MECHANISM OF THE NUCLEOPHILIC SUBSTITUTION OF HYDROGEN IN AZINES.

III.* INTERMEDIATES IN THE AMINOARYLATION OF 2-QUINOXALONE

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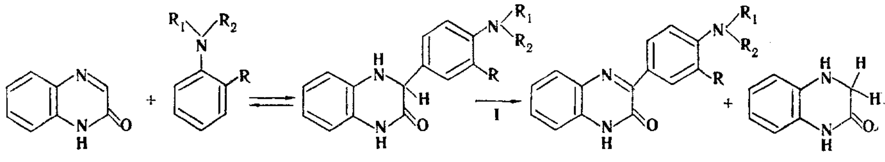
The intermediates in the replacement of hydrogen in 2-quinoxalone by arylamines were recorded by PMR spectroscopy. The synthesized model compounds — 3,4-dihydro-3-R-quinoxal-2-ones — are spectrally identical to the observed intermediates. Under the reaction conditions they undergo reversible decomposition to the starting compounds and are oxidized to give the reaction products. 6-Nitro-2-quinoxalone forms stable addition products in the reaction with arylamines. The polarographic oxidation of 3,4-dihydro-3-R-quinoxal-2-ones and the model compounds shows that primarily the dihydro fragment of the molecule is oxidized.

In [2] we reported the replacement of hydrogen in 2-quinoxalone by aromatic amines. This reaction represents a rare example of nucleophilic substitution of aromatically bonded hydrogen in "uncharged reagent—uncharged substrate" systems. In conformity with the prevailing opinions regarding the mechanism of nucleophilic aromatic substitution [3], it has been assumed that the replacement of hydrogen here proceeds as "addition–cleavage." The aim of the present research was to obtain experimental data on the mechanism of this reaction.



I VIII IIa-e IIIa-e IV

II, III a R=H, $R_1=R_2=CH_3$; b R=H, $R_1=R_2=C_2H_5$; c R=H, $R_1=R_2=CH_2C_6H_5$; d $R=R_1=H$, $R_2=CH_3$; e $R=CH_3$, $R_1=R_2=H$

It was established that the addition products (II) are recorded in the PMR spectra of the reaction mixtures when the reaction is carried out in acetic acid in the absence of oxygen. The most distinct picture is observed in the spectra of a mixture of 2-quinoxalone and N,N-dimethylaniline (Fig. 1). The singlets at 5.18 and 3.10 ppm with relative intensities of 1:6 belong to the 3-H and $N(CH_3)_2$ protons of 3-(4'-N,N-dimethylaminophenyl)-3,4-dihydro-2-quinoxalone (IIa).

Despite the fact that the spectral studies were made in an argon atmosphere, signals of final substitution product IIIa [doublet of 3,5-H protons (J = 9 Hz) at 8.41 ppm and singlet of $N(CH_3)_2$ protons at 3.04 ppm] are observed in the reaction zone. The oxidizing agent in this case is the starting heterocycle, which, owing to a hydride shift from IIa it itself converted to 3,4-dihydro-2-quinoxalone (IV). The latter is readily identified from the singlet peak at 3.96 ppm and the multiplet at 6.7 ppm, which coincides with the chemical shifts of the signals in the spectrum of authentic 3,4-dihydro-2-quinoxalone [4].

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*See [1] for communication II.

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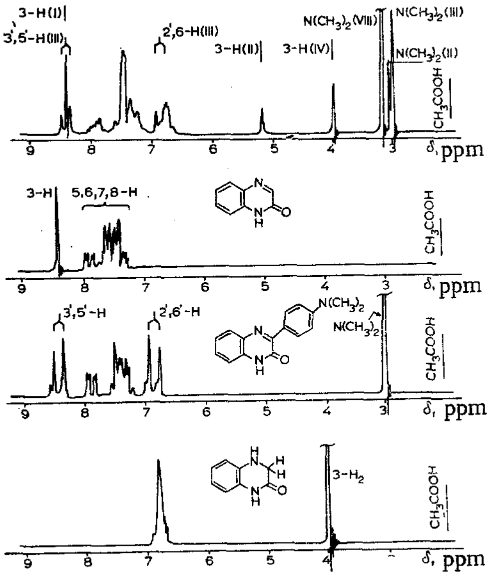
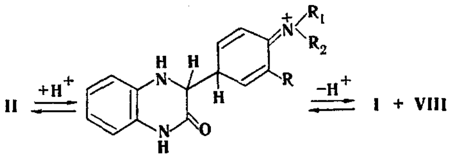


Fig. 1. PMR spectrum of a mixture of 2-quinoxalone and dimethylaniline in CH_3COOH after heating at 114°C for 20 min and spectra of model compounds.

