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Recent Advances in Several Organic Reaction Mechanisms

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Abstract: This Review is a brief account of our theoretical contributions in seven research communications in the field of reaction mechanisms. Some mechanisms were corrected as in the case of the Baeyer-Drewsen indigo synthesis. When two very different reaction mechanisms had been proposed, as in the Clemmensen Reduction, a unified theory was provided. In other cases there were no reaction mechanisms at all, as in the Baeyer-Emmerling synthesis of indigo and in the Froehde Reaction for opioids. This deficit has been solved. The reaction that controls fructosazone regiochemistry has been described, and an internal process in a mixed osazone formation has been explained. All the proposals are based on well known reactivities and we provide complete and coherent reaction series with commented steps.

Keywords: Baeyer-Drewsen, Clemmensen Reduction, Baeyer-Emmerling, Indirubin, Regiochemistry, Internal Process, Froehde Reaction

1. Introduction

In this Review we present straightforward the proposed reaction mechanism, abbreviating the justification arguments given in the original communications.

When two reaction mechanisms had been proposed for the same reaction, as in the Baeyer-Drewsen indigo synthesis or in the Clemmensen Reduction, a single and coherent reaction mechanism is presented. In other cases the reaction mechanism was missing, as in the Baeyer-Emmerling synthesis of indigo and in the Froehde Reaction. This absence has been filled. The presence of simple halochromism has been pointed out in some instances of the latter reaction.

There will be made comments about the novelty of the mechanism and which intermediates present in other sequences were discarded and why.

Only the essential references are provided, for the bulk of them the reader is sent to the original papers.

2. The Baeyer-Drewsen Synthesis of Indigo

The course of this synthesis, starting from o-nitrobenzaldehyde and acetone in alkaline medium, is presented in Wikipedia as occurring through a nitrone intermediate [1], Figure 1.

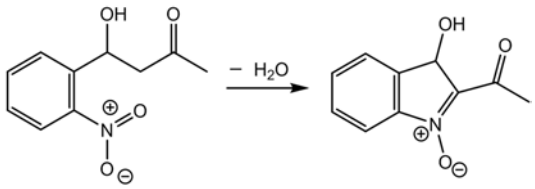


Figure 1. *Suggested nitrone formation.*

This is an error because there are no experimental examples of nitro group participations in dehydrations of this type. This misconception is mentioned in a 1932 communication [2].

Besides, the reaction between the carbanion and the nitro group can also be ruled out because the nitro group even doesn't react with a strong reducing reagent such as sodium borohydride.

Of course, we discarded the occurrence via nitrone.

In 1996 Ranganathan [3] proposed the formation of o-nitrosobenzoylacetone via an oxido-reduction step. However, in that sequence the next intermediates are very crowded and a different route with precursors with no steric hindrance is

provided, Figure 2.

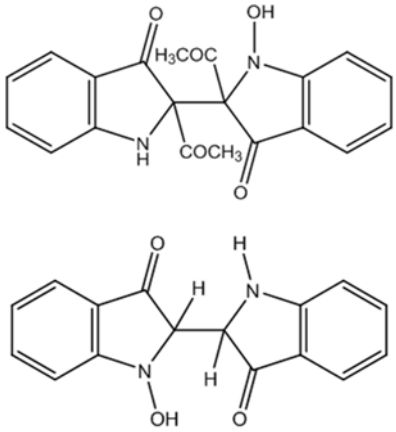


Figure 2. *Crowded intermediate and steric hindrance-free precursor.*

Thus, the complete reaction sequence we provided [4] is as follows: the first reaction product is a ketol, 4-hydroxy-4-(o-nitrophenyl)-2-butanone. This compound doesn't yield the second step of the Claisen-Schmidt Condensation, the dehydration to form the benzylidene derivative. This is due to the nitro group that creates an alternate reactivity.

It is well known that hydrogen in α-position to a nitro group is acidic. This effect is transmitted also by an intermediate double bond (vinylene bridge). An example of this redox process is the conversion of o-nitrotoluene into anthranilic acid, 2-aminobenzoic acid, in alkaline medium [5]. So, the oxidation of the obtained ketol, with the simultaneous reduction of the nitro group to nitroso is indicated in Figure 3.

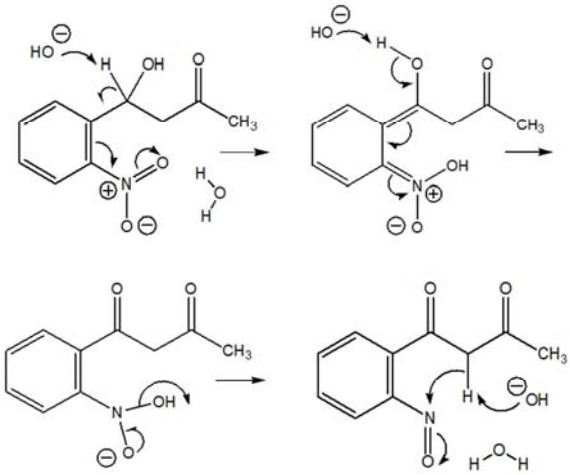


Figure 3. *Oxido reduction to a β-diketone and a nitroso group.*

The nitroso group reacts with the β-diketone active hydrogens (Ehrlich-Sachs reaction) [6, 7]. The resulting hydroxylamine, less reactive than the nitroso group, permits reaction at the outward acetyl group, i.e., a β-diketone aci break down, giving acetic acid and an enolate, Figure 4.

