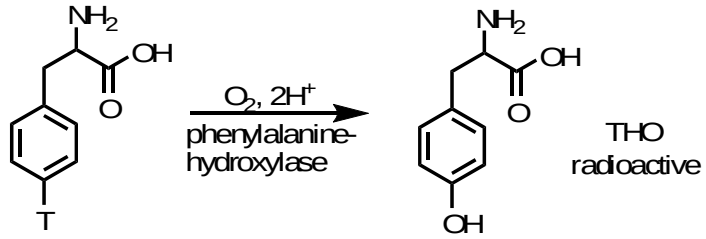
Bernhard Witkop

M. Maue

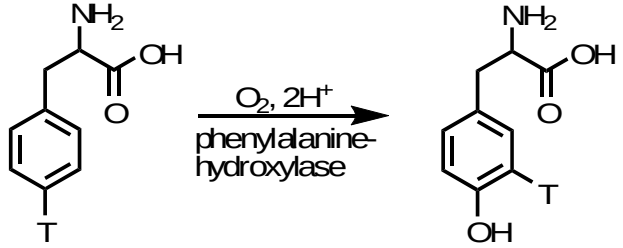
- born 1917 in Freiburg, Germany
- studied Chemistry in Munich till 1938 (diploma), 1940 (PhD)
- 1938-1946 private assistent of Prof. Wieland
- 1948-1950 lecturer at the Havard University
- US citizenship in 1953
- from 1957 Chief of the Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, Bethesda, MD
- his research interests were versatile, isolation of natural products, reaction mechanisms, synthetic organic chemistry, and biochemistry
- more than 300 publications, many of them in J. Am. Chem. Soc.

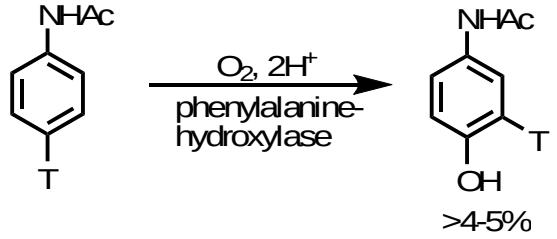
Biochemistry - NIH-Shift[1]

expected reaction



observed reactions





mechanism?

[1] G. Gruoff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, S. Udenfriend, *Science* **1967**, 157, 1524-1530.

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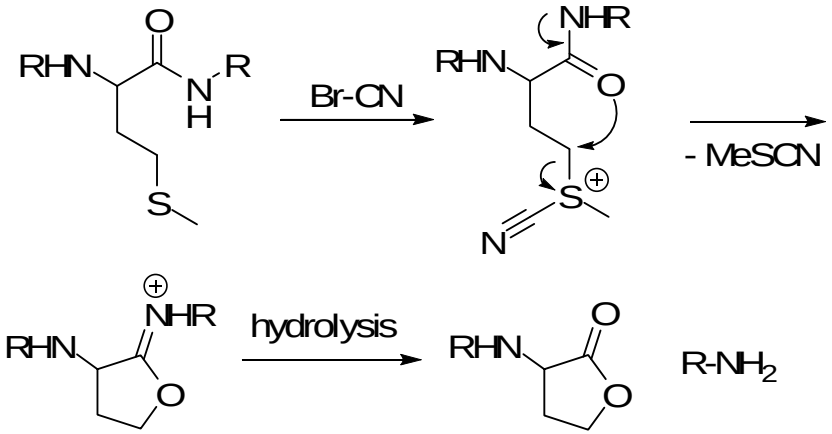
Biochemistry- protein structure[2]

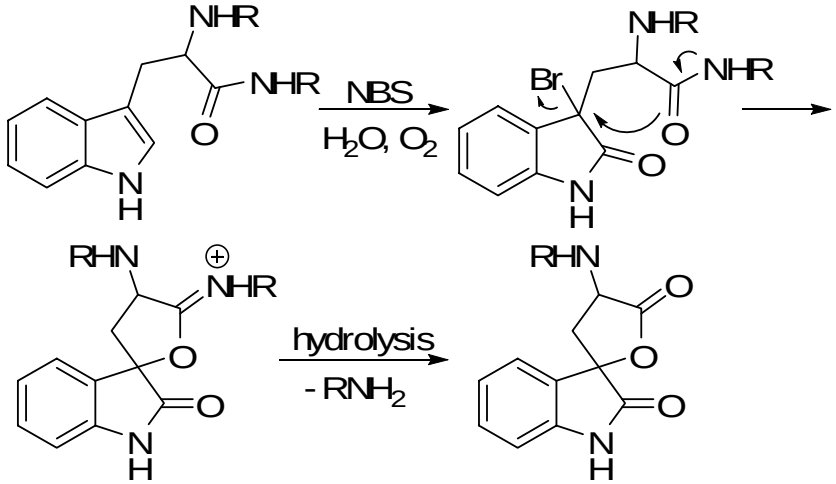
- Enzymatic and non-ezymatic pathways to cleave amide bonds selectively were important to determine the primary sequence and the reactive center of enzymes

- cyanogen bromide cleaves the amide bound next to methionine



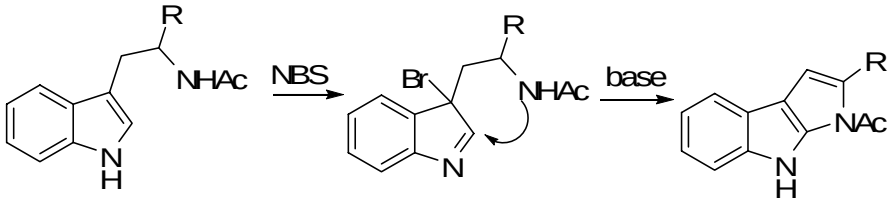
- Only a slow reaction with cysteine, no reaction with all the other amino acids

- NBS in 8.0 M urea cleaves amide bonds next to tryptophanes



- No side reactions with tyrosine or other aromatic amino acids

- interesting reaction at pH above pH 9



[2] B. Witkop, *Science* **1968**, 162, 318-326.

