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A reaction route of natural indigoids

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Abstract

Natural indigo is obtained by an empirical and traditional method, and the corresponding theoretical part is too brief: air oxidation of indoxyl in alkaline medium. The efforts were directed to the synthesis of the dye. However, the formation of indigo blue and its companion, indigo red (indirubin), is much more complex and deserves attention since there are involved interesting reactions. In this communication we provide the reaction series occurring in this process, giving the electron flow, step by step.

Keywords: Hemiaminal ether, Indigo blue, Indirubin, Indoxyl: Organic hydroperoxide, 3-Oxoindolenine

Introduction

The chemistry of natural indigoids formation has not been taken into account. Since it is a process involving air oxidation of indoxyl in alkaline medium, is common use write O_2 over an arrow and that's all. However, the case is not so simple. Indigo blue, obtained from *Indigofera tinctoria*, always contains indirubin (indigo red) as secondary companion.

Thus, a reaction route must explain the obtention of both compounds, why indigo red is obtained in minor proportion, and the formation mode of hydrogen peroxide as byproduct. In this communication we provide a route, step by step, to these bis-indole derivatives. The involved reactions are fully commented.

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

Antecedents

Indican is the glycoside, found in *Indigofera tinctoria*, from which indigoids can be obtained. The hydrolysis of indican (indoxy- β -D-glucoside) yields glucose and indoxyl, the aglycone.

According to Ballou ^[6], the alkaline hydrolysis of the phenolic glycosides consists in the ionization of the 2-hydroxi group of the sugar in the alkaline medium and this reacts with the glycosidic center, causing hydrolysis with the formation of a 1,2 epoxi derivative. Ring opening of the epoxide restores the hydroxyl group at C-2.

This ephemeral epoxide, involved in a forth and back mechanism, is very improbable. Direct attack of the base to the anomeric center, with elimination of an ambident enolate, is preferred to the invoked alcoxide formation and the multistep proposal.

Fifty years ago a radical mechanism was suggested for indigo formation. In this proposal, two indoxyl radicals can couple to form leucoindigo, but indoxyl radicals could not be detected by electron spin resonance ^[7]. Besides, indirubin was not considered, much less why the minority of this constant secondary product.

In recent years we provided the mechanism of the Baeyer-Drewsen synthesis of indigo ^[8], as well as the mechanism of the Baeyer-Emmerling first indigo synthesis ^[9, 10].

Indirubin and derivatives have attracted attention due to their healing properties. Topical indigo naturalis ointment is clinically proved to be an effective therapy for psoriasis, indirubin being the active substance ^[11]. These compounds have been used in cancer treatment, for instance in glioblastoma ^[12] and glioma ^[13].

Discussion

Indoxyl, Figure 1, a, gives in alkaline medium, $Ca(OH)_2$, the enolate. This is stabilized by resonance affording a carbanion at C-2, an ambident anion. The methylene group in the indoxyl keto form, b, is acidic due to the acidifying properties of the carbonyl group. The carbanion at C-2 is also ambident, c.

Molecular oxygen is a high energy molecule and this kind of molecules has relatively weak bonds. The double bond energy in O_2 is higher (300 kJ/mol) than the double bond energy in CO_2 [14].

In the secondary carbanion, out of four hybrid orbitals, three are involved in sigma bonds, whereas fourth hybrid orbital

contains unshared electron pair.

The indoxyl carbanion adds to the oxygen double bond forming organic peroxide, d, which is neutralized by water to a hydroperoxide, e, and a kind of hemiaminal ether is obtained.