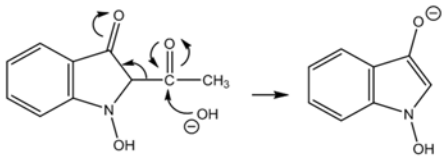


Figure 4. *Acetyl group elimination.*

The above enolate can form indolenine-3-one, Figure 5.

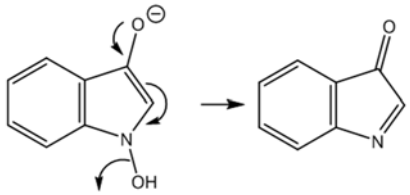


Figure 5. *Formation of a conjugated imino ketone.*

A competing reaction of this enolate is nucleophilic addition to an indolenine-3-one molecule, forming the indigo frame, Figure 6.

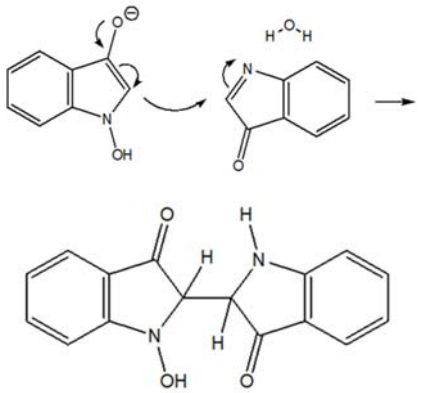


Figure 6. *Formation of leucoindigo.*

This intermediate permits the next steps occur smoothly since there is no steric hindrance like in the precursors postulated previously [3]. A dehydration followed by isomerization, both involving active hydrogens, give the indigo molecule, Figure 7.

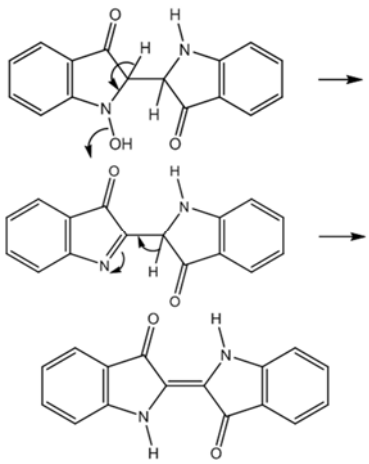


Figure 7. *Obtention of indigo blue.*

Scientific criticism has been applied in order to accept or reject each proposal. Thus, a complete and authoritative reaction sequence was provided.

3. The Clemmensen Reduction

Two principal proposals on this theme have been advanced: the 'Carbanionic Mechanism' [8] and the 'Carbenoid Mechanism' [9].

There must not be two very different mechanisms in order to explain the same reaction. So, a complete and coherent reaction mechanism is presented [10]. It involves the formation of a free carbene as well as a zinc carbene and two different carbanionic species as intermediates. This point of view is based on well known reactivities.

The reduction of an aldehyde or ketone to alkane analogs by means of amalgamated zinc and hydrochloric acid is explained as follows, Figure 8.

