

## CHEM 635

Joseph M. Fox  
Spring 2012

Tuesdays, 7-10 pm, Brown lab 207

272 Brown Lab (office), 302-831-0191  
jmfox@udel.edu

### Syllabus for CHEM 635

Spring 2012  
Tuesdays, 7-10 pm, Brown lab 207  
Joseph M. Fox, 272 Brown Lab (office), 302-831-0191  
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Papers will be posted on a week-by-week basis.  
Students should post their presentations (as pdf files, ppt, or keynote files)  
the day before lecture.

Week 1	Feb 7: Introductory lecture. Lecture notes will be posted.
Week 2	Feb 14: Group A
Week 3	Feb 21: Group B
Week 4	Feb 28: Group C
Week 5	Mar 6: Exam 1
Week 6	Mar 13: Group A
Week 7	Mar 20: Exam B Mar 27: SPRING BREAK
Week 8	Apr 3: Synthesis Week, 1-7
Week 9	Apr 10: Synthesis Week 8-14
Week 10	Apr 17: Group C
Week 11	Apr 24: Exam 2
Week 12	May 1: Group A
Week 13	May 8: Group B
Week 14	May 15: Group C

Exam 3 TBA

Group A	Group B	Group C
Ahneman, Derek Thomas	Elbaum, Michael B	Patel, Neil Virendra
Andrade, Gabriel A	Klebon, Bryan D	Rossi, Steven A
Chintala, Srinivasa Rao	Lauro, Mackenzie L	Shimkin, Kirk W
Eddy, Jennifer Wood	Liu, Jixin	Song, Ye-Geun
	Melnyk, James Edward	Wang, Yiben

### Grading

Presentations: 20%  
Exams: 60% total  
Synthesis Week 20%

### Presentations

A successful presentation should contain the following elements:

- Discuss context (importance, history, note other syntheses)
- discuss scientists involved
- show 3-D structure; use 3-D in your analysis
- retrosynthesis
- forward synthesis
- know the mechanisms in the paper
- your presentation should last for 15 minutes, with 15 minutes of Q&A

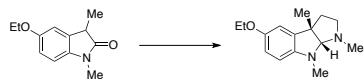
keys to the class

**mechanisms:** see it, know it  
**name reactions:** hear it, know it

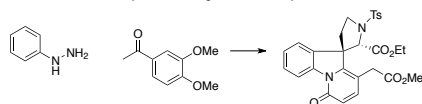
33% of exams from handouts; rest mechanisms

Chem 635 Week I  
potential exam I questions

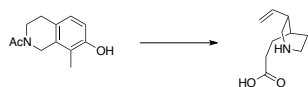
Describe Julian's synthesis of eserethole



Describe Woodward's synthesis of rings I-III & V of strychnine



Describe Woodward and Doering's synthesis of homomeroquinene



Office hours

	M	T	W	Th	F	
9						
10			✓			
11	✓		✓			
12	✓	✓	✓			
1	✓	✓				
2		✓			✓	
3					✓	
4					✓	
5				✓		

✓ blocks you can do office hrs

Your name \_\_\_\_\_

Office hours

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## Office hours

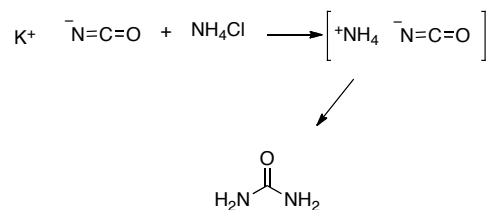
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✓ blocks you can do office hrs

Your name \_\_\_\_\_

## Wöhler synthesis of urea

Wöhler, 1928



Friedrich Wöhler *Annalen der Physik und Chemie* **1828**, 88, 253–256



Friedrich Wöhler, 1880-1882  
Polytechnic School in Berlin  
Polytechnic School at Kassel  
University of Göttingen

Significance: Wöhler was the first to make an organic substance from an inorganic substance.

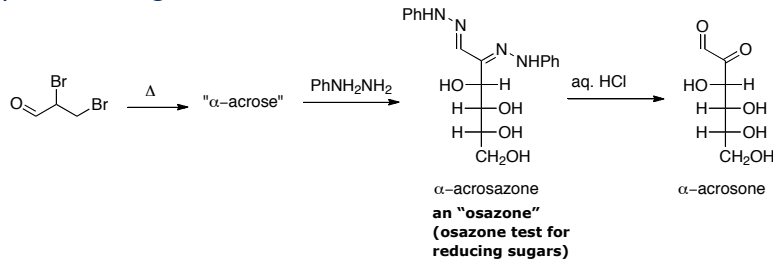
This was the beginning of the end of the theory of **vitalism**: the idea that organic and inorganic materials differed essentially by the presence of the “vital force”—present only in organic material.

To his mentor Berzelius: *“I can make urea without thereby needing to have kidneys, or anyhow, an animal, be it human or dog”*

Support for vitalism remained until 1845, when Kolbe synthesized acetic acid from carbon disulfide



## Fischer synthesis of glucose



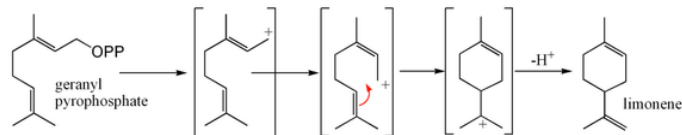
Emil Fischer, 1852-1919

University of Munich (1875-81)  
 University of Erlangen (1881-88)  
 University of Würzburg (1888-92)  
 University of Berlin (1892-1919)

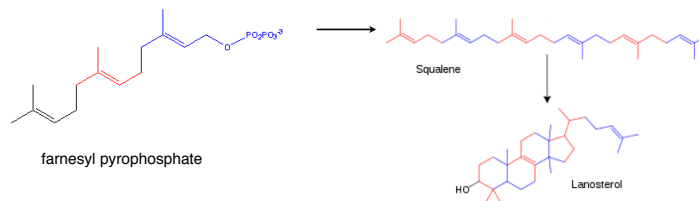
me 1 By John ApSimon

## Terpenes

- **Hemiterpenes** consist of a *single isoprene* unit. Isoprene itself is considered the only hemiterpene, but oxygen-containing derivatives such as [prenol](#) and [isovaleric acid](#) are hemiterpenoids.
- **Monoterpenes** consist of *two isoprene* units and have the molecular formula  $C_{10}H_{16}$ . Examples of monoterpenes are: [geraniol](#), [limonene](#) and [terpineol](#).

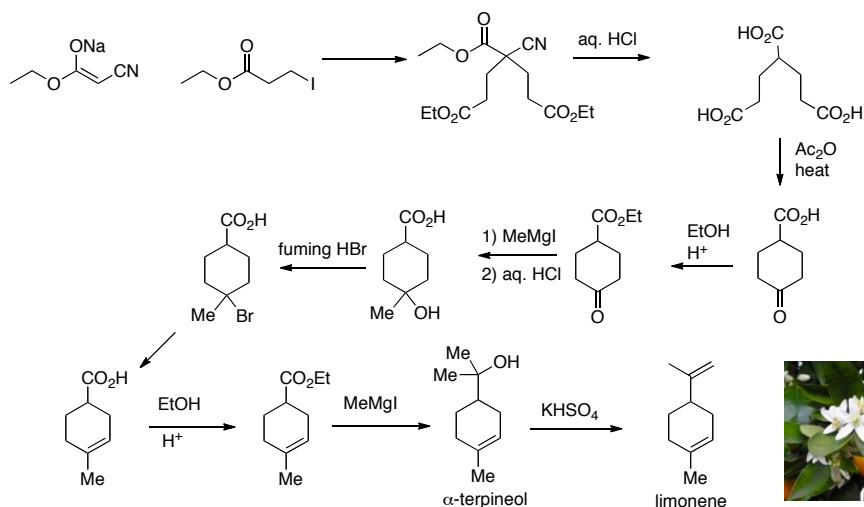


- **Sesquiterpenes** consist of *three isoprene* units and have the molecular formula  $C_{15}H_{24}$ . Examples of sesquiterpenes are: [farnesenes](#), [farnesol](#). (The *sesqui-* prefix means one and a half.)
- **Diterpenes** are composed for *four isoprene* units and have the molecular formula  $C_{20}H_{32}$ . They derive from [geranylgeranyl pyrophosphate](#). Examples of diterpenes are [cafestol](#), [kahweol](#), [cembrene](#) and [taxadiene](#) (precursor of [taxol](#)). Diterpenes also form the basis for biologically important compounds such as [retinol](#), [retinal](#), and [phytol](#). They are known to be antimicrobial and antiinflammatory.
- **Sesterterpenes**, terpenes having 25 carbons and *five isoprene* units, are rare relative to the other sizes. (The *sester-* prefix means half to three, i.e. two and a half.) Examples of sesterterpenes are [geranyl-farnesol](#).
- **Triterpenes** consist of *six isoprene* units and have the molecular formula  $C_{30}H_{48}$ . The linear triterpene [squalene](#), the major constituent of [shark liver oil](#), is derived from the reductive coupling of two molecules of [farnesyl pyrophosphate](#). Squalene is then processed biosynthetically to generate either [lanosterol](#) or [cycloartenol](#), the structural precursors to all the [steroids](#).



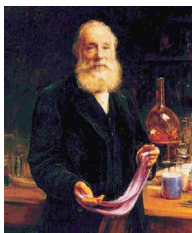
- **Tetraterpenes** contain *eight isoprene* units and have the molecular formula  $C_{40}H_{64}$ . Biologically important tetraterpenes include the acyclic [lycopene](#), the monocyclic [gamma-carotene](#), and the bicyclic [alpha-](#) and [beta-carotenes](#).
- **Polyterpenes** consist of long chains of *many isoprene* units. Natural [rubber](#) consists of polyisoprene in which the double bonds are *cis*. Some plants produce a polyisoprene with trans double bonds, known as [gutta-percha](#).

## Perkin Synthesis of $\alpha$ -terpineol and limonene

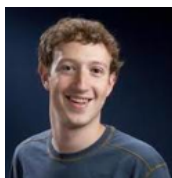


Note: use of symmetry

## Sir William Henry Perkin

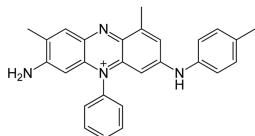


vs

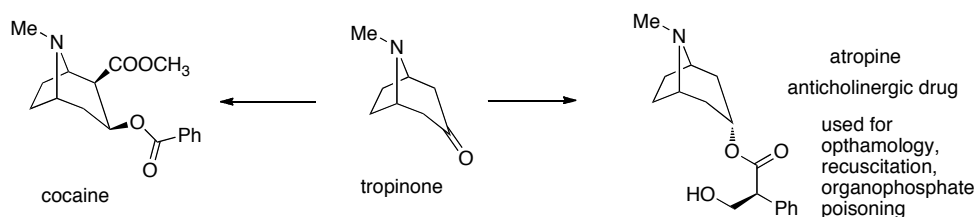


1838-1907  
began study at age of 15  
under August Wilhelm von Hofmann  
at Royal College of Chemistry in London  
(attempted study on synthesis of quinine)

made mauveine at age 18 over easter break  
launched the synthetic dye industry  
(never mind quinine. . .)