For the reliable assignment of the signals in the spectra of the reaction mixtures and to investigate the properties of the intermediates we synthesized model compounds IIa-e by reduction of the azomethine bond of the corresponding substitution products IIIa-e with zinc in acetic acid. Data on the synthesis and some of the spectral characteristics of the dihydro compounds obtained are presented in Table 1.

Model compounds II behave like intermediate σ complexes: when they are heated in acetic acid they dissociate reversibly to 2-quinoxalone and the arylamine.* The spectrum of IIa does not differ qualitatively from the spectrum of the reaction mixture after heating for 20 min in acetic acid. As the 2-quinoxalone accumulates, because of decomposition of IIa, oxidation of the latter to reaction product IIIa with the simultaneous formation of 3,4-dihydro-2-quinoxalone (IV) becomes appreciable. The addition of 2-quinoxalone to a solution of IIa leads to slowing down of the decomposition and acceleration of the oxidation.

The behavior of compounds of the II type as a function of the acidity of the medium is unusual: they are stable in trifluoroacetic acid and in neutral media, and decomposition is not observed. The differences in the behavior in the media with different acidities can be tentatively explained by the fact that the solvolysis mechanism includes an initial step involving C-protonation of the arylamine fragment via the scheme



V

The free pair of electrons of the nitrogen atom of the amino group is completely blocked in strong acid, and the basicity of the para carbon atom becomes insufficient for the addition of a proton. This scheme, when examined in the reverse order, explains the mechanism of the formation of the recordable intermediate II, which is preceded by V. The formation of particles of this sort, which bear a positive charge on the amine fragment, is usually recorded prior to the formation of Meisenheimer anionic σ complexes from polynitro compounds and amines; this can be demonstrated by means of the temperature-drop method [5]. Compounds II are not anionic in the described reaction of II but, despite the absence of a charge, structures of the II type can with good reason be considered to be σ complexes of nucleophilic heteroaromatic substitution.

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*The isolation of 3,4-dihydro-3-R-quinoxalones II from the acetic acid solutions during their synthesis therefore should be carried out rapidly (see the experimental section).

TABLE 1. 3-(4'-Aminophenyl)-3,4-dihydro-2-quinoxalones (II) and Their Spectra

Compound	R	R^1	R^2	mp, °C	Found, %			Empirical formula	Calc., %			IR spectra, ν, cm^{-1} (C=O, NH)	Electronic spectra, λ_{max} (log ε)	PMR spectra						Yield, %
					C	H	N		C	H	N			solvent	chemical shifts, ppm					
															2',6'-H	3',5'-H	3-H	N_4H	N_1H	
a	H	CH_3	CH_3	182[a]	71,8	6,3	15,6	$C_{16}H_{17}N_3O$	71,9	6,4	15,7	1684, 3410	228 (4,52); 266 (4,25); 415 (3,46)	acetone	7,24 d	6,63 d	5,00 d	5,67 s	9,37	91
b	H	C_2H_5	C_2H_5	223[a]	73,5	7,3	14,4	$C_{18}H_{21}N_3O$	73,2	7,2	14,2	1680, 3316	227 (4,54); 272 (4,29);	DMSO	7,04 d	6,51 d	4,69 s	—	—	88
c	H	$CH_2C_6H_5$	$CH_2C_6H_5$	181—182[a]	79,9	6,0	9,9	$C_{28}H_{25}N_3O$	80,2	6,0	10,0	1682, 3323	228 (4,54); 268 (4,31); 412 (3,56)	acetone	7,11 d	6,62 d	4,82 d	5,65 s	9,27	90
d	H	H	CH_3	160[c]	71,4	6,1	16,2	$C_{15}H_{15}N_3O$	71,1	6,0	16,6	1682, 3337	228 (4,49); 304 (3,79); 376 (2,16)	acetone	7,13 d	6,48 d	4,85 d	5,67 s	9,40	87
e[c]	CH_3	H	H	165[c]	71,1	6,1	16,1	$C_{15}H_{15}N_3O$	71,1	6,0	16,6	1688, 3483	228 (4,53); 301 (3,78)	CD_3OD	—	—	—	—	—	67

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a) From aqueous alcohol. b) From toluene. c) PMR spectrum of IIe (δ, ppm): 7.03 d (2'-H), 6.72 d (6'-H), 6.53 d (3'-H), and 4.74 (3-H).