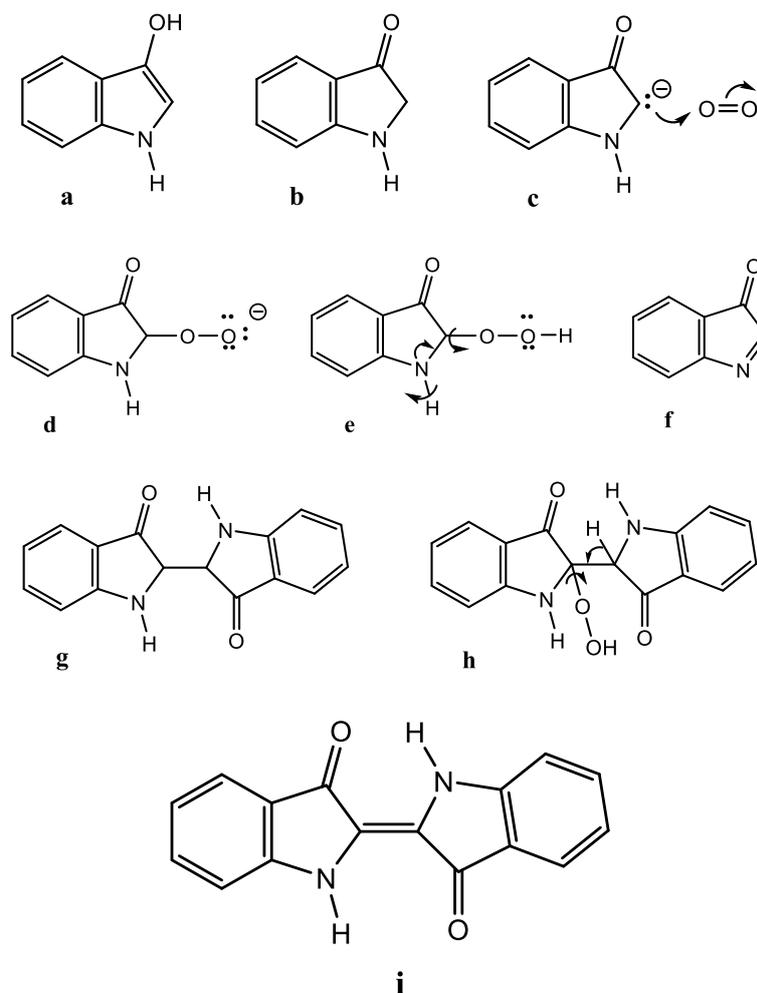


Fig 1: Reaction route to indigo blue

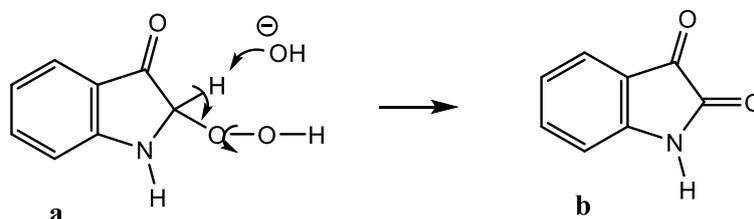
The electrodotic amino group eliminates a hydroperoxide anion, a good leaving group, e, and 3-oxo-indolenine, f, is formed (oxidation step). In this cross conjugated molecule there has been Umpolung, polarity inversion, at C-2. This position is completely free of steric hindrance and is preferred for reaction.

Since air oxygen is passed gradually through the reaction mixture, unreacted indoxyl carbanions can react with the indolenine derivative, yielding leucoindigo, g. One unit of this bis-indole intermediate repeats carbanion formation and

reaction with oxygen. Elimination of hydroperoxide anion, h, can be accomplished in the same unit as before, or by means of a carbanion generated in the other unit. This way a double bond is formed and indigo blue results, i.

The eliminated hydroperoxide anions are neutralized by water yielding hydrogen peroxide, a byproduct in the process for obtaining natural indigoids.

Now let's see the formation of the secondary product, indirubin (indigo red). Figure 2.



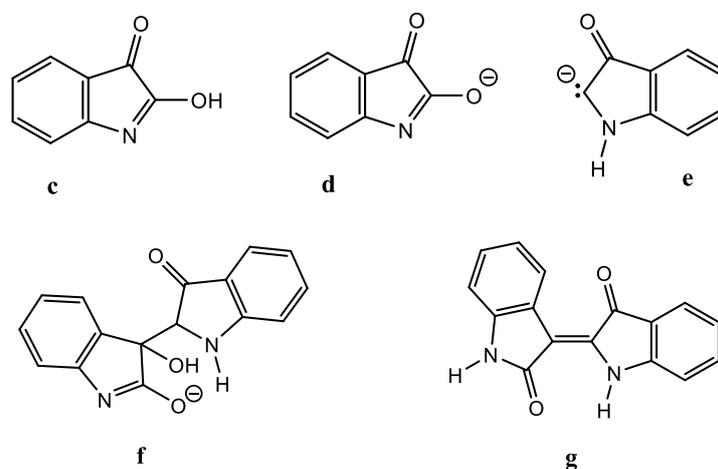


Fig 2: Reaction route of indirubin

Besides the hydroperoxide elimination by an intramolecular reaction, there is an alternative reaction: the remaining acidic proton at C-2 in the hydroperoxide intermediate can be taken by the base. The new carbanion forms a carbonyl group with concomitant hydroxyl ion elimination, a. This type of rupture is involved also in the degradation of α -keto aldehydes (Friedmann reaction) ^[15, 16]. This way an α -keto lactam results, isatin, b.

The preferred structure for this type of compounds is the lactim form, imidol, c ^[17]. In alkaline solution the respective salt turns out, d. Compare ^[18].

Indirubin is formed by condensation of indoxyl, as 3-indolinone (ψ -indoxyl), and isatin, via the carbanion, e, and the keto group of the latter, f, g. Indirubin has been synthesized likewise ^[19, 20] confirming our proposal.

Indirubin is always the secondary product, in more or less quantity. This intrigued and bothered Baeyer since he aimed to obtain only the blue compound. The minor proportion of indigo red can be explained since an additional reaction is needed for a second carbanion formation in the isatin synthesis, but the principal effect is electric hindrance ^[21, 22], due to the negative charge in the sodium salt of isatin, retarding reaction with the carbanion at ψ -indoxyl.

Conclusion

A reaction route from indican to the natural indigoids has been proposed via the following steps: alkaline hydrolysis of the glycosidic center, salt formation of the aglycone, organic peroxide, hydroperoxide, intramolecular elimination affording 3-oxo-indolenine, reaction with carbanion in 3-indolinone to leucoindigo and air oxidation to indigo blue.

Bilirubin, the secondary product, is formed via alternative hydroperoxide fission, yielding isatin, isomerization and salt formation. Finally, indigo red results by condensation of two anionic components, notwithstanding the electric hindrance, a delaying effect. This step has been confirmed by synthesis.

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.

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