## Tropinone



Tropane alkaloids occur in plants of the families Erythroxylaceae (including coca) and Solanaceae



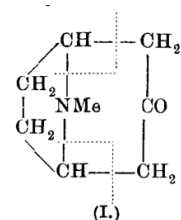
from Wikipedia

## Tropinone

First synthesis by Willstätter in 1901: arduous, 0.75% yield

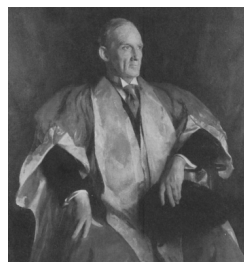
Robert Robinson, 1917: classic retrosynthetic analysis and biomimetic synthesis

Nevertheless, an inspection of the formula of tropinone (I) discloses a degree of symmetry and an architecture which justify the hope that the base may ultimately be obtained in good yield as the product of some simple reaction and from accessible materials. By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succinaldehyde, methylamine, and acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis.



... and biomimetic synthesis

'Biomimetic synthesis' (the name was invented long after 1917 and was not Robinson's although it categorizes his later intention) is similar to laboratory total synthesis with limitations. Any precursor molecular structures so used must be conceivable ones from natural products derived by known (or by possible and ultimately testable) biochemical mechanisms. Also, reaction conditions which can be used are severely limited to those which might apply in aqueous biological solutions. Such limitations pose restrictive difficulties in achieving synthetic objectives, but they may be an asset in confining thinking compared with more open 'total synthesis', in which any appropriately functionalized molecular structure from any source can be a conceivable precursor utilized under any severe laboratory conditions. With an intellectual challenge, success in 'biomimetic-synthesis' results in the satisfaction of belief that something truly 'natural' has been achieved. An implicit assumption of Winterstein and Trier and of Robinson and their successors, is that the occurrence of a specific structure has already demonstrated feasibility in nature which can be speculated, possibly imitated in the laboratory, or biochemically confirmed in broad outline.<sup>3</sup>

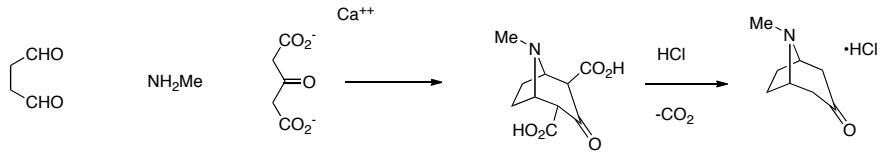


1886-1975  
Institutions  
University of Sydney  
University of Liverpool  
British Dyestuffs Corporation  
University of Manchester  
University College, London  
University of Oxford  
Alma mater  
University of Manchester

Birch, Arthur J., 'Investigating a Scientific Legend: the Tropinone Synthesis of Sir Robert Robinson, FRS', *Notes and Records of the Royal Society of London*, vol. 47, 1993, pp. 277-296

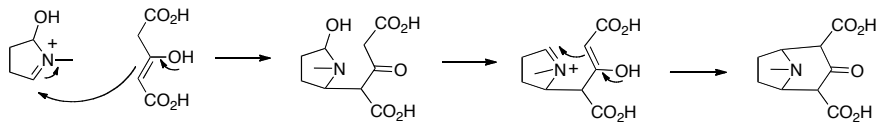
# Tropinone

Total synthesis



Robinson *J. Chem. Soc.* **1917**, 762.

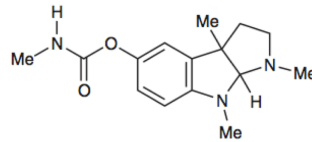
Mechanism: Double Mannich (go through entire mechanism yourself)



# physostigmine

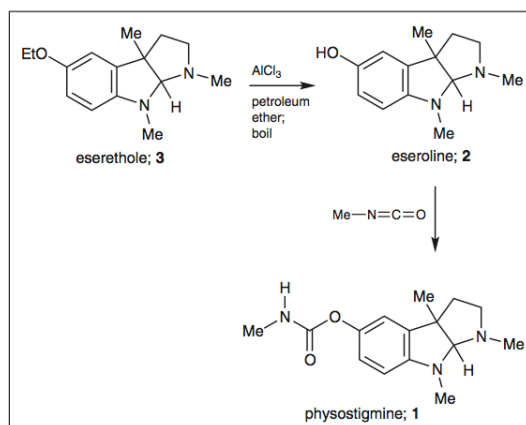


African Calabar Bean



- Potent reversible inhibitor of acetyl and butylcholinesterases
- Clinical treatment of glaucoma (reduces intraocular pressure)
- Alzheimer's disease
- Pyrrolindinoindoline

## physostigmine/eserethole

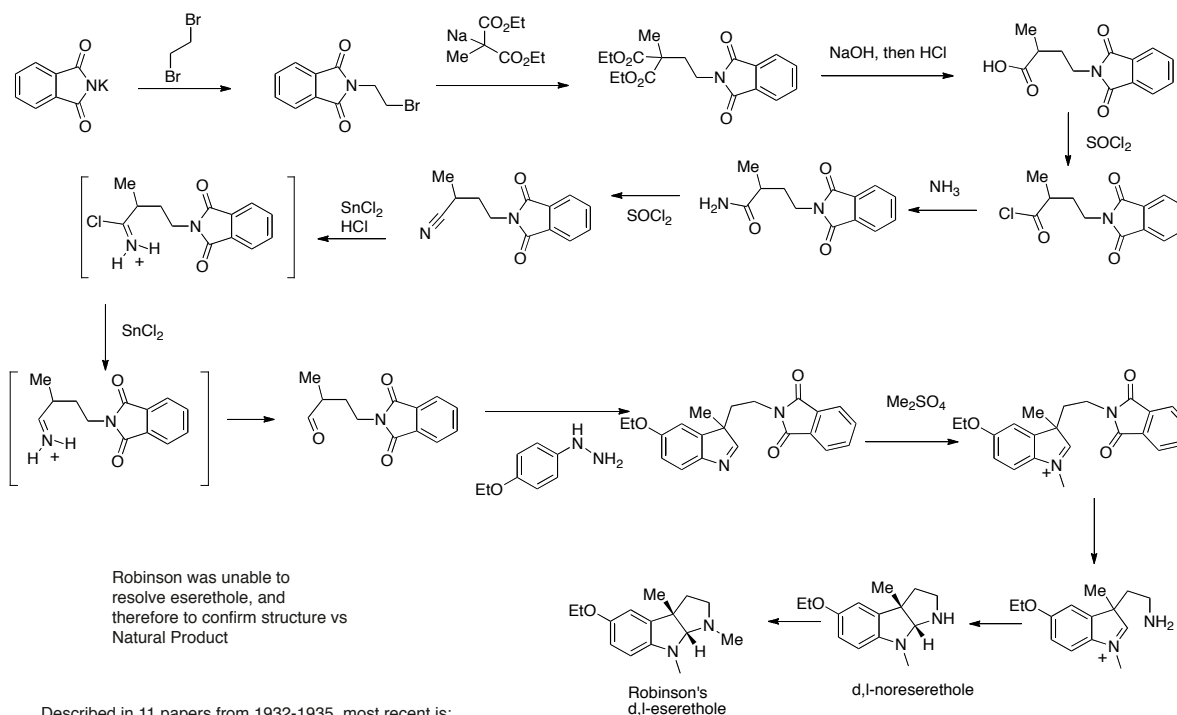


Scheme II. Formation of physostigmine from eserethole.

Polonovski and Nitzberg, *Bull. Soc. Chim.* **1916**, 19, 33.

Figure from A. Audt, *J. Chem. Educ.* **2008**, 85, 1524.

## Robinson: The first reported synthesis of physostigmine/eserethole



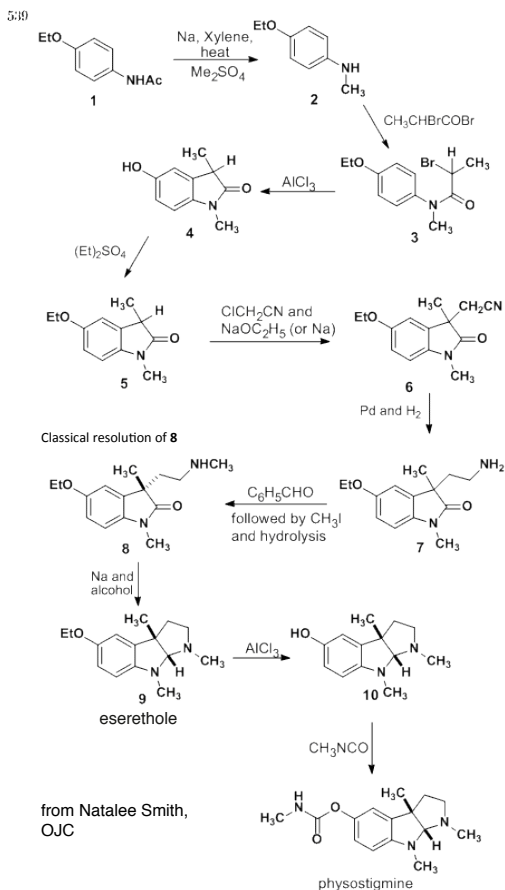
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

## Studies in the Indole Series. III. On the Synthesis of Physostigmine

BY PERCY L. JULIAN AND JOSEF PIKL

To our surprise, our product (VII) exhibited entirely different properties from those of a compound synthesized by Robinson and his co-workers and called *d,l*-eserethole. Likewise were all derivatives different. Inasmuch as our inactive material, subjected to characteristic reactions of eserethole of natural origin, yielded perfectly analogous results, we expressed the belief that our product was the real *d,l*-eserethole and that that of the English chemists must be assigned another constitution. This is now proved conclusively by synthesis of *l*-eserethole, identical with the product of natural origin.

**Reduction of *l*-Amine (VI) to *l*-Eserethole (VII).**— This reduction was carried out in exactly the same manner as described for *d,l*-eserethole:<sup>8</sup> 6.8 g. of *l*-1,β-dimethyl-5-ethoxyxindolyethyl-methylamine yielded 5.1 g. of *l*-eserethole. The picrate melted at 135° and showed with the picrate of eserethole of natural origin no depression. *Anal.* Calcd. for C<sub>21</sub>H<sub>23</sub>O<sub>3</sub>N<sub>3</sub>: C, 53.03; H, 5.30. Found: C, 52.86; H, 5.58.

