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Rearrangements during Nitrosodecarboxylation of Isomeric Dibromohydroxybenzoic Acids

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Abstract—The reaction of 3,5-dibromo-4-hydroxybenzoic acid, its sodium salt, and also sodium 3,5-dibromo-2-hydroxybenzoate with $NaNO_2$ in a glacial acetic acid at room temperature led to the formation of a mixture of dibromonitrophenol resulting from nitrosodecarboxylation accompanied by a rearrangement processes and followed by oxidation of the arising nitrosophenols.

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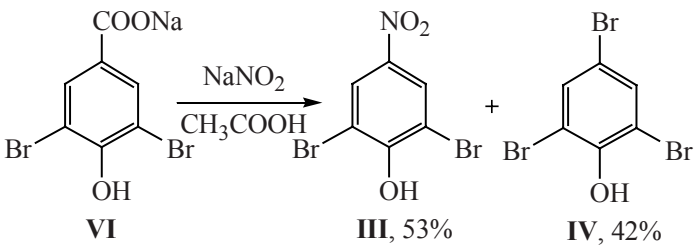
The nitrosation of hydroxybenzoic acids is known to proceed sometimes as nitrosodecarboxylation to give nitrosophenols that reacting with excess nitrous acid transform into diazo or nitro compounds depending on the process conditions [1, 2]. For instance, the nitrosation of salicylic acid in water [3] or in the presence of H_2SO_4 (pH ~2–4) [4, 5] resulted in *O*-nitrophenol, and the reaction in the acetate buffer led to the exclusive formation of *O*-diazophenol [6]. On adding sodium nitrite to the water-alcoholic solution of 3,5-dibromo-4-oxybenzoic acid an evolution of carbon dioxide was observed, and 3,5-dibromo-4-nitrosophenol formed in a quantitative yield [3, 7]. The published data suggest that these reactions may be of a certain synthetic value. For instance, the nitrosodecarboxylation of extensively brominated oxypolybromobenzoic acids may become a convenient preparative method for difficultly accessible polybromonitroso-, nitro-, and diazophenols. However the problem of the selectivity of the nitrosodecarboxylation is poorly documented, and the prevailing routes of the reaction are not clear.

In this connection we studied the features of the reaction between isomeric dibromohydroxybenzoic acids and $NaNO_2$ taken in a 10-fold excess in glacial acetic acid at 20°C (reaction period 3 h). The composition of products obtained was investigated by TLC, IR spectroscopy and in some cases by ^1H NMR spectroscopy. The preparative separation was performed using as references authentic compounds. The experiments showed that under the given conditions 3,5-dibromo-2-hydroxybenzoic acid (**I**) hardly entered into the reaction (conversion below 1%), whereas 3,5-dibromo-4-hydroxybenzoic acid (**II**) gave a mixture of 2,6-dibromo-4-nitrophenol (**III**) and 4,6-di-bromo-2-nitrophenol (**IV**) in a ratio 1.34:1 (conversion of initial acid **II** 70%). Nitrophenol **III** formed as a result of the nitrosodecarboxylation of acid **II** with the subsequent oxidation of 2,6-dibromo-4-nitrosophenol (**V**) under the reaction conditions to nitro compound [the formation of 3,5-dibromo-4-nitrophenol (**III**) from phenol **V** under the identical conditions was proved by independent experiments]. However the presence in the reaction products of a notable quantity of nitrophenol **IV** indicated the occurrence of rearrangements. No rearrangements during nitrosodecarboxylation of isomeric dibromohydroxybenzoic acids were previously observed [2, 7].

At the use of the 3,5-dibromo-4-hydroxybenzoic acid sodium salt (**VI**) the nitrosodecarboxylation accelerated (conversion 96%); therewith the ratio of the forming dibromonitrophenol isomers practically unchanged (Scheme 1).

Scheme 1.



VI **III**, 53% **IV**, 42%

† Diseased.

Sodium 3,5-dibromo-2-hydroxybenzoate (**VII**) under the reaction conditions also transformed (conversion 31%), and alongside the normal product of the nitrosodecarboxylation–oxidation, 2-nitrophenol **IV**, formed also the rearranged compound, 4-nitrophenol **III**, and isomeric nitrobromohydroxybenzoic acids **VIII** and **IX** (Scheme 2).

