Formation of 3-hydroxy-4,5-dimethyl-2(5H)-furanone (sotolon) from 4-hydroxy-L-isoleucine

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ABSTRACT

The formation of 3-hydroxy-4,5-dimethyl-2(5H)-furanone (sotolon) from 4-hydroxy-L-isoleucine (HIL) by thermally induced oxidative deamination was corroborated. Different carbonyls were reacted with HIL in a phosphate buffered model system to form sotolon. In general, α-ketoaldehydes were found to be more efficient than α-diketones. Methylglyoxal gave rise to 74 µg sotolon per mg HIL (8.6 mol%) compared to less than 1 µg/mg HIL (< 0.1 mol%) when reacted with 2,3-butanedione. The yields were significantly increased when using the lactone of HIL as precursor, i.e. 38.5 mol% and 0.3 mol%, respectively.

INTRODUCTION

3-Hydroxy-4,5-dimethyl-2(5H)-furanone (sotolon) is a powerful flavour compound (review in [1]) recently reported in coffee [2], lovage [3], condiments [4], and flor-sherry wines [5]. Sotolon was first reported in fenugreek (*Trigonella foenum-graecum* L.) by Rijkens & Boelens [6]. The structural similarity between sotolon and 4-hydroxyisoleucine (HIL), the most abundant free amino acid in fenugreek [7], was pointed out [8]. The authors suggested this unusual amino acid as a precursor of sotolon since the stereochemistry of sotolon (4S) [9] is in good agreement with that of HIL (2S,3R,4S) isolated from fenugreek [10]. As shown in the scheme, Blank et al. [4] have recently proposed a route for the formation of sotolon via oxidative deamination of HIL. The aim of this study was to verify this hypothesis.
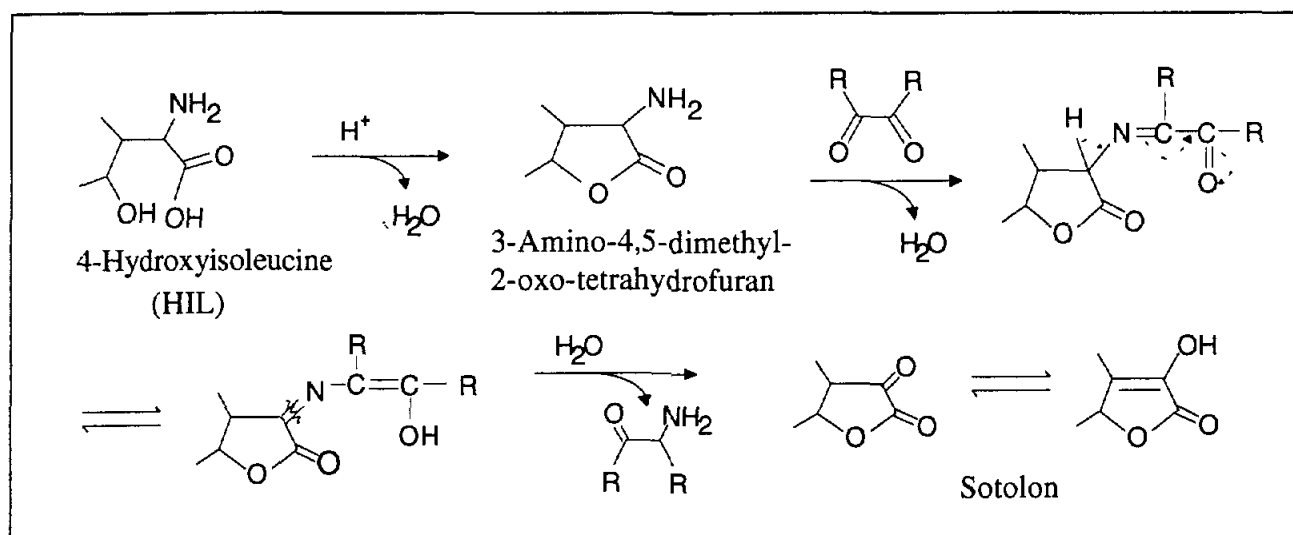
RESULTS AND DISCUSSION

The hypothesis of the formation of sotolon from HIL was checked by reacting HIL or its lactone, synthesised according to [10], with different dicarbonyls in a phosphate buffered model system (0.1 mol/L, pH 5.0) at 100°C for 1h. Sotolon was quantified by stable isotope dilution mass spectrometry using ^{13}C-labelled sotolon as internal standard [4].