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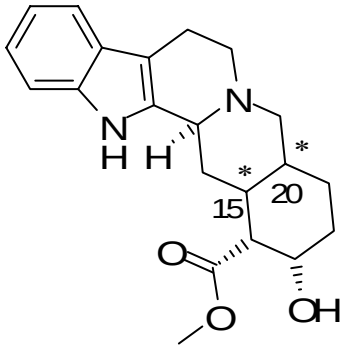
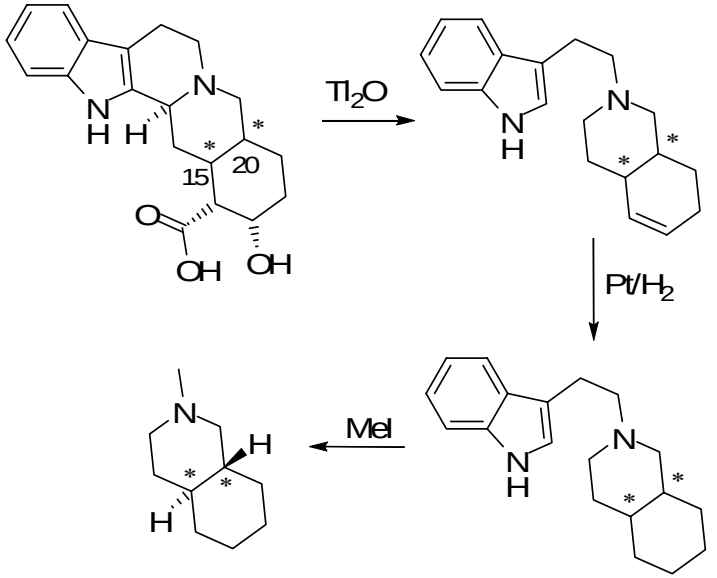
Isolation and determination of Natural Products

structure of yohimbine[3]



- The general structure was known, but not the absolute stereo-chemistry of the stereocenters at C15 and C20
- treatment of erectile dysfunction
- Increaes blood flow in extremeties
- many side affects!! (high blood pressure, anxiety….)



• by comparison of IR-data and optical activity of synthetic and the isolated decahydro-isoquinoline they could figure out the absolute stereo-chemistry of C15 and C20

[3] B. Witkop, *J. Am. Chem. Soc.* **1949**, 71, 2559-2566.

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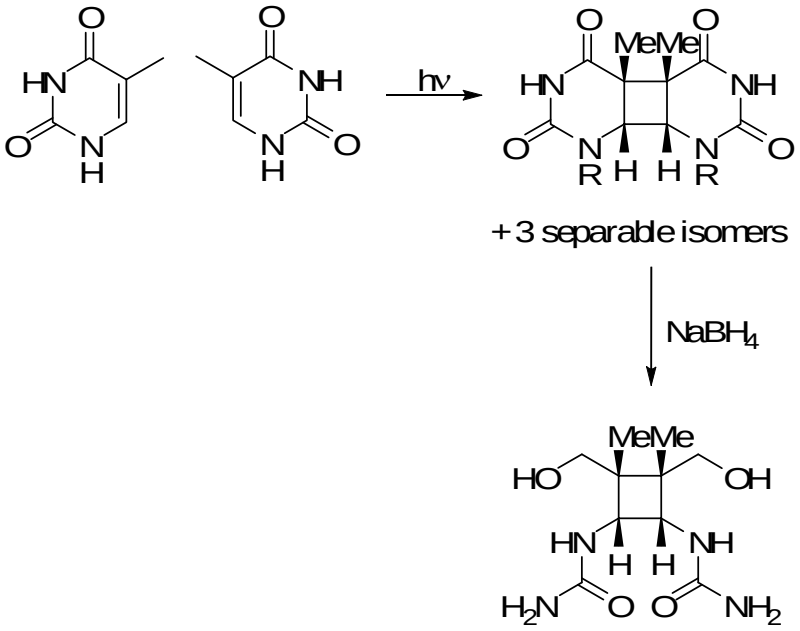
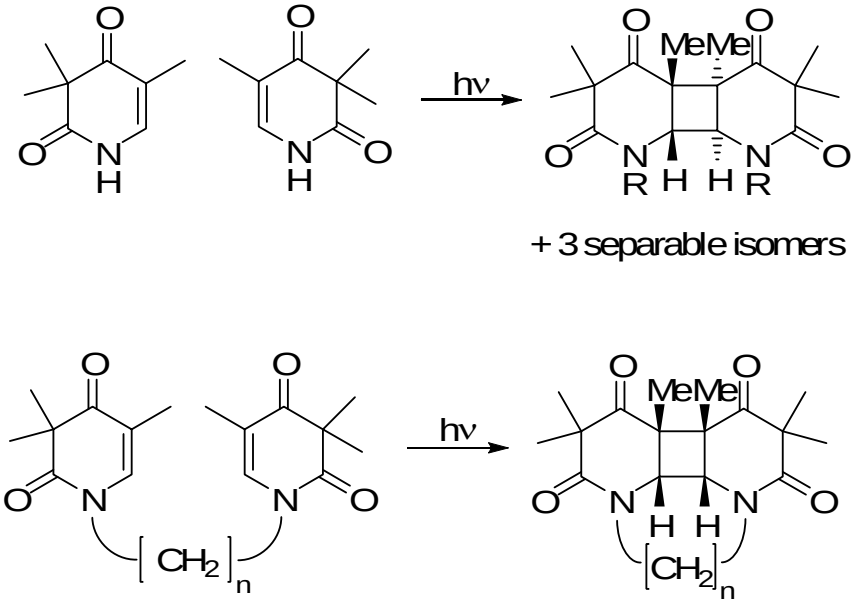
Photochemistry

