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QUINOXALINE N-OXIDES

XI. Condensation of 2-Methyl- and 2,3-Dimethylquinoxalines and Their N-Oxides with Aromatic Aldehydes

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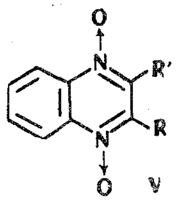
The reactions of 2-methyl- and 2, 3-dimethylquinoxalines and their N-oxides with C_6H_5CHO, p-$O_2NC_6H_4CHO$, and p-$CH_3OC_6H_4CHO$, have been investigated. It is shown that the 1, 4-di-N-oxides of 2-methyl- and 2, 3-dimethylquinoxaline do not undergo condensation with aromatic aldehydes when heated in the presence of acids, but that in the presence of strongly basic reagents they readily, without heating, undergo an aldol-type reaction, to give the corresponding carbinols. Under those conditions the di-N-oxide of 2, 3-dimethylquinoxaline and C_6H_5CHO or p-$CH_3OC_6H_4CHO$ gives only monocarbinols, whereas p-$O_2NC_6H_4CHO$ reacts with both methyl groups. Under the action of concentrated H_2SO_4 these carbinols give the corresponding styryls. The di-N-oxides of α-methyl derivatives of quinoxaline react with aromatic aldehydes more readily than the N-oxides of α- and γ-methylpyridines and quinolines. Views are put forward regarding the relationships between reactivities of α- and γ-methyl derivatives of heterocyclic N-oxides and their abilities to undergo polarization in two opposite directions.

We have previously investigated the comparative reactivities of the α-methyl group in 2-methyl- and 2, 3-dimethylquinoxaolines and their N-oxides towards hydroxymethylation with formaldehyde in neutral, acid, and alkaline media [1, 2]. The present paper sets out the results of research on the condensation of 2-methyl-(I) and 2, 3-dimethylquinoxaline (II), and their N-oxides, with aromatic aldehydes in the presence of acid and basic reagents.

By heating compound II with benzaldehyde in acetic acid containing a small quantity of hydrochloric acid (d 1.19), we obtained 2, 3-distyrylquinoxaline (III) [3]. The 1, 4-di-N-oxide of 2, 3-distyrylquinoxaline was not obtained under the same conditions from 2, 3-dimethylquinoxaline 1, 4-di-N-oxide, the starting N-oxide IV being mainly recovered unchanged, but the distyryl III was detected in the reaction products by chromatography, indicating occurrence of deoxidation of either of the reaction products, or of the starting di-N-oxide IV. The same results were obtained when the reaction was effected by heating the di-N-oxide IV with excess benzaldehyde in the presence of $ZnCl_2$. There, when heating time was increased, reaction was accompanied by marked resinification, and the distyryl III reaction product was isolated in low yield. During research on this reaction it was shown that compound IV and $ZnCl_2$ give an adduct, the analytical data for which correspond to a compound $(C_{10}H_{10}N_2O_2)_2 \cdot ZnCl_2$ (VI). Compound IV was reformed when this adduct was heated with aqueous NaOH.

The same condensation reaction proceeded quite otherwise in the presence of alkaline catalysts. Reaction of the di-N-oxide IV or of 2-methylquinoxaline 1, 4-di-N-oxide (VII) with benzaldehyde in the presence of NaOH or MeONa, resulted in condensation even without heating. In that way compound IV gave the carbinol Va, a product of an aldol-type condensation (at one methyl group only), while compound VII gave a mixture of carbinol Vb and styryl Ve.

