Notes

On the Mechanism of the Anthranilate Rearrangement[1]

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It was reported in 1900 that *o*-nitrotoluene, when heated in aqueous or alcoholic base, rearranged to anthranilic acid.[2] Since then, there has been some experimental work and a good deal of speculation on the mechanism of this reaction. The rearrangement is known not to require molecular oxygen.[3] On tenuous grounds, *o*-nitrobenzoic acid,[3] *o*-nitrosobenzyl alcohol,[4] and anthranil[4] have been proposed as intermediates in reactions involving the uptake of one or two atoms of solvent oxygen. Kukhtenko[5] carried out the rearrangement in [^{18}O]water to distinguish between these latter two possibilities. The molar ratio of base to water was about 1:2, the system was heterogeneous, and the temperature varied from 200 to 150°. He concluded that one atom of solvent oxygen was required.

Out of an interest in the metabolism of such compounds, we considered that Kukhtenko's experiments deserved repetition for two reasons. (1) Despite the lack of experimental information, it was apparent that the rearrangement was carried out under conditions comparable with those reported to cause extensive oxygen exchange in potassium anthranilate.[6] (2) The amount of solvent oxygen incorporated was found to be less than one atom per molecule by an amount greater than the estimated experimental error. Thus, although the results successfully demonstrated that the reaction does not proceed by a pathway using two atoms of solvent oxygen, they ignore the question as to whether the reaction may proceed, in part, by a pathway in which both atoms of the nitro group are transferred to the carboxyl group of anthranilic acid. This latter possibility has been reported to occur in the analogous rearrangement of 2-nitrobenzenesulfenanilide to azobenzenesulfinate.[7]

The base-catalyzed rearrangement of *o*-nitrotoluene was carried out in a 3:1 (v/v) mixture of 2-methoxyethanol and water containing approximately 10% by weight potassium hydroxide. The product was isolated after heating the reactants in an evacuated sealed tube at 100° for 9 hr in the dark. The system was homogeneous and the conditions were less vigorous than those employed previously. The isotopic composition of the carboxyl oxygen atoms was determined from the carbon dioxide formed when the anthranilic acid was quantitatively decarboxylated by heating at 200° *in vacuo*.[8] Normal anthranilic acid decarboxylated according to this procedure[8] showed an oxygen-18 content of 0.206 atom %. The mass spectrum of the carbon dioxide formed from anthranilic acid prepared by rearrangement of *o*-nitrotoluene in water containing 64.1 atom % oxygen-18 is given in Table I.

TABLE I
MASS SPECTRUM OF CARBON DIOXIDE FROM [^{18}O]ANTHRANILIC ACID

m/e	Relative abundance
44	66.1
45	1.70
46	100
47	1.13
48	2.39

The isotopic abundance of oxygen-18 derived from the results in Table I is 31.1 atom %. The low intensity at mass 48 indicates clearly that a negligible amount of *double* oxygen exchange has occurred. Further, if it is assumed that the contribution to mass 48 arises *solely* from exchange of [^{18}O]anthranilate containing one atom of ^{18}O, as is reasonable,[6] the results demonstrate that the rearrangement must proceed to the extent of 95% through the insertion of one atom of oxygen from the solvent water. Since the solvent oxygen is diluted by oxygen released from the nitro group during reaction, the above estimate is a minimal one. If this dilution is allowed for in the formation of anthranilic acid (and other possible products), the data support the above pathway virtually exclusively (99.6%), since it is known that none of the ether, alcohol,[9] or nitro-group[10] oxygen atoms exchanges with water.

This result was checked by measurement of the molecular ion peaks in anthranilic acid. Analysis of the results showed 31.5 atom % oxygen-18 and also that the oxygen-18 was contained in only one of the carboxyl oxygen atoms, which independently supports the above interpretation.

The simplest mechanism consistent with the facts is shown in Scheme I, in which anthranil (**1**) is an intermediate. It accounts for the incorporation of one atom of oxygen from the solvent. Further, the ionization of

