-1}$ mole/liter, the IIa concentrations are $6.2 \cdot 10^{-4}$ and $7.3 \cdot 10^{-4}$ mole/liter, which correspond to 83% and 97% based on the starting dihydrophenazine. As we noted above, the probability of recombination of intermediate particles IIa and V in solution to give product III decreases significantly under the indicated conditions for such low starting concentrations of the reagents and instantaneous concentrations of IIa and V, and the rate of the subsequent reactions of cation radical IIa is very low; this makes it possible to record a high degree of conversion of the substrate to the cation radical, which may approach the quantitative value.

The observed high degree of conversion of dihydrophenazine II to the cation radical in the reaction with the Vilsmeier reagent confirms the fact that cation radical IIa is the principal intermediate particle rather than a side intermediate particle in the investigated process. In addition to this, the quantitative conversion of the dihydrophenazine to cation radical IIa may also constitute evidence that the oxidation of II is realized by the Vilsmeier complex rather than by intermediate III, as one might have assumed. As a consequence of the low probability of recombination with cation radical IIa, active radicals V will evidently undergo chiefly spontaneous side transformations that do not lead to the formation of secondary intermediate III. In fact, the formation of intermediate III is not observed in the reaction of dihydrophenazine II with $POCl_3$ in dioxane—DMF at the indicated concentrations of the reagents. In addition to a number of unidentified bands, the electronic spectrum of the mixture of products formed as a result of destruction of cation radical IIa contains absorption bands with very low intensities with maxima at 362 and 443 nm, which evidently belong to trace amounts of aldehyde IV. Intermediate III cannot be detected spectrophotometrically in this case because of its low concentration.

The probability of recombination of the radical products of one-electron transfer increases as the starting concentrations of dihydrophenazine II and $POCl_3$ are increased; the rate of the subsequent conversion of cation radical IIa increases significantly in this case, as evidenced by the rapid formation of secondary intermediate III.

Preparative formylation of dihydrophenazine II in accordance with the method presented in the experimental section showed that during the process aromatic substrate II is converted to corresponding aldehyde IV in 63% yield. Under these conditions one observes only the brief appearance of intermediate cation radical IIa, which is rapidly converted to product III, whereas in dilute solutions at the same starting ratios of the reagents ($C_0^{II} = C_0^{POCl_3} = 7.5 \cdot 10^{-4}$ mole/liter) the rate of the subsequent conversion of cation radical IIa is not so high, and its maximum instantaneous concentration can be recorded spectrophotometrically and is found to be $4.0 \cdot 10^{-4}$ mole/liter, which is 53% of the initial concentration of II.

Thus our investigations show that the Vilsmeier—Haack formylation of dihydrophenazine II may include, in one of the elementary steps, electron transfer from the substrate to the electrophile with the formation of a cation radical as an intermediate particle, the subsequent recombination of which with the radical that is formed in the one-electron reduction of the

Vilsmeier complex leads to intermediate III. In addition to the data presented above, we established that one-electron oxidation of aromatic substrates by the Vilsmeier complex also occurs for other compounds that have low ionization potentials, particularly 5-methyl-10-phenyl- (VI), 5,10-diphenyl- (VII), and 5,10-dihydrophenazines in dioxane—DMF, and N,N,N',N'-tetramethyl-p-phenylenediamine (VIII) and N,N,N',N'-tetramethylbenzidine (IX) in acetonitrile—DMF. Evidence for this is provided by the appearance in the electronic spectra of absorption bands of the corresponding cation radicals VIa-IXa when solutions of VI-IX are mixed with $POCl_3$ in the indicated media (λ_{max} 375, 455, 469, 621, 672, and 742 nm for VIa, λ_{max} 378, 456, 473, 627, 678, and 750 nm for VIIa, λ_{max} 568 and 616 nm for VIIIa, and λ_{max} 439, 459, and 473 nm for IXa).

The proposed scheme of Vilsmeier—Haack substitution can evidently be realized only for easily oxidizable substrates and, in the general case, does not exclude the possibility that the process takes place via the well-known mechanism [2] for compounds with high ionization potentials.

