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THE MECHANISM OF THE CONVERSION OF *o*-NITROBENZOYLDIAZOMETHANE TO N-HYDROXYISATIN

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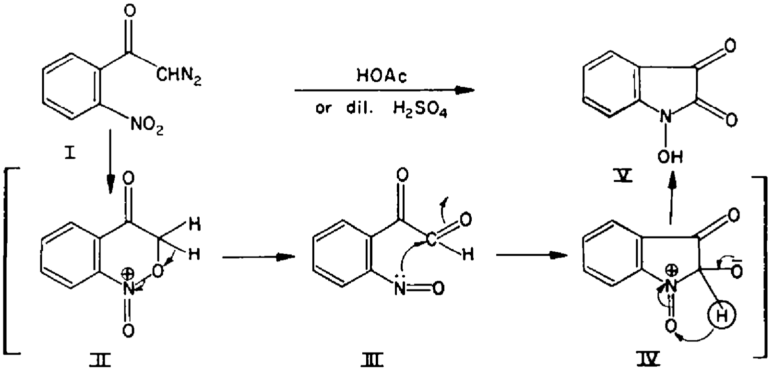
Abstract—The acid-catalyzed conversion of *o*-nitrobenzoyldiazomethane (I) to N-hydroxyisatin (V) has been studied by following the fate of the diazo carbon atom in I which was labelled with C^{14}. Degradation of V showed that all the C^{14} was in the C_2-position, thus establishing that a Wolff-type rearrangement of I (via a ketene intermediate) was not involved in the formation of V. A mechanism for the rearrangement of I to V, differing in important details from the mechanism previously proposed by Moore,[3] has been advanced.

o-NITROBENZOYLDIAZOMETHANE (I) is converted upon treatment with acetic or sulfuric acid to N-hydroxyisatin (V).[2] In this unusual transformation, the diazo group in I is lost as nitrogen, leaving a product in which the diazo carbon is oxidized (to an acid) and the nitro group is reduced (to a hydroxylamine). Moore[3] has recently proposed a mechanism in which the first step is a nucleophilic attack by a nitro oxygen atom upon the diazo carbon atom to give a benzoxazine intermediate (II), which then, through loss of a proton, suffers ring opening to give *o*-nitrosophenylglyoxal (III). Although Moore did not specify in detail the nature of the subsequent steps leading from III to V, it seems unavoidable that III must suffer nucleophilic attack by the nitroso nitrogen atom upon the aldehyde carbonyl to give IV which leads finally to N-hydroxyisatin (V) by a 1,3-hydride shift.



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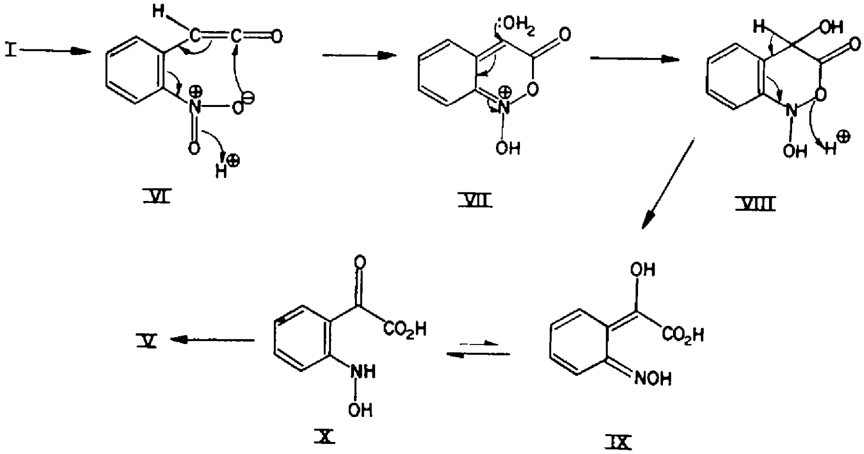
[1] NIH Predoctoral Fellow, 1962–64.

[2] F. Arndt, B. Eistert and W. Partale, *Ber. Dtsch. Chem. Ges.* **60**, 1364 (1927).