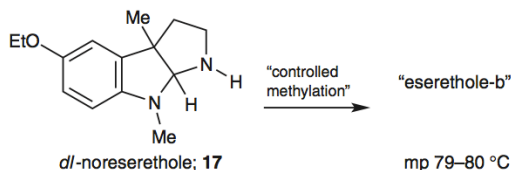


- BA. DePauw University, IN, 1920
- Fisk University, TN
- MS. Harvard University, 1923
- Howard University, (D.C.) 1929
- PhD University of Vienna, 1931  
(Rockefeller Foundation Fellowship)
- 1932 – Rosenwald Research Fellow Depauw University (Dean W. M. Blanchard)
- 1935 – Total Synthesis of Physostigmine
  - Collaboration with Josef Píkl
- 1936 – Director of Research for soya products, Glidden, Chicago
  - Large scale, cost effective production of synthetic progesterone and hydrocortisone.
  - Foam fire extinguishers WWII
- 1953 – Julian Laboratories
  - Sold for \$2M in 1961
- > 138 patents, > 160 publications before his death in 1975

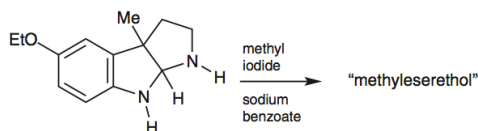


## What did Robinson do?

On controlled methylation with methyl-*p*-toluenesulphonate we found that it [*dl*-noreserethole] yielded a crystalline *dl*-eserethol (IV), m.p. 79–80 °C (J., 1934, 1416), and we then surmised that this substance would prove to be identical with a base, m.p. 80–81 °C, obtained by Hoshino and Kobayashi (*Proc. Imp. Acad. Japan*, 1934, 10, 99).



## enter Kobayashi

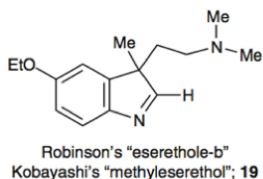


from Audt, *J. Chem. Educ.* **2008**, *85*, 1524.

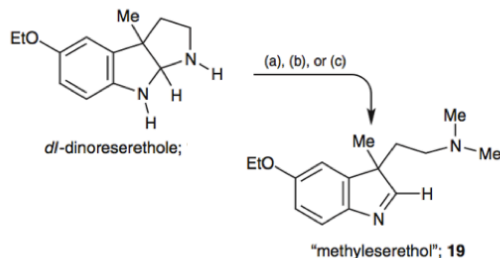
Although eserethole has a molecular formula  $C_{15}H_{22}N_2O$ , the Japanese chemists believed that the analytical results for their product indicated the presence of 16 carbons and a molecular formula of  $C_{16}H_{24}N_2O$ . It was for this reason that they named their product "methyl-*dl*-eserethol" (5, p 565). However, it was established that "methyleserethole" was the same as Robinson's "eserethole-b" by direct comparison of the melting points: the melting points were the same and the mixture melting point showed no depression (4).

Hoshino, T.; Kobayashi, T. *Proc. Tokyo* 1934, 10, 564–567.  
Kobayashi, T. *Ann.* 1938, 536, 143–163.

Robinson never published again on this subject, but Kobayashi, in 1938, identified "methyleserethole" as a constitutional isomer of eserethole (6, p 144).



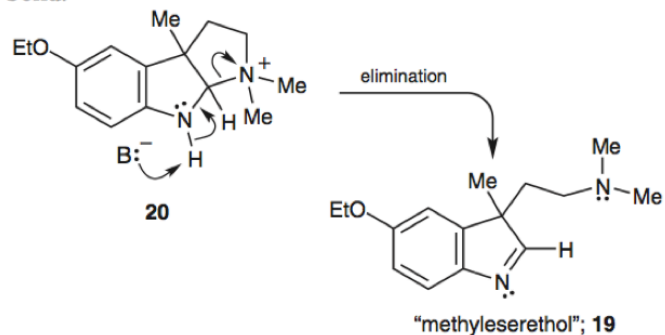
Kobayashi showed that *dl*-dinoreserethole, **18**, could be converted to "methyleserethole", **19**, by three similar procedures, methods (a), (b), and (c).



where (a) is treating the free base with methyl iodide in either alcohol or ether; (b) is treating the amine benzoate with either methyl iodide or methyl-*p*-toluenesulfonate; and (c) is treating the amine benzoate with methyl iodide or methyl-*p*-toluenesulfonate in the presence of sodium benzoate or sodium acetate (7).



A reasonable mechanism would be two successive “methyl-plus” transfers from the methyl donor to the more basic, aliphatic nitrogen to give **20**, followed by elimination to form the double bond.



“Kobayashi says, in the sentence following the one quoted just above, that “eserethole-b” is unlikely to have been formed from noreserethole, **17**, in which the indoline nitrogen bears a methyl group, although the English researchers, as mentioned above, did observe its formation.”

Audt, *J. Chem. Educ.* **2008**, *85*, 1524.

How Robinson actually make ‘eserethole b (methyleserethole)’ ?

Some time ago, in 1965, a review by Coxworth stated that “Several proposals have been advanced to account for the conversion of [*dl*-noreserethole, **17**] into [eserethol-b; **19**]” (10), making reference to work reported in the Ph.D. thesis of A. H. Jackson (11). More recently, in 2002, Brian Robinson (no relation to Robert Robinson), after reading the thesis of A. H. Jackson, reported that Jackson had been unsuccessful in his efforts to convert *dl*-eserethole to “methyleserethole” and wrote that its formation “on methylation of noreserethole thus still remains something of a mystery...” (12).

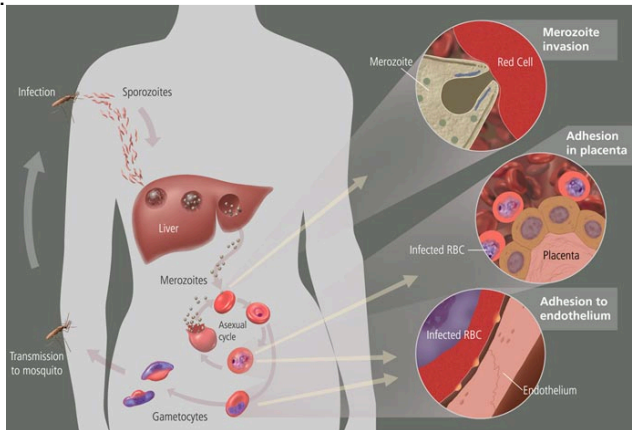
- Jackson, A. H. Ph.D. Thesis, Cambridge University, Cambridge UK, 1954.

Audt, *J. Chem. Educ.* **2008**, *85*, 1524.



## Malaria

**Malaria** is a female-mosquito-borne infectious disease caused by a eukaryotic protist of the genus *Plasmodium*. It is widespread in tropical and subtropical regions, including parts of the Americas (22 countries), Asia, and Africa. After a period of between two weeks and several months (occasionally years) spent in the liver, the malaria parasites start to multiply within red blood cells, causing symptoms that include fever, and headache. In severe cases the disease worsens leading to hallucinations, coma, and death.



The **life cycle** of malaria parasites in the human body. A mosquito infects a person by taking a blood meal. First, sporozoites enter the bloodstream, and migrate to the liver. They infect liver cells (hepatocytes), where they multiply into merozoites, rupture the liver cells, and escape back into the bloodstream. Then, the merozoites infect red blood cells, where they develop into ring forms, trophozoites and schizonts which in turn produce further merozoites. Sexual forms (gametocytes) are also produced, which, if taken up by a mosquito, will infect the insect and continue the life cycle.

-from Wikipedia

## Malaria

- References to the unique periodic fevers of malaria are found throughout recorded history, beginning in 2700 BC in China
- Malaria was the most important health hazard encountered by U.S. troops in the South Pacific during World War II, where about 500,000 men were infected. Sixty thousand American soldiers died of malaria during the North African and South Pacific campaigns.
- Europeans brought malaria to the new world in 1500's. The Peruvians would mix the ground bark of trees with sweetened water to offset the bark's bitter taste, thus producing [tonic water](#).
- Spanish Jesuit Missionaries in Peru first learned of the healing power of a tree bark in 1620. IN 1640, the Countess of Chinchon-- consort to the Spanish Viceroy of Peru-- was saved from death by administration of a native tonic made from the bark of a tree know as quina-quina (later cinchonia bark) by local people. Afterwards, tonic bark soon became widespread in popularity in Europe.



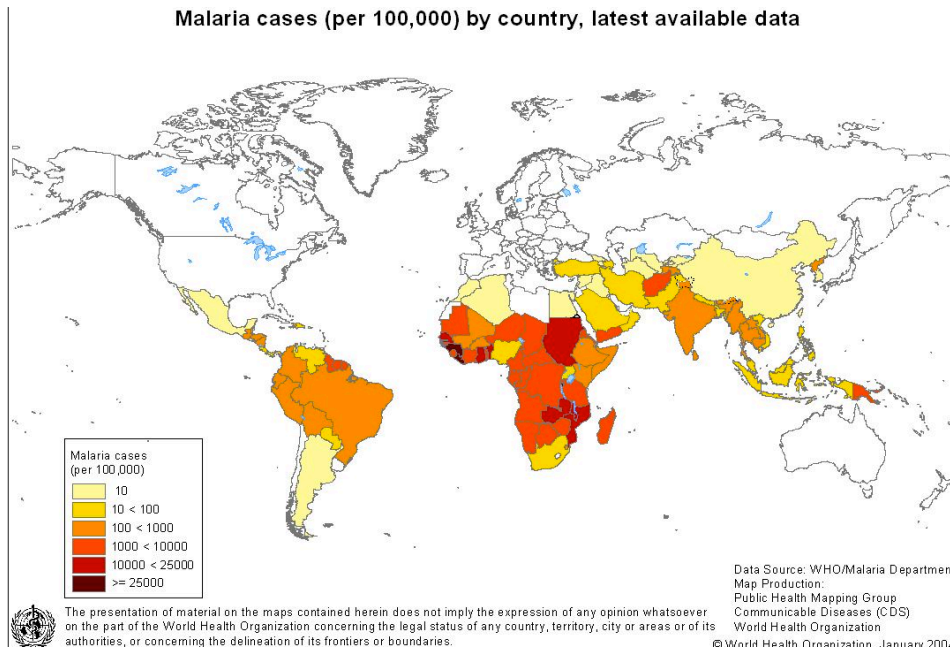
Alexander the Great



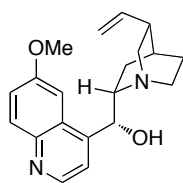
- Initially resisted in England due to the association with the papacy (bark at that time were known as Cardinal's powder or Pope's powder. Oliver Cromwell, the Puritan who overthrew King Charles I in the 17th century English Civil War, preferred to treat his fevers with mercury and bloodletting, rather than take a Jesuit powder (he died)

from Wikipedia and Molecules that Changed the World by Nicolaou

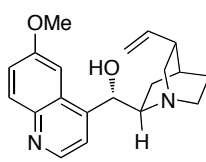
In Africa a child dies every 45 seconds of Malaria, the disease accounts for 20% of all childhood deaths.



