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(RESEARCH ARTICLE)

The chemistry of the Baeyer and Hoppe-Seyler test for glucose in urine

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Abstract

Glucose is an analyte and has drawn the attention of researchers for a long time. Baeyer accomplished several synthesis for indigo. The one under study was adapted by Hoppe-Seyler for detection of glucose in urine. The blue colour observed in the test is due to the formation of indigo. The reagent used in the test is o-nitrophenylpropiolic acid. However the route from the starting compound to indoxyl has not been cleared out. There are missing intermediates or inadequate ones have been proposed. In this communication we provide the route and the reaction mechanism involved in each step. This is in accordance with experimental data and the chemical deportment of the involved compounds.

Keywords: Glucose; Indoxyl; o-Nitrocinnamic acid; o-Nitrophenylpropiolic acid; Redox reactions

1. Introduction

In 1880 Baeyer published a synthesis of indigo starting from o-nitrocinnamic acid. The first steps were sketched, not the last ones that are missing.

In this communication we provide the route from the initial compound to indoxyl, as well as the reaction mechanisms. Both are fully commented.

Years later Hoppe-Seyler adapted this synthesis for glucose detection in urine. He used o-nitro-phenylpropiolic acid, an intermediate compound in the above route to indigo. Since glucose was used as reducing agent in the Baeyer synthesis, Hoppe-Seyler omitted it as reagent since it can be provided by diabetic urine. The test is very sensitive.

This communication is a follow up of our studies on reaction mechanism, [1-5].

2. Antecedents

The test under study is based on a 1880 synthesis of indigo by Adolph von Baeyer, [6]. This communication was commented in the United States, [7-8]. Years later Felix Hoppe-Seyler adapted this synthesis for glucose detection in urine [9-11].The test is as follows: boil 5 ml of a 0.5% solution of o-nitrophenylpropiolic acid in soda lye with 10 ml of urine. In the presence of glucose a blue colour is produced due to indigo formation.

The starting compound for the preparation of o-nitrophenylpropiolic acid is o-nitrocinnamic acid. Bromination yielded o-nitrodibromocinnamic acid, which on treatment with alkalies in the cold is converted into o-nitrophenylpropiolic acid. This substance on being warmed with a dilute solution of caustic soda and glucose is converted into indigo in 70% yield, [12].

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As it can be seen the reactions from the reagent, o-nitrophenylpropiolic acid, to the final product, indigo, are missing as well as the reaction mechanisms; especially the reduction of the nitro group by glucose and the cyclization step which has been forgotten in the chemical information dealing with the theme.

3. Discussion

The hydration of a triple bond is generally accomplished in acidic medium. However in the test under study the hydration of the triple bond in o-nitrophenylpropiolic acid took place in boiling water and alkaline medium, with concomitant decarboxylation. This manner o-nitro acetophenone is obtained. Water addition begins at the carbon atom linked to the aromatic ring. This is due to slight polarization producing an incipient carbonium ion, as well as, some negative charge vicinal to carbonyl, Fig 1, a, b. A hydroxyl group is formed and a carbanion alpha to the carboxyl which is neutralized by water, c. Keto-enol tautomerism affords a methylene ketone, d, that facilitates decarboxylation since the resulting carbanion can be stabilized by resonance to an enolate, e. The obtained product is o-nitro-acetophenone f.

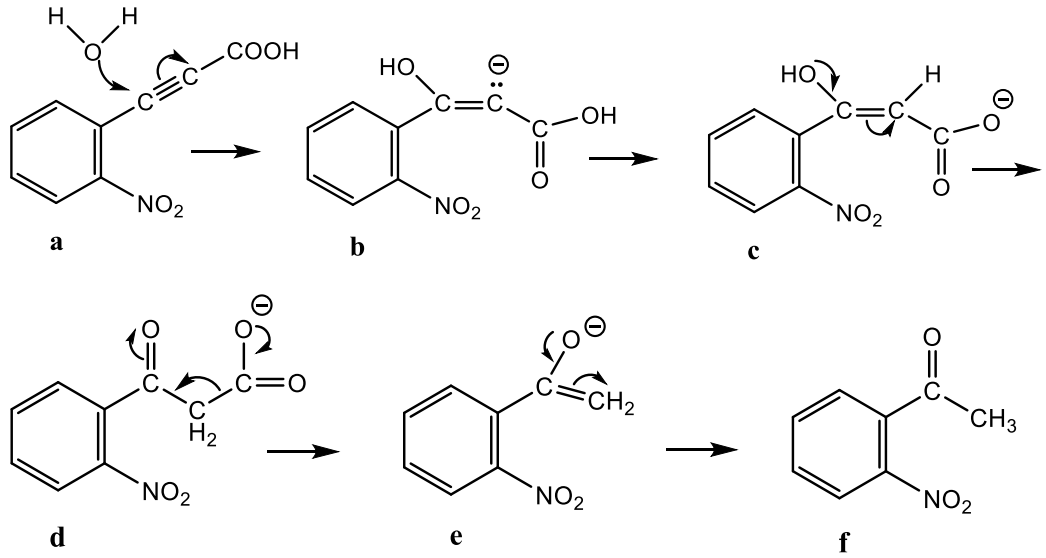

Figure 1 From **2-**nitrophenylpropiolic acid to the preliminary intermediate to indoxyl

Karrer postulated cyclization of the hydrated product, prior to decarboxylation and reduction, giving a nitrone, Figure 2, a. This intermediate was named isatogenic acid, [13]. However there are no experimental examples of nitro group participation in dehydrations of this type, [14]. Besides, there is no continuation to indoxyl and indigo formation.