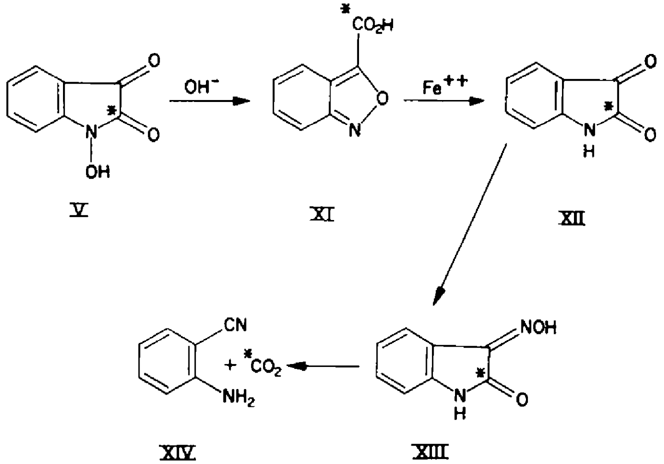
[3] J. A. Moore and D. H. Ahlstrom, *J. Org. Chem.* **26**, 5254 (1961).

A plausible alternative mechanism for the conversion of I to V, which was apparently not considered by Moore, would be a Wolff-type rearrangement of I to give the ketene (VI), followed by the sequence VI → X → V.[4]



The original diazo carbon atom would thus become attached directly to the benzene ring and would be found as C_3 in the final product (V). Since certain features of the mechanism proposed by Moore seemed unlikely, our initial objective was the examination of the possible intermediacy of a Wolff-type rearrangement by determining the fate of the diazo carbon atom labelled with C^{14}.

The requisite starting material was prepared by treatment of *o*-nitrobenzoyl chloride with labelled diazomethane (prepared from labelled methylamine *via* N-nitroso-N-methyl-*p*-tosylamide).[5] This was rearranged under the previously described conditions (glacial acetic acid) to N-hydroxyisatin, and the position of the labelled carbon atom determined by the degradative sequence V → XI → XII → XIII → XIV.



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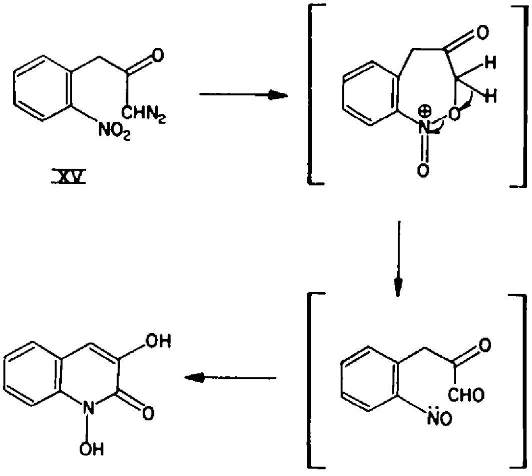
[4] In this case there is no metal ion present to catalyze a free radical Wolff rearrangement like that proposed by M. S. Newman and R. F. Beal, *J. Amer. Chem. Soc.* **72**, 5163 (1950); however, there is the possibility of a heterolytic rearrangement with concurrent nucleophilic attack of a nitro oxygen atom on the ketene carbonyl.

[5] Th. J. de Boer and H. J. Backer, *Rec. Trav. Chim.* **73**, 229 (1954).

Thus, the labelled N-hydroxyisatin was converted with alkali to anthroxanic acid (XI) which was then reduced to isatin (XII) with ferrous sulfate and ammonia.[6] (Direct reduction of N-hydroxyisatin to isatin could not be effected, in accord with the experience of previous investigators.) The labelled isatin was converted to its 3-oxime (XIII) which was subjected to a second-order Beckmann rearrangement under the conditions described by Bedford and Partridge[7] to give *unlabelled* anthranilonitrile (XIV) and *labelled* carbon dioxide. It is obvious that the diazo carbon atom became the C_2 of N-hydroxyisatin and that no Wolff rearrangement had occurred.