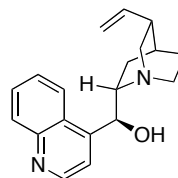
## Cinchona Alkaloids



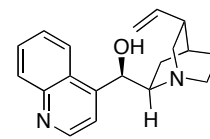
quinine



quinidine



cinchonidine

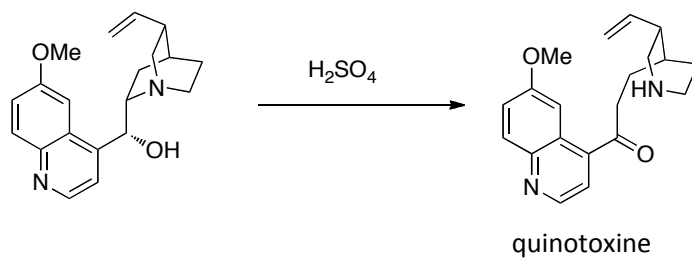


cinchonine

1820: Quinine was isolated and named in 1820 by French researchers Pierre Joseph Pelletier and Joseph Bienaimé Caventou. The name was derived from the original Quechua (Inca) word for the cinchona tree bark, "quina" or "quina-quina", which roughly means "bark of bark" or "holy bark". (from wikipedia)

quinine, equilenin (steroids?), strychnine

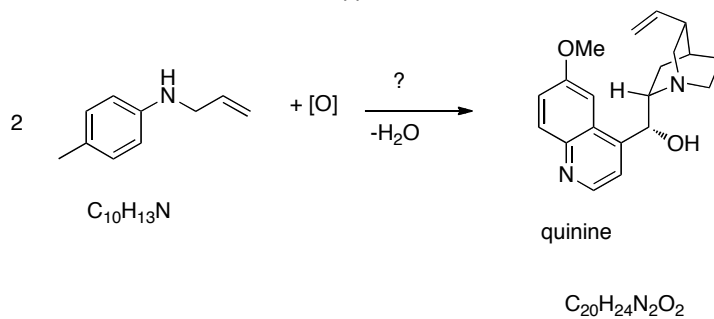
1853 Pasteur: acid catalyzed rearrangement of quinine to quinotoxine



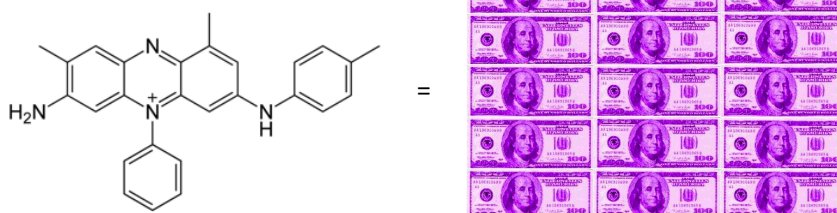
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## Studies on quinine

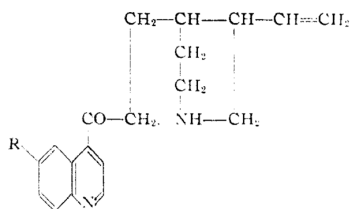
1856: Perkin and Hoffman's 'mathematical' approach



'unsuccessful' experiments led to the aniline dye industry



## Paul Rabe and Karl Kindler



• Over a 40-year period, Paul Rabe and his students published over 40 papers on the structure, chemical and physical properties, and synthesis of quinine and other cinchona alkaloids.

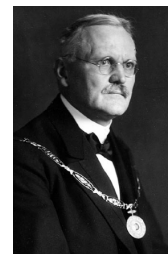
• Rabe: Universities of Jena, Prague and Hamburg

• 1908: proposed the correct structure of quinine

• 1918: Rabe and Karl Kindler synthesize quinine from quinotoxine

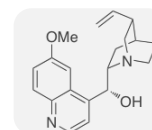
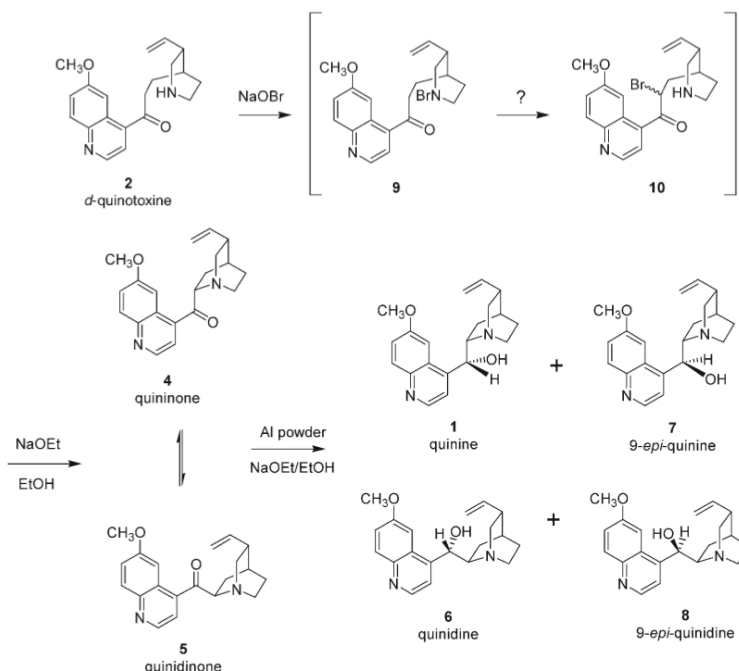
• 1935: Rabe forced by the Nazis into early retirement from his position as Director of the Institute in Hamburg. This was retaliation because Rabe had “removed a notice from the notice board notifying of a boycott against Jewish students at his Institute.” Rabe continues to conduct experiments with limited resources

• 1939: 21 years after their preliminary communication, Rabe and Kindler published a brief publication (1939) with experimental details, Rabe and Kindler report the isolation of additional quantities of quinine from the “preserved” two-decades-old reaction residues from the aluminum powder reduction of “quininone”



from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

## Paul Rabe and Karl Kindler



**Scheme 2.** Details of the conversion of *d*-quinotoxine into quinine and its isomers **6–8** by Rabe and Kindler.<sup>[7,77]</sup> In 1918 quinine was isolated and identified; **6–8** as well as additional quantities of quinine were isolated and identified in 1939 from the reaction residues from 1918. The intermediacy of the  $\alpha$ -bromoketone **9** has not been established but suggested based on the failure of analogous intermediates to react with methyl iodide. Sodium ethoxide causes epimerization about C8 of the quininone/quinidinone mixture, possibly isomerization of the bromoketones **9** and **10** as suggested by Gutzwiller and Uskokovic<sup>[119]</sup> as well as Nicolaou and Snyder,<sup>[15]</sup> and cyclization.

from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

# Robert Burns Woodward and William von Eggers Doering

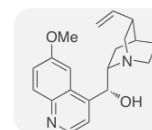


**William von Eggers Doering** (b. 1917) undergraduate and graduate student at Harvard, receiving the Ph.D. in 1943  
Columbia in 1943- 1952,  
Yale 1952-1967,  
Harvard 1968-present

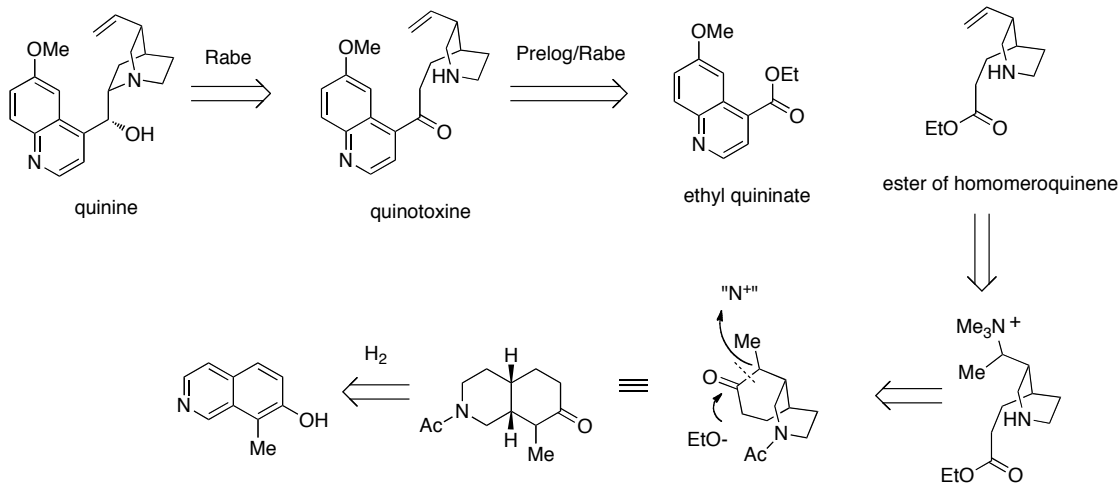
**Robert Burns Woodward**  
1917-1979  
BS (MIT) 1936  
Ph.D. (MIT) 1937  
1937: postdoc at Illinois  
1938-1979: Harvard  
1965: Nobel Prize

33

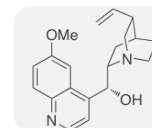
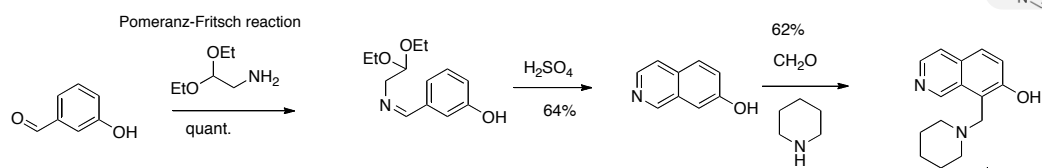
## Robert Burns Woodward and William von Eggers Doering



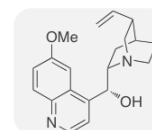
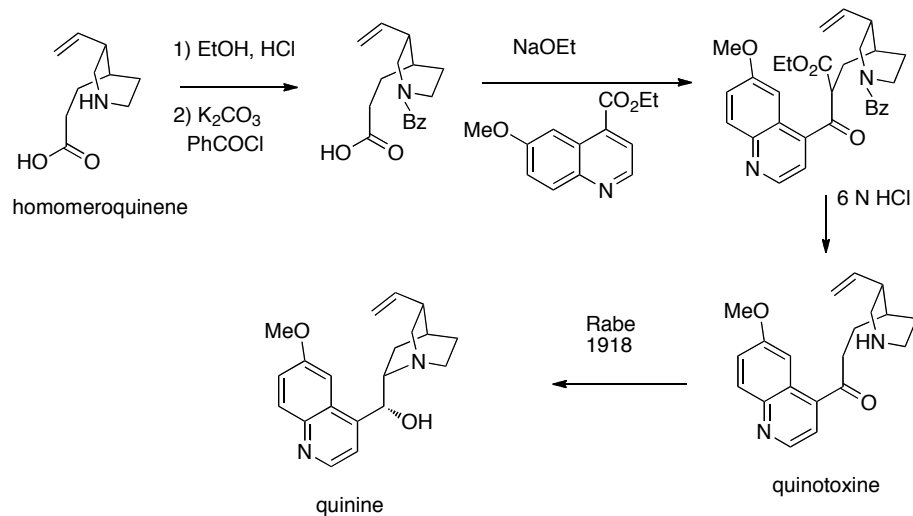
### retrosynthesis



## Woodward and Doering synthesis



## Completion of the synthesis



“In view of the established conversion of quinotoxine to quinine,<sup>[7]</sup> with the synthesis of quinotoxine [in this publication] the total synthesis of quinine was complete.”<sup>[6]</sup>



## QUININE!

Malaria was the most important health hazard encountered by U.S. troops in the South Pacific during World War II, where about 500,000 men were infected. Sixty thousand American soldiers died of malaria during the North African and South Pacific campaigns.

