NUCLEOPHILIC SUBSTITUTION OF HYDROGEN (3-H) IN QUINOXALONE BY ARYLAMINES

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When quinoxalone is heated with aromatic amines in acetic acid in the presence of ammonium nitrate, a hydrogen undergoes nucleophilic substitution to give the corresponding 3-(4'-aminophenyl)quinoxalones.

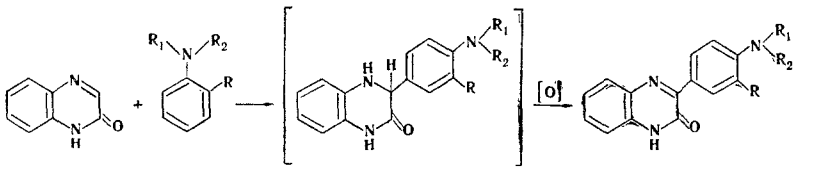
A reaction for the introduction of arylamine residues into the 2-quinazolone molecule was described in [1]. In the present study we have checked the possibility of the use of this transformation for an isomeric heterocyclic compound – quinoxalone (I).

The carbon atoms in the 2 and 3 positions in quinoxaline have pronounced electrophilic properties [2]. However, up until now, the study of nucleophilic substitution reactions in the quinoxaline series has been limited mainly to investigation of the substitution reactions of halogens in the 2 and 3 positions [3]. It is also known that quinoxalines readily react with such nucleophiles as organomagnesium compounds to give products of addition to the C=N bond; the reaction with diazomethane leads to C-methylation [5]. The participation of quinoxalines and quinoxalone in reactions with weak nucleophiles such as arylamines is unknown.

Quinoxalone proved to be inert with respect to dimethylaniline even when it was refluxed for many hours in an excess of the latter. The use of sulfur or selenium in accordance with the method in [6] requires high temperatures, in which case the yields of products are low (< 5%) because of pronounced resinification of the reaction mixture.

We have found that the reaction of I with arylamines proceeds in satisfactory yield when it is carried out with acetic acid as the solvent in the presence of equimolar amounts of ammonium nitrate. When ammonium nitrate is absent, the yield is reduced markedly. The condensation may also be carried out in fused ammonium nitrate, but the yields of products amount to only 5-10%.

On the basis of the literature data [4, 8] it might be assumed that the reaction proceeds with the initial formation of addition products II, which are then oxidized to III-XII (Table 1).



I II III-XII

The ammonium nitrate in this reaction possibly functions as a mild oxidizing agent or has a catalytic effect. The character of the oxidizing agent is of substantial significance: the use of such oxidizing agents as $KMnO_4$, $Na_2Cr_2O_7$, Cr_2O_3, H_2O_2, and $Pb(CH_3COO)_4$ leads to intensive resinification of the reaction mixture because of oxidation of the aromatic amine; on the other hand, aminoarylation does not occur when oxidizing agents of low activity such as oxygen [7] are used. Chloranil cannot be used as the oxidizing agent because of complexing with the arylamines.

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TABLE 1. 3-(4'-Aminophenyl)-2-quinoxalones (III-XII)