Chemistry with thymine dimers[4]



easy access to highly substituted diastereomerically pure cyclobutanes

Photochemistry also with 3-deazapyrimidone[5]



[4] T. Kunieda, B. Witkop, *J. Am. Chem. Soc.* **1971**, 93, 3493-3499.

[5] B. Witkop *et al.*, *Lieb. Ann. Chem.* **1988**, 979-981.

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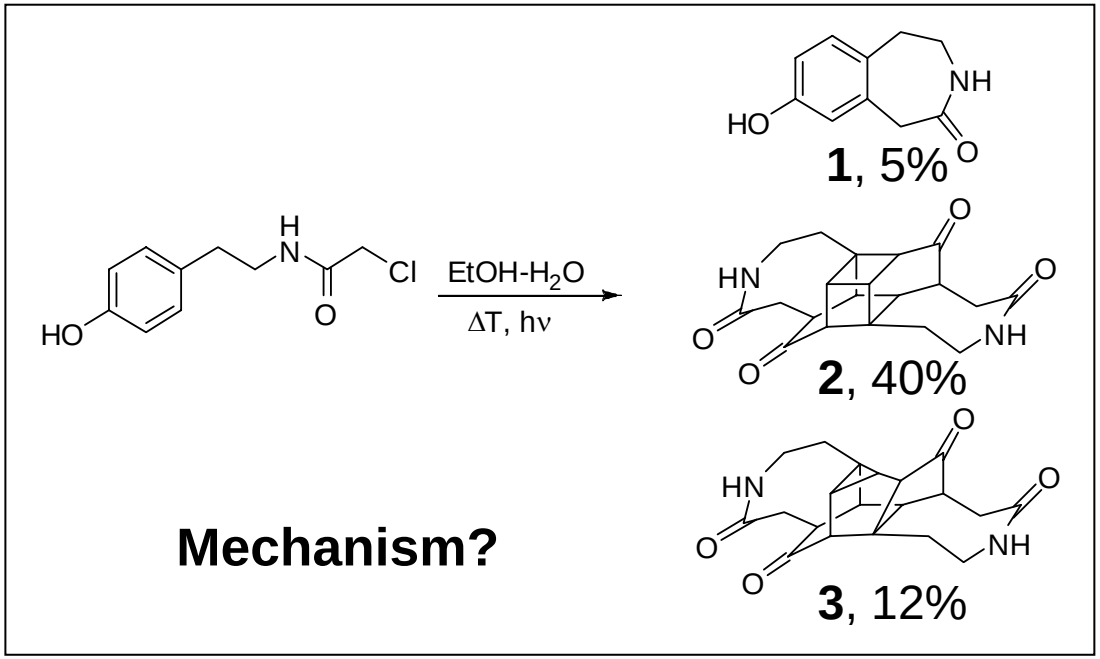
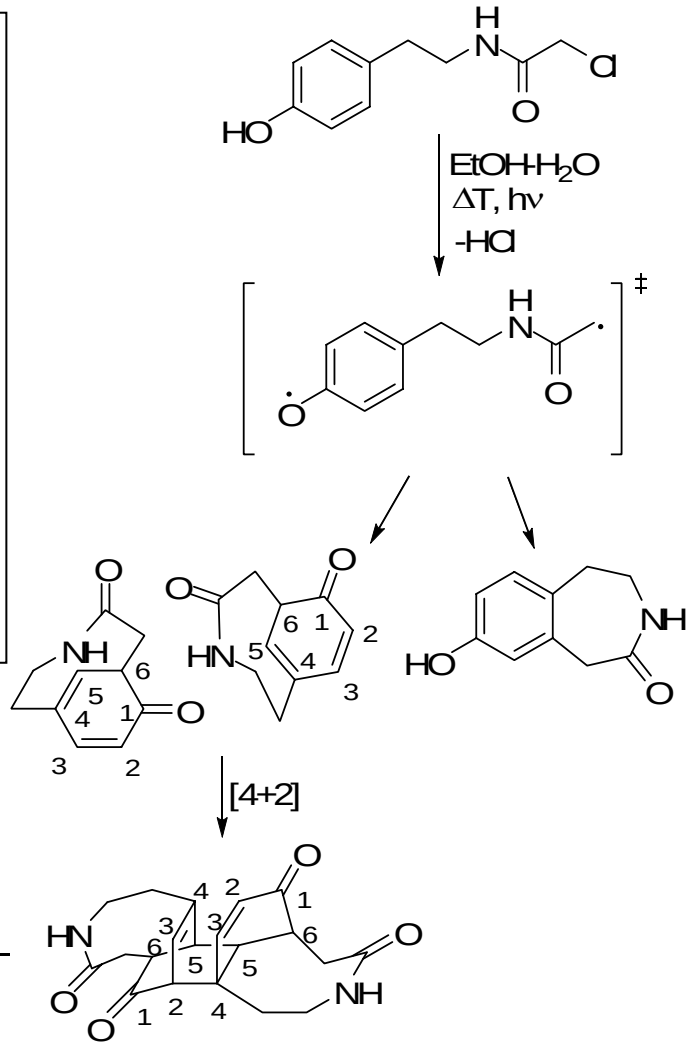
Photochemistry – cage compounds[6]