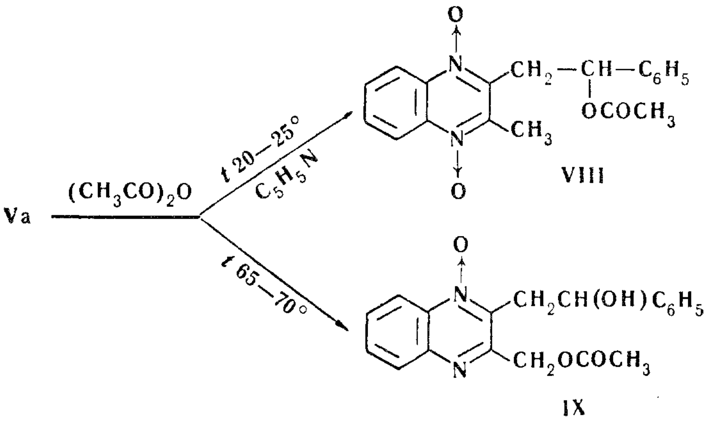
In contrast, the α-methyl derivatives of quinoxaline not oxidized at the nitrogen atom reacted with greater difficulty under the same conditions. Thus 2, 3-dimethylquinoxaline (II) did not react with benzaldehyde in the presence of NaOH (at 20–25° C, or on heating). It was only when the reaction was run in the presence of MeONa (held at 20–25° C for 15 days) that 2-methyl-3-styrylquinoxaline was obtained in low yield (36–37%). Condensation of compound IV with p-nitrobenzaldehyde and p-methoxybenzaldehyde occurred under the same conditions. With p-nitrobenzaldehyde, both methyl groups of compound IV reacted, forming the dicarbinol Vd. Condensation with p-methoxybenzaldehyde was slower, and gave the monocarbinol Vc.



V

Va $R = CH_3$, $R' = CH_2-CH(OH)C_6H_5$
Vb $R = H$, $R' = CH_2-CH(OH)C_6H_5$
Vc $R = CH_3$, $R' = CH_2-CH(OH)C_6H_4OCH_3$-(*p*)
Vd $R = R' = CH_2-CH(OH)C_6H_4NO_2$-(*p*)
Ve $R = H$, $R' = CH = CHC_6H_5$
Vf $R = CH_3$ $R' = CH = CHC_6H_5$
Vg $R = CH_3$, $R' = CH = CHC_6H_4OCH_3$-(*p*)

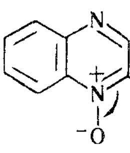
The structures of compounds Va-d were confirmed by IR spectroscopic data, which indicated that these compounds contained an OH group (bands in the 3250–3170 cm^{-1} region), as well as by preparation of the corresponding acetyl derivatives. Acetylation could be effected under mild temperature conditions in the presence of pyridine. Otherwise there was another reaction, which was a fundamental property of N-oxides of α-methyl derivatives of heterocyclic nitrogen compounds, deoxidation of the ring nitrogen, accompanied by acetoxylation of the α-methy group [4-6]. Thus the action of acetic anhydride on compound Va in the presence of pyridine at 20–25° C gave the O-acetyl derivative VIII, while heating Va with acetic anhydride gave a substance with the elementary composition $C_{19}H_{18}N_2O_4$, whose IR spectrum showed a band at 3270 cm^{-1}, characteristic of the OH group, and an ester carbonyl band at 1742 cm^{-1}. From these results the structure IX was tentatively ascribed to the compound.



Attempts to convert the carbinols Va-Vd obtained into styryls, using literature methods, did not give positive results. Styryls Ve-Vg could be obtained in almost quantitative yield by treating carbinols Va-Vc with concentrated sulfuric acid.

Thus research showed that the ability of 2-methyl- and 2,3-dimethylquinoxalines and their di-N-oxides to undergo condensation with carbonyl compounds, depends on the reaction medium. In the presence of acid catalysts the reactivities of the α-methyl groups attached to the quinoxaline ring exceed those of the α-methyl groups in the corresponding di-N-oxides. When such reactions are carried out in the presence of strong bases, the reactivities of di-N-oxides of 2-methyl- and 2,3-dimethylquinoxalines are considerably greater than those of the corresponding non-oxide compounds. Our results are in agreement with those in recently published papers [7,8] in which it is shown that the rates of exchange of hydrogen in methyl groups of N-oxides of α-picoline and quinaldine are considerably accelerated by the presence of catalytic amounts of alkoxide ions, and are higher than the rates of isotopic exchange for the corresponding bases not oxidized at the nitrogen atom.