Compound	R	R_1	R_2	mp, °C	Empirical formula	Found, %			Calculated, %			IR spectra, cm^{-1}		Electronic spectra, λ_{max}, nm (log ε)	Yield, %
						C	H	N	C	H	N	C=O	NH		
III	H	CH_3	CH_3	269[a]	$C_{16}H_{15}N_3O$	72,4	5,7	16,1	72,4	5,7	15,8	1657	—	230 (4,52), 272 (4,16), 412 (4,49)	70
IV	H	CH_2Ph	CH_2Ph	266—268[b]	$C_{28}H_{25}N_3O$	80,5	5,4	10,4	80,5	5,6	10,1	1666	—	231 (4,42), 274 (4,08), 412 (4,48)	51
V	CH_2	CH_3	$(CH_2)_2$[d]	226[b]	$C_{18}H_{17}N_3O$	74,2	6,1	14,8	74,2	5,9	14,4	1652	—	231 (4,46), 281 (4,14), 426 (4,42)	42
VI	H	CH_3	H	223[a]	$C_{15}H_{13}N_3O$	71,7	5,2	16,5	71,7	5,2	16,7	1650	3383	230 (4,50), 268 (4,10), 410 (4,44)	41
VII	H	CH_2Ph	H	227[a]	$C_{21}H_{17}N_3O$	76,9	5,4	13,1	77,0	5,2	12,8	1669	3486	231 (4,48), 272 (4,11), 410 (4,43)	35
VIII	H	C_2H_5	H	207—208[a]	$C_{16}H_{15}N_3O$	73,0	7,4	14,1	73,2	7,2	14,2	1672	3450	231 (4,49), 272 (4,10), 412 (4,42)	25
IX	H	H	H	221—223[a]	$C_{14}H_{11}N_3O$	70,6	4,9	17,5	70,9	4,7	17,7	1665	3389, 3456	228 (4,65), 258 (4,20), 393 (4,52)	51
													3488, 1616		
X	CH_3	H	H	248[b]	$C_{15}H_{13}N_3O$	71,4	5,4	16,5	71,7	5,2	16,7	1684	3462, 1618	230 (4,48), 263 (4,03), 397 (4,34)	55
XI	OCH_3	H	H	223[a]	$C_{15}H_{13}N_3O_2$	67,5	5,3	15,3	67,4	4,9	15,7	1660	3364, 3389	229 (4,48), 272 (4,04), 404 (4,31)	60
													3487, 1614		
XII	OC_2H_5	H	H	188[c]	$C_{16}H_{15}N_3O_2$	68,6	5,7	14,7	68,3	5,4	14,9	1651	3360, 3443	228 (4,48), 273 (4,03), 404 (4,32)	28
													3484, 1622		

[a]From alcohol. [b]From xylene. [c]From benzene. [d]N-Methyltetrahydroquinoline.

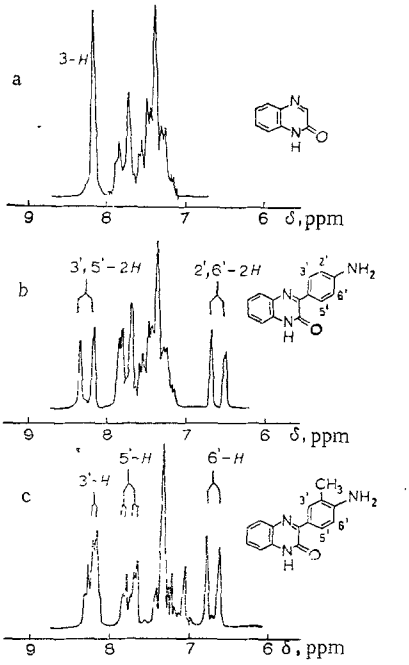


Fig. 1. PMR spectra of I, IX, and X in dimethyl sulfoxide.

Our method is a general one, and the corresponding 3-(4'-aminophenyl)quinoxalones can be readily obtained from quinoxalone by reaction with primary, secondary, and tertiary aromatic amines (Table 1).

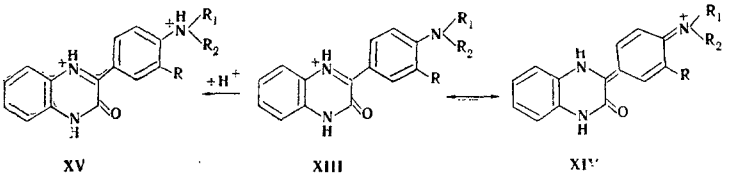
Absorption bands at 1650-1670 cm^{-1}, which are characteristic for the stretching vibrations of the C=O group, are observed in the IR spectra of III-XII. Absorption bands at 3300-3500 cm^{-1} are absent for the compound with a tertiary amino group, while a band at 3400 cm^{-1} is observed for the secondary amino group. The primary amino group of IX, XI, and XII appears as three bands at ~3360, 3440, and 3480 cm^{-1}. The appearance of a band at 3360 cm^{-1} is evidently due to strong intermolecular hydrogen bonds [9]. The bands at 1620 cm^{-1} can be assigned to the deformation vibrations of a free amino group.

