Reduction of Indolo[2,3-*a*]quinolizidines with Baker's Yeast

F. A. Farés, H. Virelizier and K. Jankowski*

*Département de chimie et biochimie, Université de Moncton, Moncton, N. B., E1A 3E9, Canada

G. W. Gribble

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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The reduction of several indolo[2,3-*a*]quinolizidines with Baker's yeast (*Saccharomyces cerevisiae*) affords novel reduction products resulting from reduction of the indole double bond, cleavage of the C-D ring junction, or reduction of a lactam to a carbinol amine, as determined by high resolution mass spectrometry.

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Although the use of Baker's yeast (BY) as a reagent in synthesis has been known since the beginning of the century [1], only in recent years have the advantages of using BY in preparative organic chemistry become apparent. Not only is BY inexpensive and simple to handle, but the propagation, as any home brewer or amateur enologist can attest, of this versatile reagent does not require a microbiological laboratory. Baker's yeast has been used for several transformations of various classes of compounds, notably involving reduction of carbon-carbon double bonds, and the reduction of carbonyl groups to alcohols [1].

The two known tetrahydro β-carbolines, 1,2,3,4,6,7, 12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) [2] and its lactam **2** [3] were chosen as substrates for the BY reduction (Scheme). The reduction was carried out by treating the substrate with an actively fermenting yeast-sugar-water suspension according to the Seebach procedure reported by Chenvert [4].

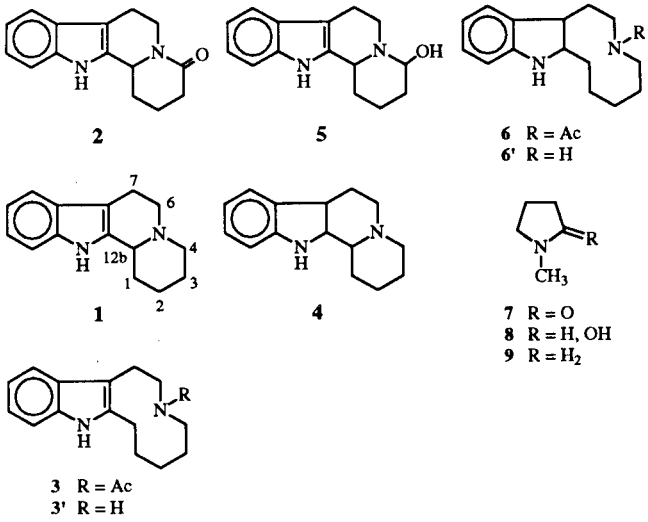
The reduction of **2** gave three products which are identified as unstable amino alcohol **5**, indoloquinolizidine **1**, and a third unknown product resulting from triple reduction of **2** (+6H). Two possible targets for such a reduction are the 2,3-indolic bond and the N_5-C_{12b} bond leading to compounds **3**, **3'** or **4**. In order to identify this reduction product, we prepared the known derivatives **3** and **4** from **1** by reduction with zinc/acetic acid and sodium borohydride/trifluoroacetic acid [5,6] and subsequently reduced them with BY. These BY reductions of **3** and **4** produced compound **6'** (or its *N*-acetyl derivative **6**) in 2.1 and 0.4% yields, respectively. In such a manner, the identity of the unknown BY reduction product of **2** (+6H) as being compound **4** was confirmed.

The reduction of a carbonyl compound to an alcohol using Baker's yeast has been reported in the literature [1]. However, to the best of our knowledge, the BY reduction of an amide to the amino alcohol has not been reported. Normally, with the exception of DIBAL, metal hydride reductions of amides afford amines rather than amino alcohol [7].

When the time of the reaction of **2** with BY was shortened from 5 days to 4 hours, the yield of amino alcohol **5** was increased and the yield of **1** had significantly decreased. These results suggest that the amino alcohol **5** is an intermediate, and is subsequently reduced to the indoloquinolizidine **1**. When **1** was submitted to the same reduction conditions, only **4** and **6** were obtained, accompanied however by traces of **5**. The amino alcohol **5** presence could then be related for carboline **1** to either the aerobic oxidation during the reaction with BY or as a by-product to a complete reduction of compound **2**. The reduction of another model lactam, *N*-methyl-2-pyrrolidone (**7**) with BY leads to the amino alcohol **8** and amine **9** in a 2:1 ratio with a total yield of 14% and traces of mono hydroxylation of **7**.