[6] B. Witkop *et al.*, *J. Am. Chem. Soc.* **1974**, 96, 2564-2569.

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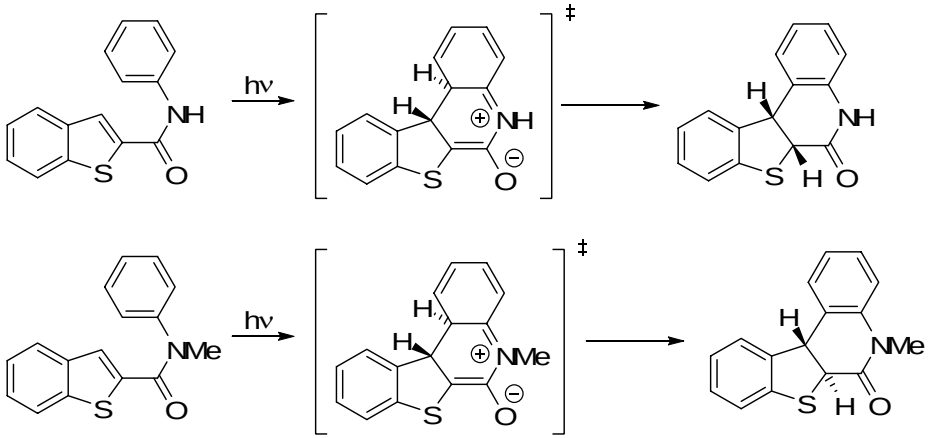
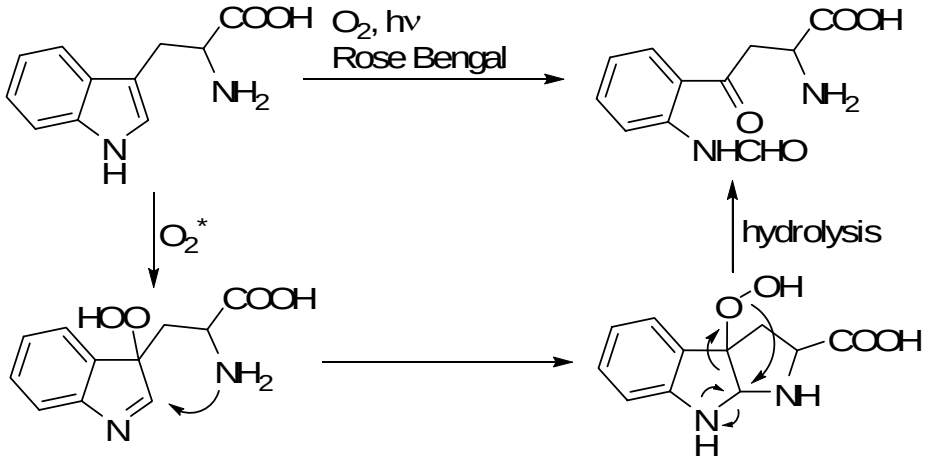
Photochemistry

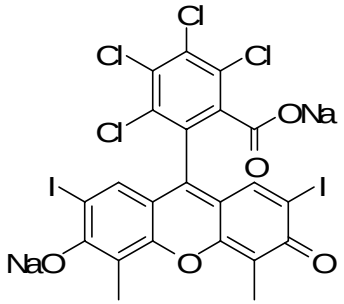
Stereochemistry of photocyclisations with heterocyclic anilides[7]



Explain the different mechanisms leading to the *cis* and the *trans* product!?

Photooxidation of Trp to kynurenine[8]





Rose Bengal

[7] B. Witkop *et al.*, *J. Org. Chem.* **1975**, 40, 3001-3003.

[8] B. Witkop *et al.*, *Proc. Natl. Acad. Sci.* **1977**, 4730-4732.

