N-OXIDES OF THE QUINOXALINE SERIES

XVI. Redox Reactions in the N-Oxides of α-Hydroxymethyl Derivatives of Quinoxaline*

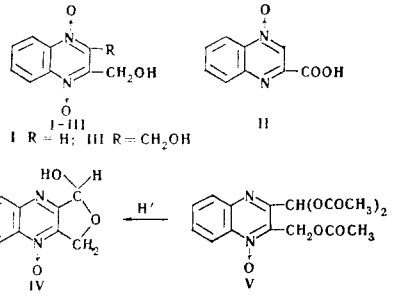
A. S. Elina, L. G. Tsyrul'nikova, and G. P. Syrova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 149–153, 1969

UDC 547.863.16:542.942.943:541.67

When di-N-oxides of α-hydroxymethyl derivatives of quinoxaline are heated with dimethyl sulfoxide, the oxidation of a CH_2OH group and the reduction of a neighboring N → O group takes place. The N-oxides of 2,3-bis(hydroxymethyl)quinoxaline undergo similar redox processes in the presence of alkaline reagents.

Recently, reports on the use of dimethyl sulfoxide (DMSO) as an oxidizing reagent have begun to appear in the literature. It is known that some haloalkanes [1, 2] and alcohols [3] are oxidized by DMSO to the corresponding aldehydes. The oxidation of 2,3-bis-(bromomethyl)quinoxaline [4] to 2-formyl-3-methyl-quinoxaline has been described. The reaction of heterocyclic N-oxides with DMSO has not previously been studied. In view of the interest in N-oxides of α-carboxy derivatives of quinoxaline, we have studied the reaction of DMSO with the 1,4-di-N-oxides of α-hydroxymethyl derivatives of quinoxaline. Heating the 1,4-di-N-oxide of 2-hydroxymethylquinoxaline (I) in DMSO led to the formation of 2-carboxyquinoxaline 4-N-oxide (II) and quinoxalinealdehyde mono-N-oxide. The latter was ascribed the most probable structure of quinoxaline-2-aldehyde 4-N-oxide.

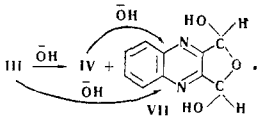


The reaction of 2,3-bis(hydroxymethyl)quinoxaline 1,4-di-N-oxide (III) with DMSO gave a substance with the elementary composition $C_{10}H_8N_2O_3$ corresponding to 3-formyl-2-hydroxymethylquinoxaline mono-N-oxide. The presence of an aldehyde group was confirmed by the preparation of its 2,4-dinitrophenylhydrazone. Nevertheless, the IR spectrum of this compound had no band characteristic for the C=O group in an aldehyde while it had the band of an associated OH group (3175 cm^{-1}). On the basis of these results, the compound obtained was ascribed the structure of the internal cyclic semiacetal of 3-formyl-2-hydroxymethylquinoxaline mono-N-oxide (IV). This was confirmed by its PMR spectra, in which there was no signal of the proton of an aldehyde group in the weak-field region; at δ 5.22 ppm (I = 16 Hz) there was a quartet belonging to the geminal protons of the CH_2 group, and doublets from the one proton of the C—H group at δ 6.35 ppm (I = 8 Hz) and from the one proton of the OH group at δ 7.42 ppm (I = 8 Hz) were observed. The assignment of the proton of the OH group was made on the basis of the shift of the doublet (δ 7.42 ppm) in the direction of stronger fields on heating (in all subsequent PMR spectra of the substances investigated, analogous assignments were made). The position of the N → O group in this compound was shown by its identity with substance IV obtained by the saponification in an acid medium of 2-acetoxymethyl-3-(diacetoxymethyl)quinoxaline (V) [5]. Thus, it was shown that the action of DMSO on di-N-oxides of α-hydroxymethyl derivatives of quinoxaline leads to a redox reaction consisting in the oxidation of one of the α-hydroxymethyl groups to an aldehyde group and the simultaneous reduction of the N → O group adjacent to the hydroxymethyl group undergoing oxidation. In contrast to the comparatively mild temperature conditions (60–90° C) in which the oxidation of 2,3-bis-(bromomethyl)quinoxaline was carried out with the aid of DMSO [4], the reactions described above took place only after I and III had been heated with DMSO at 105–110° C for several hours. The reaction, (as with subsequent ones), was followed by paper chromatography in the butanol—5% CH_3COOH (1 : 1) system. 2,3-Bis(hydroxymethyl)quinoxaline not oxidized at a nitrogen atom reacted with DMSO in a different way from 2,3-bis(bromomethyl)quinoxaline: at 60° C it gradually disappeared from the reaction mixture, but pronounced resinification took place, and a large amount of reaction products which could not be isolated in the individual state was detected chromatographically.