Other intermediate that has been proposed is isatin, b, obtained from o-nitrophenylpropiolic acid by alkaline treatment, [15]. This is impossible since isatin is an oxidation product and there is a reducer, glucose.

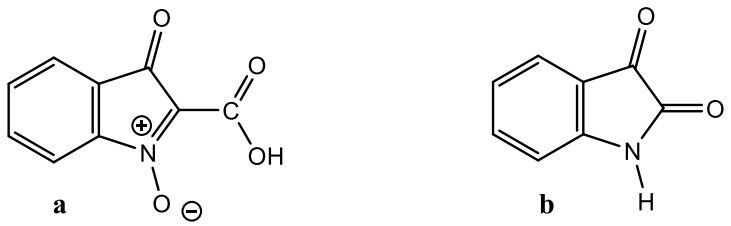

Figure 2 Discarded intermediates from experimental grounds

Reduction of the nitro group by glucose in alkaline medium takes place by addition of glucose enolate to the nitrogen double bond of the nitro group, Figure 3, a, b. Participation of the second enolate in the glucose intermediate, c, produces keto glucose (D glucosone), d, and the nitroso derivative, e, f. This intermediate can be cycled to the imino group, that is, to 3-oxo-indolenine, g. Further reduction by glucose, g, h. gives indoxyl (3-hydroxi-indol), i, via a concerted mechanism.

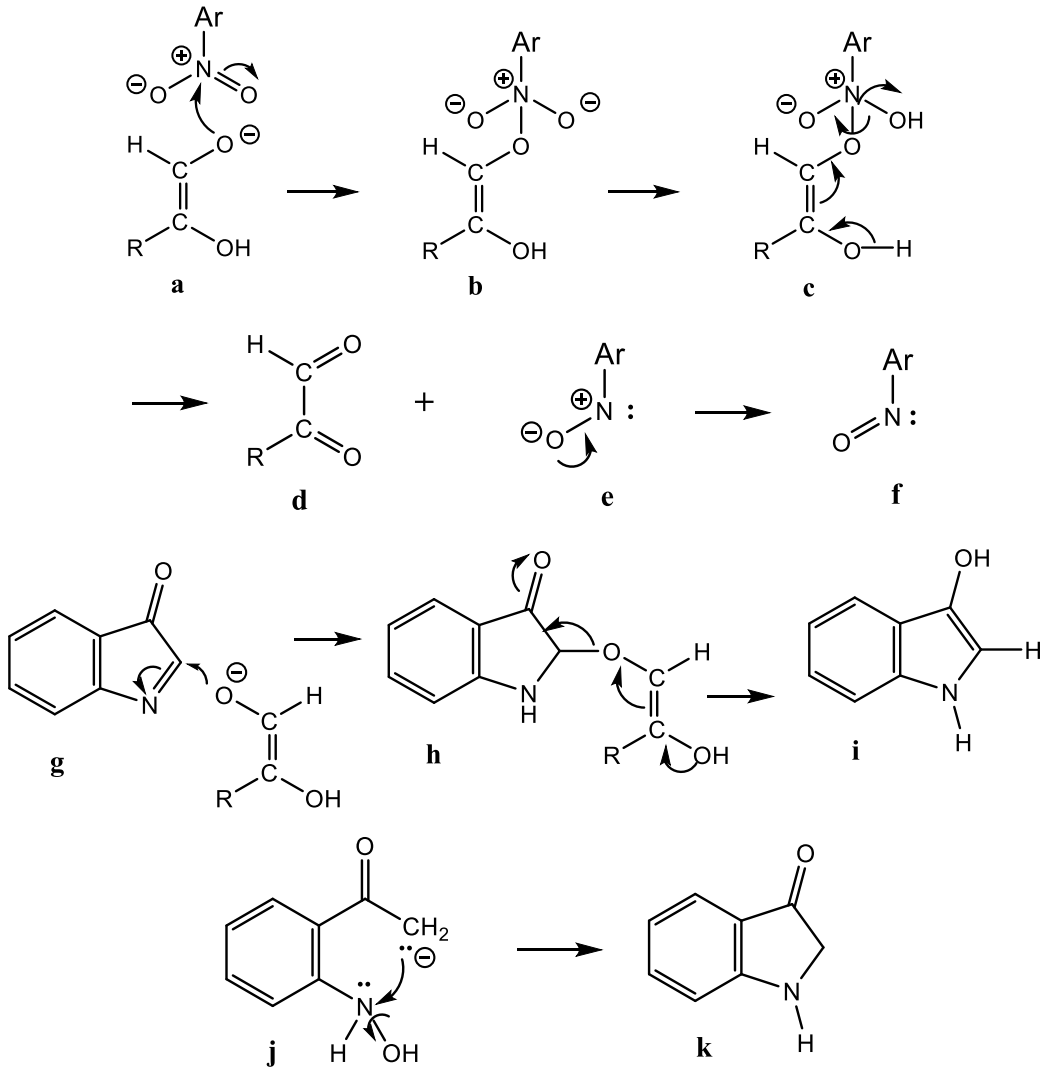

Figure 3 Indoxyl formation from 3-oxo-indolenine and from 2-hydroxylamino acetophenone in alkaline medium

