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MINI-REVIEW

Transformation of saturated nitrogen-containing heterocyclic compounds by microorganisms

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Abstract The saturated nitrogen-containing heterocyclic compounds include many drugs and compounds that may be used as synthons for the synthesis of other pharmacologically active substances. The need for new derivatives of saturated nitrogen-containing heterocycles for organic synthesis, biotechnology and the pharmaceutical industry, including optically active derivatives, has increased interest in microbial synthesis. This review provides an overview of microbial technologies that can be valuable to produce new derivatives of saturated nitrogen-containing heterocycles, including hydroxylated derivatives. The chemo-, regio- and enantioselectivity of microbial processes can be indispensable for the synthesis of new compounds. Microbial processes carried out with fungi, including *Beauveria bassiana*, *Cunninghamella verticillata*, *Penicillium simplicissimum*, *Aspergillus niger* and *Saccharomyces cerevisiae*, and bacteria, including *Pseudomonas* sp., *Sphingomonas* sp. and *Rhodococcus erythropolis*, biotransform many substrates efficiently. Among the biological activities of saturated nitrogen-containing heterocyclic compounds are antimicrobial, antitumor, antihypertensive and anti-HIV activities; some derivatives are effective for the treatment and prevention of malaria and trypanosomiasis, and others are potent glycosidase inhibitors.

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Keywords Microbial transformation · Nitrogen heterocycles · Pharmacology · Synthesis

Introduction

The microbial bioconversion of organic compounds has applications in several fields. Chemical, pharmaceutical and biotechnology industries draw on microbiological methods for the synthesis of compounds that are difficult to obtain by the methods of organic chemistry alone (Parshikov et al. 2012a, b; Petersen and Kiener 1999). Saturated nitrogen-containing heterocyclic rings serve as key moieties of many drugs. In the last 15 years, several reviews of the microbial transformation of nitrogen-containing heterocyclic compounds, such as azaarenes and quinolones, have been published (Hüttel and Hoffmeister 2010; Parshikov et al. 2012a, b; Petersen and Kiener 1999; Sukul and Spiteller 2007; Vickers and Polsky 2000).

In this review, data from the literature on saturated nitrogen-containing heterocyclic compounds have been compiled. For example, mitomycin C shows antibiotic and antitumor activities that have been related to the aziridine ring (Fürmeier and Metzger 2003), and aziridine derivatives are used in the synthesis of antimalarial drugs (D'hooghe et al. 2011). Azetidines include many molecules with biological activities (Ghorai et al. 2007). Alkaloids isolated from the ascidian *Clavelina lepadiformis* include lepadins D, E and F, which contain a piperidine ring and have antimalarial activity (Fattorusso and Taglialatela-Scafati 2009; Wright et al. 2002). Pyrrolidines and piperidines are used as substrates for the synthesis of artemisinin-based semi-synthetic antimalarial drugs (Pacorel et al. 2010). Derivatives of 3-azabicyclo[3.2.2]nonane are

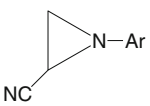
effective for the treatment and prevention of malaria and trypanosomiasis (Seebacher and Weis 2011). A derivative of azocane, guanethidine, is an antihypertensive agent in humans (Richardson and Wyso 1960).

Given the biological activity of these compounds, their use as intermediates, the lack of synthetic options and the desire to find new derivatives, the investigation of biological routes to heterocyclic nitrogen-based compounds has been undertaken by a large number of researchers (Faber 2004; Baker 1987; Duran et al. 2000; Parshikov et al. 2012c). The data in this review are presented to provide an overview of microbial technologies that can be valuable to produce new derivatives of saturated nitrogen-containing heterocycles.

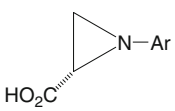
Microbial transformation of aziridine and azetidine derivatives

Aziridine groups are three-membered ring structural elements, found in a wide variety of natural products that have antibiotic and antitumor properties (Thibodeaux et al. 2012). The aziridines have been targets of investigation for synthetic chemists, both as useful intermediates and as final products (Chawla et al. 2013). Compounds having a 5-(aziridin-1-yl)-2,4-dinitrobenzyl structure were shown to have significant growth-inhibitory properties against *Trypanosoma brucei* and *Trypanosoma cruzi* (Bot et al. 2010). Clean reactions of the aziridine compounds that have exceptionally good regioselectivity and/or stereoselectivity are desirable (Chawla et al. 2013).

