N-OXIDES OF THE QUINOXALINE SERIES

XV. Mono- and Di-N-oxides of the Quinoxaline Series in Oxidation Reactions and Reactions with Acetic Anhydride*

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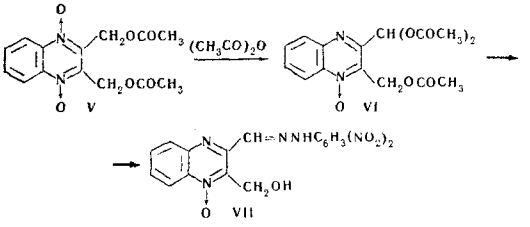
A further study of the chemical behavior of quinoxaline and its α-methyl and hydroxy derivatives and their N-oxides in oxidation reactions and reactions with acetic anhydride has been carried out. The features of these reactions connected with the structure of the reacting N-oxides are discussed.

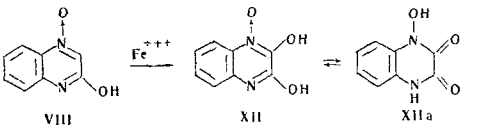
In developing our investigation of the reactions of quinoxaline N-oxides and their derivatives with anhydrides and chlorides of organic acids [1–4], it appeared of interest to study the influence of inhibitors and promoters of free-radical processes on the reaction of quinoxaline, 1,4-di-N-oxide (I) and 1,3-dimethylquinoxaline 1,4-di-N-oxide (II) with acetic anhydride. The addition of p-benzoquinone or benzoyl peroxide in the reaction of I with acetic anhydride gave results analogous to those obtained in the reaction of I with benzenesulfonyl chloride [4]: p-benzoquinone markedly lowered the yield of 2-acetoxyquinoxaline 1-N-oxide (III) (from 48.5–50 to 24–25%) while the addition of benzoyl peroxide did not appreciably affect the yield of III. These results indicated the participation of free-radical processes in the main direction of the reaction and the presence of parasitic radical processes which were also enhanced in the presence of benzoyl peroxide. Apart from compound III and quinoxaline mono-N-oxide, isolated in the form of the picrate, several other spots were detected in the reaction mixture by paper chromatography** one of which was similar to 2,3-dihydroxyquinoxaline from its R_f value (0.64–0.66) and its fluorescence in UV light (bright blue). Completely different results indicating the absence of free-radical processes in the main direction of the reaction, were obtained in the reaction of the di-N-oxide II with acetic anhydride. In this case, the addition of p-benzoquinone or benzoyl peroxide had no appreciable influence on the yield of 2,3-bis(acetoxymethyl)quinoxaline (IV). The same results permitting the authors to deny the free-radical mechanism of the reaction, were obtained earlier in a study of the influence of inhibitors of free-radical processes on the yield of 2-acetoxymethylpyridine in the reaction of α-picoline N-oxide with acetic anhydride [5].

2,3-Bis(acetoxymethyl)quinoxaline 1,4-di-N-oxide (V), on being boiled with acetic anhydride, again underwent a rearrangement with the formation of a substance having the elementary composition $C_{16}H_{16}N_2O_7$ which, on being heated with an acidified solution of 2,4-dinitrophenylhydrazine, gave a hydrazone with the composition $C_{16}H_{12}N_6O_6$. On the basis of these results, the reaction product obtained and its hydrazone have been assigned structures VI and VII, respectively.



An investigation of the reactions of 2-hydroxyquinoxaline 4-N-oxide (VIII) and 2-hydroxy(acetoxy)quinoxaline with acetic anhydride showed that the 4-oxide VIII readily reacted (on heating) with acetic anhydride, forming 2,3-dihydroxyquinoxaline (IX), while 2-hydroxy(acetoxy)quinoxaline 1-N-oxide exhibited a considerable resistance to the action of acetic anhydride. Thus, after 2-hydroxyquinoxaline 1-N-oxide (X) has been boiled with acetic anhydride for 5 hr, the main product was 2-acetoxyquinoxaline 1-N-oxide (XI), with only a small amount of a mixture of other substances one of which possessed acidic properties and, on paper chromatography, gave a spot with a R_f value close to that of compound IX but differed from it somewhat in its fluorescence in UV light: a mixture with IX gave a depression of the melting point. The study of the structure of this substance is proceeding.