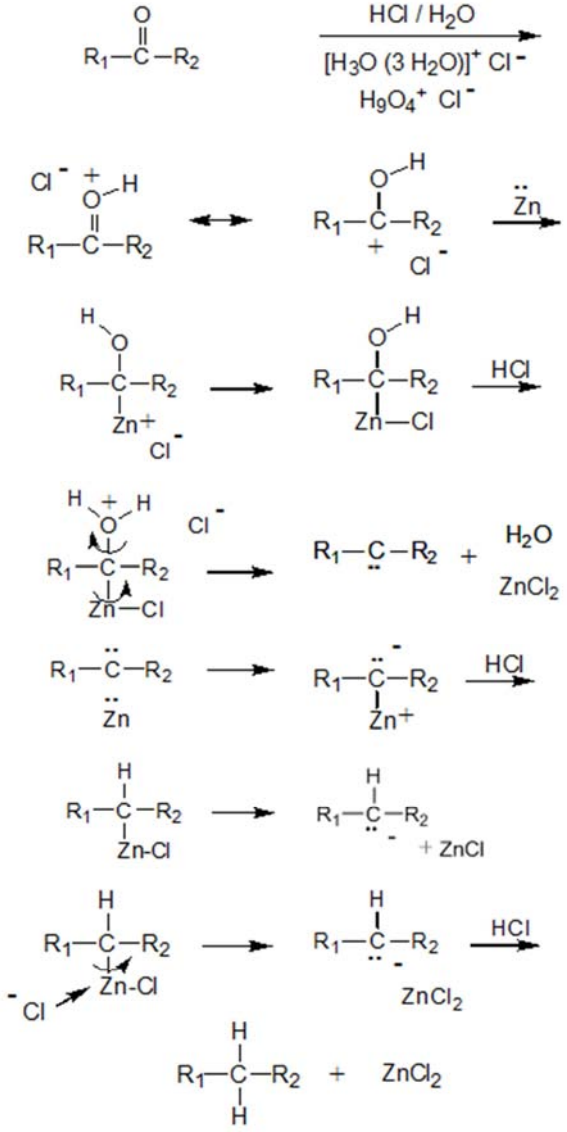


Figure 8. *Complete reaction mechanism of the Clemmensen reduction.*

The carbonyl compound is protonated by a solvated hydroxonium ion [11, 12]. The oxonium chloride is in resonance with a carbonium ion electromer. This carbocation reacts, in a chemisorptions step, with elemental zinc, an electrodoting reagent [13], leading to a two electron reduction. Reaction of the organometallic intermediate with hydrochloric acid yields a carbene, with concomitant water and zinc chloride elimination. The electron deficient species reacts with another zinc atom (metal carbene complex) giving a carbanion and an electron deficient metal. This zwitter ion reacts with hydrochloric acid and yields a deoxy organometallic derivative. A carbanion is formed by ionization, and then protonation affords the reduction product.

The ionization can be assisted by interaction with a chloride ion, eliminating zinc chloride. This is supported by the fact that zinc chloride reacts with hydrochloric acid forming the tetrachlorozincate anion, $ZnCl_4^=$, (zinc receptivity to chloride ions).

4. The Baeyer-Emmerling Synthesis of Indigo

We present highlights of our paper on this theme [14].

4.1. Oxidation of Indigo to Isatin (2,3-dioxoindoline)

The oxidation mechanisms are rarely treated in Organic Chemistry, emphasizing the utility and the experimental conditions. The nitric acid oxidation of indigo is interesting since it involves double bond addition, protolysis, epoxidation, ring opening, a second protolysis, and a carbon-carbon break down giving two carbonyl groups, i.e., two lactam groups of two isatin molecules, Figure 9.

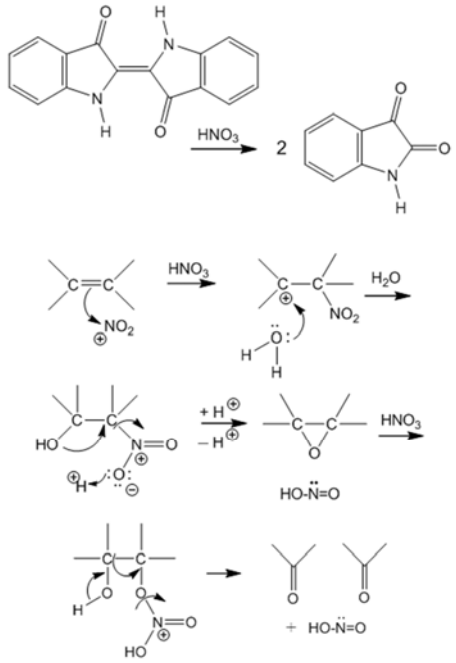


Figure 9. *Oxido-degradation of indigo by means of nitric acid.*

4.2. Cupric Chloride Oxidation of 3-aminoxindole to Isatin

This is a typical example of an ion-radical process, Figure 10.

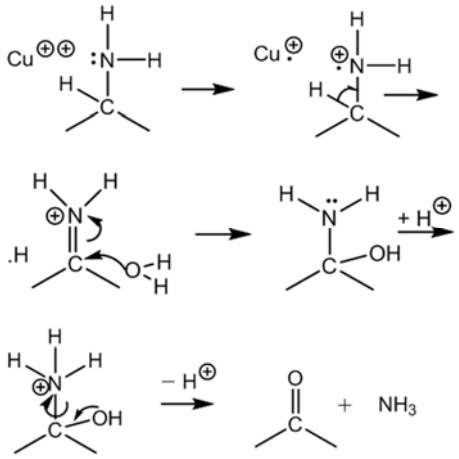


Figure 10. *Cupric chloride oxidation of the amino group to carbonyl.*

4.3. Isatin Chloride (2-chloroindolenin- 3-one) from Isatin

The chlorination mechanism via the amphion is advantageous than starting with the lactam (imidol) structure, Figure 11.