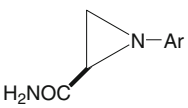
Racemic aziridine-containing carbonitriles (**I**, Ar—substituted aryl) are separated into corresponding carboxylic acids (**II**) and enantiopure isomers (**Ia**) by *Rhodococcus erythropolis* AJ270 with yields of 45–50 % (Dexian and Meixiang 2010):



I



II

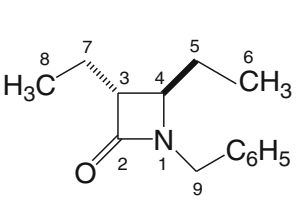


Ia

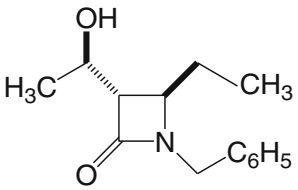
The azetidines are saturated nitrogen heterocycles containing a four-membered ring. Derivatives of azetidines have been used in traditional Asian medicine for over a thousand years (Diethelm and Carreira 2013). The skeleton of 2-azetidinone is the pharmacophore of a widely employed class of antibiotics, the β-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams and penems) (Sharma et al. 2011). The metabolism of nitrogen heterocyclics may lead to lactam formation.

Among the saturated nitrogen heterocycles, there is great interest in the transformation of monocyclic β-lactams since they often have antimicrobial activity. Furthermore, 3-azido-, 3-amino- and 3-(1,2,3-triazol-1-yl)-β-lactams have been synthesized and studied as drugs against *Plasmodium falciparum* (Singh et al. 2011). A bifunctional hybrid structure based on 7-chloroquinoline and a β-lactam recently was synthesized as a potential antimalarial agent (Singh et al. 2012).

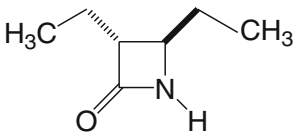
Transformation of a monocyclic β-lactam (**III**) by a growing culture of the fungus *Beauveria bassiana* ATCC 7159 produces a hydroxy derivative (**IV**) with a yield of 10 %; a second product (**V**) with a yield of 20 % is formed by elimination of the benzyl radical (Archelas et al. 1988):



III

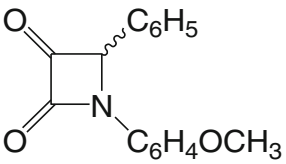


IV

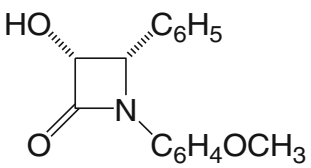


V

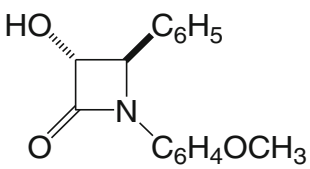
Biotransformation of an α-keto-β-lactam (**VI**) with growing cells of *Saccharomyces cerevisiae* for 5 days produces both the *cis*-hydroxy derivative (**VII**, 62 % yield) and the *trans*-hydroxy derivative (**VIII**, 38 % yield) (Mihovilovic et al. 2005)



VI

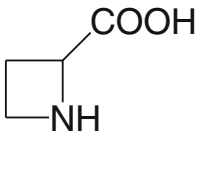


VII

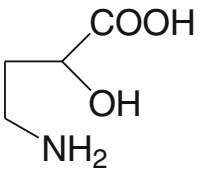


VIII

The conversion of azetidine-2-carboxylic acid (**IX**) by a hydrolase from *Pseudomonas* sp. A2C forms 2-hydroxy-4-aminobutyric acid (**X**) (Gross et al. 2008):

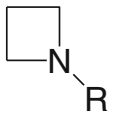


IX

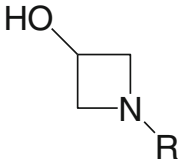


X

Hydroxylation of *N*-substituted azetidines (**XI**, R=$CO_2C_6H_5$; CO_2t-Bu) by cells of the bacterium *Sphingomonas* sp. HXN-200 leads to the formation of hydroxy derivatives (**XII**, R=$CO_2C_6H_5$; CO_2t-Bu) in position 3 of the heterocyclic ring with yields of 91–98 % (Chang et al. 2002):