EXPERIMENTAL

The 5,10-alkyl- and -aryl-substituted dihydrophenazines II, VI, and VII were obtained by the method in [10]; II was additionally purified by sublimation *in vacuo* with subsequent crystallization from ethanol. N,N,N',N'-Tetramethyl-p-phenylenediamine (VIII) was synthesized by the method in [11] and was purified by chromatography on Al_2O_3 in pentane. N,N,N',N'-Tetramethylbenzidine (IX) was synthesized by the method in [12] and was additionally purified by sublimation *in vacuo* with subsequent chromatography on Al_2O_3 in benzene and crystallization from ethanol. The melting points of II and VI-IX were in agreement with the literature values [10-12]. The tetrafluoroborate of cation radical IIa was obtained by the method in [8] and was reprecipitated several times from dichloroethane by means of ether. The positions of the maxima of the absorption bands of IIa tetrafluoroborate and their extinction coefficients were in agreement with the values described in [8]. The DMF was purified by successive maintenance over 4 Å molecular sieves and calcined Al_2O_3 and vacuum rectification, and the $POCl_3$ was fractionated *in vacuo*. The solvents used in the research were purified by the methods in [13]. The spectrophotometric measurements were made with a Specord UV-vis spectrophotometer. The concentration of cation radical IIa formed after mixing of the reagents was determined by measurement of the optical density of the investigated solution at the absorption band with λ_{max} 660 nm on the basis of the known extinction coefficient (ε $1.8 \cdot 10^3$); we demonstrated that the change in the extinction coefficient of IIa in the media used does not exceed the error in the determination of the concentration of the cation radical, which was 5%.

Formylation of 5,10-Dimethyl-5,10-dihydrophenazine (II). A 0.55-ml (6 mmole) sample of $POCl_3$ was added dropwise with stirring to a cooled (with ice water) solution of 1.26 g (6 mmole) of II in a mixture of 18 ml of dioxane and 2 ml (26 mmole) of DMF, after which the mixture was stirred at room temperature for 20 min. The temperature was then gradually raised to 90°C in the course of 50 min, and the resulting intermediate III (λ_{max} 544 nm) was cooled and decomposed by the addition of 30 ml of ice water and 30 ml of 10% NaOH solution. The resulting suspension was stirred for 15 min and extracted with benzene (six 40-ml portions). The extract was dried over Na_2SO_4, and the benzene was removed at reduced pressure to give 1.65 g of a red oil, which was dissolved in the minimum amount of boiling ether. The ether extract was cooled, and the resulting 1.0 g of substance was crystallized from methanol to give 0.90 g (63%) of 5,10-dimethyl-2-formyl-5,10-dihydrophenazine (IV) with mp 101-102°C (methanol) (mp 102°C [7]).

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ELECTROPHILIC SUBSTITUTION AND ELECTRONIC STRUCTURE OF INDOLO[2,3-b]QUINOXALINE

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UDC 547.863.1'866'752:542.944.2:543.87

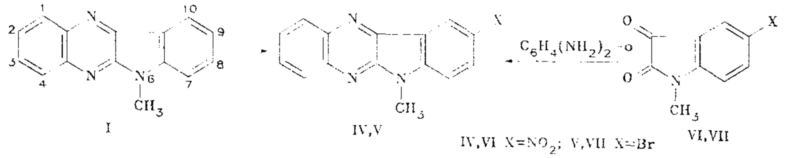
The nitration and bromination of 6-methylindolo[2,3-b]quinoxaline take place in the 9 position. The reactivity indexes were calculated within the framework of the Hückel MO and CNDO (complete neglect of differential overlap) methods. Only the π-charge distribution is in satisfactory agreement with the experimental data on electrophilic substitution in the investigated compound.

Indolo[2,3-b]quinoxalines and their analogs are attracting considerable attention [1]. In the present research we investigated the reactivity of 6-methylindolo[2,3-b]quinoxaline (I) in electrophilic substitution reactions.

In the theoretical investigation of the reactivity of I within the framework of the Hückel MO and CNDO (complete neglect of differential overlap) methods we used the following reactivity indexes [2]: the localization energy (L_r), the superdelocalizability (S_r), the boundary electron density (f_r), the distribution of the π-electron charge [$Q_r(\pi)$], and the total electron charge [$Q_r(\pi + \sigma)$] with allowance for the π and σ electrons.

It follows from an examination of the $Q_r(\pi)$ values of I (Table 1) that the aromatic ring of the indole fragment (the 7 and 9 positions) should be the most reactive, whereas, on the other hand, from the L_r, S_r, and f_r values it follows that the aromatic ring of the quinoxaline fragment (the 1 and 4 positions) should be most reactive.

We carried out two electrophilic substitution reactions (nitration and bromination) for I and found that they lead to 9-nitro- (IV) and 9-bromo-6-methylindolo[2,3-b]quinoxaline (V). The structures of IV and V were confirmed by alternative synthesis, IR and PMR spectroscopy, and mass spectrometry.



IV,VI X=NO_2; V,VII X=Br

Thus of the calculated reactivity indexes for I, only the $Q_r(\pi)$ values are in satisfactory agreement with the experimental data on the direction of electrophilic substitution. Let us note that the formation as a result of the nitration and bromination of I of 9-nitro (IV) and 9-bromo (V) derivatives rather than 7-substituted 6-methylindolo[2,3-b]-quinoxalines, as follows from the calculated $Q_r(\pi)$ values [$Q_{(7)}(\pi) = -0.027$ and $Q_{(9)}(\pi) = -0.021$], can evidently be explained by the steric effect of the methyl substituent in I.

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow 103787. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 840-842, June, 1984. Original article submitted January 13, 1983; revision submitted September 13, 1983.