During the war, the U.S. had been cut off from the Dutch East Indies, its major sources of cinchona bark



Figure 5. Cartoon from the Portland Oregon Journal, May 28, 1944.

Woodward and Doering was celebrated on radio in a broadcast “which originated in the studios of our key station WEAJ in New York [and] was also heard from coast to coast over the NBC network”<sup>[23]</sup> on May 8, 1944. According to the script, Robert St. John reported:

“I have an exciting story for you, today ... a story with war as its background ... but a story about the saving of lives, rather than the taking of lives!!! ...

“The Polaroid Corporation was interested in quinine, because they used quinine in manufacturing light-polarizing material. And so they set Bob Woodward to work, trying to create synthetic quinine ... Woodward chose as his collaborator on the project 26-year-old Bill Doering ... These two mere boys set to work, with common chemicals, and just a few days ago they were proudly able to announce that they had succeeded, where generations of great scientists had failed!! They had succeeded in creating synthetic quinine!! A substance which may snatch whole hospitals’ full of malaria-ridden soldiers in Pacific jungles out of the shadow of death!!! Bob Woodward, 27! Bill Doering, 26! Mere boys! I wish you could meet them, face to face!”<sup>[24]</sup>

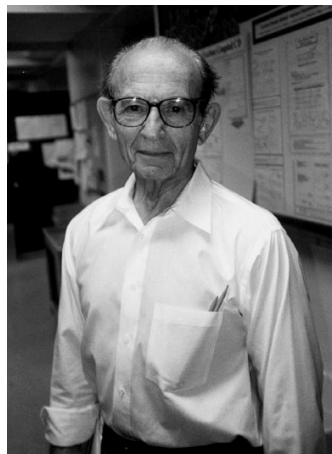
Many articles appeared in the news media, including a front-page article in *The New York Times* on May 4, 1944<sup>[45]</sup> as well as another article and an editorial a few days later.<sup>[46,47]</sup> Further articles appeared in *Life* magazine,<sup>[48]</sup> *The New Yorker*,<sup>[49]</sup> *Business Week*,<sup>[50,51]</sup> *Newsweek*,<sup>[52]</sup> *Time*,<sup>[53]</sup> *Reader’s Digest*,<sup>[54]</sup> *Science News Leader*,<sup>[55]</sup> as well as the *Virginia Gazette*, Alexandria,<sup>[56]</sup> the *Philadelphia Inquirer*,<sup>[57]</sup> *Drug Trade News*,<sup>[58]</sup> *Kentucky Messenger*,<sup>[59]</sup> and a remarkable cartoon from the *Oregon Journal* (Figure 5).<sup>[60]</sup> Most of the news reports were overwhelmingly positive

from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

## The quinine myth?

**2000-2001:** Gilbert Stork characterized the impression of the achievement of the synthesis of quinine by Woodward and Doering as a “widely believed myth.”

Stork concluded that the claim by Woodward and Doering is a “myth” because they had synthesized only homomeroquinene and d-quinotoxine; no synthetic quinine had been made in Cambridge. In fact, Rabe and Kindler never published the experimental details of their conversion of d-quinotoxine into quinine.



### Gilbert Stork

Born in Brussels, Belgium, 1921  
University of Florida, B.S. 1942;  
University of Wisconsin–Madison, PhD  
1945 with Samuel M. McElvain  
1946 Harvard University: Instructor  
1948 Assistant Professor  
1953 Columbia University

from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

## The quinine myth?

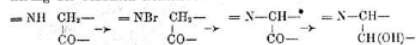
### 48. Paul Rabe und Karl Kindler: Über die partielle Synthese des Chinins. Zur Kenntnis der China-Alkaloide XIX.

[Vorläufige Mitteilung aus dem Chem. Staatslaboratorium zu Hamburg.]

(Eingegangen am 8. Januar 1918.)

Die Versuche des einen von uns über die Verwandlung der Chinatoxine in die Chinaalkaloide<sup>1)</sup> sind nach längerer Unterbrechung 1917 wieder aufgenommen und durch die schließlich geglückte Synthese des Chinins aus dem Chinin zum Abschluß gebracht worden. Da die klinische Identifizierung des so synthetisierten Chinins mit dem natürlichen Fiebermittel noch vorgenommen werden soll, so schicken wir die kurze Beschreibung der Chinin-Synthese der zusammenfassenden Abhandlung über die partielle Synthese der acht Chinaalkaloide und weiterer, mit ihnen stereoisomerer, in der Natur bisher nicht aufzufindender Basen voraus.

Die Synthese vollzieht sich in drei Schritten: Das Chinin geht bei der Einwirkung von unterbromigsaurem Natrium in das *N*-Bromchinin über; ihm wird mittels Alkalis Bromwasserstoff unter Bildung des Chininons entzogen; endlich liefert das Chininon bei der Behandlung mit Aluminiumpulver in alkoholischer Lösung bei Gegenwart von Natriumäthylat das Chinin. In der Auffindung dieses eigenartigen Reduktionsgemisches besteht der wesentliche Fortschritt bei den Synthesen in der Reihe der Chinaalkaloide. Was die genauere Formulierung der benutzten Reaktionen:



angeht, so verweisen wir auf die XV. Mitteilung: Über die partielle Synthese des Cinchonins, B. 44, 2088 [1911].

Das *N*-Bromchinin, in analoger Weise wie der Bromkörper<sup>2)</sup> aus dem Cinchonidin bereitet, kommt aus Äther in farblosen Nadeln vom Schmp. 123°. Das aus ihm hervorgegangene Chininon vom Schmp. 108° war in allen seinen Eigenschaften identisch mit dem Chininon aus Chinin.

16.3 g synthetisiertes Chininon gaben bei der Behandlung mit dem genannten Reduktionsgemisch neben 0.9 g Chinidin das Chinin in einer Ausbeute von 2 g analysenreiner Substanz. Es schmolz wie verlangt bei 177° und besaß in absolut-alkoholischer Lösung das optische Drehungsvermögen  $[\alpha]_D^{25} = -158.7^\circ$  ( $c = 2.1432$  bei 20°), während Rabe<sup>1)</sup> für das natürliche Alkaloid  $[\alpha]_D^{25} = -158.2^\circ$  ( $c = 2.136$  bei 15°) gefunden hat.

0.1164 g Subst.: 0.3174 g CO<sub>2</sub>, 0.0801 g H<sub>2</sub>O.  
C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>. Ber. C 74.03, H 7.46.  
Mol.-Gew. 324.21. Gef. » 74.87, » 7.70.

<sup>1)</sup> Rabe, B. 41, 62 [1908]; 44, 2088 [1911]. Vortrag auf der 55. Versammlung der Gesellschaft Deutscher Naturforscher und Ärzte, Wien 1913; siehe die Eigenberichte in den Verhandlungen dieser Gesellschaft 1913, II, 1, 293, in Ch. Z. 1913, 1237 und Z. Ang. 1913, I, 548.

B. R. 44, 2088 [1911]

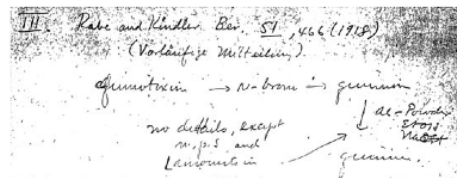


Figure 26. Excerpt from handwritten literature search notes (ca. 1943) of Robert B. Woodward on the 1918 Rabe and Kindler article.<sup>[1]</sup> Note the words, "no details, except m.p.s and amounts in".<sup>[159]</sup>

"no details, except m.p.s and amounts in ..."<sup>[159]</sup>

we refer to paper XV: The partial synthesis of cinchonine. Ber. 44, 2088 [1911].

The *N*-bromquinotoxine, prepared in the same way as the bromo compound obtained from cinchotoxine,<sup>2)</sup> crystallizes from ether as colorless needles with m.p. 123°. The quinone obtained from it with m.p. 108° is in all respects identical to the quinone obtained from quinine.

16.3 g synthetic quinone when treated with the aforementioned reducing mixture yielded, besides 0.9 g quinidine, 2 g of analytically pure quinine. Quinine melted as required at 177° and had an optical rotation in absolute alcohol of  $[\alpha]_D^{25} = 158.7^\circ$  ( $c = 2.1432$  at 20°C) while Rabe<sup>1)</sup> for the natural alkaloid had found  $[\alpha]_D^{25} = 158.2^\circ$  ( $c = 2.1362$  at 15°C).

Sample 0.1164 g: 0.3174 g CO<sub>2</sub>, 0.0801 g H<sub>2</sub>O

C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> .	Observed	C 74.03, H 7.46.
Mol. Wt. 324.21	Calculated	C 74.37, H 7.70.

<sup>1)</sup> Rabe, Ber. 41, 62 [1908]; 44, 2088 [1911].

from: J. I. Seeman, Angew. Chem. Int. Ed. 2007, 46, 1378 – 1413

## The quinine myth?

Gilbert Stork  
Chemistry Department  
University of Wisconsin  
Madison 3, Wisconsin

September 19, 1944

Dr. R. B. Woodward  
Chemistry Department  
Harvard University  
Cambridge, Massachusetts

Dear Dr. Woodward:

I am to give a talk to the graduate students and faculty members of the organic chemistry department at the University of Wisconsin next October 4, on the subject of quinine--proof of structure, synthetic approaches.

I intend, of course, to present the brilliant synthesis which you accomplished with Dr. Doering. However, the communication to the Editor published in the JACS, although presenting the successive steps, does not indicate the yields for the various transformations.

I wonder if you could find the time to let me know the yields on the various steps leading to homoserquinone. If you could only fill them in on the adjoined sheet and send it back to me, I would be very thankful.

Would you also tell me whether Rabe's conversion of quinotoxine into quinine has been repeated by you in your present work?