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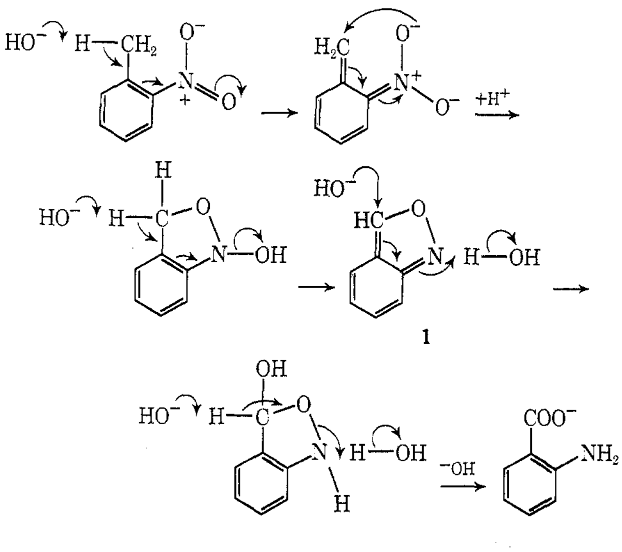
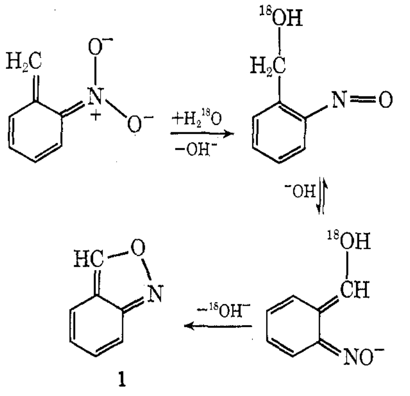
Scheme I



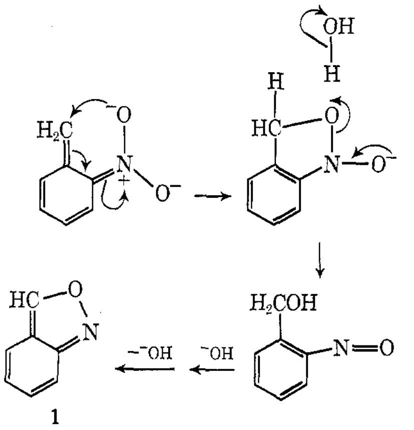
the methyl group and the hydrolysis of anthranil to anthranilic acid are well established.[5,11]

However, while anthranil is a reasonable intermediate, the present work does not comment on the detailed mechanistic pathway to this intermediate. Alternate versions of the mechanism shown, in which only one oxygen atom of the nitro group is transferred to anthranilate, would allow the involvement either of labeled[12] (Scheme II) or unlabeled (Scheme III) o-nitrosobenzyl alcohol. If o-nitrosobenzyl alcohol were an obligatory reaction intermediate and it was possible to remove it from the system as it formed, oxygen-18 analysis may enable a distinction between these latter possibilities.

Scheme II



Scheme III



Experimental Section

o-Nitrotoluene was fractionally distilled twice, the second distillation being performed under dry nitrogen, bp 94° (9.3 mm) [lit.[13] bp 94° (9.3 mm)]. 2-Methoxyethanol was redistilled three times, bp 124° (lit.[14] bp 124.4°). [^{18}O]Water (81.52 atom % ^{18}O, 0.254 atom % ^{17}O, 83.7 atom % D) was supplied by Yeda Research and Development Co., Rehovoth, Israel.

Rearrangement of o-Nitrotoluene in [^{18}O]Water.—o-Nitrotoluene (0.511 g) and potassium hydroxide (0.591 g, Baker Analyzed Reagent) were mixed with [^{18}O]water (1.071 g) and 2-methoxyethanol (3 ml). The reaction vessel was flushed rapidly with dry nitrogen, the contents were frozen, and the vessel was evacuated and sealed. The reaction was allowed to proceed for 9 hr at 100° in the dark. After the solvent was removed *in vacuo*, the residue was dissolved in water and extracted with ether. The pH was reduced to 3.4 and the extraction was repeated. This fraction was dried (Na_2SO_4), the solvent was removed, and the product was sublimed *in vacuo* to give 53 mg (10.4%) of anthranilic acid, mp 136.5–139°. Recrystallization from ether–hexane and benzene–hexane gave anthranilic acid, mp 143.8–144.2° (lit.[3] mp 145.5°). This purification procedure ensured that the product was in contact with normal water for only 30 min, under conditions unlikely to cause exchange.

Anthranilic acid was decarboxylated by heating *in vacuo* at 200–220° for 30–45 min and the carbon dioxide was purified by distillation from −80 to −196°. Isotopic ratios were measured in a Nier-type mass spectrometer.[15] The mass spectrum of anthranilic acid was determined on an AEI MS902 spectrometer at 70 eV using the direct insertion probe.

Registry No.—o-Nitrotoluene, 88-72-2; anthranilic acid, 118-92-3.

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A New Synthesis of Benzocyclobutene and Bicyclo[4.2.0]octa-1(6),3-diene

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There are several methods available for the synthesis of benzocyclobutene[2] (**1**). We required large quantities of **1** and were not satisfied with presently published methods such as the improved pyrolysis of 1,3-dihydroisothionaphthene 2,2-dioxide (**2**).[3] We were not satisfied with this route as it involved the use of rather noxious compounds as synthetic intermediates and special apparatus for the final thermal decomposition. We also had a need for large amounts of bicyclo[4.2.0]octa-1(6),3-diene (**3**). We therefore have de-

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