

On the Mechanism of the Baeyer-Drewsen Synthesis of Indigo

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Abstract The Baeyer-Drewsen synthesis of indigo involves an interesting reaction series. Besides the incomplete and erroneous former attempts to explain the indigo formation process, there are recent contributions that are unsatisfactory from the theoretical point of view. Some are interesting but partially incorrect, others are incomplete and with stoichiometric errors, another is mere nonsense. We provide an up-dated and consistent reaction series, with comments on each step proposed by us, and also on those proposed by the others. These comments are based on well known reactions and reactivities. Since most names were lacking and others were unsuitable, not systematic or wrong, the appropriate nomenclature regarding the reaction intermediates is also given.

Keywords Baeyer-Drewsen, Indigo, Indoles, Reaction mechanisms, Reactive intermediates

1. Introduction

The Baeyer-Drewsen synthesis of indigo [1-3], from o-nitrobenzaldehyde and acetone, in alkaline medium, is an outstanding synthesis in Organic Chemistry. (Figure 1). In fact, from only two reactants, a reaction series occurs. However, until now there is no a complete and correct theoretical treatment of the involved steps in this synthesis, nor comments on the reaction mechanisms.

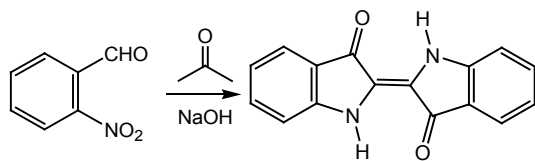


Figure 1. Baeyer-Drewsen Indigo synthesis

2. Early Approaches and Recent Theories

An attempt to explain the indigo formation by this method is in Gattermann's "Preparative Organic Chemistry" [4]. The condensation product of o-nitrobenzaldehyde with acetone in alkaline solution forms the so-called o-nitrophenyllactic acid ketone; i.e., 4-hydroxy-4-(2-nitrophenyl)-2-butanone. According to Gattermann, this compound loses acetic acid to

give o-nitrostyrene and by further loss of a molecule of water is changed into "indolone", which corresponds to half of the indigo molecule and polymerises to the dye. Figure 2.

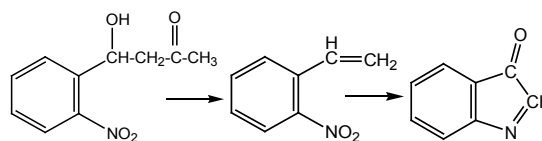


Figure 2. Gattermann's proposal

The formation of 2-nitrostyrene is very improbable since this splitting is proper to β -diketones because the second carbonyl group stabilizes the resulting carbanion in this break down, forming an enolate. The next step, a dehydration, is impossible. However, the 'indolone', i.e., indolenine-3-one, is considered also as intermediate in modern theories; of course, it is formed via a much longer route.

The Romanian researchers Tanasescu and Georgescu presented in the "Bulletin de la Societe Chimique de France" a then generally admitted reaction sequence for indigo formation [5]. Figure 3.

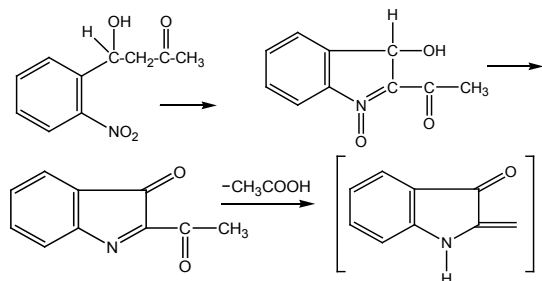


Figure 3. Suggested indigo formation

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The not named cyclization product is the old-fashioned way to represent a nitron, an imine N-oxide. However, nitrones are formed by reaction of a hydroxylamine and a carbonyl compound, not directly from a nitrocompound. If so, a simultaneous reduction of this group is necessary. Besides, there are no experimental examples of nitro group participations in dehydrations of this type. Notwithstanding, there are actually similar proposals.

The Henry Reaction, the nitro-aldol reaction, is the combination of a nitroalkane and an aldehyde or a ketone in the presence of a base to form β -nitro alcohols that can be dehydrated. The nitro group remains intact [6]. As it can be seen, these reactions are very different to the proposed nitron formation.