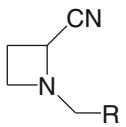


XI

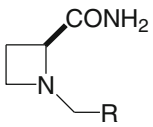


XII

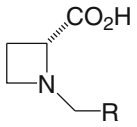
Later, it was shown that the resolution of racemic 1-benzylazetidine-2-carbonitriles (**XIII**, R=C_6H_5; 4-Me-C_6H_4; 4-MeO-C_6H_4; 4-Br-C_6H_4; 3-Br-C_6H_4; 2-Br-C_6H_4) in phosphate buffer by *R. erythropolis* AJ270 produces isomers **XIV** and **XV** with yields up to 46 % (Leng et al. 2009)



XIII



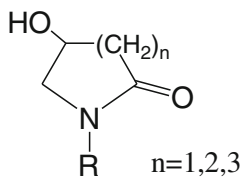
XIV



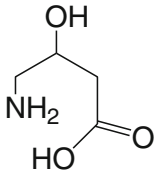
XV

Microbial transformation of pyrrolidine and its derivatives

Pyrrolidine forms a part of the molecule of an antibiotic, clindamycin, which has antimalarial properties (Bertrand and Kremsner 2002). Furthermore, pyrrolidine derivatives inhibit the growth of chloroquine-resistant strains of *P. falciparum* (Mendoza et al. 2011). There are several pharmacologically interesting compounds with the general formula (**XVI**) (Archelas et al. 1986):



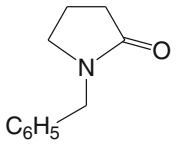
XVI



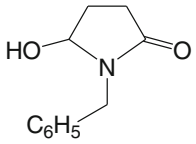
XVII

They can also be regarded as analogs of γ-amino-β-hydroxybutyric acid (**XVII**), which has great medical importance (Archelas et al. 1986).

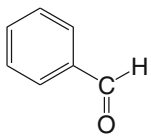
N-Substituted pyrrolidines and their analogs may be hydroxylated by growing cultures of *B. bassiana* ATCC 7159. As a result of the transformation of 1-benzylpyrrolidone-2 (**XVIII**), optically active 1-benzyl-5-hydroxypyrrolidone-2 (**XIX**, 12 % yield) and benzaldehyde (**XX**, 2 % yield) are formed (Srairi and Maurey 1987):



XVIII

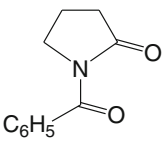


XIX

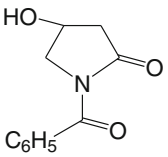


XX

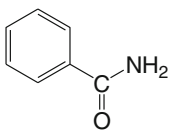
During the transformation of 1-benzoylpyrrolidone-2 (**XXI**), the optically active 1-benzoyl-4-hydroxypyrrolidone-2 (**XXII**, 21 % yield) has been detected in a mixture with benzamide (**XXIII**) (Srairi and Maurey 1987):



XXI

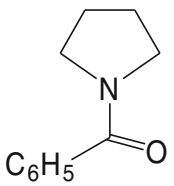


XXII

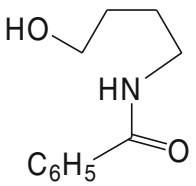


XXIII

In the transformation of 1-benzoylpyrrolidine (**XXIV**) by *B. bassiana*, however, a carbon atom at position 2 is hydroxylated with ring opening and formation of *N*-(4-hydroxybutyl)benzamide (**XXV**, 8 % yield) (Archelas et al. 1986):

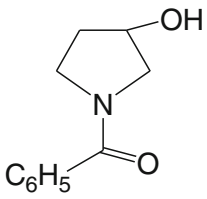


XXIV



XXV

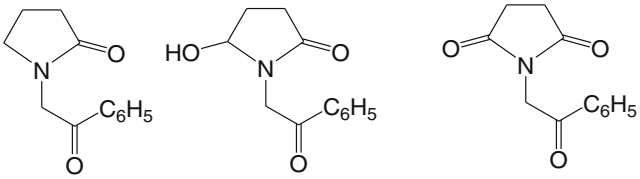
During the transformation of 1-benzoylpyrrolidine (**XXIV**) or 1-benzoylpyrrolidone-2 (**XXI**) in growing cultures of the fungus *Cunninghamella verticillata* VKPM F-430, the optically active (−)-1-benzoyl-3-hydroxypyrrolidine (**XXVI**, 38 % yield) or benzamide (**XXIII**), respectively, is produced (Parshikov et al. 1992):