The published data suggest [2, 7] that the nitrosodecarboxylation of hydroxybenzoic acids proceeds by the mechanism of electrophilic substitution in the aromatic ring. Our results may be understood from the viewpoint of rearrangements occurring in the intermediately formed cationic *ipso*-nitroso complexes (Schemes 3 and 4).

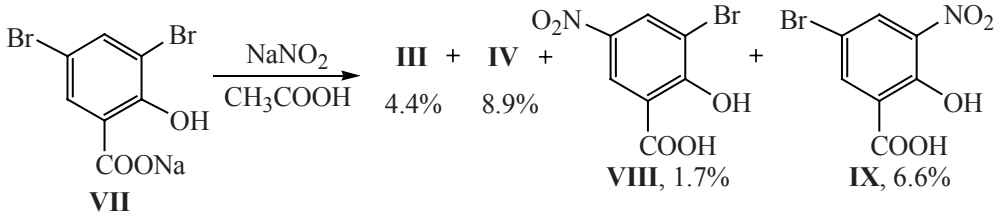
In the nitrosation of the 3,5-dibromo-4-hydroxybenzoic acid two isomeric *ipso*-nitroso complexes **A** and **B** may form; therewith the calculated enthalpy of formation of complex **B** is by 7 kcal/mol less (Scheme 3). Moreover, its rearrangement may result in the formation of *ipso*-bromo complex **C** that is even more stable (> 4 kcal/mol), and its decarboxylation and further oxidation lead to 4,6-dibromo-2-nitrophenol (**IV**). The decarboxylation of *ipso*-bromo complexes is a well-known reaction that easily occurs at treating with bromine in dilute acetic acid isomeric dibromohydroxybenzoic acids [8].

The nitrosation of 3,5-dibromo-2-hydroxybenzoic acid may provide three *ipso*-nitroso complexes **D**–**F** (Scheme 4). The formation of 4,6-dibromo-2-nitrophenol (**IV**) may take two routes: decarboxylation of *ipso*-nitroso complex **D** or of the rearranged of *ipso*-bromo complex **G**.

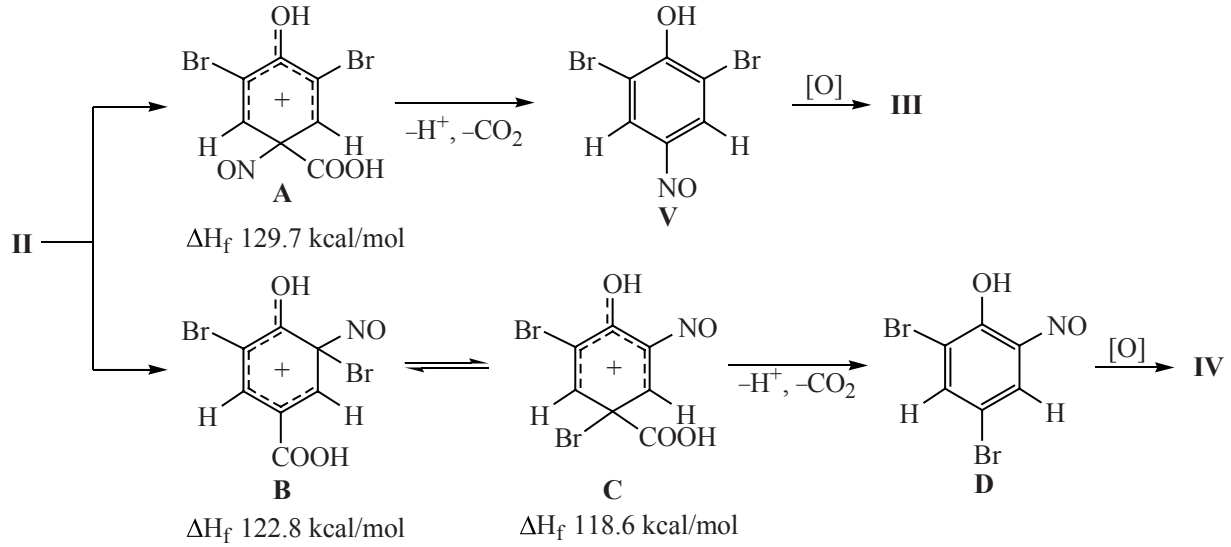
2,6-Dibromo-4-nitrophenol (**III**) may arise only from the rearrangement of complex **F** followed by the decarboxylation of the formed *ipso*-bromo complex **H**. In this case reactions of nitrosodebromination are also presumable yielding nitrobromohydroxybenzoic acids **VIII** and **IX** from *ipso*-complexes **F** and **E** respectively in agreement with the experiment (Scheme 2).