Very sincerely yours,

*Gilbert Stork*  
Gilbert Stork



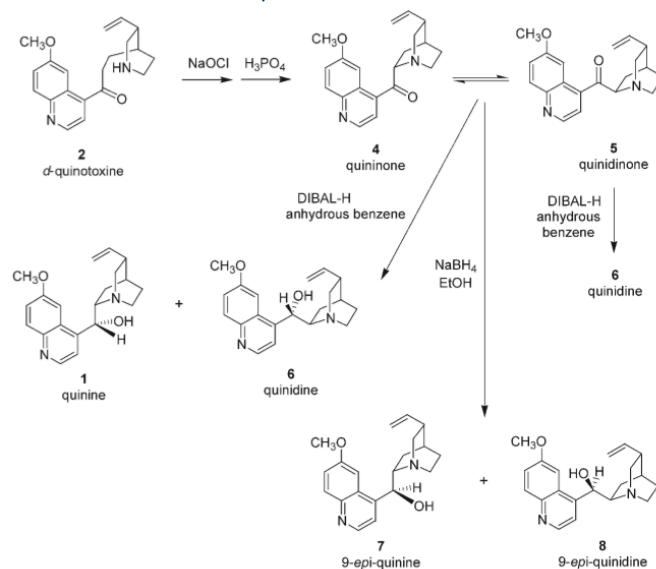
Figure 19. Gilbert Stork as a graduate student at the University of Wisconsin, ca. 1944. The photograph is reproduced with permission from Gilbert Stork.

from: J. I. Seeman, Angew. Chem. Int. Ed. 2007, 46, 1378 – 1413



## The quinine myth?

### Hoffmann-La Roche Synthesis



**Scheme 5.** Gutzwiller and Uskoković published<sup>[19]</sup> the closest analogous modern transformation of *d*-quinotoxine to quinine to that used by Rabe and Kindler<sup>[2,77]</sup> (Scheme 2). In both the diisobutylaluminum hydride (DIBAL-H) and sodium borohydride reductions, an equilibrated mixture of quinone and quinidinone was prepared prior to their exposure to the reductant. Furthermore, reduction of quinidinone by DIBAL-H (under conditions in which there is no equilibration with quinone) resulted in 94% yield of quinidine exclusively.

“In the very last phase of the Rabe pathway, one has to reduce a ketone, quinone and quinidinone, to alcohol ... . We tried to repeat it but we were not successful to obtain quinine in a yield that one can consider successful. One obtained a mixture: quinine was one of the components but not in substantial amount that in my point of view we could call a practical yield.”  
Milan Uskokovic

from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

## The quinine myth?



from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

## The Woodward–Doering/Rabe–Kindler Total Synthesis of Quinine: Setting the Record Straight

Jeffrey I. Seeman\*

Keywords:  
alkaloids · heterocycles · history of  
science · quinine · total synthesis

Dedicated to Professors Otto Theodor Rabe,  
Ernest L. Eitel, and Rolf Huisgen.

**1918**  
48. Paul Rabe und Karl Kindler: Über die partielle Synthese des Chinins. Zur Kenntnis der China-Alkaloide XIX. [Vorläufige Mitteilung aus dem Chem. Staatslaboratorium zu Homburg.]

**The Total Synthesis of Quinine**  
BY R. B. WOODWARD AND W. E. DOERING

**1945**  
The culmination of the structural investigations on quinine in the proposal of the correct structure (I in 1908<sup>1</sup>) may be considered the point at which rational efforts toward total synthesis could be initiated.<sup>2</sup> These efforts first took the form of an attack on the synthesis of substances containing the quinoline moiety of the quinine molecule. First success was achieved independently by Pietet and Mianer,<sup>3</sup> and by Kaufmann and Peyer,<sup>4</sup> in 1912 with the synthesis of quininic acid

had shown<sup>5</sup> in 1853 that the cinchona alkaloids on heating with tartaric or sulfuric acid, were transformed into isomeric substances, *e. g.*, cinchonidine (cinchonidine) and quinotoxine<sup>6</sup> (quinotoxine) from cinchonine and quinine, respectively. Subsequent investigations by other workers resulted in the verification of these early results,<sup>7</sup> in improvements in the mode of effecting the isomerization,<sup>8</sup> and in the successful formulation<sup>9</sup> of quinotoxine as (IV, R = OCH<sub>3</sub>) and cinchonidine as (IV, R = H). It was now apparent that these

**2001** The First Stereoselective Total Synthesis of Quinine  
Gilbert Stork,<sup>10</sup> Dejiang Niu, A. Fujimoto,<sup>11</sup> Emil R. Kofl,<sup>12</sup> James M. Balkovec,<sup>13</sup> James R. Tata,<sup>14</sup> and Gregory R. Duke<sup>15</sup>

Contributed from the Department of Chemistry, Columbia University, New York, New York

Angewandte Chemie

from: J. I. Seeman, *Angew. Chem. Int. Ed.* 2007, 46, 1378 – 1413

## Rabe Rest in Peace: Confirmation of the Rabe–Kindler Conversion of *d*-Quinotoxine Into Quinine: Experimental Affirmation of the Woodward–Doering Formal Total Synthesis of Quinine\*\*

Aaron C. Smith and Robert M. Williams\*

*Angew. Chem. Int. Ed.* 2008, 47, 1736–1740

**Table 1:** Conditions for reducing quinidinone/quininone to quinine.

Entry	Reducing conditions	T [°C]	Yield of isolated quinine/quinidine	Yield of quinine <sup>[f]</sup>
1 <sup>[a]</sup>	DIBAL-H benzene	20	72%	33%
2 <sup>[b]</sup>	NaBH <sub>4</sub> , EtOH	0	11%	4%
3	Al powder (new) <sup>[c]</sup> NaOEt, EtOH	reflux	trace	trace
4	Al powder (new) <sup>[c]</sup> NaOEt, EtOH	reflux	30% (1.1:1)	16%
5	Al powder + Al <sub>2</sub> O <sub>3</sub> NaOEt, EtOH	reflux	26% (1.1:1)	14%
6	Al powder (aerated) <sup>[c]</sup> NaOEt, EtOH	reflux	24% (1.1:1)	13%
7	Al powder MeOH, NaOMe	reflux	8% (1.2:1)	4%
8	Al powder (sonication) NaOEt, EtOH	reflux	22% (1.1:1)	12%
9	Al powder, Na(OiPr), <i>i</i> PrOH	reflux	32% (1:1.2)	15%
10	Al(OiPr) <sub>3</sub> , <i>i</i> PrOH	reflux	28%	16%
11	LiAlH <sub>4</sub> , ether	–78	45%	trace
12	LiAlH <sub>4</sub> , ether	0	59%	trace
13	LiAlH <sub>4</sub> , ether	20	56%	trace
14	LiAlH <sub>4</sub> , ether <sup>[d]</sup>	0	40% (1:1.5)	16%

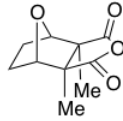
[a] Experiment from Ref. [11]. [b] General reaction conditions here.  
[c] Bottle #1. [d] Bottle #2. [e] After epimerization. [f] Calculated based on <sup>1</sup>H NMR spectra.



**Figure 1.** Crystals of quinine tartrate obtained directly from quinotoxine according to the Rabe–Kindler protocol<sup>[2]</sup> without the use of any modern isolation, chromatographic, or analytical techniques.

“Our validation of the formal total synthesis of quinine as originally reported by Woodward and Doering in 1944<sup>[1]</sup> should serve to remove the blemish asserted<sup>[6,7]</sup> on the reputations of Rabe and Kindler as well as those of Woodward and Doering.”

## cantharidin



poisonous chemical compound secreted by many species of blister beetle, and most notably by the Spanish fly, *Lytta vesicatoria* (a beetle).



The beetle contains up to 5% cantharidin



Cantharidin was first isolated in 1810 by Pierre Robiquet,

LD<sub>50</sub> is around 0.5 mg/kg, with a dose of as little as 10 milligrams being potentially fatal

## cantharidin

Various preparations of desiccated Spanish flies have been used as some of the world's oldest alleged aphrodisiacs, with a reputation dating back to the early western mediterranean classical civilizations:

- In Roman times, Livia, the scheming wife of Augustus Caesar, slipped it into food hoping to inspire her guests to some indiscretion with which she could later blackmail them.
- Henry IV (1050–1106) is known to have consumed Spanish fly at the risk of his health.
- It was slipped into the food of Louis XIV to secure the king's lust for Madame de Montespan.
- In the 18th century, cantharides became fashionable, known as *pastilles Richelieu* in France.

-wikipedia



Madame de Montespan

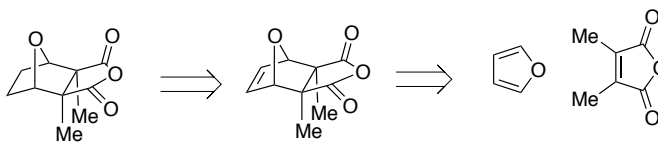


Maquis had invited either a small select number, or a large one, of guests who were either local innocents or local libertines (or both), and with the intention of inciting them all to a friendly sexual frenzy he fed them either aniseed comfits or chocolate pastilles (or both) laced with "Spanish Fly" and/or other more "genuine" aphrodisiacs.

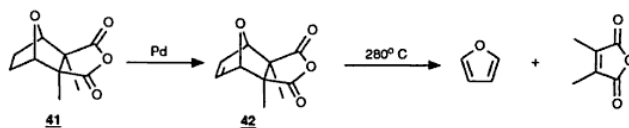
The planned fun backfired in the worst possible way for both the guests (who became seriously compromised and/or seriously ill) and the Maquis who was arrested and charged with poisoning.