However, Tanasescu and Georgescu [5] considered the above sequence rather complex, without other comments, and proposed the formation of o-nitrosobenzoylacetone as a better intermediate. They named this compound γ -keto- γ -methyl- α -keto- α -nitrosophenyl-propane. Then the cyclization was proposed and no more suggestions were made. Figure 4.

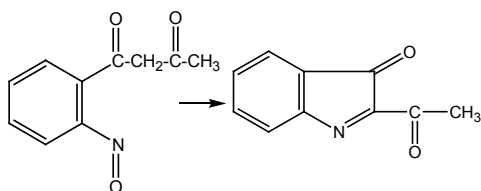


Figure 4. o-Nitrosobenzoylacetone as intermediate

Later, Paul Karrer [7] included in his textbook on Organic Chemistry (1947) the wrong sequence discarded by the Romanians.

It was until 1996 that Ranganathan [8] proposed a modern point of view on the subject. After the enolate condensation of acetone with o-nitrobenzaldehyde he correctly proposed an oxido-reduction step conducting to o-nitrosobenzoylacetone, or 1-(o-nitrosophenyl)-1,3-butane-dione (no name was given). This reaction was proposed previously by the Romanian researchers [5], but without any mechanism. The cyclization of the nitroso compound now gives two products, a saturated and an unsaturated indole nucleus, Figure 5, unlike in Figure 4.

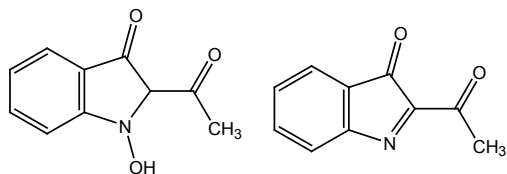


Figure 5. Resulting products from the nitroso compound

However, this author delays acetic acid elimination until the very late stages, thus including a series of very crowded intermediates, with high steric hindrance. One of these intermediates is presented in a 3D molecular model. Figures 6a and 6b.

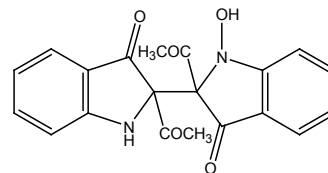


Figure 6a. A proposed crowded intermediate

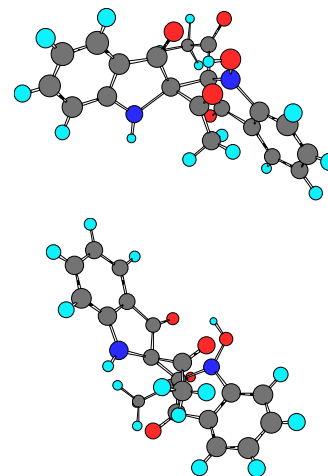


Figure 6b. 3D views of the crowded intermediate

Thus, the second part of the reaction series results improbable since such steric hindrance would greatly increase the reaction time which in fact demands just minutes.

Notwithstanding this communication and the papers on nitron preparations [6] there are still in books and Online sequences for the Baeyer-Drewsen synthesis starting with the unfeasible nitron formation [9-11]. The first error in these communications is the change of the name Drewsen to Drewson. The British abstracts retain 'Drewsen'.

In a modern (2010) 'Organic Chemistry' [9], there is a nonsensical sequence of reactions regarding the indigo formation. Only a few examples: an alcohol as a hydride donor, a nitroso group as an oxygen-base, unnecessary four-member reactions. No more comments.

Other communication [10] begins with the incorrect nitron formation from the aldol condensation product. However, in the reaction sequence the acetyl group loss is proposed before the condensation of two heterocyclic moieties, which is very probable. Nevertheless, there is an unnecessary hydration of an intermediate. In the Baeyer-Drewsen indigo synthesis various dehydrations take place, not hydrations.

In the book by the Parikhs [11] they speak on the Baeyer-Drewson Indoxyl Synthesis. It is the Indigo Synthesis. They provide a brief scheme with many missing intermediates. The resulting one from a supposed cyclization is wrong since the molecule lost an oxygen atom. (Figure 7) After elimination of acetic acid in the above hydroxylamine, there is an inexplicable oxidation of the alcohol to the ketone, Figure 8.