The rearrangements of *ipso*-nitroso complexes occur presumably via intramolecular successive 1,2-shifts of bromine atoms through "bromonium" transition states [9]. However the formation of final rearranged products by intermolecular exchange of intermediate *ipso*-nitroso complexes **A**, **B**, **D**–**F** with the initial dibromohydroxybenzoic acids **I** and **II** cannot be excluded; as a result *ipso*-bromo complexes may form (for instance, **I** and **J** in the cases shown on Scheme 5).

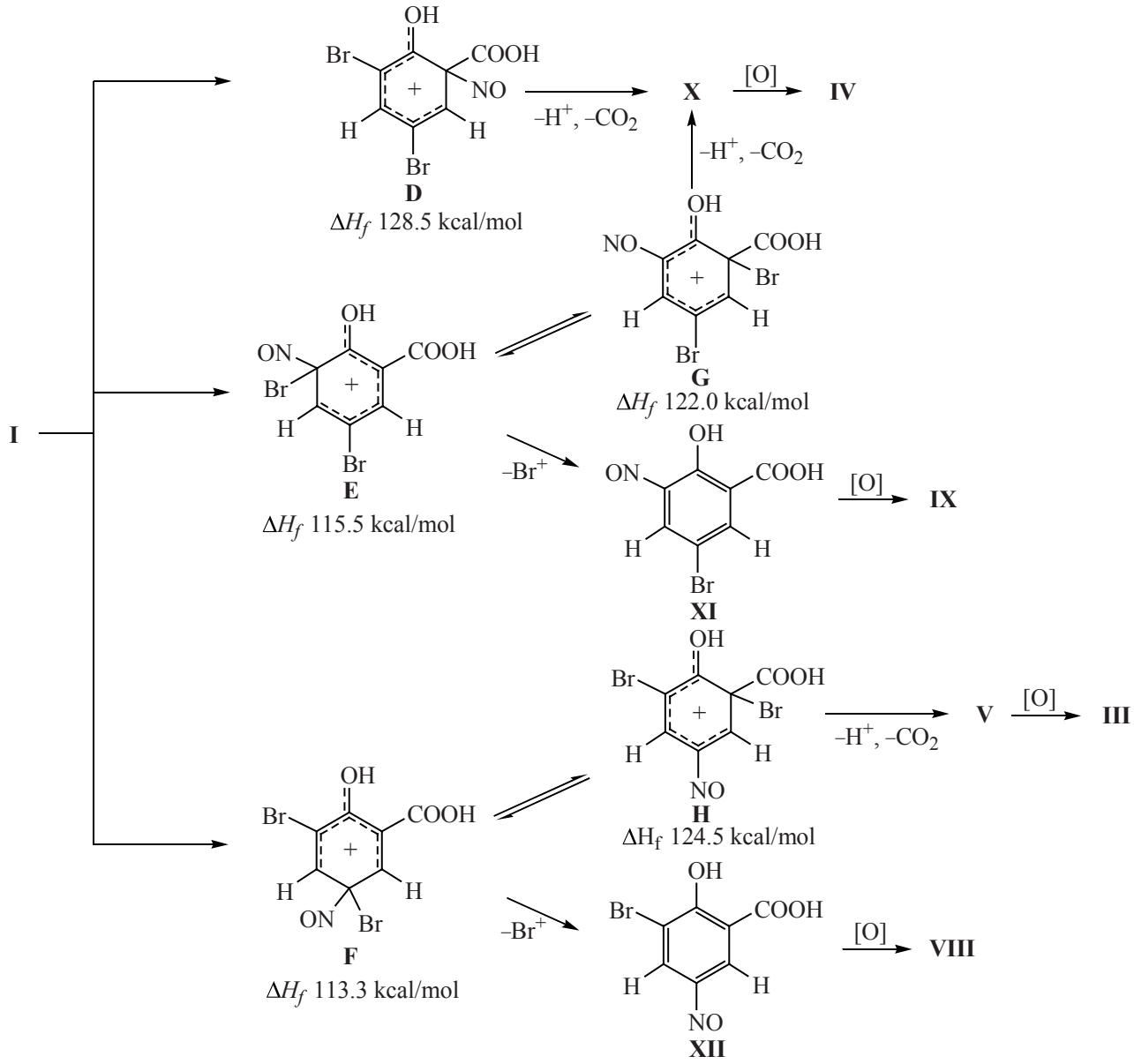
Scheme 2.