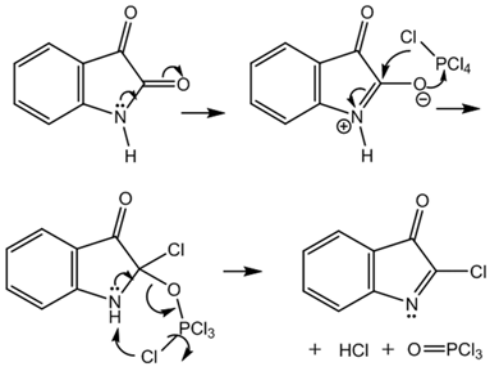
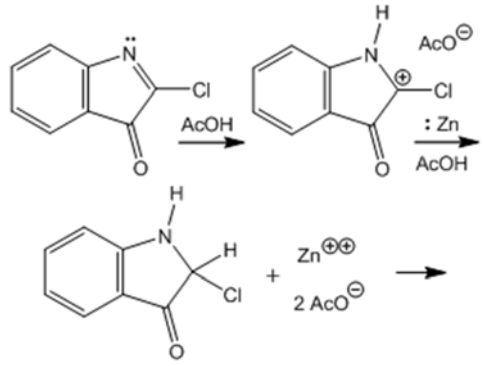


Figure 11. *Mechanism of isatin chlorination by means of phosphorous pentachloride.*

4.4. Zinc Reduction

The reduction mechanism of the above obtained isatin chloride is in Figure 12.



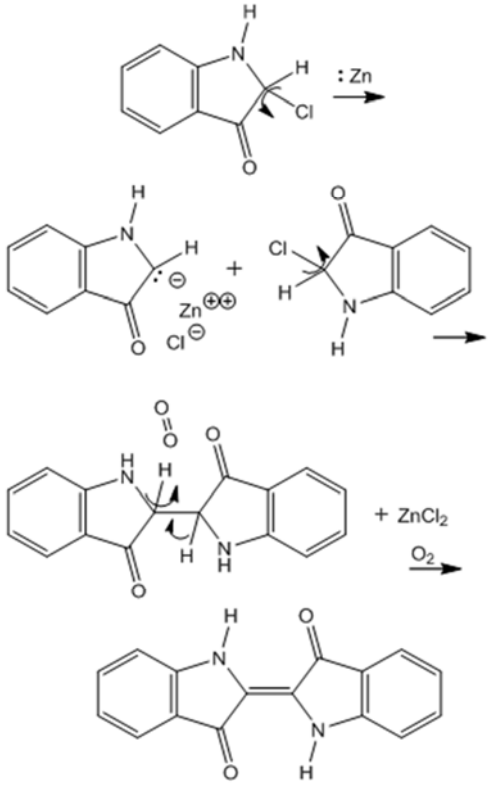


Figure 12. *Reduction of the imino chloride to indigo blue.*

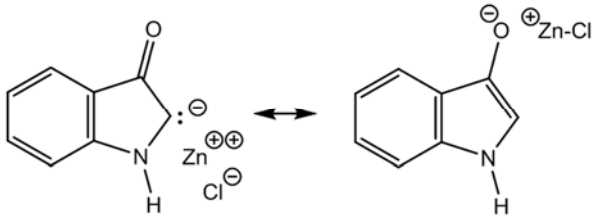


Figure 13. *Key electromeric intermediates.*

The first neutral intermediate is the chloro ketone resulting from double bond saturation via acid catalysis and reduction with zinc. A second reduction step yields an electrodoting carbanion that can react with a remaining chloro ketone molecule to give the indigo frame. Finally, aereal oxidation of leucoindigo gives indigo blue.

The reactive carbanin can be stabilized by resonance as a chloro zinc enolate with O-metallation, Figure 13.

5. Indirubin Formation in the Baeyer-Emmerling Synthesis

There was no mechanism explaining how indigo red (indirubin) is formed in this synthesis. Two routes to this important co-product of indigo blue were advanced [15]. Indirubin is actually employed in cancer treatment, [16].

5.1. First Route to Indirubin

This consist in the reaction of the carbanion arose from the reduction steps of isatin chloride, with the intermediate α-chloro ketone, Figure 14.