The ease of oxidation of $C_{(3)}$ in compound VIII has been observed in other reactions, as well. Thus, it was found that solutions of VIII containing $FeCl_3$ and not at first giving a color reaction acquired a gradually deepening blue coloration on standing. It has been shown that this phenomenon is connected with the oxidation of compound (VIII) by the Fe^{3+} cation with the formation of 2,3-dihydroxyquinoxaline 1-N-oxide (XII ⇄ XIIIa) for which a blue-red coloration with $FeCl_3$ is characteristic.



Earlier, in an attempt to obtain the N-oxides of 2,3-dicarboxy- and 3-carboxy-2-hydroxyquinazolines

*For part XIV, see [10].

**Here and below, paper chromatography was carried out in the butanol–5% acetic acid system.

by oxidizing the corresponding quinoxaline derivatives with hydrogen peroxide in acetic acid, the oxidation of the α-carbon atoms of the ring accompanied by cleavage of the C—C bond and the resulting formation of 2,3-dihydroxyquinoxalines was observed [6].

We found an analogous phenomenon in the oxidation of compound IV with a solution of peracetic acid. In this reaction, together with the di-N-oxide V, compound IX was isolated as one of the by-products with a yield of 5–5.5%. We also observed the formation of compound IX (yield 7.5–8%) in the oxidation of quinoxaline with a solution of peracetic acid.

I express my deep gratitude to Prof. O. Yu. Magidson for the attention which he has devoted to this work.

EXPERIMENTAL

Reaction of quinoxaline di-N-oxide (I) with acetic anhydride. a) A mixture of 4.5 g (0.028 mole) of I and 23 ml of acetic anhydride was boiled with stirring for 1 hr and then the acetic anhydride was driven off in vacuum and the reaction product was separated from resinous substances by distillation, a fraction boiling between 120 and 150° C (2 mm), which rapidly crystallized being collected. After recrystallization from 5 ml of methanol, 2.37 g (41.5%) of 2-acetoxyquinoxaline 1-N-oxide (III) with mp 111–112°C [2], was obtained The methanolic solution was evaporated and the residue was treated with 5 ml of 2.5 N NaOH solution and left for 15–20 min, after which all the substance had gone into solution. From the alkaline solution chloroform extracted quinoxaline mono-N-oxide (0.3 g), after which it was acidified and the substance that separated out was reprecipitated from an aqueous solution of $NaHCO_3$. This gave 0.31 g (7%) of 2-hydroxyquinoxaline 1-N-oxide (X), mp 210–211°C [2].

b) The reaction was carried out in the same way as in experiment (a) except that 0.1 g of p-benzoquinone was added to the mixture before the beginning of the reaction. The yield of compound III was 1.13 g (19.8%) and that of compound X was 0.2 g (4.4%).

c) The reaction was carried out in a similar manner to experiments (a) and (b) with the addition of 0.1 g of benzoyl peroxide to the reaction mixture. The yield of compound III was 2.33 g (40.9%) and that of compound X 0.4 g (9.0%).

Reaction of 2,3-dimethylquinoxaline di-N-oxide (II) with acetic anhydride. a) With stirring, 20 ml of acetic anhydride was added to a solution of 5 g (0.024 mole) of II in 15 ml of glacial acetic acid heated to 115–116°C over 7–10 min and then the temperature was raised to the boiling point over 10 min and the mixture was boiled for 20 min. After the end of the reaction vacuum distillation yielded a fraction boiling between 140 and 170° C (1 mm), which rapidly crystallized on standing. After recrystallization from 5 ml of methanol, 4.26 g (69.6%) of 2,3-bis(acetoxymethyl)quinoxaline (IV), mp 90–91°C [1], was obtained.

b) The reaction was carried out in the same way as in experiment (a) but 0.1 g of p-benzoquinone was added to the reaction mixture before the beginning of the reaction. The yield of compound IV was 4.27 g (69.8%), mp 89–90°C.

c) The reaction was carried out as in experiments (a) and (b), but 0.1 g of benzoyl peroxide was added to the reaction mixture before the beginning of the reaction. The yield of compound IV was 4.6 g (67%), mp 92–93°C.

Reaction of 2,3-bis(acetoxymethyl)quinoxaline 1,4-di-N-oxide (V) with acetic anhydride. A solution of 1.5 g (0.005 mole) of V in 10 ml of acetic anhydride was boiled for 2 hr and then the acetic anhydride was distilled off in vacuum and the residue was triturated with ether. This gave 0.8 g (50%) of 2-acetoxymethyl-3-diacetoxymethylquinoxaline 1-N-oxide (VI), mp 136–137°C (from methanol). Found, %: C 55.37; H 4.58; N 8.27. Calculated for $C_{16}H_6N_2O_7$, %: C 55.17; H 4.63; N 8.04.