However, reduction of 2-nitroso-acetophenone to the 2-hydroxylamino derivative yields the most suitable intermediate for easy cyclization to the keto form of indoxyl, j, k, by elimination of hydroxyl group by carbanion,

The transformation of indoxyl to indigo has been described recently by us [16].

In 1882 Baeyer brought out a variant of the synthesis under study, using ferrous sulphate in ammonia as reducer to o-aminophenylpropiolic acid. Decarboxylation by heat leads to ortho-aminophenylacetylene whose hydration gives o-aminoacetophenone, [17, 18].

Two years later Baeyer published the reduction of o-nitrophenylacetylene by means of zinc dust and ammonia to the o-amino compound [19-21].

4. Conclusion

The synthesis of indigo starting from o-nitrocinnamic acid, due to Baeyer, was adapted byHoppe-Seyler as test for glucose in urine. Since important steps in this route are missing, as well as, the mechanistic theory, we provided them. Especially the reaction mechanism for reduction of the nitro group by glucose in alkaline medium was supplied. Two reduced products are most suitable for ring closure to the target molecule, indoxyl. Other two proposed intermediates were discarded on experimental grounds.

A not previously proposed intermediate for easy cyclization to indoxyl is o-hydroxylamino-acetophenone and this is a novel contribution to the theme.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest among the authors or any other person.

References

[1] Sánchez-Viesca F, Gómez R. The mechanism of the morphine-apomorphine rearrangement. Am. J. Chem. 2022; 12(4): 73-75.

[2] Sánchez-Viesca F, Gómez R. The chemistry of the Heller's test for urine indican detection. Magna Scientia Adv. Res. & Rev. 2022; 05(01): 025-029.

[3] Sánchez-Viesca F, Gómez R. The mechanism of the oxido-degradation of the Cinchona alkaloids. Am. J. Chem. 2022; 12(1): 18-21.

[4] Sánchez-Viesca F, Gómez R. The chemistry of Crismer's test for glucose in urine. OAR J. Chem. & Pharm. 2021; 01(02): 005-008.

[5] Sánchez-Viesca F, Gómez R. The mechanism of the Davy test for strychnine. Int. Res. J. Pure & Appl. Chem. 2021; 22(10): 36-39.

[6] Baeyer A. Ueber die Beziehungen derZimmtsäure zu der Indigogruppe. Ber. 1880; 13(2): 2254-2263.

[7] King J, Felter HW, Lloyd JU. King's American Dispensatory, 18th. ed., Cincinnati: Ohio Valley Co. 1898.

[8] Cohn AI. Tests and Reagents. New York: J. Wiley & Sons, 1903; 10.

[9] Felix Hoppe-Seyler (1825-1895). https://es.wikipedia.org>wiki>Felix_Hoppe_Seyler

[10] Schneider A, Altschul J. Reagents and Reactions known by the names of their authors. Milwaukee, Wis.: Pharm. Review Publ. Co. 1897; 32.

[11] Merk E. Merck's Reagienten-Verzeichnis. Darmstadt: Springer. 1903; 66.

[12] Perkin FM. The present condition of the indigo industry. Nature, Nov. 1, 1900; 7-9.

[13] Karrer P. Organic Chemistry, 3rd ed. Amsterdam: Elsevier. 1947; 556-557.

[14] Sánchez-Viesca F, Berros M, Gómez R. On the mechanism of the Baeyer-Drewsen synthesis of indigo. Am. J. Chem. 2016; 6(1): 18-22.

[15] Nadir SH. Indigo synthesis by A. v. Baeyer starting from cinnamic acid.https://commons.wikimedia.org>

[16] Sánchez-Viesca F, Gómez R. On the formation mechanism of indigo blue and indigo red from vegetable source. Modern Chemistry. 2021; 9(4): 88-91.

[17] Baeyer A, Bloem F. Ueber o-amidophenylpropiolsäure und ihre Derivate. Ber.1882; 15(2): 2147-2154.

[18] Baeyer A, Bloem F. Sur l'acide orthoamidophenylpropiolique et ses derives. Bull. Soc. Chim. Paris, 1883; 39(1): 340-343.

[19] Baeyer A, Bloem F. Ueber die Bildung von Indigo durch amido-Acetophenon. Ber. 1884; 17(1): 963-967.

[20] Baeyer A, Bloem F. Sur la formation de l'indigo par l'o-amido-acetophenone. Bull. Soc. Chim. Paris, 1885; 44(2); 136-138.

[21] Morton AA. The Chemistry of Heterocyclic Compounds. New York: McGraw-Hill. 1946; 122.