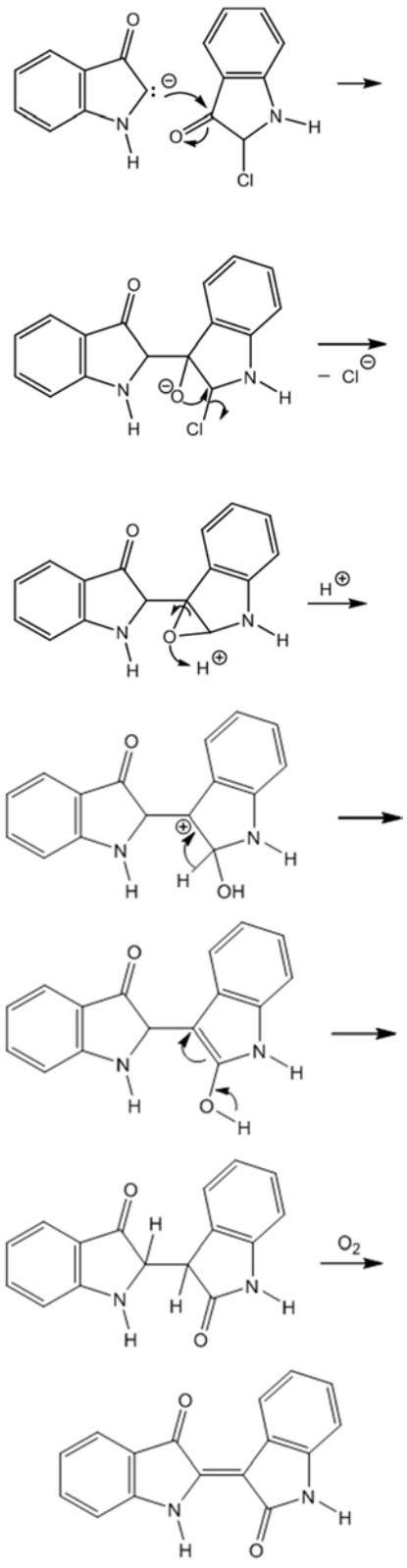


Figure 14. *Indirubin synthesis with the intermediate α-chloro ketone.*

This is a rather complex six step synthesis that involves: 1, nucleophilic addition to the carbonyl group (second option to chlorine substitution); 2, intramolecular epoxide formation; 3, ring opening by protolysis; 4, enol formation; 5, isomerization; and 6, aereal oxidation.

5.2. Second Route to Indirubin

The other way to indigo red in this synthesis is reaction of the carbanion from zinc/acetic acid reduction of isatin chloride with remaining isatin chloride, Figure 15.

In this secondary condensation reaction, the resulting alkoxide reacts with acetic acid and the hydroxy group is dehydrated. Finally, the reactive chloro imine is hydrated and the unstable 2,2-chloroalcohol yields the carbonyl group (lactam).

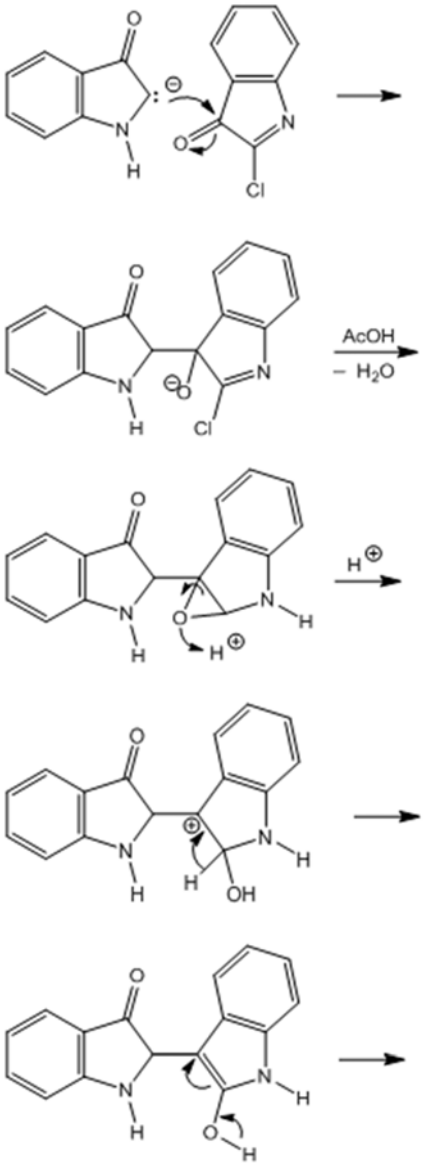


Figure 15. *Indirubin synthesis from isatin chloride.*

6. Mechanism of the Heyns Rearrangement

A retro-Amadori type or Heyns-variant rearrangement has been proposed [17, 18] in order to explain osazone formation, Figure 16.

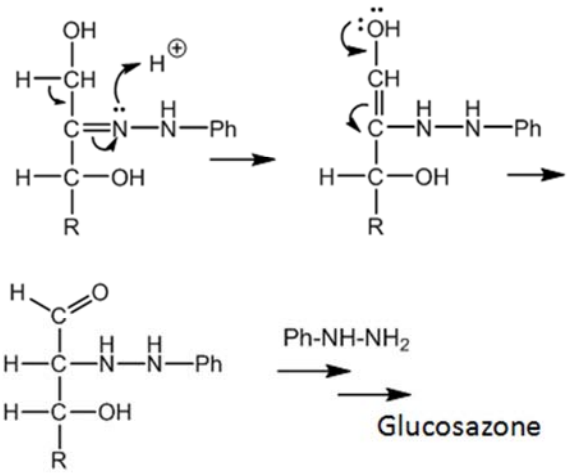


Figure 16. *Suggested oxido-reduction step.*

The fructose phenylhydrazone is isomerized to an enolhydrazine that gives 2-deoxy-2-phenylhydrazino D-glucose.

However, this mechanism does not account for the regiochemistry, i.e., why the reaction proceeds to C-1 and not to C-3.

The explanation given in our paper [19] is as follows: after the phenylhydrazone formation, the only existing difference is that at C-1 there is a primary alcohol, whereas at C-3 there is a secondary one, being the primary alcohol more reactive in the presence of the base than the secondary one. Since nitrogen is a Lewis base, the β-nitrogen can react with the primary alcohol, a better hydrogen donor than the secondary one. Then an oxido-reduction occurs at C-1 and C-2, i.e., a 1,4-hydrogen transfer via a cyclic, concerted five-member reaction mechanism (internal catalysis).