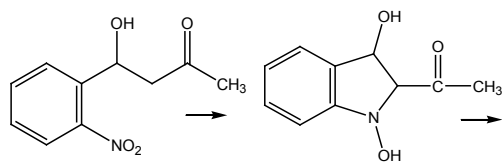


Figure 7. Mistaken cyclization

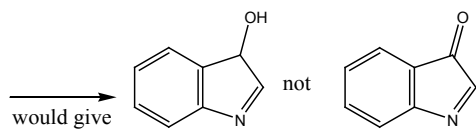


Figure 8. Correct and incorrect products after acetic acid elimination

In this section we have commented old misconceptions that however still persist. Also, we pointed out wrong nomenclature as well as seriously mistaken proposals found in current text books. Two interesting but partially incorrect theories were discussed too.

After all this, our subject deserves a complete and well established theory. This will be presented in the next section.

3. Discussion

After the preceding proposals, we can present a coherent and consistent reaction series, with the most probable reaction course. We have taken into account the different points of view, as well as, known reactivities, experimental data and results from molecular modelling.

In order to clear up the starting point of this reaction series, we must draw a comparison of the internal and the external chemical deportment of the nitro group. As example of the latter, this group does not react with a hydride donor such as sodium borohydride. On the other hand, as example of internal reactivity, *o*-nitrotoluene can be converted into anthranilic acid (2-aminobenzoic acid) by heating with aqueous sodium hydroxide, by internal oxido-reduction [12].

The above comparison is very useful because it explains 1) the failure of the nitro group to react with the chain and form a nitron; and 2) the facility to undergo reduction, even to the amine, by an internal process. The electron transfer occurs obviously through the benzene ring, since there is no chain to be invoked.

A cyclization, although intramolecular, can be considered external because it is through space. On the other hand, electron transfer is immediate in a conjugated system (internal, in strict sense).

Thus, we are in agreement with an oxido-reduction step through the benzene ring, and not with a cyclization involving the nitro group.

It is well known that vicinal hydrogen to a nitro group is acidic. This effect is transmitted also by an intermediate double bond (vinylene bridge). This is the case in the aldol condensation product. The oxidation of the ketol and the simultaneous reduction of the nitro group to nitroso, via an *o*-semiquinoid nitronate, is detailed in Figure 9.

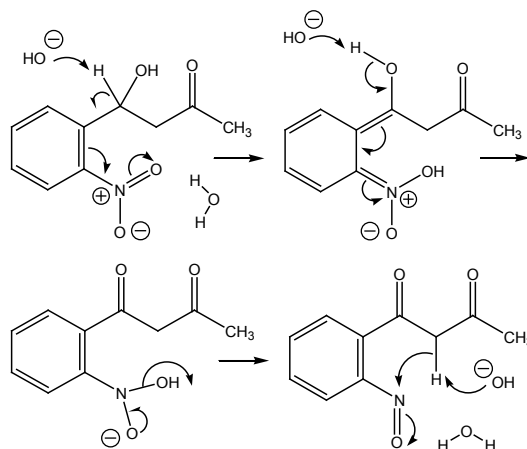


Figure 9. Oxido-reduction to diketone and nitroso group, starting from the nitro ketol

The nitroso group, a good electrophile, reacts with the β -diketone active hydrogens, via the enolate (Ehrlich-Sachs reaction) [13, 14]. Figure 9. The oxyamino adduct, the less reactive hydroxylamine, is thus formed. Then other reaction takes place at the outward acetyl group: the β -diketone aci break down, giving acetic acid and an enolate, Figure 10.

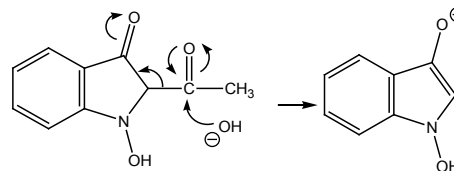


Figure 10. Elimination of acetic acid

The above enolate can form indolenine-3-one, Figure 11.

