ELECTROPHILIC SUBSTITUTION REACTIONS IN 2, 3-DIMETHYLQUINOXALINE AND ITS N-OXIDE

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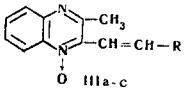
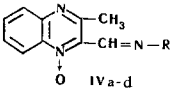
The reaction of 2, 3-dimethylquinoxaline and its mono-N-oxide with aromatic aldehydes and nitroso and diazo compounds has been studied. It has been found that the introduction of the N-oxide group increases the reactivity of a methyl group in the α-position with respect to it. Some properties of the compounds obtained have been studied.

It is known that hydrogen atoms of a methyl group conjugated with a heteroatom possess mobility and are capable of reacting with aldehydes and nitroso and diazonium compounds [1]. The binding of the unshared electron pair on the nitrogen of the heterocycle by its conversion into a quaternary or onium salt causes a considerable increase in the mobility of the hydrogen atoms of the methyl group. The formation of the N-oxide group leads to the appearance of a positive charge on the nitrogen, partially compensated by the electron-donating capacity of the oxygen atom. Depending on the nature of the heterocycle, a N-oxide group may both raise and lower the reactivity of a neighboring methyl group [2]. Such investigations have not been performed in the quinoxaline field.

We have studied the reaction of 2, 3-dimethylquinoxaline (I) and its mono-N-oxide (II) with aromatic aldehydes and nitroso and diazonium compounds. When II was condensed with aromatic aldehydes in ethanol in the presence of sodium methoxide the corresponding styryl derivatives (III) were formed after 30–45 minutes' heating. Since I does not give styryl derivatives with aromatic aldehydes under these conditions, it can be stated that it is the methyl group adjacent to the N-oxide group that takes part in the reaction with aldehydes:



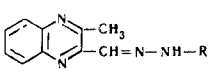
IIIa-c



IVa-d

IIIa R=C_6H_5
IIIb R=p-ClC_6H_4
IIIc R=p-$NO_2C_6H_4$

IVa R=p-$(CH_3)_2NC_6H_4$
IVb R=p-$(C_2H_5)_2NC_6H_4$
IVc R=p-$COOHC_6H_4$—NH
IVd R=p-$C_2H_5OOCC_6H_4$—NH



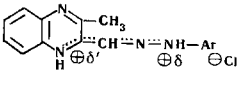
Va-d

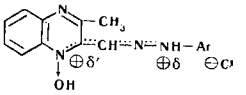
Va R=C_6H_5
Vb R=p-$NO_2C_6H_4$
Vc R=p-$COOHC_6H_4$
Vd R=p-$C_2H_5OOCC_6H_4$

The reaction of I and II with nitroso compounds and diazonium salts have not been described in the literature but there is information [3] that the methyl group in 2-methylquinoxaline reacts with nitroso and diazonium compounds only when the hydrogen is activated by the introduction of a nitrile group into the compound. From II and nitroso compounds we succeeded in obtaining the corresponding azomethines and from II and diazonium salts, azo dyes, provisionally called azoquinoxalines [4] (IV). From I and diazonium salts we obtained the azo dyes (V).

The reaction of I with nitroso compounds was carried out in methanolic sodium methoxide. In this case, the formation of the azomethine was observed only after prolonged boiling and in very small amounts. Under the same conditions, on gentle heating compound II very readily gave a copious dark red precipitate of the azomethine which, from the analytical data and molecular weight, corresponded to IV, i.e. only one methyl group, that in the α-position to the N-oxide group, took part in the reaction.

The azo coupling reactions of I and II with diazonium salts was carried out in glacial acetic acid in the presence of concentrated HCl, in pyridine, and in aqueous alkali. Compound I forms azo dyes in both acid and alkaline media. The structure of the compounds obtained was shown by independent synthesis by the reaction of 3-methylquinoxaline-2-aldehyde with phenyl- and p-nitrophenylhydrazines. Compounds IV were obtained from II and diazonium salts in an alkaline medium. They are yellow or yellow-orange crystalline substances. In an acid medium, IV acquire intense red-violet colorations. The depth of the coloration can be explained by the appearance of an ion with equalized bonds which is formed from the azo and hydrazone structures of the azoquinoxalines and their N-oxides [4].





EXPERIMENTAL

3-Methyl-2-styrylquinoxaline N-oxide (IIIa). A mixture of 1.76 g (0.01 mole) of II [5] and 2.12 g (0.02 mole) of benzaldehyde with a solution of 1.15 g of metallic sodium in 20 ml of methanol was heated in the boiling water bath for 1 hr, the solution assuming a brown color. After the solvent had been distilled off, the residue was twice crystallized. Yellow crystalline powder, soluble in benzene and chloroform and, on heating, in alcohols, ether, and acetone; insoluble in water.

Compounds IIIb and IIIc were obtained similarly.