Thus, the regiochemistry has been explained, Figure 17.

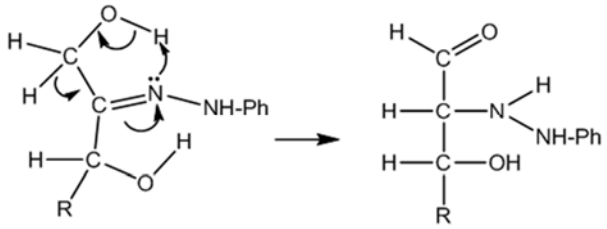


Figure 17. *Concerted oxido-reduction step in fructose phenylhydrazone.*

This proposal has been sustained in other communication [20] since our intermediate is in accordance with the results of Russian experiments on fructosazone formation employing ^{15}N and two aryl hydrazines [21].

7. Reactivities Involved in a Mixed Osazone Formation

The reaction of D-mannose phenylhydrazone with p-bromophenylhydrazine was accomplished in order to settle to which of the Weygand´s proposed routs for osazone formation the reaction was in accordance with the study [22].

The resulting intermediate splits off p-bromoaniline and aniline (70/30). However, this experimental ratio has not been explained.

The reactions involved in an acid catalyzed process are in Figure 18.

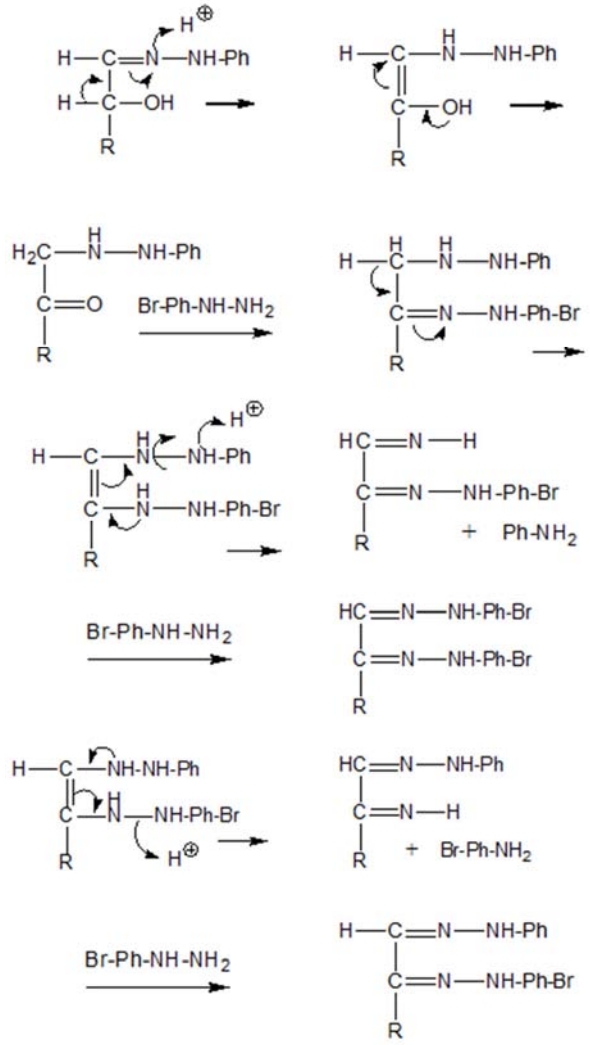


Figure 18. *Mixed osazone formation reactions via acid catalysis.*

In a previous paper [20] these reactions are discussed. In the mixed ene-bis-hydrazine, the α-nitrogen in the aniline fragment is more basic than the other α-nitrogen in this molecule. This can be deduced since aniline (pKa=4.60) is more basic than p-bromoaniline (pKa=3.86) [23]. Figure 18 shows the preferred protonation in the ene-bis-hydrazine, i.e., in the aniline segment. This protonation would favour a ratio aniline/p-bromoaniline. But the experimental ratio is the opposite: p-bromoaniline/aniline, 70/30. Thus, this step must be an internal process without acid catalysis; the enamine reactivity and the leaving group being of utmost importance, as we will see.

In the mixed ene-bis-phenylhydrazine, the inductive effect of the bromine atom is transmitted to the end of the π-system creating a δ+ at the α-nitrogen since the p-orbital of Br and N are both involved in the π-system (long distance effect),

Figure 19.