In view of the experimental facts set out above, and a number of previously known ones [9, 10], it is impossible to agree with the view expressed by some authors regarding the depressed reactivity of α- and γ-methyl groups in heterocyclic N-oxides, ascribed to a static conjugation effect between a free electron pair of the oxygen in the group N → O and π-electrons in the ring [11, 12]. Rather, all the experimental results indicate that the reactivities of α- and γ-methyl groups in heterocyclic N-oxides depend mainly on dynamic electronic effects arising mainly at the moment of reaction, and in particular connected with the widely known ability of this class of compound to polarize in two opposite directions, depending on the nucleophilic or electrophilic character of the approaching reagent. In the light of these ideas, the role of the basic reagent (OH^- or OMe^-) can comprise not only ability to extract a proton from the α- and γ-methyl groups, but also polarization, evoked by its approach, of the N-oxide molecule in a direction facilitating formation of an active intermediate anion (X and XI) which undergoes condensation. With α- and γ-methyl derivatives of heterocyclic compounds not oxidized at the nitrogen atom, the similar polarization in the presence of OH^- and OR^- will be less marked, and therefore compounds of that type, as compared with their N-oxides, will be less prone to undergo condensation in alkaline medium. It should be noted that the reactivity of α- and γ-methyl groups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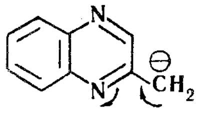
XI

Results of Reactions of 1, 4-Di-N-Oxides of 2-Methyl- and 2,3-Dimethylquinoxalines with Aromatic Aldehydes in the Presence of Bases

Starting Compound	Alkaline reagent	Aldehyde	Ouantity of aldehyde in mole per 1 mole N-oxide	Reaction Time, hr	Reaction product	Yield, %	Mp, ° C	Formula	Found, %			Calculated, %			Band of OH group in IR spectrum, cm^{-1}
									C	H	N	C	H	N	
IV	NaOH	Benzaldehyde	1	18	Va	70.7	191—192 ex benzene	$C_{17}H_{16}N_2O_3$	69.23	5.68	9.55	68.91	5.44	9.46	3230
"	"	"	2	"	"	91.5	"	Identified, by mixed mp and chromatographically,* as Va, prepared above							
"	"	"	"	3	"	90.7	"								
"	CH₃ONa		"	18	"	87.7	"								
"	NaOH	p-Nitrobenzaldehyde	"	18	Vd**	73.0	241.5 decomp	$C_{24}H_{20}N_4O_6$	58.61	4.24	11.24	58.54	4.09	11.38	3250
"	"	Anisaldehyde	"	11 days	Vc	18.4	192—193 ex EtOAc	$C_{18}H_{18}N_2O_4$	66.38	5.61	8.75	66.26	5.56	8.59	3250
"	"	"	"	20 days	"	36.2	"	Identified, by mixed mp as Vc, prepared above							
VII	"	Benzaldehyde	"	18	Ve***	19.0	231 decomp; ex EtOH	$C_{16}H_{12}N_2O_2$	72.47	4.66	10.40	72.71	4.58	10.56	—
					Vb	31.9	168—168.5	$C_{16}H_{14}N_2O_3$	68.14	5.16	10.05	68.08	5.00	9.93	3170
"	"	"	"	3 days	Mixture Ve and Vb	37.9	ex Me_2CO								

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* Chromatographed with the systems BuOH-5% AcOH, using Leningrad Factory No. 2 paper for chromatography. Visualizer, UV light.

** As compound Vd could not be recrystallized on account of its very low solubility in ordinary organic solvents, it was purified by repeated treatment with AcOH.

*** After removing compound Ve, the reaction products solution was evaporated, to give Vb.

**** The mixture of Ve and Vb was treated with concentrated H_2SO_4 as described below, to give Ve, yield of styryl 28.8%

in di-Noxides of 2-methyl- and 2,3-dimethylquinoxalines is considerably greater than in N-oxides of α- and γ-methylated quinolines. Thus under identical conditions, i.e., in the presence of basic reagents, N-oxides of α- and γ-methylpyridines or quinolines condense with benzaldehyde only when heating at 80–90° C is continued for long enough [11], while the corresponding α-methyl derivatives of di-N-oxides of quinoxaline, as was previously mentioned above, undergo the same reaction practically at room temperature.