<http://www.theoldfoodie.com/2006/06/orgy-of-bon-bons.html>

## cantharidin



Heating **cantharidin 41** together with palladium asbestos at 280°C in order to accomplish **dehydrogenation** to give **42** afforded furan and dimethyl-maleic anhydride as the only products (Scheme 10).<sup>37</sup>



Von Bruchhausen, F; Bersch, H. W. *Arch. Pharm.* **1928**, 266, 697

from *Gas phase reactions in organic synthesis* By Yannick Vallée

## cantharidin

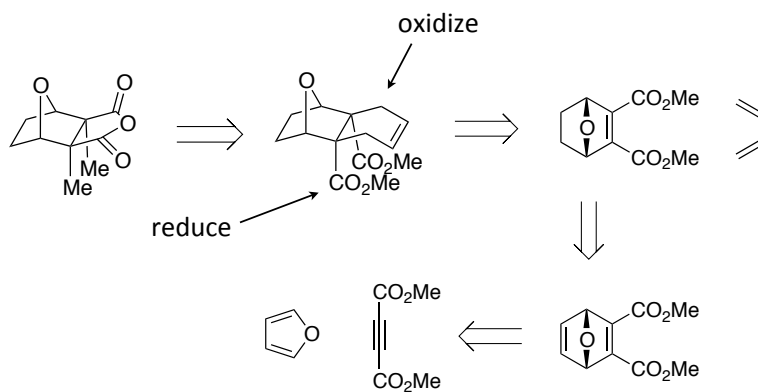
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

### A Stereospecific Synthesis of Cantharidin

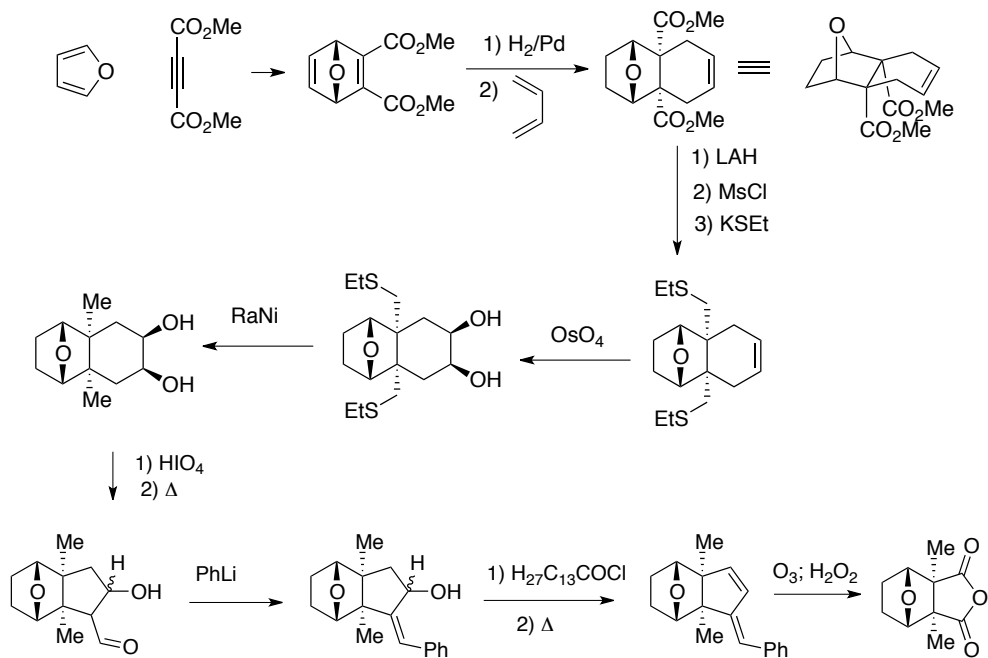
BY GILBERT STORK, EUGENE E. VAN TAMELEN, LEONARD J. FRIEDMAN AND ALBERT W. BURGSTAHLER<sup>1</sup>

RECEIVED AUGUST 13, 1952

the first planned stereospecific synthesis

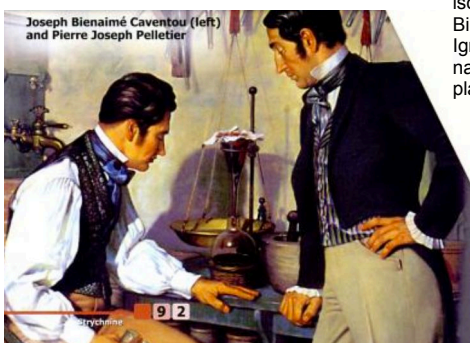


## cantharidin



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## strychnine



isolated by Pierre Joseph Pelletier and Joseph Bienamé Caventou in 1818 from the Saint Ignatius bean of the *Strychnos ignatii* tree, named by Jesuit missionaries who named the plant medicinally. Indigenous to the Philippines



Decades of experimentation, particularly by Robinson (250 papers!) and Hermann Leuchs led to structure elucidation by Robinson in 1946.

The **Strychnine tree** (*Strychnos nux-vomica* L.) also known as **Nux vomica**, **Poison Nut**, **Semen strychnos** and **Quaker Buttons**with, is native to [India](#), [southeast Asia](#)

It is a major source of the highly poisonous [alkaloids strychnine](#) and [brucine](#), derived from the seeds inside the tree's round, green to orange fruit. The seeds contain approximately 1.5% [strychnine](#), and the dried blossoms contain 1.023%.<sup>[1]</sup> However, the tree's bark also contains brucine and other poisonous compounds.



from wikipedia and *Molecules that changed the world* by Nicolaou

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## strychnine

Strychnine acts as a blocker or antagonist at the inhibitory or strychnine-sensitive glycine receptor (GlyR), a ligand-gated chloride channel in the spinal cord and the brain



Strychnine causes muscular convulsions and eventually death through asphyxia or sheer exhaustion.

-wikipedia

### AMERICAN PRACTITIONER AND NEWS: VOLUMES XIII AND XIV—1892.

#### Abstracts and Selections.

##### ALCOHOLISM AND ITS TREATMENT.—

Irwin and Rippe's intensive care medicine By Richard S. Irwin, James M. Rippe, 2008

#### STRYCHNINE

The use of **strychnine** as a pesticide dates back to the 16th century, when an extract of the Filipino St. Ignatius bean (*Strychnos ignatii*) was introduced as a rodenticide in Europe. **Strychnine** was used as a tonic, cathartic, and aphrodisiac as late as 1970, and resulted in numerous deaths [122–124]. It is also found as an adulterant in illicit drugs, such as cocaine and heroin. The only "**legitimate**" uses of **strychnine** today are as a pesticide and in research study of neural transmission [124–126].

Dr. Branthwaite, the resident physician of the Dalrymple Home in London, has also used strychnine in combination with other remedies in a number of cases with excellent results. Dr. J. L. Gray, of Laporte, Indiana, gives chloride of gold and sodium with nitrate of strychnine and a small quantity of atropia internally, and also injects gold and strychnine under the skin. The patients are seen four times a day, and the gold and strychnine are rapidly increased until the limits of tolerance are reached. Whisky is given in carefully regulated doses. The treatment lasts from three to six weeks. Dr. Gray has treated more than two hundred cases in this manner, and believes that about seventy per cent are cured.

## strychnine

LD50 = 1-2 mg/kg orally in humans

### Notable strychnine poisonings

- Strychnine poisoning (in contaminated wine) is one of the theories concerning the death of [Alexander the Great](#).
- Strychnine was used in several of the murders committed by serial killer [Thomas Neill Cream](#), who poisoned prostitutes on the streets of London
- Famous [Delta Blues](#) legend [Robert Johnson](#)'s whiskey bottle was laced with strychnine, resulting in pneumonia.
- A childhood friend of [Vincent Van Gogh](#), Margot Begemann, attempted suicide by ingestion of strychnine.
- [Belle Guinness](#) of La Porte, Indiana, also known as *Lady Bluebeard*, reportedly used strychnine to murder her victims at the turn of the last century.<sup>[6]</sup>
- [Hannes Hirtzberger](#), Mayor of Spitz in Lower Austria was reported to have been poisoned by Helmut Osberger, a local wine producer.<sup>[7]</sup>
- [Jane Stanford](#), co founder of [Stanford University](#) may have died from strychnine poisoning.<sup>[8]</sup>
- [Oskar Dirlewanger](#), the notorious WWII leader of the [SS-Sturmbrigade Dirlewanger](#), a penal battalion composed of German criminals, was known to have murdered several Jewish girls in the Lublin Ghetto in Poland by having them stripped naked and injected with strychnine. This was done for the entertainment of himself and his officers who watched their fatal convulsions while relaxing.<sup>[citation needed]</sup>
- A woman in San Diego, California was a victim of strychnine poisoning in 1990 at the hands of her husband, who had dialed 911 but hung up the telephone without leaving his name or address. Persistence on the part of the dispatcher and the rescue workers allowed them to locate and extract the victim, but she eventually died in the hospital.<sup>[9]</sup>



### Fictional strychnine poisonings

- Mrs. Emily Inglethorp in [Agatha Christie's](#) *The Mysterious Affair at Styles*
- Inmates in the popular TV series [The Wire](#) were given heroin doses laced with strychnine.
- Norman Bates' mother and her lover were killed with strychnine in [Alfred Hitchcock's](#) *Psycho*. The sheriff comments: "Ugly way to die."
- Chief Constable Riddle's daughter, Emily was killed with an accidentally lethal case of strychnine-laced cocaine in [Peter Robinson's](#) "[Cold Is The Grave](#)".
- Herb in *Die Softly* by [Christopher Pike](#).
- In [Cape Fear](#) Max Cady poisons Sam Bowden's dog with strychnine.
- Rio Takeuchi in the manga *Spiral*: Suiiri no Kizuna threatens main character, Ayumu Narumi in a game to test his luck using strychnine poisoning.
- In "[All Things Wise and Wonderful](#)", [James Herriot](#), the main character and local veterinarian, deals with several victims of strychnine poisoning when a dog-killer attacks the neighborhood dogs.
- The murder in the *Monk* episode *Mr. Monk and the Secret Santa* is carried out through a bottle of port poisoned with strychnine.
- The Joker makes a cameo appearance in the Elseworld graphic novel *Gotham* by *Gaslight* as a serial killer who tries to kill himself with strychnine, leaving him with a permanent grin.

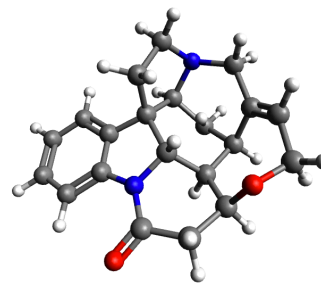
text from wikipedia; photo from smithsonian



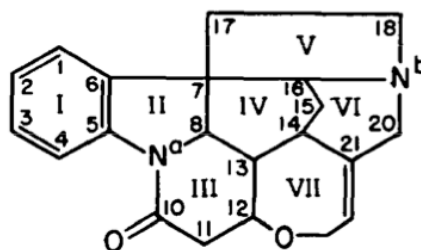
## strychnine

It was now possible to contemplate the synthesis of the substance of which it has been said: "For its molecular size it is the most complex substance known."<sup>‡§</sup>

<sup>‡</sup> Admittedly, by one whose special familiarity with the intricacies of its structure and behavior might excuse a certain prejudice,<sup>§</sup> but with six nuclear asymmetric centers and seven rings constituted from only twenty-four skeletal atoms, the case is a good one.