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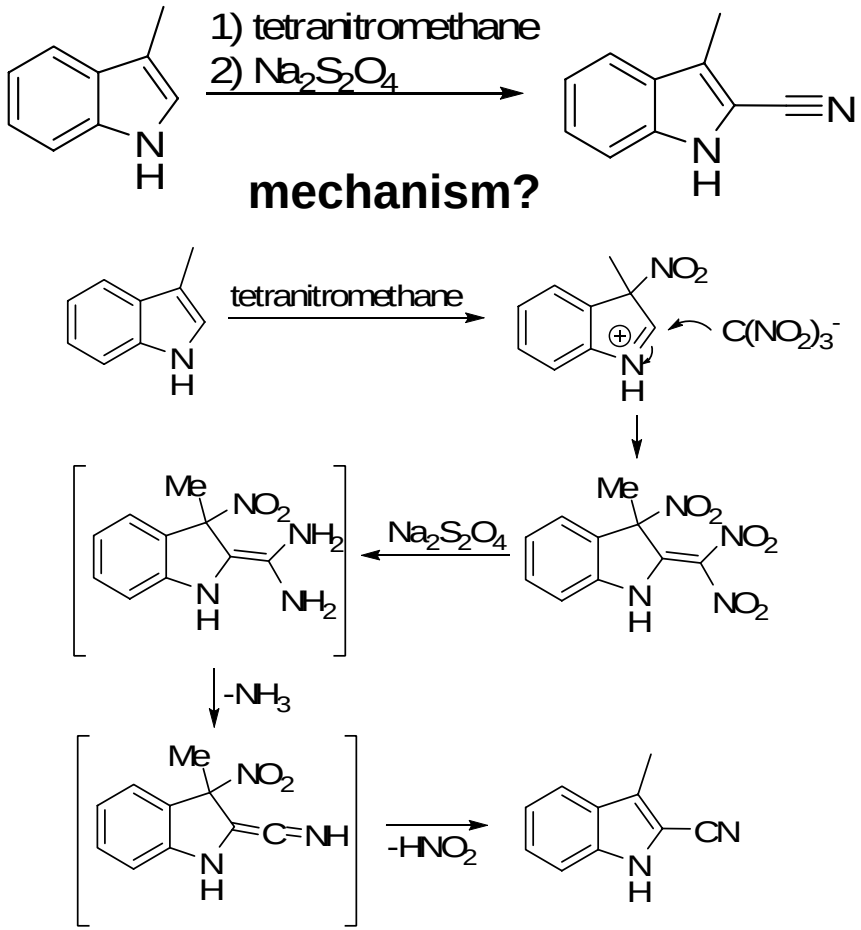
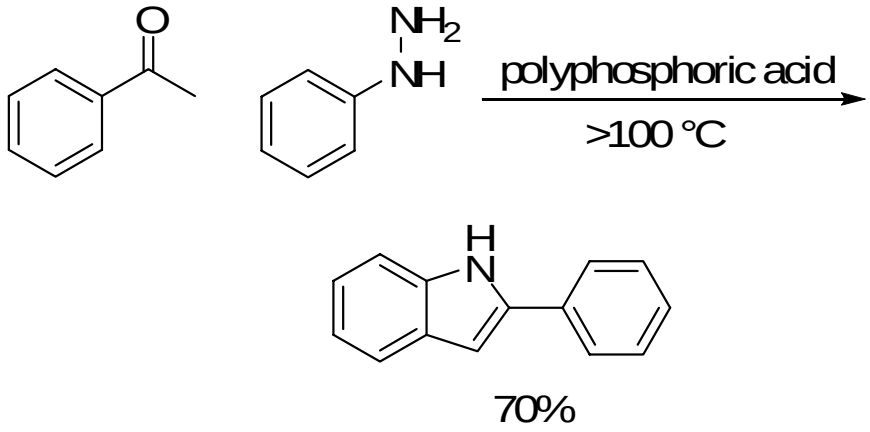
Synthesis and Mechanisms

Living on the edge….[9]



Fischer indole synthesis in polyphosphoric acid[10]



Good yields, easy workup

Limitation: only the synthesis of 2-substitued indoles possible

[9] B. Witkop *et al.*, *J. Am. Chem. Soc.* **1969**, 91, 6199-6200.

[10] B. Witkop *et al.*, *J. Am. Chem. Soc.* **1952**, 74, 3948-3949.