We wish to express our thanks to Professor O. Yu. Magidson, for the interest which he has taken in the present work.

Experimental

Reaction of 1, 4-di-N-oxides of 2-methyl-(VII) and 2, 3-dimethylquinoxaline (IV) with aldehydes in the presence of alkaline reagents. To VII or IV, suspended in 10–12 times its own weight of dry EtOH, was added the aldehyde and the alkaline reagent, NaOH (as a 1 N aqueous solution), the amount of the latter being 0.12 mole per 1 mole di-N-oxide taken for reaction, or else 0.2 mole MeONa (as a 10% MeOH solution) per 1 mole di-N-oxide. The reaction mixture was kept at 25–30° C under nitrogen, and the precipitate formed filtered off. The reaction product was purified by recrystallizing from the appropriate solvent (for results see table).

Reaction of 2, 3-dimethylquinoxaline (II) with benzaldehyde in the presence of alkali. A mixture of 1.58 g (0.01 mole) compound II, 22 ml dry EtOH, 2.03 ml (0.02 mole) benzaldehyde, and 1 ml 1 N NaOH was kept at 25–30° C under nitrogen for 7 days. The reaction products were evaporated, the residue treated with ether, and the insoluble material filtered off, yield 1.15 g (78%) unchanged compound II, mp 101–102° C, identified by mixed mp.

Reaction of 2, 3-dimethylquinoxaline 1, 4-di-N-oxide (IV) with benzaldehyde in the presence of hydrochloric acid. A mixture of 0.95 g (0.005 mole) compound IV, 2.03 ml (0.02 mole) benzaldehyde, 5 ml AcOH, and 3 drops concentrated HCl was refluxed for 5 hr, then the reaction products evaporated under reduced pressure. The tarry residue gave, on recrystallization from MeOH, 0.46 g (48.4%) unchanged compound IV, mp 186–187° C, identified by mixed mp, and chromatographically. The mother liquor gave a spot with R*f* 0.89 (emerald green in UV), R*f* and fluorescence identical with those of compound III.

2, 3-Distyrylquinoxaline (III). A mixture of 1.58 g (0.01 mole) compound II, 2.03 (0.02 mole) benzaldehyde, 9 ml AcOH, and 5 drops concentrated HCl, was refluxed for 5 hr, the reaction products evaporated to dryness under reduced pressure, and the tarry residue treated with 1 N NaOH, to give 1.3 g (38.9%) compound III, mp 191–192° C (ex petrol ether-benzene). Identified chromatographically and by mixed mp with known compound [3].

2-Methyl-3-styrylquinoxaline. A mixture of 1.58 g (0.01 mole) 2,3-dimethylquinoxaline, 22 ml dry EtOH, 2.03 ml (0.02 mole) benzaldehyde, and 1 ml 10% MeONa in MeOH was kept for 15 days at 20–22° C. The reaction mixture was evaporated, the residue extracted with hot benzene, the extract evaporated to small volume, and petrol ether added to it. The precipitate formed was filtered off and triturated with MeOH, to give 0.24 g (37.4%) 2 methyl-3-styrylquinoxaline, mp 136.5–137.5° C (ex MeOH). Found: C 83.04; H 5.87; N 10.87%. Calculated for $C_{17}H_{14}N_2$: C 82.90; H 5.73; N 11.38%.

From the mother liquor there was obtained a spot with R*f* 0.93, identical with that of 2, 3-dimethylquinoxaline.

2, 3-Dimethylquinoxaline 1, 4-di-N-oxide (IV) adduct with zinc chloride (VI). 1.36 g (0.01 mole) anhydrous $ZnCl_2$ was added to a suspension of 1.9 g (0.01 mole) compound IV in 15 ml dry EtOH, and the mixture left at 20–25° C for 3 hr. Cooling gave 2.32 g (45%) adduct VI, mp 227° C (decomp, ex dry EtOH). Found: C 46.32; H 4.02; Cl 13.64%. Calculated for $C_{20}H_{20}N_4O_4 \cdot ZnCl_2$: C 46.85; H 3.90; Cl 13.67%.