XXVI

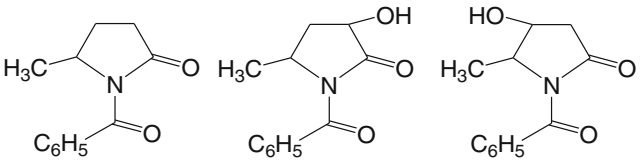
3-Hydroxy derivatives in yields of 66.4–93.5 % also are formed in the transformation of *N*-substituted pyrrolidines by cells of the bacterium *Sphingomonas* sp. HXN-200; the substituent on the nitrogen atom may be $CH_2C_6H_5$, COC_6H_5, $CO_2CH_2C_6H_5$, $CO_2C_6H_5$ or CO_2t-Bu (Li et al. 2001).

During hydroxylation of 1-phenacylpyrrolidone-2 (**XXVII**) by *B. bassiana* ATCC 7159, an intermediate compound, 1-phenacyl-5-hydroxypyrrolidone-2 (**XXVIII**), and the final product, 1-phenacylpyrrolidinedione (**XXIX**), are formed with a yield of 23 % (Srairi and Maurey 1987):



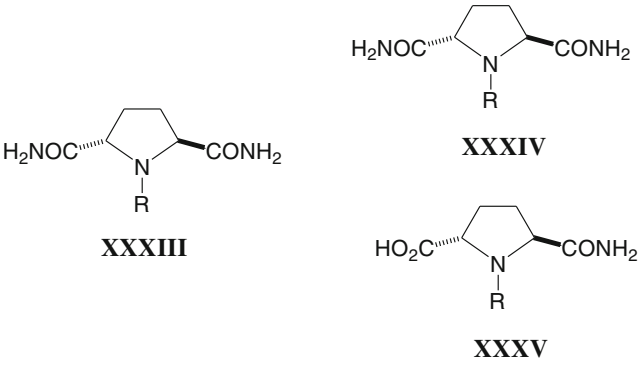
XXVII **XXVIII** **XXIX**

Further study of the biotransformation of substituted pyrrolidones in growing cultures shows that *B. bassiana* ATCC 7159 hydroxylates 5-methyl-1-benzoylpyrrolidone-2 (**XXX**) in either position 3 (**XXXI**, 11 % yield) or position 4 (**XXXII**, 12 % yield) of the hetero ring, in a process accompanied by the formation of benzamide (**XXIII**) (Srairi and Maurey 1987):



XXX **XXXI** **XXXII**

Separation of racemic *trans*-pyrrolidine-2,5-dicarboxamides (**XXXIII**, R=Bn; allyl; H), using the amidase of *R. erythropolis* AJ270, produces (2*S*,5*S*)-pyrrolidine-2,5-dicarboxamides (**XXXIV**) and (2*R*,5*R*)-5-carbamoylpyrrolidine-2-carboxylic acids (**XXXV**) in high yields (up to 52 %) with excellent enantioselectivity (Chen et al. 2012):

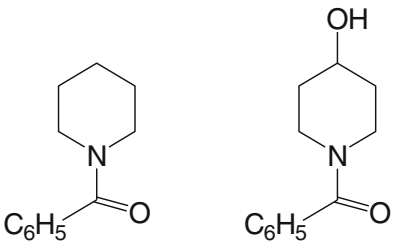


XXXIII **XXXIV** **XXXV**

Microbial transformation of piperidine and its derivatives

Some substituted piperidine rings are found in natural and synthetic compounds that have biological activity (Sun et al. 2000). Over the past 20 years, thousands of piperidine derivatives have been tested in pre-clinical and clinical studies (Weintraub et al. 2003), and some piperidine derivatives, such as febrifugine, are antimalarial drugs (Taniguchi and Ogasawara 2000).