A study of the PMR spectra of some of the compounds obtained in this research confirmed that substitution proceeds in the 3 position of the heteroring and also made it possible to establish that arylamines react at the para position. The 3-H methylidyne proton which appears as a singlet at 8.2 ppm (Fig. 1, spectrum a), is not present in the spectra of the substitution products. The two doublets at 8.2 ppm and 6.6 ppm with J=8 Hz (Fig. 1, spectrum b) are characteristic for p-disubstituted aromatic compounds. A three-spin system of the AMX type, which can be readily analyzed according to the rules for spectra of order 1, is observed for compounds with o-substituted arylamines (Fig. 1, spectrum c).

The electronic spectra of the investigated 3-(4'-aminophenyl)quinoxalones contain three absorption bands at 228-231, 260-320, and 390-425 nm, which can be assigned to π-π* transitions. The introduction of an aromatic amine residue into the quinoxalone molecule (λ_{max} 230, 282, and 348 nm)

leads to a pronounced shift of the long-wave maximum and an increase in the molar extinction coefficient by a factor of about four. The medium-wave maximum sustains an appreciable hypsochromic shift, during which the absorption intensity also increases. The position of the short-wave band lies in approximately the 230 nm range. The expected bathochromic shift of the long-wave maximum is observed as the degree of alkylation of the nitrogen atom of the amino group increases.

Bases III-XII are yellow and form mono- and diprotonation products; they are red in acetic acid and yellow in concentrated H_2SO_4. An additional absorption (λ_{max} 520-540 nm, log ε 2.9-3.4) appears in the spectrum of an acetic acid solution in the visible region as a shoulder on the long-wave maximum, which disappears in concentrated H_2SO_4. The mesomeric structure of ion XIV, which has a p-quinoid system of bonds, explains the bathochromic effect observed in weakly acidic solutions. The unshared pair of electrons of the amino group is blocked (XV) in strong acid, and the formation of a mesomeric p-quinoid structure becomes impossible.



XV XIII XIV

EXPERIMENTAL

The electronic absorption spectra of $4 \cdot 10^{-4}$ mole/liter solutions of the compounds in alcohol were recorded with a Specord spectrophotometer. The IR spectra of mineral-oil suspensions (NaCl prism) and perfluorocarbon oil suspensions (LiF prism) of the compounds were recorded with an IKS-14 spectrometer. The PMR spectra of 5% solutions in dimethyl sulfoxide were recorded with a Varian-60T spectrometer.

3-(4'-N,N-Dimethylaminophenyl)quinoxalone (III). A mixture of 1 g (6.8 mmole) of quinoxalone, 0.86 ml (6.8 mmole) of dimethylaniline, and 0.54 g (6.8 mmole) of ammonium nitrate was refluxed in 12 ml of acetic acid for 2 h, and the resulting hot solution was poured into 100 ml of 1 N HCl. The resulting intensely red solution was allowed to stand for ~5 h in order to precipitate unchanged I. The solution was then copious filtered, and the filtrate was neutralized to pH 6-7. The copious yellow precipitate was removed by filtration, washed on the filter with warm water, and dried at 100°.

3-(4'-N,N-Dibenzylaminophenyl)quinoxalone (IV). A mixture of 1 g (6.8 mmole) of quinoxalone, 2.05 g (7.5 mmole) of dibenzylaniline, and 0.54 g (6.8 mmole) of ammonium nitrate was refluxed in 12 ml of acetic acid for ~5 h until a copious precipitate formed. The suspension was cooled, and the crystalline precipitate was removed by filtration, washed with ether, and dried at 100°.

Compounds V-XII. A 0.82-ml (13.6 mmole) sample of glacial acetic acid was added to a mixture of 6.8 mmole of quinoxalone, 7.5 mmole of arylamine, and 6.8 mmole of ammonium nitrate, and the mixture was heated on an oil bath to 130-135° and stirred for 2 h. The reaction mass was dissolved by heating in 50 ml of alcohol, and the alcohol solution was separated with a 30 × 1000 preparative column filled with activity II Al_2O_3 (elution with chloroform). The unchanged arylamine and the resinification products were eluted with chloroform (the first red-violet zone), and the substitution products were eluted with acetone–chloroform (1:1) or alcohol. The solvent was removed by distillation, and the dry residue was crystallized from a suitable solvent (Table 1).

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