4 ml 15% NaOH was added to 0.5 g adduct VI, the mixture heated to 45° C, and after 20 min the reaction products were extracted with $CHCl_3$, to give 0.2 g compound IV, mp 189–190° C, identified chromatographically and by mixed mp.

Reaction of 2, 3-dimethylquinoxaline 1, 4-di-N-oxide (IV) with benzaldehyde in the presence of zinc chloride. a) A mixture of 0.95 g (0.005 mole) compound IV, 5 ml benzaldehyde, and 0.5 g anhydrous $ZnCl_2$ was heated at 125–130° C for 3 hr. Then the reaction products were evaporated under reduced pressure, the residue treated with 15% NaOH, extracted with $CHCl_3$, and the tars separated off. Evaporation of the extract gave 0.23 g (24.2%) unchanged compound IV, mp 188–189° C, R*f* 0.69. Identified by mixed mp and mixed chromatography. Chromatography of the tars gave a spot with R*f* 0.88 (emerald green fluorescence in UV), identical in R*f* and UV fluorescent color with III.

b) A similar reaction was run at 130–135° C (5 hr). After distilling off the benzaldehyde, treatment of the residue with 15% NaOH, and extraction with $CHCl_3$, gave a viscous tar which was boiled with EtOH. On cooling the EtOH extract deposited 2, 3-distyrylquinoxaline (III), yield 0.19 g (11.3%), mp 187–188° C. Identified by mixed chromatography with authentic product [3]. Paper chromatography of the reaction products did not show a compound with R*f* 0.69, characteristic of compound IV.

2-Methyl-3-styrylquinoxaline 1, 4-di-N-oxide (Vf). 0.9 ml concentrated H_2SO_4 was added with cooling to 0.5 g compound Va, heat being evolved, and the temperature of the reaction mixture rising to 50–55° C. After 30 min the reaction products were poured into ice water and neutralized with 2.5 N NaOH. Yield 0.46 g (97.7%) compound Vf, mp 173–174° C (ex MeOH). Found: C 73.24; H 4.97; N 10.27%. Calculated for $C_{17}H_{14}N_2O_2$: C 73.36; H 5.07; N 10.07%. The IR spectrum does not show an absorption band characteristic of the OH group in the 3200–3300 cm^{-1} region.

Compound Vg was prepared similarly, mp 176–177° C (ex MeOH), yield 95.8%. Found: C 70.12; H 5.07; N 9.26%. Calculated for $C_{18}H_{16}N_2O_3$: C 70.13; H 5.23; N 9.09%. No absorption band characteristic of the OH group in the IR spectrum at 3200–3300 cm^{-1}.

2-Methyl-3-(β-acetoxy-β-phenyl) ethylquinoxaline 1, 4-di-N-oxide (VIII). 3.5 ml Ac_2O was added to a suspension of 0.5 g compound Va in 3.5 ml dry pyridine, and the mixture left for 18–20 hr at 20–22° C. The reaction products were poured into water, and after 1 hr, the whole brought to pH 2–3 by adding 2.5 N HCl. The oily material was extracted with $CHCl_3$, the extract gave 0.57 g tarry material, which was boiled with benzene-petrol ether (1:100). Cooling the solution gave 0.2 g (35.2%) compound VIII, mp 88.5–90° C (ex benzene-petrol ether). Found: N 8.45%. Calculated for $C_{19}H_{18}N_2O_4$: N 8.28%. No OH band in the 3200–3300 cm^{-1} region in the IR spectrum, but there is a band at 1740 cm^{-1} (C=O).

2-Acetoxymethyl-3-(β-hydroxy-β-phenyl) ethylquinoxaline 4-N-oxide (IX). A mixture of 2 g compound Va and 20 ml Ac_2O was heated at 65–70° C (4 hr 30 min), the reaction products then cooled, and the precipitate filtered off, to give 0.82 g (35.9%) IX, mp 176.5–177.5° C (ex benzene). Found: C 67.47; H 5.47; N 8.40%. Calculated for $C_{19}H_{18}N_2O_4$: C 67.43; H 5.36; N 8.28%. The IR spectrum has a band at 3270 (OH) and another at 1724 cm^{-1} (C=O in ester).

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