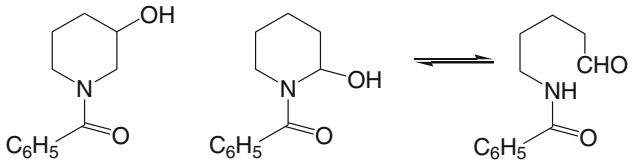
In recent decades, the microbial chemistry of piperidines has flourished. Studies of the transformation of 1-benzoylpiperidine (**XXXVI**) by various research groups under different experimental conditions have resulted in the isolation of 1-benzoyl-4-hydroxypiperidine (**XXXVII**) with a yield of 18 % after transformation with *B. bassiana* ATCC 7159 (Johnson et al. 1968a), 7 % after transformation with *B. bassiana* ATCC 7159 (Archelas et al. 1986), 80 % after transformation with *Aspergillus niger* VKM F-1119 (Parshikov et al. 1992) and 91–98 % after transformation with *Sphingomonas* sp. HXN-200 (Chang et al. 2002):



XXXVI **XXXVII**

After the transformation of 1-benzoylpiperidine (**XXXVI**) by growing cultures of *B. bassiana* VKM F-3111D and *Penicillium simplicissimum* KM-16, 1-benzoyl-4-hydroxypiperidine (**XXXVII**) was isolated with yields of 60 and 3 %, respectively, and the optically active (+)-3-hydroxy-1-benzoylpiperidine (**XXXVIII**) with yields of 1 and 3 %, respectively (Parshikov et al. 1992). Furthermore, among the biotransformation products of 1-benzoylpiperidine (**XXXVI**)

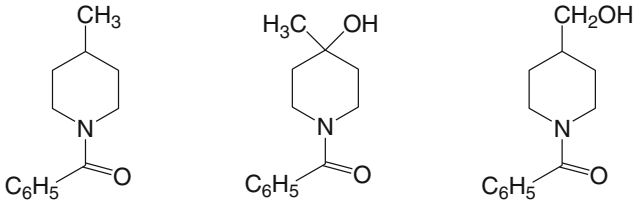
produced by *P. simplicissimum* KM-16, 2-hydroxy-1-benzoylpiperidine (**XXXIX**) was detected with a yield of 12 % (Parshikov et al. 1992):



XXXVIII **XXXIX**

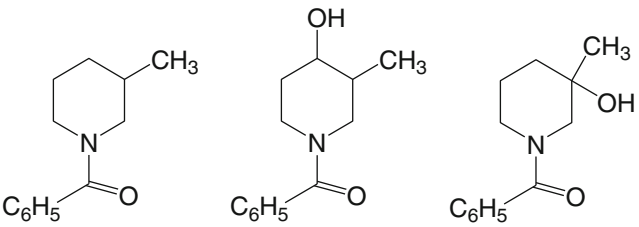
Transformation of 1-(4-acetylphenyl)piperidine by *B. bassiana* ATCC 7159 was similarly accompanied by the formation of 4-hydroxy-1-(4-acetylphenyl)piperidine with a yield of 20 % (Johnson et al. 1992). Later, this result was confirmed by others (Osorio-Lozada et al. 2008).

With the introduction of a methyl substituent on the heterocyclic ring, the transformation process is different. In the transformation of 1-benzoyl-4-methylpiperidine (**XL**) in growing cultures of *B. bassiana* ATCC 7159, a 4-hydroxy compound (**XLI**, 13 % yield) is obtained with 1-benzoyl-4-hydroxymethylpiperidine (**XLII**, yield 23 %) (Johnson et al. 1969):



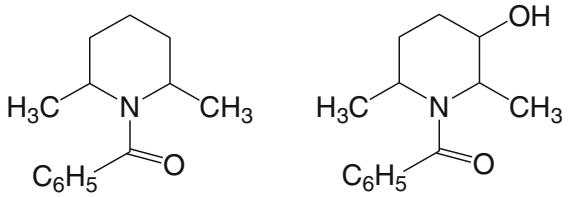
XL **XLI** **XLII**

At the same time, 1-benzoyl-3-methylpiperidine (**XLIII**) is hydroxylated in position 4 (**XLIV**, yield 6 %) and position 3 (**XLV**, 7 % yield) of the heterocyclic ring (Johnson et al. 1969):



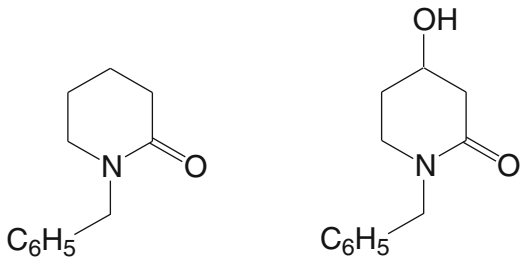
XLIII **XLIV** **XLV**

For a compound with two methyl substituents on the heterocyclic ring, 1-benzoyl-2,5-dimethylpiperidine (**XLVI**), the hydroxylation by *B. bassiana* ATCC 7159 occurs in position 3 of the ring (**XLVII**, 49 % yield) (Johnson et al. 1969):