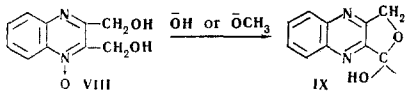
Further investigation of the chemical properties of N-oxides of α-hydroxymethyl derivatives of quinoxaline showed that in the presence of alkaline reagents these compounds undergo analogous redox processes. Thus, when 2,3-bis(hydroxymethyl)quinoxaline 1,4-di-N-oxide (III) was treated with alkali in ethanol, a mixture consisting of substance IV and the product of its further redox transformations—the cyclic hydrate of 2,3-diformylquinoxaline (VII)—was formed. When the amount of alkali was increased, compound VII was formed almost quantitatively. Its structure was established on the basis of the results of elementary analysis, its IR and PMR spectra, and also by the isolation

*For part XV, see [5].

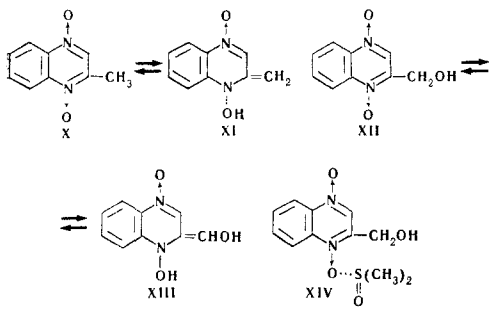
from it on sublimation of 2,3-diformylquinoxaline:



Since in the PMR spectrum of compound VII in place of the expected one doublet there are two doublets of protons of C—H groups at δ 6.40 ppm (I = 8 Hz) and 6.17 ppm (I = 8 Hz), and the doublet belonging to the proton of the O—H group at 7.21 ppm (I = 8 Hz) is split further, the assumption was made that compound VII is a mixture of spatial isomers, the ratio of the intensities of the doublets at δ 6.40 and 6.17 ppm showing that one of the isomers predominates. Apparently this also explains why the melting point of compound VII is somewhat lower than the figures given in the literature [4]. It is an interesting fact that the oxidation of compound IV with hydrogen peroxide in an alkaline medium led to the deoxidation of the N → O group and to the formation of 2,3-dicarboxyquinoxaline. 2,3-Bis(hydroxymethyl)quinoxaline 1-N-oxide (VIII) underwent analogous redox processes under the same conditions, forming compound IX:



It was established that atmospheric oxygen is not involved in the processes taking place, since when III was heated in methanol in the presence of alkali in a current of nitrogen (with previous evacuation of the air from the apparatus) the yield of compound VII was practically unchanged. The mechanism of the processes studied might be connected with some previously-observed features of the structure and chemical behavior of the N-oxides of α-alkyl derivatives of quinoxaline. Thus, the acidic properties of 2-methylquinoxaline di-N-oxide and its rapid irreversible conversions in an alkaline medium have been ascribed to the possibility of tautomerism of the **X** ⇄ **XI** type [6].