2-(p-Diethylaminophenyliminomethyl)-3-methylquinoxaline N-oxide (IVb). A mixture of 0.88 g (0.005 mole) of II and 1.78 g (0.01 mole) of p-nitrosodiethylaniline was mixed with 20 ml of a solution of 0.57 g of metallic sodium in methanol and heated in the boiling water bath for 30 min. The color of the solution became dark red and, after cooling, a precipitate deposited. Dark red needles,

Quinoxaline Derivatives

Compound	Mp, °C (solvent for crystallization)	λ_{max}, nm (log ε) in ethanol	Empirical formula	N, % found	N, % calculated	Yield, %
IIIa	177 (Ethanol)	245 (4.00); 315 (3.78)	$C_{17}H_{14}N_2O$	10.56	10.68	60
IIIb	174 (Ethanol)	240 (4.12); 285 (3.92); 340 (3.77)	$C_{17}H_{13}N_2OCl$	9.71[3*]	9.44	65
IIIc	196 (Butanol)	240 (4.15); 275 (3.34); 315 (3.71)	$C_{16}H_{13}N_3O_3$	13.53	13.68	55
IVa	160 (Methanol)	245 (3.98); 265 (4.01); 315 (3.88); 445 (3.75)	$C_{18}H_{18}N_4O$	18.33	18.29	60
IVb	134 (Ethanol)	245 (3.94); 265 (3.95); 315 (3.88); 445 (4.03)	$C_{20}H_{22}N_4O$	16.92	16.76	68
IVc	268 (Decomp., butanol)	305 (3.65); 335 (3.65); 405 (3.86); 410 (4.23); 516 (4.00)[2*]	$C_{17}H_{14}N_4O_3$	17.50[4*]	17.39	58
IVd[1*]	188 (Methanol)	420 (4.45); 520 (4.34)[2*]	$C_{19}H_{18}N_4O_3$	15.65	16.00	62
Va[1*]	197 (Ethanol)	415 (3.82); 600 (3.71)[2*]	$C_{16}H_{14}N_4$	21.39	21.36	55
Vb[1*]	247 (Ethanol)	426 (4.50); 490 (3.82)[2*]	$C_{16}H_{13}N_5O_2$	23.01	22.79	50
Vc	>270 (Butanol)	305 (4.03); 335 (3.92); 412 (4.01); 510 (4.04)[2*]	$C_{17}H_{14}N_4O_2$	18.45	18.29	60
Vd	205 (Methanol)	250 (3.99); 310 (3.96); 335 (3.84); 390 (4.22); 416 (4.52); 520 (4.14)[2*]	$C_{19}H_{18}N_4O_2$	16.80	16.76	64

1*UV spectra not recorded.
2*Spectra recorded in ethanol with the addition of conc. HCl (1 : 1).
3*Found, %: C 68.61; H 4.52. Calculated, %: C 68.81; H 4.42.
4*Found, %: C 68.34; H 4.62. Calculated, %: C 68.35; H 4.38.

readily soluble in chloroform, ethyl acetate, and methyl formate and, on heating, in alcohols and ether. Insoluble in water. Found, %: C 71.72; H 6.62; N 16.92; Mol. wt. 339.07. Calculated for $C_{20}H_{22}N_4O$, %: C 71.83; H 6.63; N 16.76; Mol. wt. 334.40.

Compound **IVa** was obtained under similar conditions.

3-Methyl-2-(phenylazomethyl)quinoxaline (Va). a) With stirring, a solution of 0.02 mole of benzenediazonium sulfate in 5 ml of concentrated HCl was added in small portions to a cooled solution of 1.6 g (0.001 mole) of **I** in 20 ml of glacial acetic acid; the color became intense red and after some hours a red-violet precipitate deposited, which was crystallized. Microcrystalline orange powder soluble in dioxane and acetone and, on heating, in ethanol; sparingly soluble in benzene; insoluble in water.

b) To a solution of 1.72 g (0.01 mole) of 3-methylquinoxaline-2-aldehyde in 20 ml of ethanol was added an ethanolic solution of an equimolar amount of phenylhydrazine; an orange precipitate of the phenylhydrazone precipitated, and this was crystallized. A mixture with the **Va** obtained by method (a) gave no depression of the melting point.

Compound **Vb** and the corresponding hydrazone were obtained similarly.

2-(p-Ethoxycarbonylphenylazomethyl)-3-methylquinoxaline (Vd). A solution of 0.04 mole of diazotized anesthesine was added in small portions to a cooled solution of 3.2 g (0.02 mole) of **I** in 20 ml of pyridine. The solution became dark red, and when it was acidified with concentrated HCl, an orange precipitate deposited which was filtered off after 48 hr and crystallized. The **Vd** consisted of yellow crystals. Found, %: C 68.27; H 5.51; N 16.80; Mol. wt. 335.09. Calculated for $C_{19}H_{18}N_4O_2$, %: C 68.25; H 5.43; N 16.76; Mol. wt. 334.36.

The azo dyes **IVc, IVd,** and **Vc** were obtained similarly.

The molecular weights were determined by the method of isothermal distillation.

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