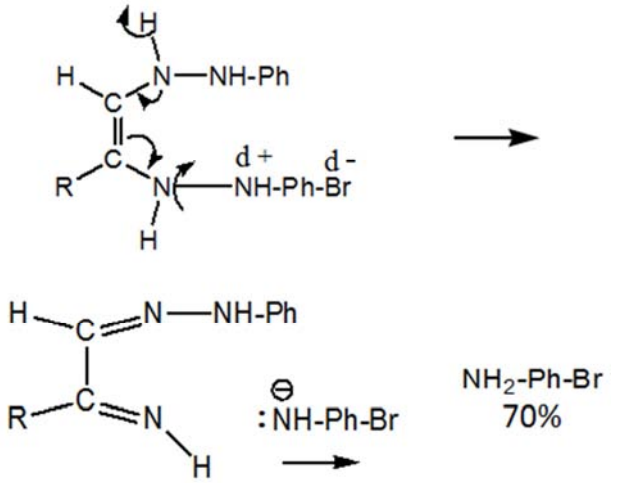


Figure 19. *p-Bromoaniline as main product via an internal process involving a vinylene bridge.*

The electron donor effect of the enamine vicinal to the aniline group, combined with the δ+ in the p-bromoaniline fragment, con form a phenylhydrazone at C-1 and an imino group at C-2, with the concomitant elimination of a good leaving group, since the negative charge is in the nitrogen with a previous δ+, as indicated in Figure 19.

On the other hand, the δ+ at the α-nitrogen decreases the reactivity of the vicinal enamine group since the formation of an adjacent positive charge is hampered or unfavourable, leading to the secondary product, Figure 20.

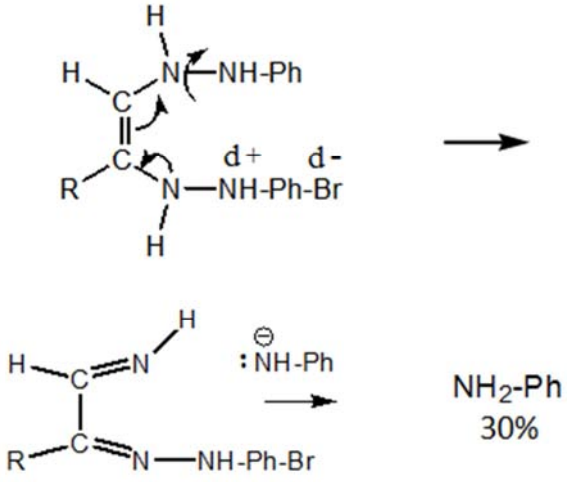


Figure 20. *Formation of aniline as secondary product.*

The ketimino hydrazone and aldimine hydrazone above formed react as indicated in Figure 21, yielding two different osazones.

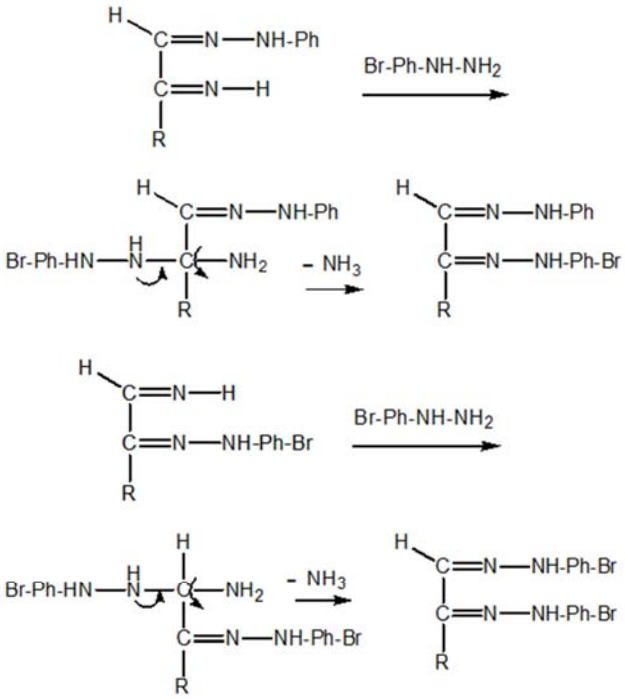


Figure 21. *Formation of the monobromo and dibromo osazone.*

8. The Mechanism of the Froehde Reaction

The Froehde reagent, prepared from molybdic acid or sodium molybdate dissolved in sulphuric acid is reduced by phenols and some alkaloids, especially morphine, Figure 22.

This colour test is used for the preliminary identification of opioids, morphine gives blue. Since the reaction course and the end products were not known, we advanced a reaction mechanism in accordance with established reactivities and the chemical deportment of the inorganic reagent, molybdic acid [24].

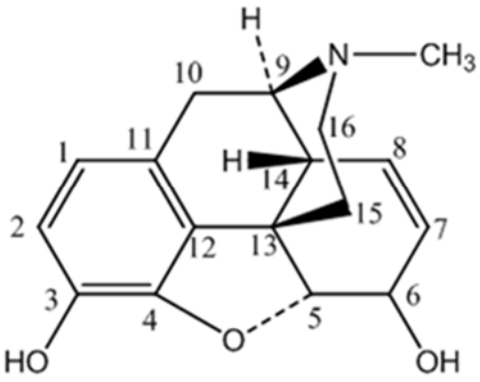


Figure 22. *Morphine structure.*

There can be two redox steps. The first is a hydroxylation process, Figure 23.