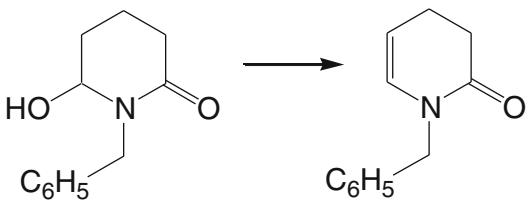


XLVI **XLVII**

The introduction of a ketone group to the heterocyclic ring partially changes the site of hydroxylation. During growth of *B. bassiana* ATCC 7159 in the presence of 1-benzylpiperidone (**XLVIII**), in addition to 1-benzyl-4-hydroxypiperidone-2 (**XLIX**, 10 % yield), the unstable 1-benzyl-6-hydroxypiperidone-2 (**L**, 5 % yield) was detected but then was spontaneously converted to its dehydration product (1-benzyl-2-oxo-1,2,3,4-tetrahydropyridine) (**LI**) (Archelas et al. 1986):

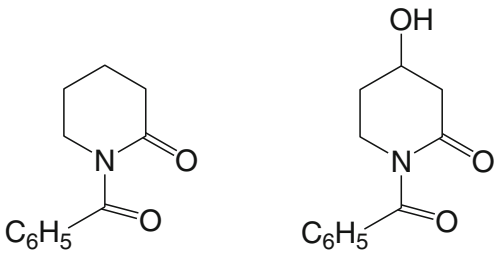


XLVIII **XLIX**



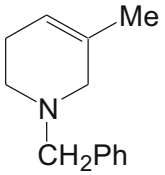
L **LI**

During 1-benzoylpiperidone-2 (**LII**) hydroxylation in growing cultures of *B. bassiana* ATCC 7159, along with benzamide (**XXIII**), the optically active 1-benzoyl-4-hydroxypiperidone-2 (**LIII**) was isolated with a yield of 27 % (Archelas et al. 1986):

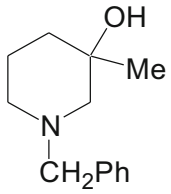


LII **LIII**

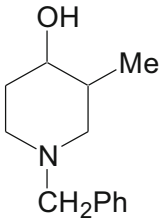
During the transformation of 1-benzyl-3-methyl-Δ^3-piperidine (**LIV**) by growing mycelia of *C. verticillata* VKPM F-430, three products were observed in a ratio of **LV**/**LVI**/**LVII** = 1:2:16 (Terent'ev et al. 1997):



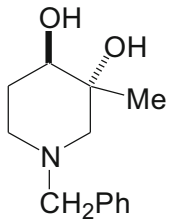
LIV



LV

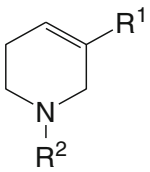


LVI

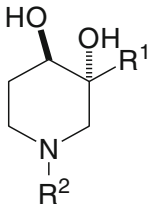


LVII

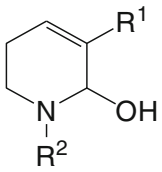
Other analogs of 1-benzyl-3-methyl-Δ^3-piperidine (**LIV**), 1,2,5,6-tetrahydropyridines (**LVIII a** = R^1 = Bn; R^2 = H; **b** = R^1 = Bn, R^2 = H; **c** = R^1 = Pr, R^2 = Me), were also converted by *C. verticillata* VKPM F-430 with formation of the isomers **LIX a** (97.6 % yield), **LIX b** (100 % yield), **LIX c** (19.0 % yield) and **LX c** (59.0 % yield) (Terent'ev et al. 2003):



LVIII a, b, c

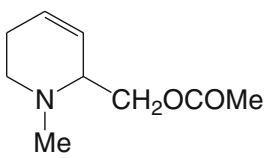


LIX a, b, c

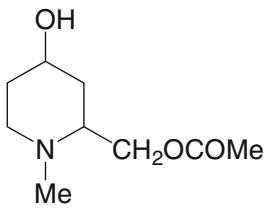


LX c

Also, in growing cultures of *C. verticillata* VKPM F-430, 2-acetoxymethyl-l-methyl-l,2,5,6-tetrahydropyridine (**LXI**) was transformed into a 4-hydroxy derivative (**LXII**) with a low yield (Modyanova et al. 1999):



