REDOX TRANSFORMATIONS OF 2-FORMYLQUINOXALINE HYDRATE AND DIETHYLACETAL N,N'-DIOXIDES

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Depending on the pH of the medium, when 2-formylquinoxaline hydrate N,N'-dioxide is subjected to attack by the OH^- anion, it undergoes redox transformations to give 2-carboxyquinoxaline 4-oxide or quinoline N,N'-dioxide and the formate ion. In the case of attack by the OH^- anion 2-formylquinoxaline diethylacetal N,N'-dioxide undergoes only the first reaction, regardless of the pH.

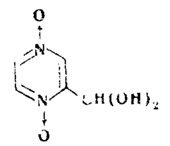
It is known that N-oxides of α-monohydroxyalkyl derivatives of azines or diazines are capable, when they are subjected to attack by the OH^- anion, of undergoing redox transformations that consist in oxidation of the monohydroxyalkyl group to a carbonyl group and simultaneous deoxidation of the ring nitrogen atom in the ortho or para position relative to it [1-3].

We have observed that 2-formylpyrazine hydrate N,N'-dioxide (I), when it is subjected to attack by the OH^- anion, undergoes a reaction of the same type to give 2-carboxypyrazine 4-oxide (II) (Reaction A) at various pH values. At the same time, 2-formyl-1,5-naphthyridine hydrate N,N'-dioxide (III) is capable of undergoing reaction in two directions and, depending on the pH, is converted to 2-carboxy-1,5-naphthyridine 5-oxide (IV) (Reaction A) or unsubstituted 1,5-naphthyridine N,N'-dioxide (V) [4, 5] (Reaction B).

In this connection, the subject of the present research was a study of the transformations of 2-formylquinoxaline hydrate and diethylacetal N,N'-dioxides (VI and VII) in alkaline media in order to compare their reactivities with the reactivities of the corresponding 1,5-naphthyridine and pyrazine derivatives.

Compounds VI and VII were obtained from 2-formylquinoxaline N,N'-dioxide (VIII) [6].

It was shown that VI, like III, is capable of undergoing reaction in two directions (Reactions A and B) to give, respectively, 2-carboxyquinoxaline 4-oxide (IX) or quinoxaline 1,4-dioxide (X).



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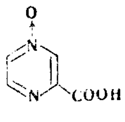

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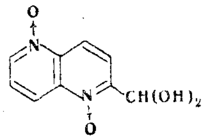

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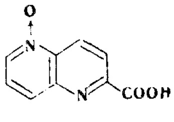

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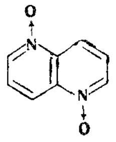
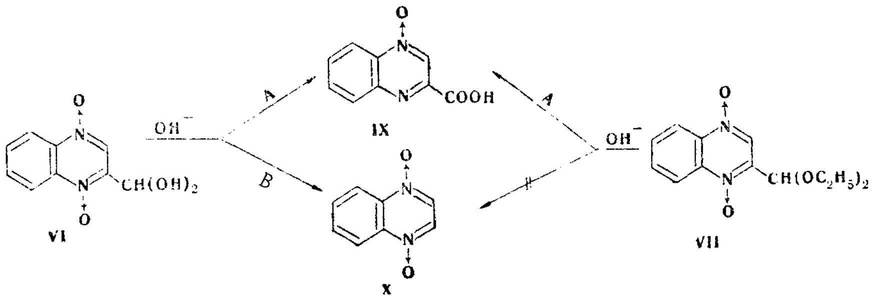


V



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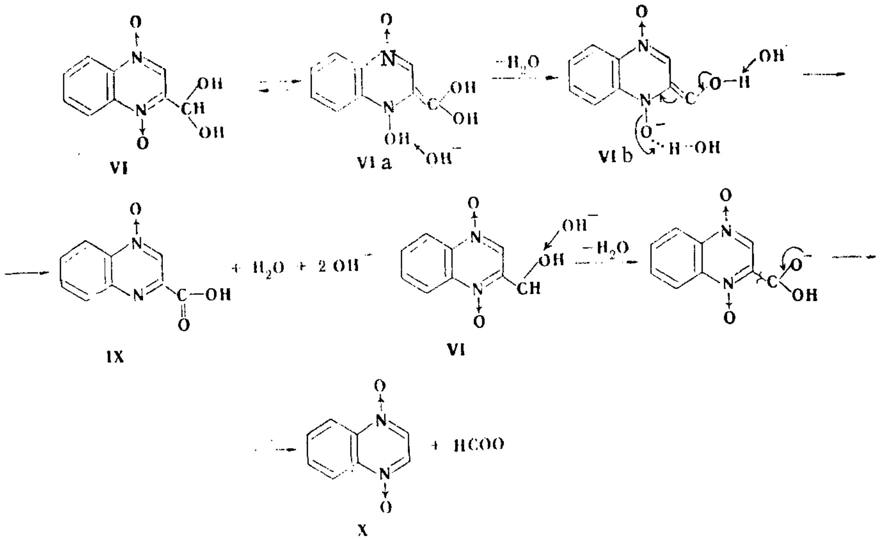
In addition, experiments carried out with N,N'-dioxides III and VI under identical conditions revealed differences in their behavior. They react identically (via a reaction of the B type) only at high pH values (≥13). At pH 12.3-12.5 VI reacts only via a reaction of the B type, whereas under the same conditions III also undergoes reaction A (to give IV in ~8% yield) in addition to reaction B. At low pH values (8.3-8.5) VI undergoes reaction in two directions (A:B = 6:1), in contrast to III, which undergoes a reaction of only the A type.