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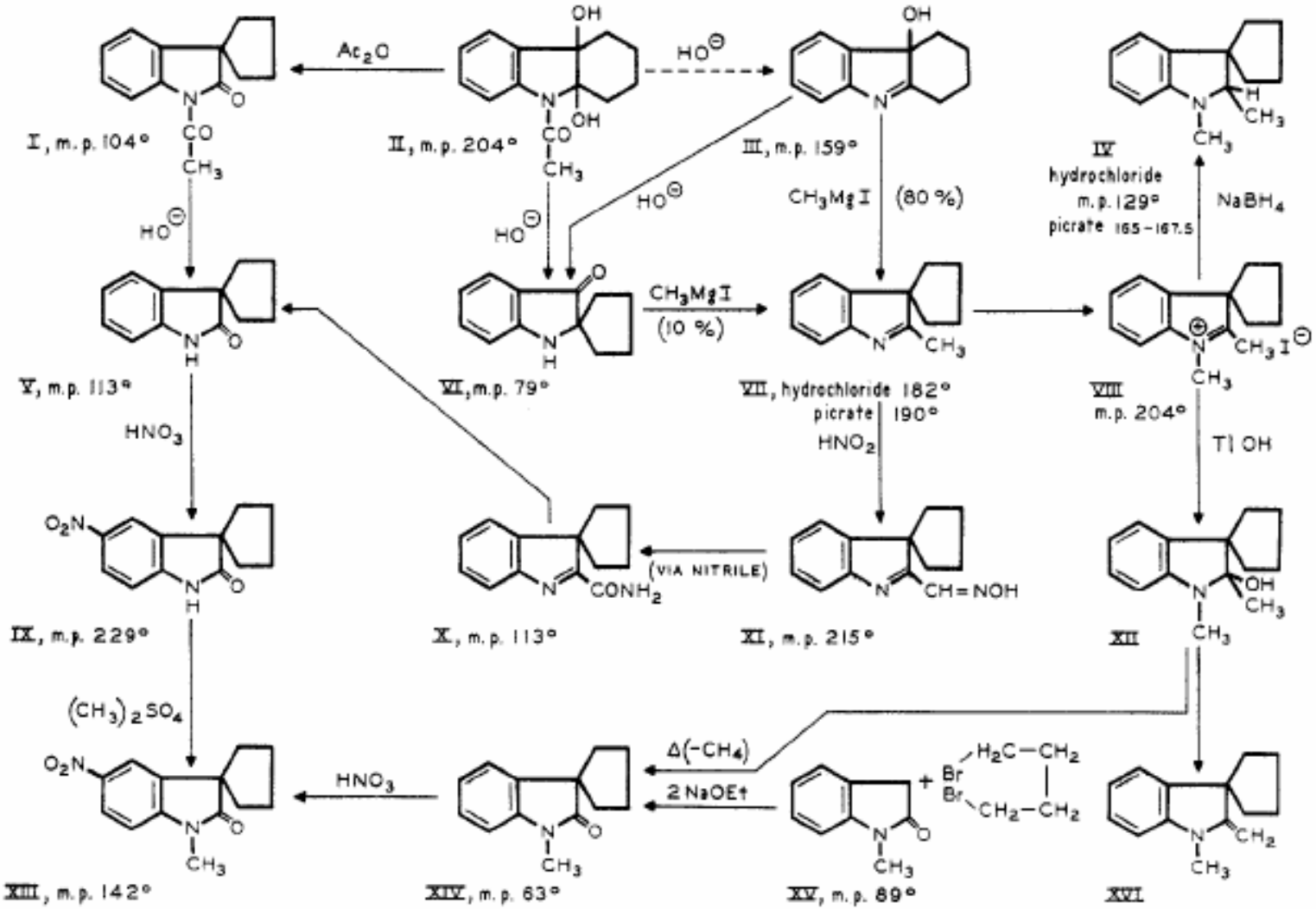
Synthesis and Mechanisms - Chemistry of Spirooxindoles



[11] J. B. Patrick, B. Witkop, *J. Am. Chem. Soc.* **1952**, 75, 2572-2576.