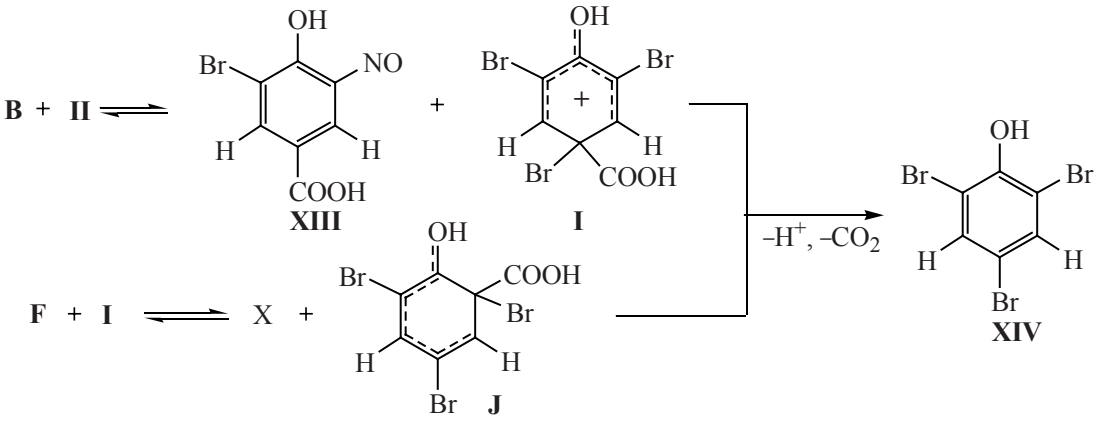
Scheme 3.



Scheme 4.



Scheme 5.



In this event due to the decarboxylation of *ipso*-bromo complexes [8] 2,4,6-tribromophenol (**XIV**) should be present in the reaction mixtures.

In the products of the reactions under investigation we did not detect even traces of phenol **XIV**. It was found however that 2,4,6-tribromophenol in the glacial acetic acid at room temperature in the presence of sodium nitrite quickly transformed into a mixture of 2,6-dibromo-4-nitro- (**III**) and 4,6-dibromo-2-nitro- (**IV**) phenols in a ratio 1:2.16. It was also established that under similar conditions the nitrosodebromination rate of phenol **XIV** is greater than the rate of the nitrosodecarboxylation of the dibromohydroxybenzoic acids (conversion 100% in 2 h). Thus the experimental data obtained do not permit the choice between the possible rearrangement routes.

Unsubstituted 2-hydroxy- and 4-hydroxybenzoic acids and sodium 2-hydroxybenzoate did not undergo rearrangements under the action of sodium nitrite at 20°C both in the glacial and dilute (75%vol) acid. 4-Sodium hydroxybenzoate was also stable in the glacial acetic acid, whereas in dilute CH_3COOH it formed insignificant quantity of 4-nitrophenol (conversion of the initial salt within 3 h reached 0.5%).

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer InfraLYUM FT-02 from pellets with KBr, ^{1}H NMR spectra, on a spectrometer Bruker AC-200 (200 MHz) in $CDCl_3$, internal reference HMDS. TLC was carried out on Silufol UV-254 plates, eluent hexane–acetone, 7:3, development in iodine vapor or under UV irradiation.

Quantum-chemical calculations were performed using software package HyperChem 7.0. The enthalpy of formation of *ipso*-complexes was calculated by semiempirical PM3 method [10] with optimization of all geometrical parameters of all molecular systems under consideration. According to the calculations performed in most cases the complexes are characterized by conformational nonuniformity (the existence of local minima). The data presented in Schemes 3 and 4 correspond only to the most stable conformations.

Acids **I** [11], **II** [12], phenol **III** [13], **IV** [14], V [5], and **XIV** [15] were prepared by published procedures.