We have shown the considerable increase in the mobility of the hydrogen atoms of the α-methyl group in the corresponding quinoxaline N-oxides in the presence of alkaline reagents [7,8]. It may be assumed that under the reaction conditions the N-oxides of the α-hydroxymethyl derivatives of quinoxaline exist predominantly in the form of type **XIII**; the subsequent splitting out of the elements of water must lead to the deoxidation of one of the cyclic nitrogen atoms and conversion of the neighboring hydroxymethyl group into an aldehyde group. In the reactions with DMSO, activation of the reacting molecules possibly takes place through the formation of complexes of type **XIV**. It must also be mentioned that the products of the reactions of compounds I and III were isolated in the form of sulfur-containing adducts the composition of which it has not been possible to determine because of their instability.

We express our deep gratitude to Prof. O. Yu. Magidson for the attention devoted to the present work.

EXPERIMENTAL

Reaction of 2-hydroxymethylquinoxaline 1,4-di-N-oxide (I) with DMSO. A solution of 1.2 g (0.006 mole) of compound I in 24 ml of DMSO (mp 16.5° C) was heated at 105–110° C for 40 hr. The reaction solution was evaporated in vacuum to small volume. The residue was poured into water. The precipitate that formed was separated off and dissolved in aqueous $NaHCO_3$ solution. The alkaline solution was extracted with chloroform, whereupon a precipitate of the sodium salt of 2-carboxyquinoxaline 4-N-oxide precipitated. It was filtered off and dissolved in water, and a 2.5 N solution of hydrochloric acid added (pH 1–2). This gave 0.2 g of 2-carboxyquinoxaline 4-N-oxide (II), mp 186.5–187° C (from acetone). A mixture with the compound **II** obtained previously [9] gave no depression of the melting point. Found, %: C 57.04; H 3.34; N 14.53. Calculated for $C_9H_6N_2O_3$, %: C 56.84; H 3.18; N 14.74. The alkaline solution remaining after the chloroform extraction was treated with a 2.5 N solution of hydrochloric acid (pH 1–2). This gave another 0.2 g of compound **II**, mp 184–185° C. The total yield of II was 30.7%.

The chloroform extract was evaporated. The resinous residue was treated with an ethanolic solution of 2,4-dinitrophenylhydrazine and three drops of 2.5 N hydrochloric acid solution. The mixture was heated in the water bath for 5 min, to give 0.2 g of quinoxaline-2-aldehyde 4-N-oxide 2,4-dinitrophenylhydrazone, mp 286.5° C (decomp.). Found, %: C 51.01; H 2.96; N 23.96. Calculated for $C_{15}H_{10}N_6O_5$, %: C 50.86; H 2.84; N 23.73. The combined mother liquors yielded a further 0.5 g of quinoxaline-2-aldehyde 4-N-oxide 2,4-dinitrophenylhydrazone, the total yield of hydrazone being 0.7 g which corresponds to 0.35 g (31.6%) of quinoxaline-2-aldehyde 4-N-oxide.

Reaction of 2,3-bis(hydroxymethyl)quinoxaline 1,4-di-N-oxide (III) with DMSO. A solution of 8 g (0.036 mole) of compound **III** in 160 ml of DMSO was heated at 105–119° C for 50 hr. The reaction mixture was evaporated in vacuum to a small volume, and the residue was poured into water. The precipitate formed was filtered off and dissolved with cooling in 2.5 N NaOH solution; the solution was rapidly purified with carbon, filtered, and treated with 2.5 N hydrochloric acid (pH 1–2). The precipitate that deposited was filtered off to give 5 g (68%) of 1-hydroxy-1,3-dihydrofuro[3,4-b]quinoxaline (**IV**), mp 212.5° C (decomp., from water), R_f 0.64 (violet in UV). Found, %: C 58.68; H 3.98; N 13.87. Calculated for $C_{10}H_8N_2O_3$, %: C 58.81; H 3.95; N 13.75.