If the mechanism proposed by Moore for the transformation of I to V were operative, it seems reasonable that it should permit the conversion of 1-diazo-3-(*o*-nitrophenyl)acetone (XV), a homolog of I, to 1,3-dihydroxycarbostyril (XVI), the corresponding homolog of N-hydroxyisatin. However, Moore has shown that this conversion does *not* take place.[3]



XVI

We propose a mechanism for the conversion of I to V which does not involve the nitroso aldehyde intermediate (III) proposed by Moore, and which accounts for all of the experimental evidence. We suggest that the benzoxazine (II), as proposed by Moore, is initially formed by nucleophilic attack by a nitro oxygen atom upon the diazo carbon atom with loss of nitrogen. Subsequent acid-catalyzed enolization to give XVII allows for attack by acetate (in glacial acetic acid) or water (in dilute sulfuric acid) to give the quinoid-like intermediate (XVIII), which upon loss of a proton would give *o*-hydroxylaminophenylglyoxylic acid (X) (or its mixed anhydride with acetic acid (XIX)), which is known to undergo spontaneous cyclization to N-hydroxyisatin.[8] The failure of XV to undergo rearrangement to XVI then becomes explicable, for XX, the intermediate analogous to XVII, cannot undergo cleavage with acetate or water to afford *o*-hydroxylaminobenzylglyoxylic acid.

If *o*-nitrosophenylglyoxal (III) were indeed an intermediate in the conversion of I to V as proposed by Moore, then its formation *in situ* by another route, but under

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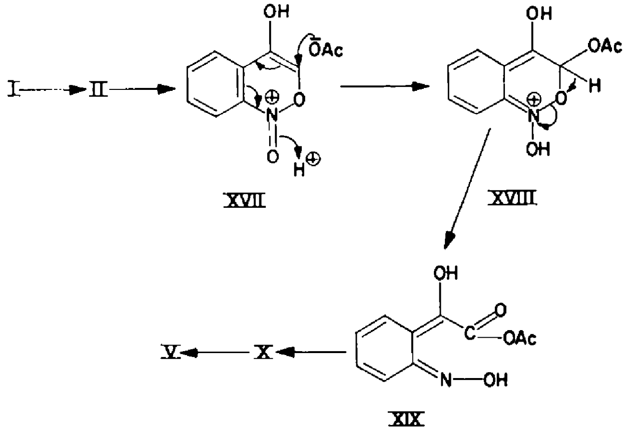
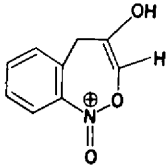
[6] A. Reissert, *Ber. Dtsch. Chem. Ges.* **41**, 3921 (1908).

[7] G. R. Bedford and M. W. Partridge, *J. Chem. Soc.* 1633 (1959).

[8] E. Bamberger and A. Lindberg, *Ber. Dtsch. Chem. Ges.* **43**, 122 (1910); G. Heller, *Ibid.* **44**, 2418 (1911).





XX

analogous reaction conditions, should likewise lead to N-hydroxyisatin. Our attempts to demonstrate its possible intermediacy were inconclusive; however, numerous catalytic and chemical reductions[9] of *o*-nitrophenylglyoxal in glacial acetic acid gave complex, unidentified colored products, but neither N-hydroxyisatin nor isatin was found.

EXPERIMENTAL[10]

o-*Nitrobenzoyl chloride.* A slurry of 100 g *o*-nitrobenzoic acid and 91 g freshly distilled thionyl chloride was gently heated until a clear solution was obtained. The excess thionyl chloride was removed under water pump press. The residue was distilled *in vacuo* (using a water trap to protect the pump). A pale yellow oil was collected; yield 95 g, (89·6%) b.p.$_{0\cdot7\ \mathrm{mm}}$ 139–141°.[11]

o-*Nitrobenzoyldiazomethane* (I). To an ethereal solution of diazomethane, prepared by the method of de Boer and Backer[6] from 32·0 g (0·68 mole) *p*-toluenesulfonyl chloride and a mixture of 20 ml (0·177 mole) 30% methylamine aq and 3·7 mg ($5\cdot5 \times 10^{-5}$ mole) methylamine hydrochloride (Nuclear Research Chemicals) containing 0·5 millicurie of C^{14}, was added 8·9 g (0·048 mole) *o*-nitrobenzoyl chloride. Considerable gas evolution took place. Evaporation of the solution to approximately half its volume resulted in the separation of 2·8 g yellow crystals of *o*-nitrobenzoyldiazomethane, m.p. 98° (lit[3]. m.p. 105–106°). Attempted recrystallization of this material frequently resulted in explosive decomposition; it was therefore used in the next step without further purification.