2-Acetoxymethyl-3-formylquinoxaline 2,4-dinitrophenylhydrazone (VII) was obtained by heating compound VI with an acidified solution of dinitrophenylhydrazine for 10–15 min; bright yellow crystalline substance, mp 219–220°C. Found, %: C 50.32; H 3.30; N 21.76. Calculated for $C_{16}H_{12}N_6O_6$, %: C 50.00; H 3.14; N 21.87.

Reaction of 2-hydroxyquinoxaline 4-N-oxide (VIII) with acetic anhydride. A mixture of 0.5 g (0.004 mole) of compound VIII and 5 ml of acetic anhydride was boiled for 1 hr 30 min, and the solid matter (0.48 g) was filtered off and crystallized from acetic acid. The substance obtained did not melt below 360° C; on paper chromatography with a reference sample (compound IX) [7], it gave a spot identical with IX in R_f value (0.66) and fluorescence in UV light (bright blue-violet). Found, %: C 59.32; H 3.79; N 17.28. Calculated for $C_8H_6N_2O_2$, %: C 59.27; H 3.73; N 17.28.

Reaction of compound VIII with $FeCl_3$. A concentrated aqueous solution of $FeCl_3$ was added to a solution of 0.3 g of compound VIII in 100 ml of ethanol and the mixture was left at 20–25°C for 48 hr. The reaction solution gradually acquired a coloration which toward the end of the period became dark lilac. The ethanol was distilled off. The residue was treated with 2–3 ml of 2.5 N NaOH solution and the mixture was boiled for 5–10 min and filtered, after which the filtrate was acidified to pH 1–2. This gave 0.18 g of a substance with mp 280–281°C (decomp., from aqueous methanol) identical with the 2,3-dihydroxy-quinoxaline 1-N-oxide (XII) obtained by known methods [8, 9] (a mixture gave no depression of the melting point, R_f 0.65—pink spot on ordinary illumination, dark cherry-red color reaction with $FeCl_3$).

Production of 2,3-dihydroxyquinoxaline (IX) in the oxidation of 2,3-bis-(acetoxymethyl)quinoxaline (IV) and quinoxaline with peracetic acid. a) To a 9% solution of peracetic acid prepared from 180 ml of 30% hydrogen peroxide and 840 ml of acetic anhydride in the presence of 8.4 ml of H_2SO_4 (d 1.84) were added 15 g of CH_3COONa, 1 g of $Na_4P_2O_7$, and 94 g of compound IV. Oxidation was carried out for 19 hr at 55–60°C. At the end of the reaction, the amounts of unconsumed hydrogen peroxide and peracetic acid were determined and they were decomposed at 10–15°C with the calculated quantity of Na_2SO_3. The reaction solution was evaporated to small bulk, neutralized with aqueous $NaHCO_3$ solution, and extracted with chloroform. The 2,3-bis(acetoxymethyl)quinoxaline 1,4-di-N-oxide (V) passed into the chloroform. The residue, insoluble in the chloroform weighing 2.8 g (5%) did not melt below 360°C and on paper chromatography gave a spot identical in R_f value and fluorescence in UV light with 2,3-dihydroxyquinoxaline [7].

b) Fifty grams of quinoxaline was oxidized and the reaction solution was treated in the same way as in experiment (a). The residue, insoluble in chloroform (4.9 g, 7.8%), was identical with 2,3-dihydroxyquinoxaline [7].

Reaction of 2-hydroxyquinoxaline 1-N-oxide (X) with acetic anhydride. A mixture of 1 g of X and 5 ml of acetic anhydride was boiled for 6 hr and cooled, and the precipitate that had separated out was filtered off, weight 0.20 g. The substance obtained was treated with alkali and after 15–20 min the resin insoluble in the alkali was filtered off and the filtrate was acidified. This gave 0.15 g of a substance with mp 307–309°C a mixture of which with IX melted at 303–305°C. The acetic anhydride was distilled off from the reaction solution in vacuum and the residue was treated with 2 N NaOH solution, the mixture was filtered, and the filtrate was acidified. The crystalline substance obtained was reprecipitated from $NaHCO_3$ solution giving 0.6 g of X, mp 209–210° C.

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