Reaction of sodium 3,5-dibromo-4-hydroxybenzoate with $NaNO_2$. A mixture of 1 g (3.1 mmol) of sodium 3,5-dibromo-4-hydroxybenzoate and 50 ml of glacial acetic acid was stirred at room temperature till complete dissolution of the salt, and then was added at stirring by small portions 2.14 g (31 mmol) of $NaNO_2$ within 2 h. Then the reaction mixture was kept at room temperature for 1h and afterwards poured into 200 ml of 10% solution of Na_2CO_3. The formed precipitate was 2-nitro-4,6-dibromophenol (**IV**) (0.39 g) containing trace impurity of phenol **III** (TLC data). After filtering off compound **IV** the separated precipitate was filtered off and dried to obtain 0.28 g of 4-nitro-2,6-dibromophenol (**III**). The filtrate was diluted with water to the volume of 500 ml and extracted with ether. The ether extract was washed with water, dried, and the solvent was evaporated. The residue (0.25 g) was a mixture of compound **III** (85%) with initial acid **II**.

Reaction of sodium 3,5-dibromo-2-hydroxybenzoate with $NaNO_2$. The reaction was carried out in a similar way. The reaction mixture was diluted with 200 ml of 10% solution of Na_2CO_3, the formed precipitate (0.69 g) was a mixture of the initial salt and 2-nitro-4,6-dibromophenol (**IV**) that was separated from the salt by extraction with ether (we obtained 0.06 g of compound **IV**). The filtrate was acidified with concn. HCl to pH 1–2, the separated precipitate was filtered off and dried to obtain 0.15 g of pure 3,5-dibromo-2-hydroxybenzoic acid (**I**). The filtrate after isolating acid **I** was diluted with water to the volume of 500 ml and extracted with ether. The ether extract was dried, the ether was evaporated. The residue (0.11 g according to TLC and IR spectrum consisted of phenols **III** and **IV**, acid **I**, and nitro group containing hydroxybenzoic acids [in the IR spectrum additional absorption bands appeared at 1342, 1516, and 1524 cm^{-1}, characteristic of aromatic nitro group, and also at 1671, 2500–3100 (series of wide bands) and 3371 cm^{-1}, characteristic of aromatic hydroxyacids]. The composition of the residue was established from the ^{1}H NMR spectrum that contained in the region of aromatic protons pairs of doublets of equal intensity at 7.59 and 7.74 ppm (*J* 2.3 Hz) (acid **I**), 8.35 and 8.53 ppm (*J* 2.3 Hz) (acid **IX**), 8.49 and 8.72 ppm (*J* 2.3 Hz) (acid **VIII**), 7.77 and 7.99 ppm (*J* 2.3 Hz) (phenol **IV**), and a singlet at 8.13 ppm (phenol **III**). From the ratio of the overall integral intensity of aromatic protons in these compounds their content in the residue was calculated as 18, 36, 9, 6, and 31% respectively.

The reactions with $NaNO_2$ of isomeric dibromo- and unsubstituted hydroxybenzoic acids and the workup of the reaction mixture and isolation of products were carried out as described above.

Reaction of 2,4,6-tribromophenol (XIV) with $NaNO_2$. A mixture of 1 g (3 mmol) of compound **XIV** and 50 ml of glacial acetic acid was stirred at room temperature till complete dissolution of tribromophenol. Then was added at stirring by small portions 2.07 g (30 mmol) of $NaNO_2$ within 1.5 h. The stirring of the reaction mixture was continued for 0.5 h more, then it was poured into 150 ml of 10% solution of Na_2CO_3. The precipitated 2-nitro-4,6-dibromophenol (0.52 g) was separated, washed with water, and dried. The filterate was acidified with concn. HCl to pH 1–2, diluted with water to 500 ml, and extracted with ether. The ether extract was washed with water, dried, and the solvent was evaporated. We obtained 0.28 g of 4-nitro-2,6-dibromophenol containing traces of 2-nitro isomer (TLC data).

Oxidation of 2,6-dibromo-4-nitrosophenol (V). A mixture of 1 g (3.56 mmol) of compound **V**, 50 ml of glacial acetic acid, and 2.48 g (3.59 mmol) of $NaNO_2$ was stirred at room temperature for 3 h, then the reaction mixture was diluted with 450 ml of water. The separated precipitate (0.52 g) was filtered off, washed with water, and dried. It was 4-nitro-2,6-dibromophenol (**III**). The filtrate was extracted with ether. The ether extract was washed with water, dried, and the solvent was evaporated. We obtained additionally 0.27 g of compound **III** containing traces of 2-nitro isomer (TLC data). Overall yield 75%.

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