The ability of III and VI to undergo two types of reactions under the influence of alkaline reagents may be associated with attack by the OH^- anion on the electrophilic centers of the molecule, which may be the protons of the hydroxy group of the dihydroxymethyl group or the carbon atom of the same group.

We have shown that in the presence of any amount of alkali acetal VII, which does not contain protons of hydroxy groups, reacts only via pathway A. Thus, the probable electrophilic center of VII and VI that determines a reaction of the A type is the proton attached to the α-carbon atom. It might be assumed that the first step in Reaction A is attack on this proton by the OH^- anion or, which seems more likely, prior migration of it to the oxygen atom of the adjacent N → O group (VIa) with the subsequent liberation of a molecule of water and the formation of anion VIb, which is stabilized by secondary attack by an OH^- anion with conversion to IX.



As regards a reaction of the B type, one should here establish the character of the cleavage of the C—C bond and the structure of the secondary reaction product. It was found that the dihydroxymethyl group is split out in the form of a formate ion, which was converted quantitatively to carbon monoxide, which is the only gaseous product in the dehydration of formic acid with acetic anhydride in the presence of sulfuric acid.

It may be assumed that the first step in reaction B is attack by the OH^- anion on the proton of one of the hydroxy groups of the dihydroxymethyl group with subsequent cleavage of the C—C bond and the formation of X (or V in the case of III), which is accompanied by the liberation of the formate anion.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin—Elmer 457 spectrometer. Chromatography was carried out on Silufol UV-254 plates in a chloroform—methanol system (9:1) and on paper in a butanol—5% acetic acid system (1:1) only for IX with development in UV light.

2-Formylquinoxaline Diethylacetal 1,4-Dioxide (VII). A 2.4-g (12.6 mmole) sample of VIII was refluxed in 12 ml of a 19% solution of HCl in anhydrous alcohol for 1 h, after which the alcohol was removed, and the residue was neutralized with $NaHCO_3$ solution and extracted with chloroform. Workup gave 1.58 g (47%) of a product with mp 119-120°C (from alcohol) and R_f 0.85. Found: C 59.4; H 6.0; N 10.7%. $C_{13}H_{16}N_2O_4$. Calculated: C 59.2; H 5.9; N 10.6%.

2-(Dihydroxymethyl)quinoxaline 1,4-Dioxide (VI). A 1.46-g (5.5 mmole) sample of VII was heated in 14.6 ml of 1 N HCl at 85°C until it dissolved, after which the solution was cooled and filtered to give 1.04 g (90%) of VI with mp 209-210°C (dec., from water). Found: C 52.1; H 3.8; N 13.7%. $C_9H_8N_2O_4$. Calculated: C 51.9; H 3.9; N 13.5%.

Transformations of VI, VII, and III in Alkaline Media. A) A 2-ml sample of 2.5 N NaOH (pH > 14) was added to 0.4 g (1.19 mmole) of VI, and the mixture was stirred at 22°C for 20 min. According to the results of TLC, after 10 min the mixture contained only X: spots of starting VI (R_f 0.6) and IX (R_f 0.4) were absent. The mixture was filtered to give 0.306 g (98%) of X, which was identical to a sample of X obtained by a known method [7]. Compound V (96%) was obtained from N,N'-dioxide III under similar conditions (after 30 min).

B) In the presence of 26 ml of 0.1 N NaOH (pH ~ 12.35) under the same conditions III gave 8% IV and 87% V, while N,N'-dioxide VI gave 96% X.

C) A 0.4-g sample of VI was allowed to stand in 30 ml of 8% $NaHCO_3$ solution (pH 8.3) at 22°C for 6 days, during which VI vanished in the reaction mixture, and X and IX were detected. The mixture was extracted with chloroform, and the chloroform was evaporated to give 0.04 g (13%) of X. The aqueous alkali layer was acidified and worked up to give 0.3 g (82%) of IX, which was identical to the compound obtained by a known method [6]. An experiment with III was similarly carried out to give IV (99%).

D) A 0.26-g (0.98 mmole) sample of VII was placed in 13 ml of 1 N NaOH in anhydrous alcohol, and the mixture was allowed to stand at 22°C for 24 h until the spot of VII vanished in the reaction solution. The alcohol was removed, and the residue was dissolved in water. The aqueous solution was acidified and worked up to give 0.18 g (96%) of IX. An experiment with VI was carried out similarly. After 30 min, the spot of VI vanished in the reaction mixture, and only the spot of X was detected. A total of 0.196 g (97%) of X was isolated from 0.26 g of VI.

Quantitative Determination of the Formate Ion. An accurately weighed sample (5-10 mg) of VI was placed in a 15-ml reaction flask equipped with a bubbling tube, a gas-exhaust tube, and a dropping funnel, 0.3 ml of 1 N NaOH was added, and the mixture was allowed to stand for 20 min. Acetic acid (5 ml) and 5 ml of acetic anhydride were added, and the flask was connected to an azotomer filled with 50% KOH. A stream of carbon dioxide was passed through the bubbler until the size of the bubbles passing through the microgasometer became vanishingly small, after which 0.2 ml of concentrated H_2SO_4 was added dropwise from the dropping funnel. As a result of this procedure, 99.4% CO was obtained.

The determination was carried out similarly in an experiment with III, except that the mixture was allowed to stand for 1.5 h after treatment with alkali. As a result of this procedure, 98.5% CO was obtained.

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