LXI

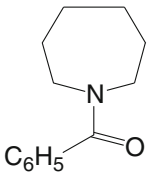


LXII

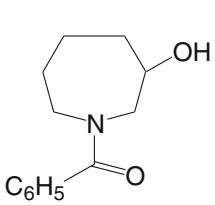
Microbial transformation of azepane, azocane and their derivatives

Over the past 50 years, transformations of azepane (hexamethyleneimine) derivatives have been studied by several groups of researchers (Seebacher and Weis 2011).

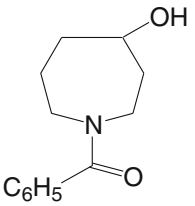
During the transformation of 1-benzoylhexamethyleneimine (**LXIII**) by growing cultures of *B. bassiana* ATCC 7159, two optically active 3- and 4-hydroxy derivatives (**LXIV**, 3 % yield; **LXV**, 11 % yield) and a ketone (**LXVI**, 10 % yield), with a carbonyl group at position 3 of the heterocyclic ring, are obtained (Archelas et al. 1986):



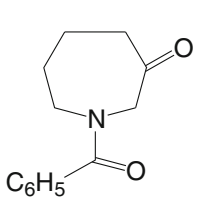
LXIII



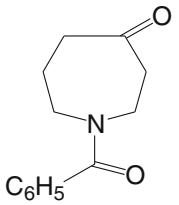
LXIV



LXV



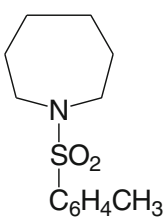
LXVI



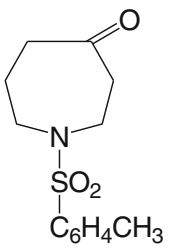
LXVII

Other authors (Johnson et al. 1968a) reported that *B. bassiana* ATCC 7159 oxidizes 1-benzoylhexamethyleneimine (**LXIII**) to a mixture of 3- and 4-oxo-1-benzoylhexamethyleneimines (**LXVI** and **LXVII**) and the 4-hydroxy derivative (**LXV**).

Transformation of 1-(4-tolylsulfonyl)-hexamethyleneimine (**LXVIII**) by *B. bassiana* ATCC 7159 was accompanied by formation of only the 4-oxo derivative (**LXIX**) (Johnson et al. 1968a):



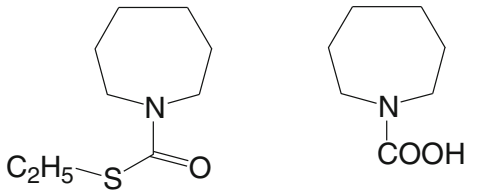
LXVIII



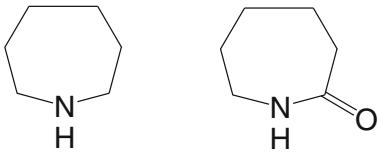
LXIX

The bacterium *Gulosibacter molinativorax* ON4 oxidizes molinate (**LXX**) in several stages: azepane-1-carboxylic acid (**LXXI**), hexamethyleneimine (**LXXII**), and caprolactam

(**LXXIII**), followed by the opening of the hetero ring (Barreiros et al. 2008):

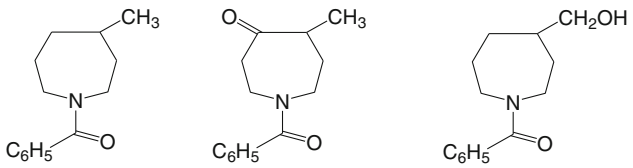


LXX **LXXI**



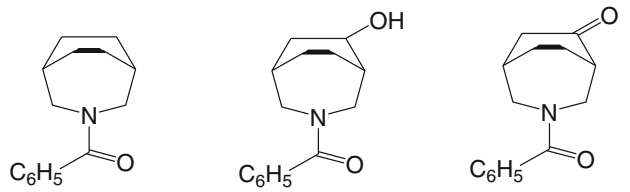
LXXII **LXXIII**

Transformation of 4-methyl-1-benzoylhexamethyleneimine (**LXXIV**) in growing cultures of *B. bassiana* ATCC 7159 produces an oxo derivative (**LXXV**, 11 % yield) and a second product of oxidation (**LXXVI**, 29 % yield) that has a hydroxymethyl group (Johnson et al. 1968a):



