Bernhard Witkop

• born 1917 in Freiburg, Germany
• studied Chemistry in Munich till 1938 (diploma), 1940 (PhD)
• 1938-1946 private assistant of Prof. Wieland
• 1948-1950 lecturer at the Harvard 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-Shift¹

expected reaction

\[
\text{expected reaction}
\]

observed reactions

\[
\text{observed reactions}
\]

mechanism?

Biochemistry - protein structure

- Enzymatic and non-enzymatic 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.

\[
\begin{align*}
RHN\_CO\_NHR & \xrightarrow{\text{Br-CN}} RHN\_NHR \xrightarrow{-\text{MeSCN}} \\
RHN\_S\_NHR & \xrightarrow{\text{hydrolysis}} RHN\_CO\_NH\_R
\end{align*}
\]

- 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.

\[
\begin{align*}
\text{NBS} \xrightarrow{\text{H}_2\text{O}, \text{O}_2} \text{hydrolysis} \xrightarrow{-\text{RNH}_2} \\
\text{NBS}\_\text{NHAc} \xrightarrow{\text{base}} \text{hydrolysis} \\
\end{align*}
\]

- No side reactions with tyrosine or other aromatic amino acids.

- Interesting reaction at pH above pH 9.

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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
- Increases blood flow in extremities
- 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

Photochemistry

Chemistry with thymine dimers

\[ \text{Photochemistry also with 3-deazapyrimidone} \]

\[ \text{easy access to highly substituted diastereomERICly pure cyclobutanes} \]

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Photochemistry – cage compounds

Mechanism?

1, 5%
2, 40%
3, 12%

Sterechemistry of photocyclisations with heterocyclic anilides

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

Photooxidation of Trp to kynurenine

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Synthesis and Mechanisms

**Living on the edge....**

1. **tetranitromethane**
2. **Na₂S₂O₄**

**mechanism?**

Fischer indole synthesis in polyphosphoric acid

- **polyphosphoric acid**
- **>100 °C**

Good yields, easy workup

Limitation: only the synthesis of 2-substituted indoles possible

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Synthesis and Mechanisms - Chemistry of Spirooxindoles

Synthesis and Mechanisms - Twofold Wagner-Meerwein-Rearrangements\textsuperscript{12-13}

Expected reaction with Lithiumorganyl

\[
\text{Expected reaction with Lithiumorganyl}
\]

Unexpected reaction with Grignard reagent

\[
\text{Unexpected reaction with Grignard reagent}
\]

Rearangement can be induced by an excess Grignard reagent, acid or BF\textsubscript{3}OEt\textsubscript{2}


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Synthesis and Mechanisms

Deketopiperazines of 3,4-dehydroproline – unique structural properties

\[ \text{HCl} \xrightarrow{\text{SOCl}_2, \text{MeOH}} \text{OMe} \xrightarrow{\text{NET}_3} \]

either D,D- or L,L-diketopiperazines

Stereodagram of the \textit{L,L}-diketopiperazine

\[ 14 \text{ B. Witkop et al., J. Am. Chem. Soc. 1972, 96, 539-543.} \]
Synthesis and Mechanisms

**Batrachotoxin**

- a cardiotoxic alkaloid from the colombian arrow poison frog *Phyllobates aurotaenia* (LD$_{50}$ = 2 µg/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](image1)
![Batrachotoxin unknown residue R](image2)

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

![Derivative with fully substituted pyrrol](image3)

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

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