Formation of sotolon from 4-hydroxy-L-isoleucine (HIL) using α-dicarbonyls

Both 2,3-butanedione and 2,3-pentanedione formed low amounts of sotolon (tabl. 1). Higher amounts of sotolon were obtained with methylglyoxal (74 μg) and phenylglyoxal (16 μg) revealing 30-150 times more sotolon compared to the α-diketones. The data show that α-dicarbonyls are capable of generating sotolon from HIL and that α-ketoaldehydes are more efficient. The reactivity of the dicarbonyl is an important parameter, particularly for the formation of the Schiff base (scheme).

Table 1. Formation of sotolon from 4-hydroxyisoleucine (HIL) using α-dicarbonyls [1]

α-Dicarbonyl	Molar ratio HIL/Carbonyl	Sotolon [μg/mg HIL]	Yield [mol%]
2,3-Butanedione	1:12.5	0.7	< 0.1
2,3-Pentanedione	1:12.5	0.5	< 0.1
Methylglyoxal [2]	1:12.5	73.7	8.6
Phenylglyoxal	1:12.5	15.7	1.9

[1] Control experiment (without α-dicarbonyl) yielded 0.04 mg sotolon/mg HIL (< 0.01 mol%)
[2] Control experiment (reaction without HIL) yielded 0.07 mg sotolon

Formation of sotolon from 3-amino-4,5-dimethyl-2-oxotetrahydrofuran

The role of the lactonisation step was studied by reacting α-dicarbonyls with the lactone of HIL. Significantly higher amounts of sotolon were generated from the lactone compared to the amino acid (tabl. 2). Using methylglyoxal, the yields were increased by a factor of 4 to about 300 μg which corresponds to 38.5 mol% yield. The intermediate 3-amino-4,5-dimethyl-2-oxotetrahydrofuran was found to be a better precursor than the amino acid. Lactonisation is apparently one of the rate limiting steps of the reaction (scheme).

Table 2. Formation of sotolon from the lactone of HIL [1]

α-Dicarbonyl	Molar ratio Lactone/Carbonyl	Sotolon [μg/mg HIL lactone]	Yield [mol%]
Methylglyoxal	1:12.5	298.0	38.5
2,3-Butanedione	1:11	2.1	0.3

[1] Control experiment (reaction without carbonyl) yielded 0.03 mol% sotolon

Effect of the α-dicarbonyl concentration on the formation of sotolon from HIL

The efficiency of transforming HIL into sotolon can be enhanced by using higher amounts of the α-dicarbonyl (tabl. 3). Increasing the concentration of methylglyoxal six-fold doubled the amount of sotolon produced. The results with glyoxal, which is another reactive carbonyl forming sotolon from HIL, also indicate that the concentration of sotolon does not increase linearly with the amount of α-dicarbonyl.

Table 3. Formation of sotolon from HIL as affected by the concentration of α-dicarbonyl

α-Dicarbonyl	Molar ratio HIL/Carbonyl	Sotolon [µg/mg HIL]	Yield [mol%]
Methylglyoxal	1:10	64.2	7.4
Methylglyoxal	1:1.6	33.7	3.8
Glyoxal	1:12.5	44.9	5.2
Glyoxal	1:4.3	28.8	3.3

Formation of sotolon from HIL using other carbonyls containing an α-function

As shown (tabl. 4), the α-dicarbonyl function is not essential for the formation of sotolon from HIL. However, the yields were rather low when using α-keto acids or ascorbic acid. The high efficiency of dehydroascorbic acid was most likely due to its more reactive α, β-tricarbonyl structure. The yields obtained with glycerinaldehyde might be explained by the formation of methylglyoxal via phosphate catalysed β-elimination of water.

Table 4. Formation of sotolon from HIL using other α-functionalised carbonyls

Carbonyl	Molar ratio HIL/Carbonyl	Sotolon [µg/mg HIL]	Yield [mol%]
Pyruvic acid	1:12.5	1.0	0.1
2-Ketobutyric acid	1:12.5	4.0	0.5
Ascorbic acid	1:12.5	6.2	0.7
Dehydroascorbic acid	1:12.5	46.3	5.4
Glycerinaldehyde	1:12.5	14.1	1.6

ACKNOWLEDGEMENTS

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