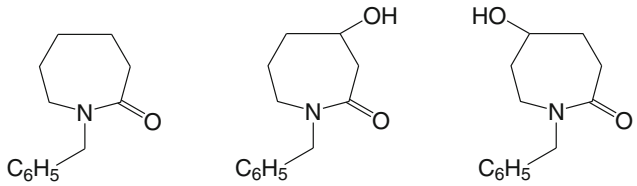
LXXIV **LXXV** **LXXVI**

Increasing the complexity of the molecular structure of hexamethyleneimine may still lead to similar results. For example, transformation of 3-benzoyl-3-azabicyclo[3.2.2]nonane (**LXXVII**) by *B. bassiana* ATCC 7159 also produces hydroxy and oxo derivatives (**LXXVIII**, 50 % yield and **LXXIX**, 22 % yield) (Johnson et al. 1968b):



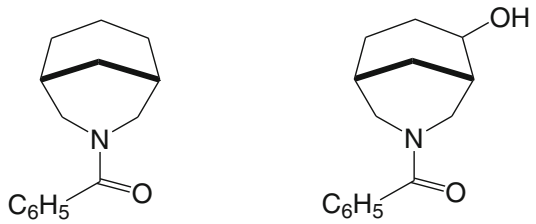
LXXVII **LXXVIII** **LXXIX**

1-Benzylcaprolactam (**LXXX**) hydroxylation in cultures of *B. bassiana* ATCC 7159 produces two optically active isomeric hydroxy derivatives (**LXXXI** and **LXXXII**) (Archelas et al. 1986):



LXXX **LXXXI** **LXXXII**

Despite the fact that azocanes (and their derivatives) include drugs with antiviral and antimalarial properties (Hocart et al. 2011), such as reactivators of phosphorylated cholinesterases (Radic et al. 2012), their microbiological transformations have rarely been investigated. During the transformation of 3-benzoyl-3-azabicyclo[3.2.2]nonane (**LXXXIII**) in growing cultures of *B. bassiana* ATCC 7159, only one product (**LXXXIV**, 60–70 % yield) is detected (Johnson et al. 1968b):



LXXXIII **LXXXIV**

Conclusion

Organic chemists and pharmacologists have a great interest in the stereochemistry and regiochemistry of synthetic processes (Hassner 2009), such as the molecular stereochemistry of aziridines (Keifer et al. 1988) and the hydroxylation of azetidine, pyrrolidine and their derivatives (Romanova et al. 1995; Feula al. 2010).

Some mono- and bi-cyclic polyhydroxylated alkaloids are known as potent glycosidase inhibitors; for instance, castanospermine and deoxynorjirimycin are promising anticancer and anti-HIV compounds, respectively. Some stereoisomers of 2-(hydroxymethyl)pyrrolidine-3,4-diols also have been reported as glycosidase inhibitors (Ahn and Shin 1997). The 3-hydroxypyrrolidine moiety is found in a range of naturally occurring bioactive alkaloids, and many synthetic approaches to produce 3-hydroxypyrrolidines also have been developed (Aurrecoechea et al. 2009; Hodgson et al. 2006; Rios et al. 2007).

Many hydroxylated piperidine alkaloids are potent inhibitors of glycosidases and related enzymes (Grishina et al.

2011). 4-Hydroxypiperidines are present in many drugs, such as the antidiarrhoeal loperamide and the schizophrenia medications haloperidol and benztropine (McKay et al. 2010). Polyhydroxypiperidines and polyhydroxyazepanes have attracted attention of researchers due to their biological importance in the development of glycosidase inhibitors (Shih et al. 2007; Shih et al. 2011).

Azocanes used in the asymmetric synthesis of α-alkylated α-amino acids also demonstrate potential biological activities as potent inhibitors of some enzymes (Georg and Guan 1992).

Microbial technologies for hydroxylation in different positions of molecules may help in creating a series of new drugs; for instance, hydroxylated derivatives of saturated nitrogen-containing heterocycles may be obtained using microbial technologies and used to create hybrid molecules of artemisinin, quinine or chloroquine (Walsh et al. 2007).

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