N-*Hydroxyisatin* (V). A mixture of 2·8 g labelled *o*-nitrobenzoyldiazomethane, 4·5 ml glacial acetic acid and 0·1 ml formic acid was heated to boiling for 1 min. Vigorous gas evolution took place.

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[9] The three reduction methods employed were: (1) Pd–C and 3½ atm H_2; (2) Zn–NH_4Cl, $Na_2Cr_2O_7$–H_2SO_4; G. H. Coleman, C. M. McCloskey and F. A. Stuart, *Org. Syn.* **25**, 80 (1945); (3) Zn–$FeCl_3$, E. Hecker, *Chem. Ber.* 88, 1666 (1955).

[10] All the radioactive samples were counted on a Nuclear Chicago C-101 apparatus, with low background counting system (approximately 2 counts per min). The counting head was set at 1350 volts, under 7 lb press of Q gas (98·7% He and 1·3% butane), with a counting efficiency for C^{14} calculated to be 22%.

[11] Charles W. Jefford, Ph.D. Thesis, Princeton University (1962). p. 96.

The red crystals which separated on cooling were collected and washed with 60 ml ether to give 0·58 g (24%), m.p. 193° dec (lit[2]. m.p. 193°).

Correcting for background count, 0·09472 mg recorded 239·5 cts/min.

$$\text{Mol. wt. of V} = 163{\cdot}13\,\frac{163{\cdot}13}{0{\cdot}09472} \times 239{\cdot}5 = 412{\cdot}5 \times 10^6 \text{ cts/min/mole}$$

1 microcurie = 2·22 × 10^6 cts/min.[12]

412·5/2·22 = 186 microcuries/mole

Anthroxanic acid (XI). To a mixture of 0·58 g labelled N-hydroxyisatin and 0·80 g unlabelled N-hydroxyisatin was added 50 ml 2N NaOH aq, and the resulting solution was allowed to stand at room temp for 20 hr. A 55-ml portion of 2N HCl aq was added and the resulting suspension allowed to stand at room temp for 4 hr. The nearly colorless precipitate of anthroxanic acid was filtered and dried over Drierite in a vacuum desiccator to give 1·23 g (89%), m.p. 198°, followed by resolidification and remelting at 245° (lit. m.p. 197–198°, with resolidification and remelting at ca. 240°).

Correcting for background count, 0·09878 mg recorded 109·1 cts/min.

$$\text{Mol. wt. of XI} = 163{\cdot}13\,\frac{163{\cdot}13}{0{\cdot}09878} \times 109{\cdot}1 = 180{\cdot}2 \times 10^6 \text{ cts/min/mole}$$

180·2/2·22 = 81·2 microcuries/mole XI.

Predicted activity of XI (from activity of V) is

58/(58 + 80) × 186 = 78·1 microcuries/mole XI

Isatin (XII). To a solution containing 6 ml water and 2·4 ml conc. NH_4OH was added 1·2 g labelled anthroxanic acid, followed by 6 g $FeSO_4 \cdot 7H_2O$. The solution was allowed to stand at room temp for 30 min, after which time 20 ml water was added. The mixture was shaken, filtered, and the filtrate acidified with 25 ml 2N HCl. The red crystals of isatin which separated upon standing were collected by filtration to give 0·78 g (72%), m.p. 202° (lit[6]. m.p. 202–204°).

Correcting for background count, 0·09920 mg recorded 120·6 cts/min.

$$\text{Mol. wt. of XII} = 147{\cdot}13\,\frac{147{\cdot}13}{0{\cdot}09920} \times 120{\cdot}6 = 174{\cdot}8 \times 10^6 \text{ cts/min/mole}$$

174·8/2·22 = 78·7 microcuries/mole of XII.