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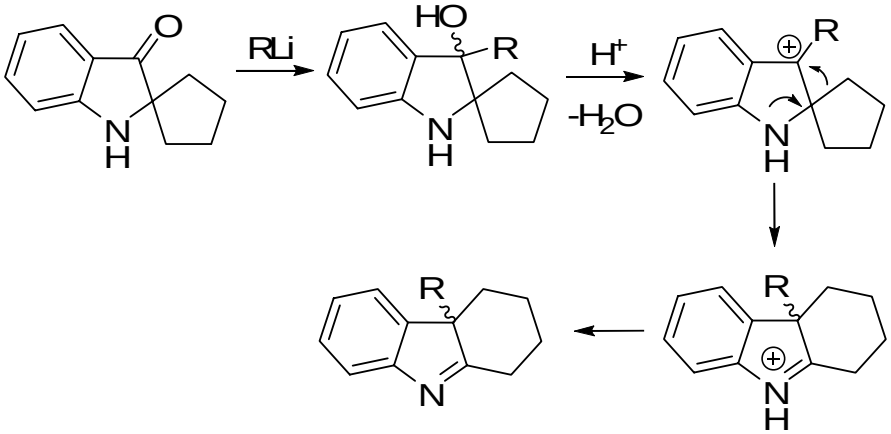
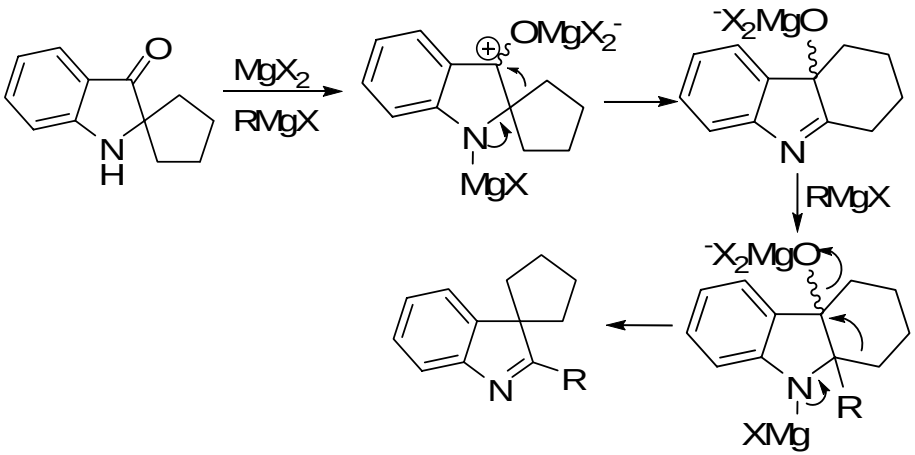
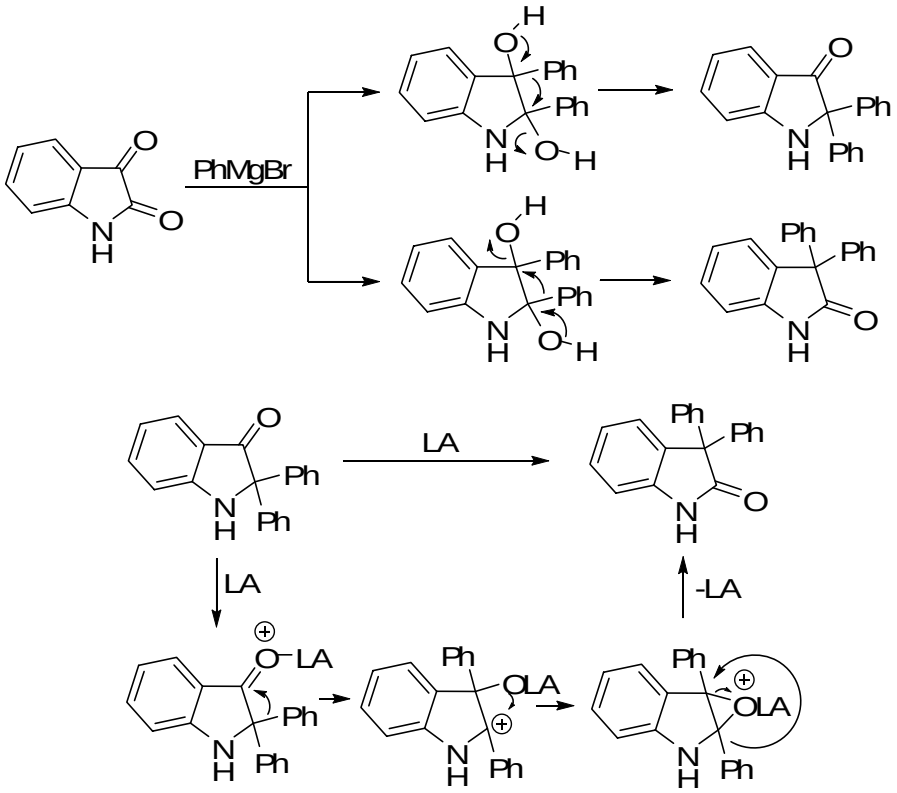
Synthesis and Mechanisms -Twofold Wagner-Meerwein-Rearangments[12-13]

Expected reaction with Lithiumorganyl



Unexpected reaction with Grignard reagent





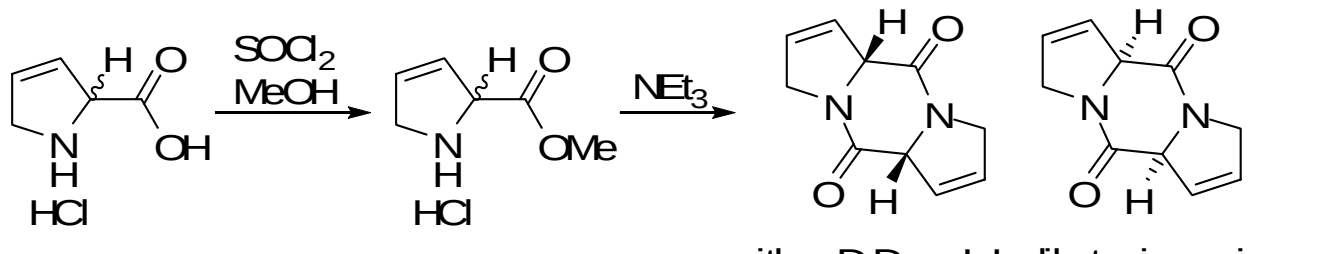
Rearangement can be induced by an excess Grignard reagent, acid or BF_3OEt_2

