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Investigation of the Mechanism of the Anthranilic Rearrangement Using the Oxygen Isotope O^{18}

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When aqueous alkali acts on *o*-nitrotoluene, a number of products are formed, of which the most important is anthranilic acid ([1]). The mechanism of this reaction, called the anthranilic rearrangement, is important for understanding the processes of oxidation, reduction, isomerization, and condensation of aromatic nitro compounds. It has been investigated by a number of authors; however, none of the proposed reaction schemes has so far been either unambiguously confirmed or rejected on the basis of the data available in the literature.

The purpose of the present work was to clarify a question important for understanding the rearrangement mechanism: whether the oxygen of the carboxyl group of anthranilic acid originates from the nitro group of the initial *o*-nitrotoluene or from the aqueous alkali. For this purpose we investigated the conversion of *o*-nitrotoluene into anthranilic acid and of the potassium salt of *o*-nitrotoluene-*p*-sulfonic acid into *p*-sulfoanthranilic acid under the action of aqueous KOH labeled with O^{18}. From the O^{18} content in the anthranilic and *p*-sulfoanthranilic acids formed in this process, we judged the reaction mechanism.

The results of typical experiments are given below.

To 0.24 g/mol of *o*-nitrotoluene, heated in a flask with a reflux condenser to 200°, a solution of 0.45 g/mol KOH^{18} in 0.90 g/mol H_2O^{18} was added. The temperature of the reaction mixture thereby decreased over 15 min to 150°. This temperature was maintained by heating until the end of the reaction. Then unreacted *o*-nitrotoluene and *o*-toluidine were removed from the reaction mixture by steam distillation, and the residue was neutralized with dilute H_2SO_4. A stream of CO_2 was passed through the liquid to remove hydrocyanic acid, and the mixture was filtered; the filtrate was acidified with acetic acid, and after the addition of cupric acetate, the copper salt of anthranilic acid precipitated from it. The latter was decomposed with hydrogen sulfide; the anthranilic acid formed was extracted with ether and, after removal of the ether, was sublimed. The melting point was 148°. In different experiments we varied the duration of addition of alkali from 20 to 90 min and the duration of subsequent heating of the reaction mixture from 15 to 120 min. The excess O^{18} content in the isolated anthranilic acid varied only slightly and amounted to 41-48% of the excess O^{18} content in the initial aqueous alkali, equal to 0.60 at.%.

To a solution of 0.16 g/mol KOH^{18} in 1.40 g/mol H_2O^{18}, heated in a flask with a reflux condenser on a boiling water bath, 0.04 g/mol of the potassium salt of *o*-nitrotoluene-*p*-sulfonic acid was added over a period of 15 to 60 min, and heating of the reaction mixture was continued at 100° for another 60-150 min. Then the reaction mixture was neutralized with dilute hydrochloric acid, and by the action of copper sulfate the copper salt of *p*-sulfoanthranilic acid was precipitated from it (over the course of 24 hours). Its decomposition with hydrochloric acid gave *p*-sulfoanthranilic acid, of whose purity we veri—

were carried out by titrating one weighed portion with alkali and the other with sodium nitrite. The excess content of O^{18} in *n*-sulfoanthranilic acid amounted to 44-48% of the excess content of O^{18} in the initial aqueous alkali, which in different experiments ranged from 0.80 to 2.00 atom %.

The data obtained show that, in the carboxyl group of anthranilic and *n*-sulfoanthranilic acids, one oxygen atom originates from *o*-nitrotoluene, and the second from the aqueous alkali. This observation agrees with the reaction mechanisms proposed by Scholl (^{2}), Shukina and Predvoditeleva (^{3}), and with one of the variants of the scheme of Porai-Koshits (^{4}). All these authors assumed that the anthranilic rearrangement proceeds with the intermediate formation of anthranil:

$$\textit{o}\text{-nitrotoluene} \longrightarrow \text{anthranil} \xrightarrow[(+\mathrm{KOH})]{\mathrm{O}^{18}} \text{potassium anthranilate, } \mathrm{COOK}^{18} \quad (1)$$

Our data reject the scheme of Lock (^{1}):

$$\textit{o}\text{-nitrotoluene} \xrightarrow[(-3\mathrm{H}_2)]{(+3\mathrm{KOH}^{18})} \textit{o}\text{-nitrophenyl } \mathrm{C}\left(\mathrm{OK}^{18}\right)_3 \xrightarrow[(-\mathrm{H}_2\mathrm{O})]{(+3\mathrm{H}_2)} \text{potassium anthranilate, } \mathrm{COOK}^{18,18}$$

and also that variant of the Porai-Koshits scheme in which the formation of the ortho form of the acid was assumed, as well as the sometimes proposed (^{5}) mechanism of intramolecular oxidation of the methyl group by the oxygen of the nitro group.

In order to confirm a mechanism of type (1), we studied the hydrolysis of anthranil to anthranilic acid with heavy-oxygen aqueous alkali. It was found that the acid contained 40-46% of that amount of excess O^{18} which was present in the aqueous alkali, which serves as further evidence in favor of a rearrangement mechanism of type (1).

Control experiments showed that isotope exchange of anthranilic and *n*-sulfoanthranilic acids during the reaction does not significantly distort their isotopic composition. Isotope exchange of anthranil with H_2O^{18} at 100° does not occur at all.

In addition to investigating the mechanism of the anthranilic rearrangement, we studied the structure of anthranil, for which a number of formulas had been proposed, the three most substantiated of which were the following:

(I)	(II)	(III)
benzene-fused ring with CN and N→	benzene-fused ring with C=O and NH	benzene-fused ring wit

The choice between them could not previously be made definitively. We found that anthranil does not exchange its hydrogen with heavy water even at 100° for 3 hours, which unambiguously refutes the amide formula (II) of Friedländer and Heller (^{6}), since hydrogen in an $N-H$ grouping exchanges very rapidly.

In the reduction of *o*-nitrobenzaldehyde labeled with O^{18} in the carbonyl group, it was found that the anthranil formed does not contain an excess of O^{18}

and that, consequently, its oxygen originates from the nitro group, and not from the carbonyl group of *o*-nitrobenzaldehyde, which corresponds to the scheme:

(scheme showing o-nitrobenzaldehyde labeled C=^{18}O $\xrightarrow[CH_3COOH]{Sn}$ hydroxylamine intermediate labeled C=^{18}O

These data refute the assumption that the carbonyl oxygen is retained in anthranil, advanced by Bamberger [7], but not the structure (III) proposed by him. We believe that formula (I), proposed [8] and recently given new substantiation [3], best corresponds to the properties of anthranil.

The results of our experiments with *o*-nitrobenzaldehyde show, on the other hand, that this substance may be, as has sometimes been assumed [4], an intermediate product of the anthranil rearrangement preceding anthranil, since, in accordance with our data, the oxygen of the nitro group, which does not exchange with aqueous alkali, passes into anthranil. The determination of the content of O^{18} in water and in organic substances was carried out with the aid of a mass spectrometer by methods developed in our laboratory [9,10]. The accuracy of the analyses was 3%.

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