1-Hydroxy-1,3-dihydrofuro[3,4-b]quinoxaline 4-N-oxide (IV). 0.6 g (1.7 mM) of 2-acetoxymethyl-3-(diacetoxymethyl)quinoxaline 1-N-oxide (V) was added to 8 ml of 2.5 N hydrochloric acid solution heated to 90° C. The reaction mixture was heated at the same temperature for 5 min and cooled, and the precipitate was filtered off. This gave 0.34 g of compound IV, mp 212.5° C (decomp., from water), R_f 0.64 (violet). A mixture with the compound IV obtained above gave no depression of the melting point, and the IR spectra of the two compounds coincided.

Action of alkali on 2,3-bis(hydroxymethyl)quinoxaline 1,4-di-N-oxide (III). a) A mixture of 1 g (4.5 mM) of compound III, 7 ml of ethanol, and 0.25 ml of 8% methanolic NaOH was boiled for 30 min. After cooling, the precipitate that had deposited was filtered off, giving

0.28 g (33%) of compound IV, mp 211° C (decomp.), R_f 0.64 (violet). A mixture with the compound IV obtained above gave no depression of the melting point, and the IR and PMR spectra of the two compounds coincided.

The mother solution remaining after the separation of compound IV was evaporated at room temperature. The residue was treated with water and neutralized with 2.5 N hydrochloric acid solution. This gave 0.22 g (24%) of 1,3-dihydroxy-1,3-dihydrofuro[3,4-b]quinoxaline (VII) [4], mp 171.5–172.5° C (from aqueous methanol), R_f 0.88 (dark violet). Found, %: C 58.94; H 3.83; N 14.00. Calculated for $C_{10}H_8N_2O_3$, %: C 58.81; H 3.95; N 13.75.

2,4-Diformylquinoxaline [4] was obtained by the sublimation of compound VII at a bath temperature of 115–120° C (2 mm), mp 175–176° C (decomp.). Found, %: C 64.70; H 3.20; N 15.32. Calculated for $C_{10}H_6N_2O_2$, %: C 64.52; H 3.25; N 15.06.

b) A mixture of 1 g (4.5 mM) of compound III and 10 ml of 2.5% methanolic NaOH solution was kept at 22–24° C for 3 hr 30 min. The reaction solution was evaporated at the same temperature, and the residue was treated with water and neutralized with 2.5 N hydrochloric acid. This gave 0.85 g of compound VII, mp 170–171° C (decomp., from aqueous methanol), R_f 0.88 (dark violet).

c) The reaction was performed as in paragraph (b) with the difference that the air was previously evacuated from the apparatus and it was twice purged with oxygen-free nitrogen. The reaction was carried out in a current of nitrogen. This yielded 0.82 g of compound VII, mp 170–171° C (decomp., from aqueous methanol).

Action of alkali on 1-hydroxy-1,3-dihydrofuro[3,4-b]quinoxaline 4-N-oxide (IV). A mixture of 1 g (5 mM) of compound IV and 8 ml of 2.5% methanolic NaOH was kept at 22–24° C for 2 hr. The reaction solution was treated as in paragraph (b) of the preceding experiment. This gave 0.88 g (88%) of 1,3-dihydroxy-1,3-dihydrofuro[3,4-b]quinoxaline (VII), mp 170–171° C (decomp., from aqueous methanol), R_f 0.88 (dark violet). A mixture with the compound VII obtained above gave no depression of the melting point.

Action of alkali on 2,3-bis(hydroxymethyl)quinoxaline 1-N-oxide (VIII). A mixture of 0.4 g (2 mM) of compound VIII, 4 ml of methanol, and 0.12 ml of 8% ethanolic NaOH solution was boiled for 30 min. After cooling, the precipitate that had deposited was filtered off to give 0.10 g of unchanged compound VIII, mp 141–142° C (from ethanol), R_f 0.52 (violet). The mother solution was evaporated and the residue was treated with water and neutralized with 2.5 N hydrochloric acid. This gave 0.16 g of 1-hydroxy-1,3-dihydrofuro[3,4-b]quinoxaline (IX), mp 158–159° C (from water). R_f 0.78 (violet). Found, %: C 63.87; H 4.35; N 14.45. Calculated for $C_{10}H_8N_2O_2$, %: C 63.80; H 4.28; N 14.88.