TABLE 2. Polarographic Oxidation Potentials of 3,4-Dihydro-3-R-2-quinoxalones (II) and 3-R-2-Quinoxalones (III)

Index	R	$E_{ox.p.}$, V	
		II	III
a	4'-Dimethylaminophenyl	1,28	1,36
b	4'-Diethylaminophenyl	1,26 1,40 shoulder	1,36 1,58 shoulder
c	4'-Dibenzylaminophenyl	1,32 1,54	1,52
d	4'-Methylaminophenyl	1,34	1,37
e	2'-Methyl-4'-aminophenyl	1,34 1,47 shoulder	1,42 1,65 shoulder
*	H	1,23 shoulder 1,38	—

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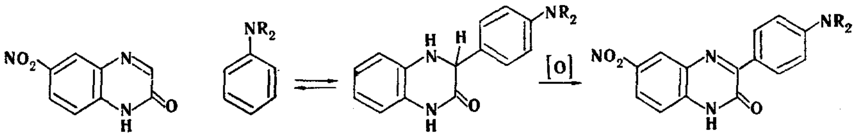
*3,4-Dihydro-2-quinoxalone.

In the case of aminoarylation of 2-quinoxalone one observes clearly expressed acid catalysis: the addition of up to 5% CF_3COOH to the reaction mixture appreciably accelerates the reaction and raises the yields of products by about 40%. Activation of 2-quinoxalone by protonation in the addition step is hardly a necessary condition for the occurrence of the reaction. As previously established in [2], the reaction may also take place in neutral media but under more severe conditions and in the presence of an oxidizing agent. Considering the ionization constants of aromatic amines ($pK_a \approx 5$) and 2-quinoxalone ($pK_a = -1.37$), it should be assumed that an increase in the acidity of the medium should more likely lead to deactivation of the components in the first step of the reaction.

If acid catalysis seems problematical in the addition step, it is clearly expressed in the dehydrogenation step. The protonated form of the 2-quinoxalone evidently acts as the dehydrogenating agent here. In fact, model intermediates II are not oxidized by quinoxalone II in a neutral medium [dimethyl sulfoxide (DMSO] but are appreciably oxidized by it when they are heated in acetic acid and are very rapidly oxidized in practically quantitative yield at room temperature in CF_3COOH.

As a result of the introduction of a nitro group into the 6 position of 2-quinoxalone we were able to separately observe the first step of the reaction — the formation of addition products VIa-c. In the case of N,N-diethylaniline we were able to isolate both an addition product and substitution product VII. Despite the fact that the nitro group in the 6 position is not conjugated with the 3-C center of nucleophilic attack, its effect on the reactivity of 2-quinoxalone and the stability of the addition product is considerable. In the case of 6-nitro-2-quinoxalone the equilibrium is shifted to favor the formation of the addition products, in contrast to 2-quinoxalone, for which intermediate dihydro compounds II are formed in concentrations insufficient for their isolation.



VIc VIIb

VI a $R=CH_3$; VI, VII b $R=C_2H_5$; VI c $R=CH_2C_6H_5$

We have already noted that the choice of oxidizing agent plays an important, and sometimes decisive, role in reactions involving nucleophilic substitution of hydrogen [6]. If the equilibrium in the addition step is shifted to favor the starting materials and is established rapidly, the rate-determining step in the reaction as a whole will be dehydrogenation, i.e., it will be limited by the ratio of the redox potentials of the dihydro compound of the II type and the oxidizing agent. The dehydrogenating agent must be introduced into the reaction mass, and one should therefore exclude the possibility of oxidation of the starting nucleophile. The data on the oxidation potentials of the intermediate dihydro compounds give a quantitative approach to the selection of the dehydrogenating agent. With this in mind, we subjected II to anode oxidation on a rotating platinum electrode. Compounds II have two centers at which oxidation may occur — the cyclic and exocyclic amino groups. As models for oxidation we therefore studied final substitution products III, in which the 3-C—4-N bond is already oxidized. Most of the polarographic curves of electrochemical oxidation on the differential and integral polarograms have a distinct form and are suitable for analytical purposes. The potential range of electrochemical oxidation lies at 1.25-1.75 V.

A comparison of the capacity for oxidation (Table 2) of 3,4-dihydro-2-quinoxalone (IV) and 2-quinoxalone (which is not oxidized) provides evidence that the dihydro fragment of the molecule undergoes oxidation. In the case of R-substituted III oxidation undoubtedly takes place at the exocyclic amino group. Compounds III are oxidized at potentials that are 30-70 mV higher than those observed for II.

The oxidation potentials of the R derivatives of dihydro compounds II are close to those for 3,4-dihydro-2-quinoxalone. This, in conjunction with the data for chemical oxidation, during which the exocyclic amino group is not involved, makes it possible to assert that the oxidation potentials found for II pertain to the oxidation of the ring 3-C—4-N bond.