Isatin-3-oxime (XIII). A solution of 0·75 g labelled isatin in 11 ml ethanol was added to a solution of 0·38 g hydroxylamine hydrochloride dissolved in 4 ml hot water. The resulting solution was refluxed with stirring for 20 min. The yellow crystals which separated on cooling were collected to give 0·79 g, (95%), m.p. 247°. (Found: C, 59·38; H, 3·91; N, 17·02; Calc. for $C_8H_6N_2O_2$: C, 59·26; H, 3·73; N, 17·28%).

Our observed m.p. for isatin-3-oxime (247°) differs significantly from previous lit. claims.[13] Repetition of a number of independent preparations of this material confirms our higher m.p.; its structure is confirmed both by analysis and by its conversion (*vide infra*) to anthranilonitrile. We will comment in detail on this discrepancy in a separate communication.

Correcting for background count, 0·08842 mg recorded 101·9 cts/min.

$$\text{Mol. wt. of XIII} = 162{\cdot}14\,\frac{162{\cdot}14}{0{\cdot}08842} \times 101{\cdot}9 = 186{\cdot}7 \text{ cts/min/mole}$$

186·7/2·22 = 84·1 microcuries/mole of XIII.

Anthranilonitrile (XIV). Labelled isatin-3-oxime (200 mg) was placed in a 2 ml flask which was connected to an apparatus similar to that used by Bedford and Partridge.[7] A $Ba(NO_3)_2$ trap (pH 7·25) was placed between the ether trap and the water-pump aspirator to capture the evolved CO_2. The reaction was started by melting the oxime in an oil bath at 245°, and it was then allowed to proceed spontaneously. From this decomposition, anthanilonitrile in the Drechsel bottle was

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[12] D. Taylor, *The Measurement of Radio Isotopes* (2nd Edition) p. 12. J. Wiley, N.Y. (1957).

[13] The upper and lower limits appear to be 223–225° (R. Schachat, E. Becker and A. McLaren, *J. Org. Chem.* **16**, 1349 (1951)) and 191–192° (M. Kohn and A. Ostersetzer, *Monatsh.* **34**, 1741 (1913)).

collected in ether. The ether solution was filtered and evaporated; the residue was sublimed to furnish 12 mg (8·2%) pure anthranilonitrile, m.p. 49° (lit.[7] m.p. 49–50°).

Correcting for background count, the anthranilonitrile recorded no radioactivity.

Approximately 10 mg $BaCO_3$ was isolated by filtration from the $Ba(NO_3)_2$ trap. Because radioactive $BaCO_3$ exhibits intensive self-absorption, the counting procedure outlined by Calvin[14] was used.

Each weighed sample was suspended in 50 ml $Ba(NO_3)_2$–$BaCO_3$ mother liquor and filtered on a 2·4 cm diameter. Whatman No. 50 filter paper. The paper was dried and counted.

Correcting for background count,

0·2	mg	7	cts/min
0·3195	mg	14·0	cts/min
0·5423	mg	15·2	cts/min
0·9981	mg	23·4	cts/min
1·6275	mg	44·4	cts/min
2·1080	mg	64·4	cts/min

These points were plotted with cts/min as the abscissa and wt (in mg) as the ordinate. The reciprocal of the curve (i.e., $y = 1/f(x)$), extrapolated to 0·0 mg, gives the correction for self-absorption: 850–900 cts/min/mg.

$$\text{Mol. wt. of } BaCO_3 = 197{\cdot}30 \, \frac{197{\cdot}30}{0{\cdot}001} \times 850 = 167{\cdot}7 \times 10^6 \text{ cts/min/mole}$$

$$\text{Mol. wt. of } BaCO_3 = 197{\cdot}30 \, \frac{197{\cdot}30}{0{\cdot}001} \times 900 = 177{\cdot}5 \times 10^6 \text{ cts/min/mole}$$

$$167{\cdot}7/2{\cdot}22 = 75 \text{ millicuries/mole } BaCO_3$$

$$177{\cdot}5/2{\cdot}22 = 80 \text{ millicuries/mole } BaCO_3$$

Acknowledgement—This research was supported in part by a grant (CY-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

[14] M. Calvin, *Isotopic Carbon.* J. Wiley, N.Y. (1949).