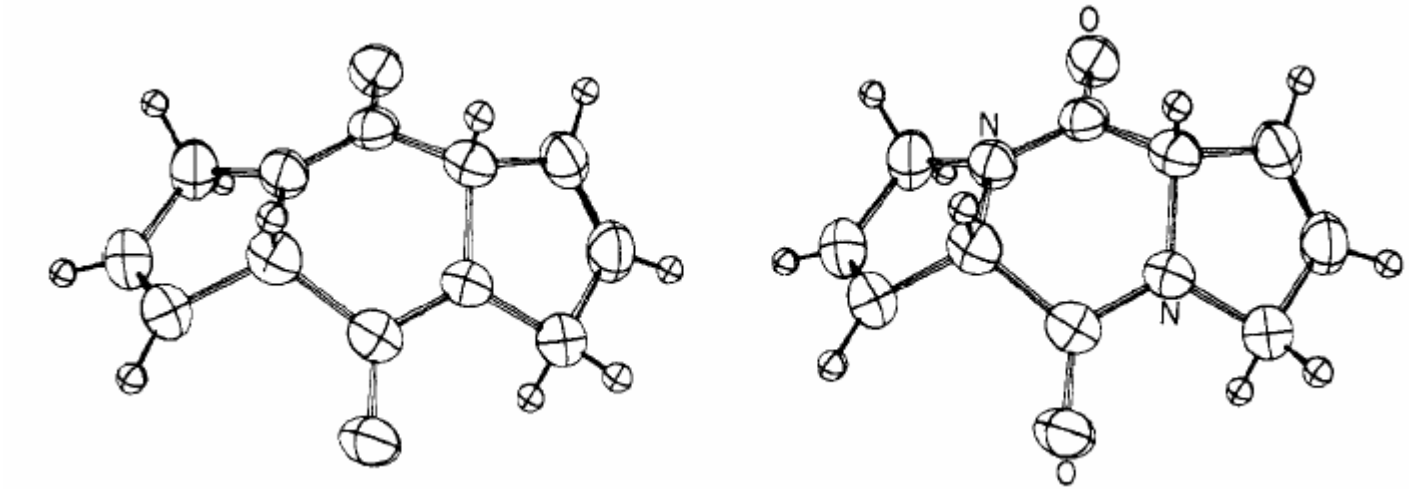
[12] J. B. Patrick, B. Witkop, *J. Am. Chem. Soc.* **1951**, 73, 1558-1564.

[13] A. Ek, B. Witkop, *J. Am. Chem. Soc.* **1951**, 73, 5664-5669.

Synthesis and Mechanisms

Deketopiperazines of 3,4-dehydroproline – unique structural properties[14]





Stereodiagram of the *L,L*-diketopiperazine

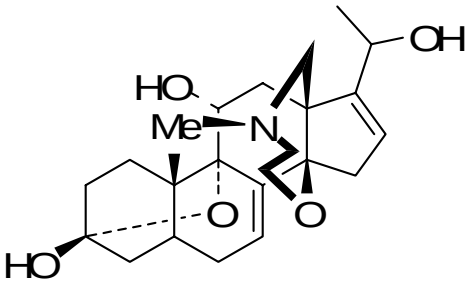
[14] B. Witkop *et al.*, *J. Am. Chem. Soc.* **1972**, 96, 539-543.

Synthesis and Mechanisms

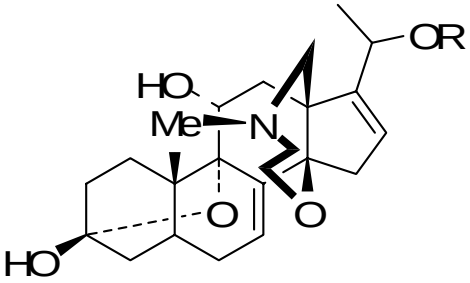
Batrachotoxin[15]

• a cardiotoxic alkaloid from the colombian arrow poison frog *Phyllobates aurotaenia* (LD_{50} = 2μg/kg mice)

• very labil venom (4 expeditions to Colombia were necessary) and most of the experiments were carried out in μg-quantities



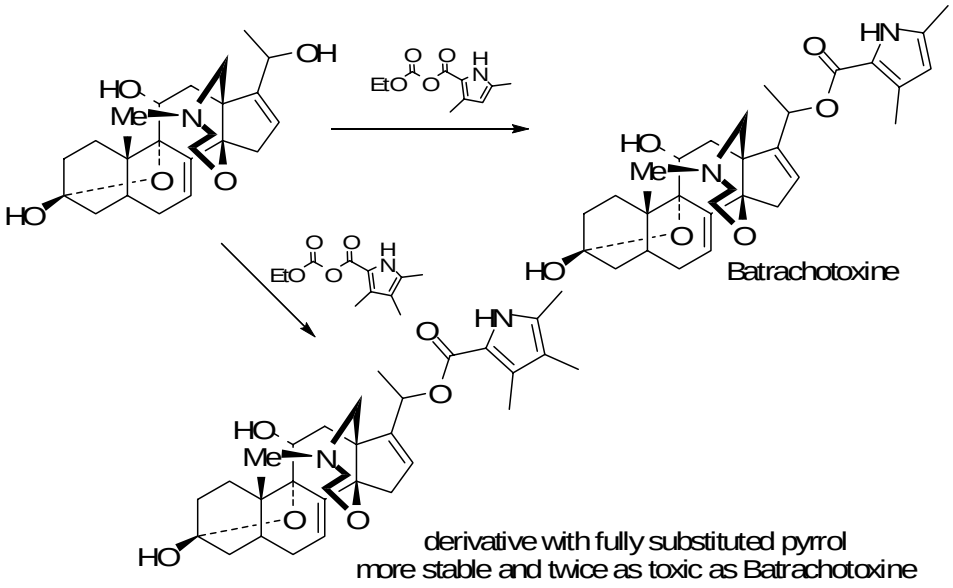
Batrachotoxin A
known structure



Batrachotoxin
unknown residue R

• by NMR, UV/Vis and MS they found that R is 2,4-dimethylpyrrole-3-carboxylic acid

• ultimate proof of their hypothesis was the partial synthesis of Batrachotoxine from Batrachotoxine A and activated 2,4-dimethylpyrrole-3-carboxylic acid



[12] T. Tokuyama, J. Daly, B. Witkop, *J. Am. Chem. Soc.* **1969**, 91, 3931-3938.