Amines: Finishing Up and a Historical Vignette
April 8, 2019

• The Hofmann and Cope elimination reactions.
• Two Chemists, One Molecule: Percy Julian, Robert Robinson, and the Synthesis of Physostigmine.

The Hofmann Rearrangement: \( R\text{-C(O)NH}_2 \) to \( R\text{-NH}_2 \) conversion.

The Curtius Rearrangement: \( R\text{-CO}_2H \) to \( R\text{-NH}_2 \) conversion.
Hofmann Elimination

Review:

\[
\begin{align*}
\text{KOH} & \quad \text{EtOH/}\Delta & 82\% & 12\% \\
\text{tBuOK} & \quad \text{tBuOH/}\Delta & \text{minor} & \text{major}
\end{align*}
\]

The ‘actual’ Hofmann Elimination:

\[
\begin{align*}
\text{NH}_2 & \xrightarrow{\text{CH}_3\text{I (x.s.)}} \text{N} & \xrightarrow{\text{Ag}_2\text{O} \text{H}_2\text{O}} & \Delta & 95\% & 5\%
\end{align*}
\]

Rationale:

1. pK\text{a} differences (Me > RCH\text{2} > R\text{2}CH)
2. conformational bias
3. anionic TS

*C.2-C.3 bond:*

*C.2-C.1 bond:*

*“Hofmann Rule: In quaternary amine hydroxides, the loss of H is easiest from Me > RCH\text{2} > R\text{2}CH.”*

Phphysostigmine

- Isolated from the seed (éséré, or Calabar bean) of the West African plant *Physostigma venenosum*
- A reversible acetylcholinesterase inhibitor
- Ordeal Poison: used in the administration of “divine justice”
  - Innocent: vomits
  - Guilty: has seizures, asphyxiates, dies.
- An early (1876) glaucoma treatment.
- Has been more recently explored as an Alzheimer’s disease therapy.

\[
\begin{align*}
\text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

l-physostigmine

*l-esonine*

C\text{15}H\text{21}N\text{3}O\text{2}

mp 105-106 °C

\[\alpha\] = −76°
Two Chemists

One Molecule

Percy Julian

born

1899

DePauw U.

1920

Ph.D.

1927

U. Vienna

1931

Professor

1933

Howard U.

1936

Director of Research

Glidden Soya Products

Robert Robinson

born

1886

Manchester U.

1905

Ph.D.

1912

U. Sydney

1920

Professor

1922

St Andrews U.

1928

Professor

1930

Manchester U.

1947

Professor

UCL

Oxford U.

Nobel Prize

Chemistry

\[
\begin{align*}
\text{d,l-Eserethole} &
\end{align*}
\]

Julian's synthesis

d,l-Eserethole

mp 38 °C

\[
\begin{align*}
\text{sodium metal} & \quad \text{xylene} \\
\text{dimethyl sulfate} & \quad \text{base} \\
\text{diethyl sulfate} & \quad \text{base} \\
\text{sodium ethoxide} & \\
\text{1. methyl iodide} & \quad \text{1. H+ hydrolysis} \\
\text{sodium metal} & \quad \text{ethanol} \\
\end{align*}
\]
In a series of ten beautiful papers Robinson and his co-workers have described syntheses of compounds which they call “d,l-esonethole” and “d,l-eseremethole.” Their “d,l-esonethole” is not the compound (XII) described in this communication as d,l-eserethole, and the constitution of which can hardly be questioned. We believe that the English authors are in error, that the compound they describe as d,l-eserethole is not the substance, and that we are describing for the first time the real d,l-eserethole.

Indeed, this conclusion finds strong support in the reactions of eserethole with methyl iodide, which we have described above. The English authors depend upon methylation of their d,l-noreserethole (which seems to be identical with our product (XII)) with methyl p-toluenesulphonate and at times methyl sulfate. This could well lead to a substance whose structure is represented by (XVII). A substance with this formula assigned to it has been obtained by Hoshino and Kobayashi through methylation by various procedures of dinoreserethole. Its melting point appears to be identical with the “d,l-eserethole” of Robinson and his co-workers and likewise the melting points of the two picrates seem identical. The English authors, themselves, express the opinion “that reinvestigation will show that the bases are identical,” but “that action of alkali on trimethyl-dinoreserethole iodide results in the loss of a methyl group.” Our results tend to substantiate, however, the claim of the Japanese chemists.

Final proof that we have completed the synthesis of physostigmine will be forthcoming when resolution experiments now in progress are completed.

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Robinson proposes the discrepancy is due to different ring junctions.

Physostigmine: possible stereoisomers

\[ \text{\textit{L}-physostigmine} \]
\[ [\alpha]_D = -76^\circ \]

\[ \text{\textit{D}-physostigmine} \]
\[ [\alpha]_D = +76^\circ \]

\[ \text{\textit{L}-eserine} \]
\[ [\alpha]_D = -76^\circ \]

\[ \text{\textit{D}-eserine} \]
\[ [\alpha]_D = +76^\circ \]

Text excerpted from:
Robert Robinson
(biographical memoir written by two fellow members of the Royal Society)
Julian takes some heat for structural representations...

with that secured from eserethole of natural origin. Also, like l-esserethole, our d,l-esserethole takes up two atoms of hydrogen on catalytic reduction yielding 1,3-dimethyl-3-β-methy laminoethyl-5-ethoxy-2,3-dihy droindole (XIV).