The PMR spectrum has a quartet from the two protons of the CH_2 group (δ 5.16 ppm, I = 16 Hz), a doublet of the proton of the C–H group (δ 6.35 ppm, I = 8 Hz), and a doublet of the O–H proton (δ 7.28 ppm, I = 8 Hz). (The PMR spectra were recorded on a JNM-4H-100 instrument in solution in a mixture of DMSO + CCl_4 with TMS as internal standard; the chemical shifts are given in the δ scale.)

The IR spectrum exhibits the absorption band of an associated O–H group (3220 cm^{-1}).

3-Formyl-2-hydroxymethylquinoxaline 2,4-dinitrophenylhydrazone was obtained in the usual way, mp 204° C (decomp.). The substance was purified by repeated boiling with ethanol. Found, %: N 21.94. Calculated for $C_{16}H_{12}N_6O_4$, %: N 22.22.

Action of alkali on 2,3-bis(hydroxymethyl)quinoxaline (VI). A mixture of 0.1 g (0.6 mM) of VI (mp 165–165.5° C), 1.5 ml of methanol, and 0.04 ml of 8% methanolic NaOH was boiled for 30 min. After cooling, the precipitate was filtered off to give 0.08 g of unchanged starting material VI, mp 164.5–165° C, R_f 0.62 (violet).

Oxidation of 1-hydroxy-1,3-dihydrofuro[3,4-b]quinoxaline 4-N-oxide (IV). A mixutre of 0.8 g of compound IV, 10 ml of 3% hydrogen peroxide solution, and 12 ml of 2 N NaOH solution was heated at 42–45° C for 4 hr. Then another 10 ml of 3% hydrogen peroxide solution was added, and the mixture was heated at the same temperature for another 6 hr. The reaction solution was cooled and extracted with chloroform. The aqueous layer was treated with 2.5 N hydrochloric acid (pH 2–3), and the precipitate that formed was separated off to give 0.75 g (87.5 %) of 2,3-dicarboxyquinoxaline, mp 189.5° C (decomp., from water) [10]. Found, %: C 54.78; H 2.77; N 12.84. Calculated for $C_{10}H_6N_2O_4$, %: C 55.05; H 2.77; N 12.85. The 2,3-diethoxycarbonylquinoxaline had mp 82.5–83.5° C (from aqueous acetic acid). A mixture with a sample of 2,3-diethoxycarbonylquinoline obtained by another method [11] gave no depression of the melting point. Found, %: C 61.57; H 5.02; N 10.22. Calculated for $C_{14}H_{14}N_2O_4$, %: C 61.27; H 5.14; N 10.22.

REFERENCES

1. N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, J. Am. Chem. Soc., **79**, 6562, 1957.

2. J. M. Hunsberger and J. M. Tien, Chem. Ind. (London), 88, 1959.

3. V. J. Traynelis and W. L. Hergenrother, J. Am. Chem. Soc., **86**, 298, 1964.

4. E. J. Moriconi and A. J. Pritsch, J. Org. Chem., **30**, 1542, 1965.

5. A. S. Elina, KhGS [Chemistry of Heterocyclic Compounds], **4**, 545, 1968.

6. H. McIlwain, J. Chem. Soc., 322, 1943.

7. A. S. Elina and L. G. Tsyrul'nikova, KhGS [Chemistry of Heterocyclic Compounds], **2**, 432, 1966.

8. A. S. Elina and L. G. Tsyrul'nikova, KhGS [Chemistry of Heterocyclic Compounds], **2**, 272, 1966.

9. A. S. Elina and O. Yu. Magidson, ZhOKh, **25**, 161, 1955.

10. F. D. Chattway and W. G. Humphrey, J. Chem. Soc., 645, 1929.

11. A. S. Elina, L. G. Tsyrul'nikova, and M. I. Medvedeva, ZhOrKh, **1**, 147, 1965.

24 October 1966

Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute, Moscow