With regard to these reductions with Baker's yeast, we considered the possibility that oxidation was accompanying the reduction, since such concomitant oxidation, during BY reductions, has been reported in the literature

Scheme



Table

Product Profiles for Reduction of **1** and **2** with BY (%)

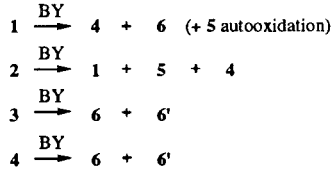
Substrate	4 hours					5 days				
	Total indolic material recovered %	[a]	+2H [b]	+4H [b]	+6H [b]	Total indolic material recovered %	[a]	+2H [b]	+4H [b]	+6H [b]
2	4	65 **2**	33 **5**	1 **4**	0.5 **6**	11	25 **2**	10 **5**	57 **4**	8 **6**
1	6.5	92 **1**	7 **4**	1 **6**	—	15	90 **1**	9 **4**	0.5 **6**	—

[a] Substrate recovered. [b] +2H, +4H, +6H means single, double or triple reduction of the substrate.

[1,8]. As it was observed several times for biological or biochemical oxidation, the BY is a complex system which can give both reduction and oxidation reactions [7].

The autooxidation level under these conditions, especially for air-sensitive indolic bases, were evaluated and, consequently, the yield of **5** in this reaction was lower than expected. In order to clarify this point, the anaerobic (under a nitrogen atmosphere) reaction of **1** and **2** with BY was carried out (for 4 hours and for 5 days) leading to the conclusion that the reduction of both compounds is accompanied by oxidation, which accounted for up to

Reaction Summary

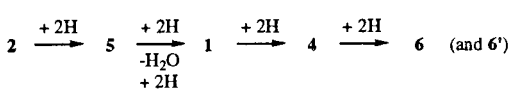


12% of **5**, due to the autooxidation under BY condition.

The reduction of **1** and **2** with K-Selectride and DIBAL-H leads to generally inaccessible model compounds whose structures were established by gc-ms. The reduction of **2** with DIBAL-H produced the amino alcohol **5** as well as the carboline **1** (ratio 1:9, total yield of 2.5%) but K-Selectride reduction performed on the same compound leads to an equimolar mixture of **5** and **1**, but with the yield not exceeding 0.7%. Both of these control reductions on **1** showed only traces of **4**.

The reaction of indolic base with BY provides for the synthesis several interesting alkaloid derivatives and metabolites. Despite the generally low yield of these reactions, these intermediates can be very difficult to synthesize by conventional routes. The BY reduction of more complex indolic alkaloid ajmaline and yohimbine produces at most 0.2 and 2% of the corresponding dihydro derivatives, respectively.

Reaction Sequence



EXPERIMENTAL

Mass spectrometric analysis were carried out on Riber 30-10 Nermag spectrometer, electron impact, positive ions, 70 eV, using GC Delsi DC 700 and the CPSIL 50 m column, ID 0.3 μ.

General Procedure for Baker's Yeast Reduction.

A mixture of sucrose (1.5 g) and fresh baker's yeast (1 g) in water (8 ml) gave, after 1 hour at 30°, a rapid evolution of carbon dioxide. The substrate (0.5 mmol) was added, and the fermenting suspension was stirred for another 24 hours at room temperature. A warm (40°) solution of 1 g of sucrose in 3 ml of water was then added. Stirring was continued for 5 days at room temperature. The mixture was worked up by first adding 1 g of Celite and then filtering. The filtrate was extracted with chloroform (multiple extraction). The extract was dried over magnesium sulphate, filtered, and concentrated. The residue was submitted to analysis by gc-ms using available model compounds [9].

Reduction using the Zinc/Acetic Acid System.

Compound **1** (200 mg) and Zn powder (3 g) were refluxed in acetic acid (glacial 25 ml) for 5 days under argon. The mixture was then filtered and evaporated and the residue partitioned between aqueous acetic acid and chloroform. The dried chloroform extract was evaporated to give the amide **3**, crystallized from methanol, mp 212-216°.

Reduction using the Trifluoroacetic Acid/Sodium Borohydride System.

A solution of **1** (226 mg) in trifluoroacetic acid (44 ml) was stirred and cooled with an ice-bath. To this was added sodium borohydride powder (354 mg) in small portions under argon atmosphere. The mixture was stirred for 4 hours at room temperature. The mixture was worked up by first adding ice and then neutralized with concentrated ammonium hydroxide, then extracted with methylene chloride. The extract was washed with

brine, dried over magnesium sulphate, filtered, and concentrated to give a yellow oil which was identified as **4**.

Reduction using DIBAL-H or K-Selectride.

The reductions were modeled on Baran [10] and Fortunato [11] experimental procedures.

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* Author to whom correspondence should be addressed.

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