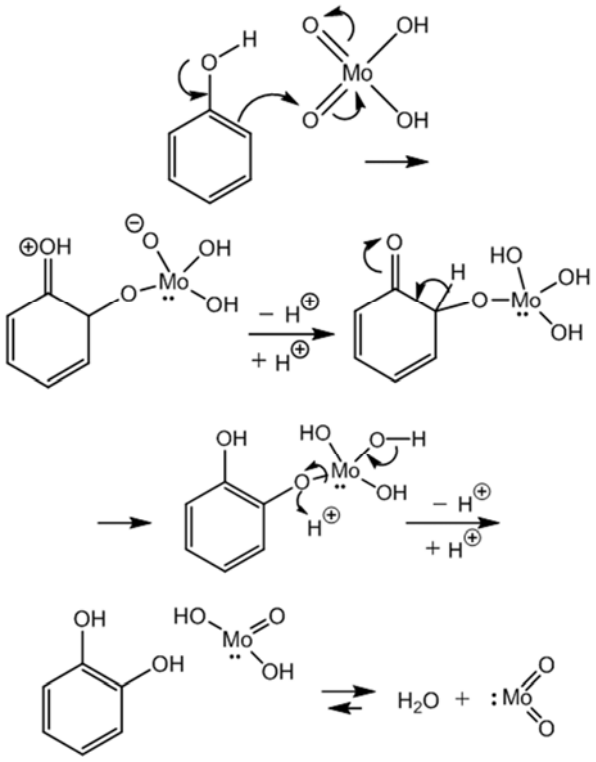


Figure 23. *Aromatic hydroxylation by a redox mechanism.*

The electron donor phenolic section reacts with the electron acceptor molybdic acid. Proton transfer and aromatization yields an organometallic intermediate. Finally protolysis affords a pyrocatechol derivative and molybdene dioxide hydrate. The dioxide is coloured violet.

The second reduction step is oxidation to the ortho quinone, Figure 24.

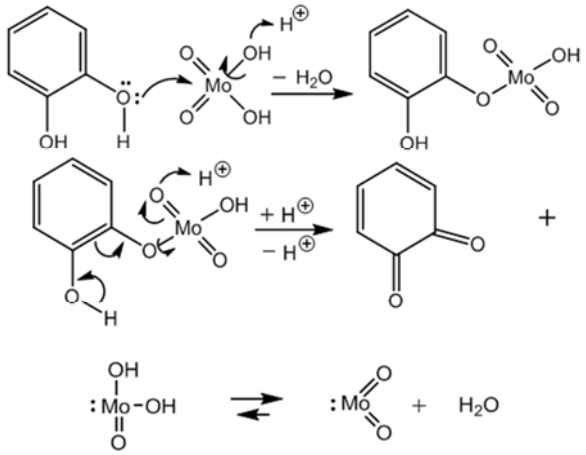


Figure 24. *ASecond oxidation-reduction step.*

After an acid catalyzed esterification, a redox reaction is promoted by protolysis. A yellow ortho quinone is obtained plus hydrated molybdene dioxide. The mixture is green due to the blue/yellow combination.

In the original communication there is a discussion about the colours obtained with synthetic opioids with a methoxy group at C-3. These compounds give different colours and we concluded that these results are probably due to halochromism (coloured salts).

9. Conclusion

Discarding clearly erroneous ancient routes on the Baeyer-Drewsen indigo synthesis, there were two more recent proposals. A careful study of the involved reactivities permitted us discriminate between the correct and the erroneous ones. This was done on the basis of known experimental work. Thus, it was possible establish a single and complete reaction mechanism for this synthesis.

A more complex situation was found in the case of the Clemmensen Reduction because there were two very different reaction mechanisms: the 'Carbanionic Mechanism' and the 'Carbenoid Mechanism'. Notwithstanding that both routes had some experimental evidence; there must not be two different reaction mechanisms for the same reaction. However, it was possible present a unified theory involving both carbenes and carbanions as well.

The ancient Baeyer-Emmerling synthesis of indigo had no reaction mechanisms at all. So, this route was updated giving this missing item. The reactivity of each functional group was carefully taken into account in accordance with the specialized literature. Another communication related to this synthesis deals with the formation mechanism of indigo red (indirubin), a co-product of indigo blue. This red product is of actual importance since it is used in cancer treatment.

Other group of compounds studied in this communication is the Carbohydrates. The regiochemistry of the Heyns Rearrangement has been elucidated. Thus, the missing theory of osazone formation has been provided and it is in accordance with experimental results realized in Russia employing sophisticated materials such as mixed phenyl-hydrazines, one of them with radioactive nitrogen.

The reactivity in a case of mixed osazone formation has been explained. These important reactions involve an unusual 'internal process'.

Finally, the Froehde Reaction mechanism has been proposed for the first time. This was done after a careful study of molybdenum chemistry since the reagent in this colour test is molybdic acid which is reduced to several oxides and salts. Some synthetic opioids give very different colours to the blue obtained with morphine. This is because there is no phenolic group in their molecules, and there is just halochromism, salt formation with the sulphuric acid used in the test.

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