EXPERIMENTAL

The electronic spectra of $5 \cdot 10^{-4}$ mole/liter alcohol solutions of the compounds were measured with a Specord UV-vis spectrophotometer. The IR spectra of the compounds were recorded with an IKS-14 spectrometer with NaCl (mineral oil suspensions) and LiF (perfluorocarbon suspensions) prisms. The PMR spectra of DMSO, acetone, and CD_3OD solutions were recorded with a Perkin—Elmer R-12B spectrometer. The chemical shifts were measured relative to hexamethyldisiloxane as the internal standard.

Polarographic oxidation was carried out on a rotating platinum electrode (1400 rpm) in a 1 M solution of lithium perchlorate in acetonitrile as the base electrolyte. The comparison electrode was an external aqueous saturated calomel electrode. The depolarizer concentration was $8 \cdot 10^{-3}$ mole/liter. The volume of the solution in the cell was 2.5 ml. The polarographic curves were recorded with an LP-7 polarograph at a rate of polarization of the indicator electrode of 400 mV/min.

3-(4'-Aminophenyl)-3,4-dihydro-2-quinoxalones (IIa-e). A 3.78-mmole sample of the starting 3-(4'-aminophenyl)-2-quinoxalone was dissolved by heating in 30-50 ml of acetic acid, after which the solution was cooled to room temperature and filtered through a layer of zinc dust (about 3 cm) into a Bunsen flask containing 50 g of ice and 80 ml of NH_4OH. The filtration was carried out at such a rate that the filtrate was slightly pink in color. The resulting flocculent precipitate was removed by filtration, dried at no higher than 100°, and crystallized.

3-(4'-N,N-Dimethylaminophenyl)-3,4-dihydro-6-nitro-2-quinoxalone (VIa). A mixture of 1.2 g (6.2 mmole) of nitro-2-quinoxalone, 1.2 ml (10.0 mmole) of dimethylaniline, and 10 ml of acetic acid was heated for 4 h, the resulting suspension was cooled, and the solid material was removed by filtration and crystallized from CH_3COOH to give VIa, with mp 254-256°, in 80% yield. PMR spectrum* (DMSO), δ: 7.58 d (5-H), 7.53 dd (7-H), 6.86 d (8-H), 4.94 d (3-H), 6.63 d (2'6'-H), 7.07 d (3'5'-H), 11.0 s (N_1-H), and 7.13 s (N_4-H) ppm. Electronic spectrum in alcohol (c 10^{-5} mole/liter), λ_{max} (log ε): 202 (4.52), 269 (4.43), and 400 nm (3.52). Found, %: C 61.4 ;H 5.5. $C_{16}H_{16}N_4O_3$. Calculated, %: C 61.5; H 5.2.

3-(4'-N,N-Diethylaminophenyl)-3,4-dihydro-6-nitro-2-quinoxalone (VIb) and 3-(4'-N,N-Diethylaminophenyl)-2-quinoxalone (VIIb). Compound VIa, with mp 286-288° (from xylene), was obtained in 34% yield by the method used to prepare VIa. Found, %: C 64.2; H 5.4; N 16.2. $C_{18}H_{18}N_4O_3$. Calculated, %: C 63.9; H 5.4; N 16.5. Compound VIb was obtained after isolation of VIIb by neutralization of the filtrate with concentrated ammonium hydroxide, removal of the precipitate by filtration, drying, and crystallization from petroleum ether—benzene. A product with mp 207° was obtained in 15% yield. PMR spectrum (DMSO), δ: 4.88 d (3-H), 6.87 d (8-H), 7.53 dd (7-H), 7.58 d (5-H), 7.00 s (N_4-H), 7.05 d (3',5'-H), 6.56 d (2',6'-H), and 10.92 s (N_1-H) ppm. Found, %: C 63.2; H 5.7. $C_{18}H_{20}N_4O_3$. Calculated, %: C 63.5 ;H 5.9.

3-(4'-N,N-Dibenzylaminophenyl)-3,4-dihydro-2-quinoxalone (VIc). This compound, with mp 262-263° (from acetic acid), was obtained in 66% yield by the method used to prepare VIa. PMR spectrum (DMSO), δ: 4.85 d (3-H), 6.84 d (8-H), 7.49 dd (7-H), 7.54 d (5-H), 6.48 d (2',6'-H), 6.57 d (3',5'-H), 7.27 s (N_4-H), and 10.94 s (N_1-H) ppm. Found, %: C 72.7; H 5.3; N 12.5. $C_{28}H_{24}N_4O_3$. Calculated, %: C 72.4; H 5.2; N 12.1.

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*Abbreviations: s is singlet, d is doublet, and dd is doublet of doublets.