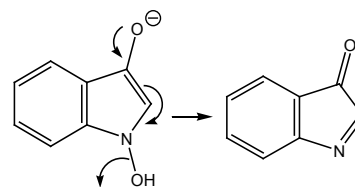


Figure 11. Formation of indolenine-3-one, a reactive 1,2-iminoketone

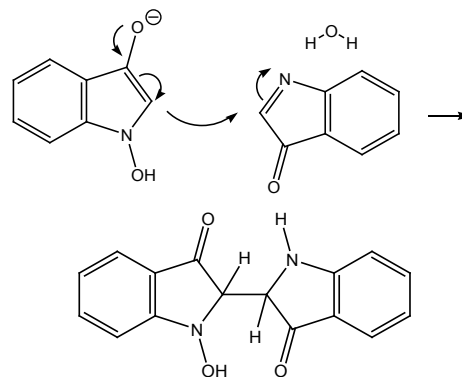


Figure 12. Formation of the tetra-annular frame

In this enolate the double bond is conjugated with the benzene ring, unlike when the diketone is external to the

nitroso compound. This conjugation stabilizes the enolate, lowering its reaction rate and retarding the second step of the Ehrlich-Sachs reaction. This permits the reaction, by electromeric effect, with a preformed indolenine molecule. This way the indigo frame is formed, Figure 12.

This and the next intermediates are not crowded, unlike those proposed in the Indian paper [8]. The above intermediate is represented in 3D, Figure 13.

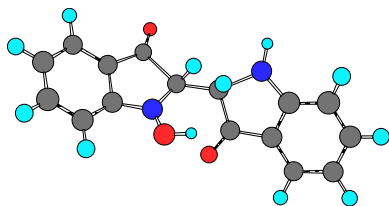


Figure 13. Coupled indole moieties in 3D, without steric hindrance

This intermediate permits the next steps occur smoothly. These are a dehydration and an isomerization, both involving active hydrogens, originating the chromophoric group of the blue dye. Figure 14.

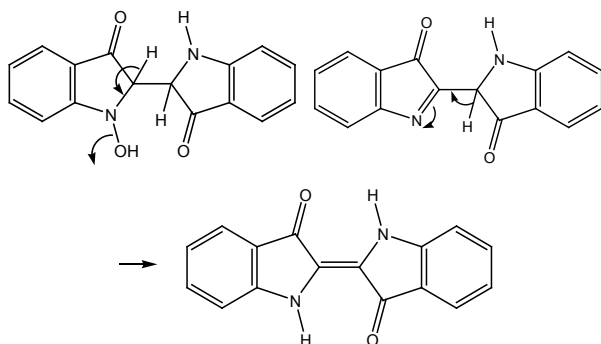


Figure 14. Base catalyzed dehydration and isomerization to form indigo.

For those interested in the Experimental Part of this synthesis, the following references are given.

One striking aspect of the Baeyer-Drewsen synthesis is its laboratory simplicity: just mix the reactants, no heating, and add drop by drop sodium hydroxide solution. After a short time the dye separates in crystalline flakes, [4]. For laboratory details see [15, 16].

The starting compound, 2-nitrobenzaldehyde, can be prepared from 2-nitrotoluene by the Fournier method, oxidation with manganese dioxide and diluted sulphuric acid [17-19].

Other method to obtain 2-nitrobenzaldehyde, also from 2-nitrotoluene, is by isonitrosation to form 2-nitro-benzaldehyde oxime, and subsequent hydrolysis to the aldehyde. A detailed procedure is the cognate preparation of the 4-bromo analog, in order to obtain Tyrian Purple, 6,6'-dibromoindigo [20]. A recent experimental variant is found in reference [21].

o-Nitrotoluene can be obtained by toluene nitration with acetyl nitrate, in 90% yield [22, 23], instead of the separation of the ortho and para isomers that result employing sulphonic mixture. Toluene gives o-nitro-toluene when treated with a mixture of $\text{Fe}(\text{NO}_3)_3$ and acetic anhydride at

40°C (Menke's method) [24, 25]. In this preparation AcONO_2 is formed in situ. The reaction mechanism with acetyl nitrate has been provided recently [25].

4. Conclusions

- We have reviewed both the early approaches and the recent theories on the mechanism of the Baeyer-Drewsen indigo synthesis.
- Comments on all the steps involved in the reaction sequence have been made.
- Scientific criticism has been applied in order to accept or reject each proposal.
- We have looked also at the pros and cons of each step.
- In this communication a complete and authoritative reaction sequence is provided.
- Well known reactions and reactivities have been taken into account.
- Molecular modelling has also been of help.

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