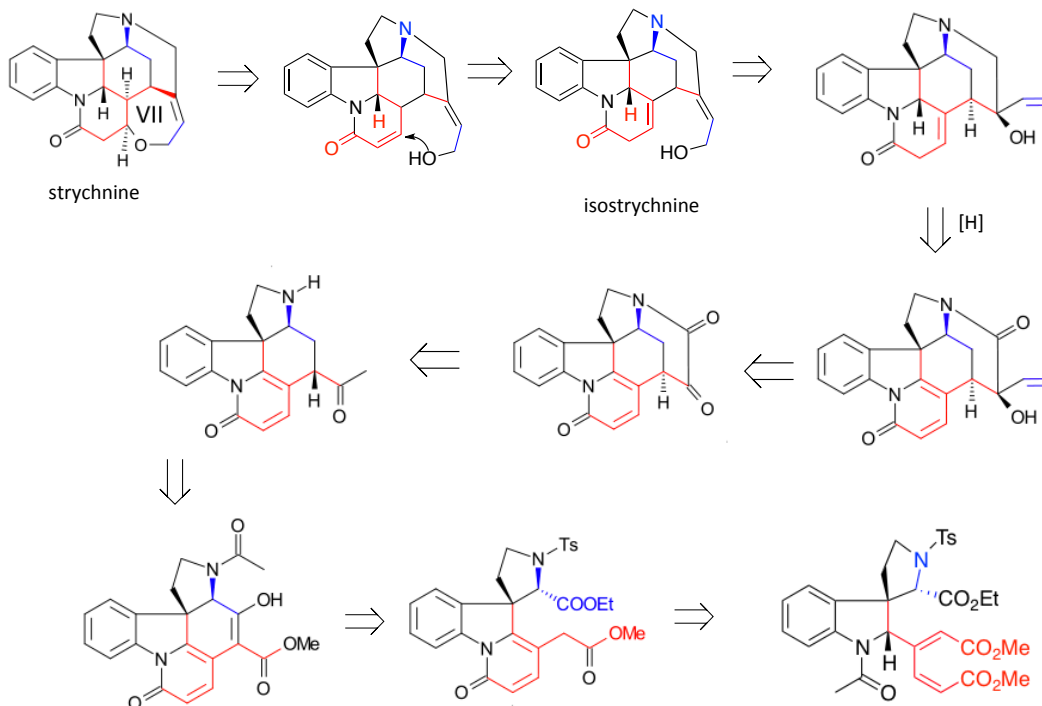


\* The accompanying diagram shows the numbering system used for strychnine throughout this paper.

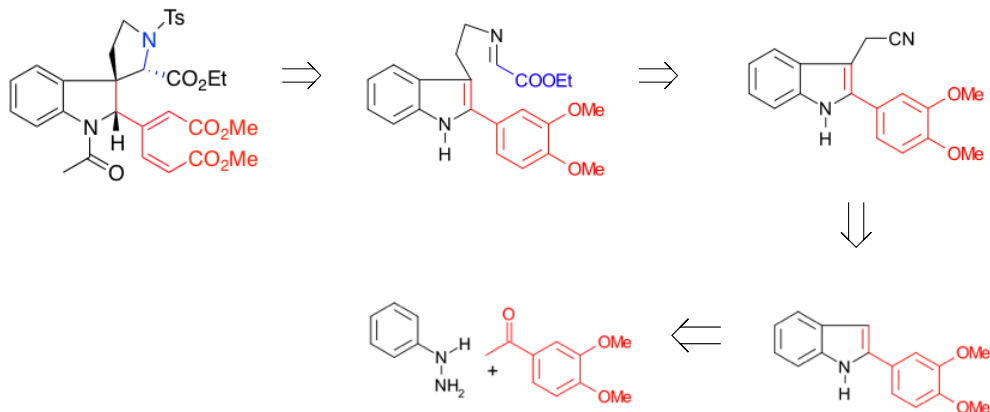


R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker *Tetrahedron*, **1963**, *19*, Pages 247-288  
Communication: *J. Am. Chem. Soc.* **1954**, *76*, 4749

## strychnine-retrosynthesis

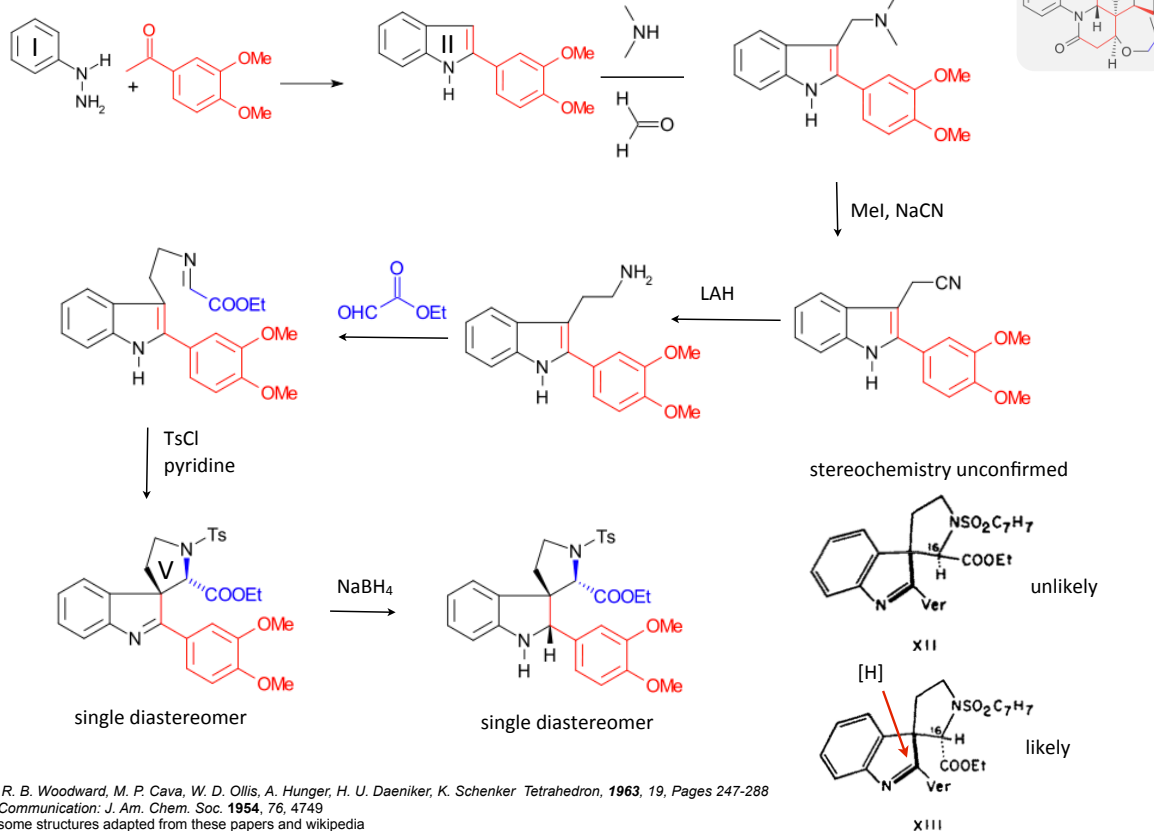


# strychnine- retrosynthesis



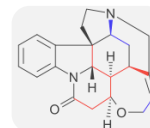
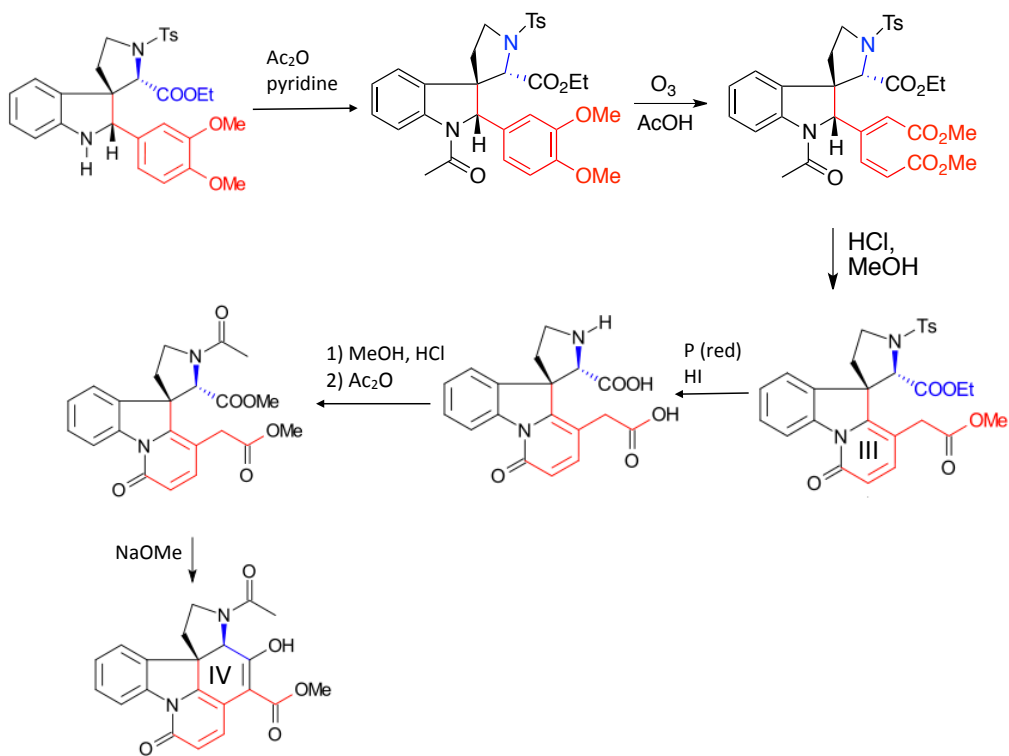
55

## strychnine

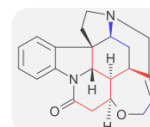
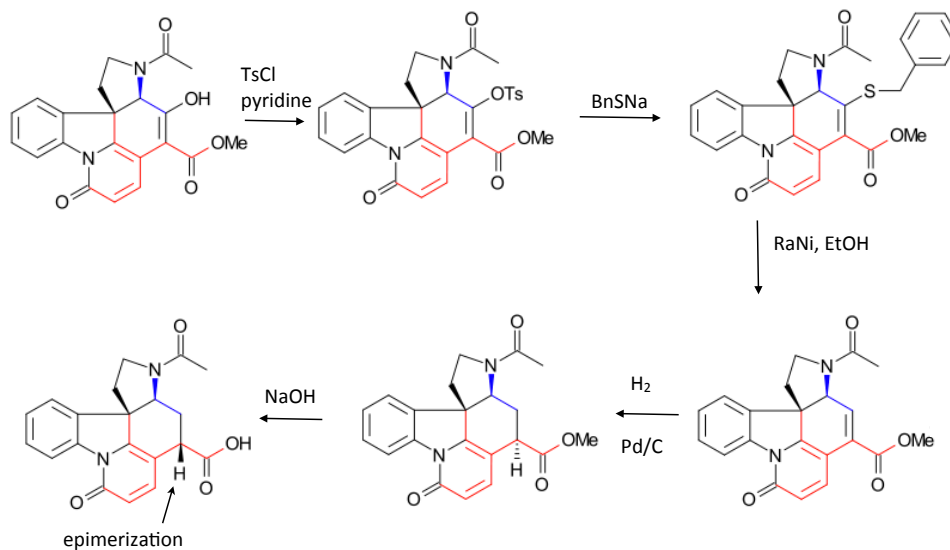




## strychnine

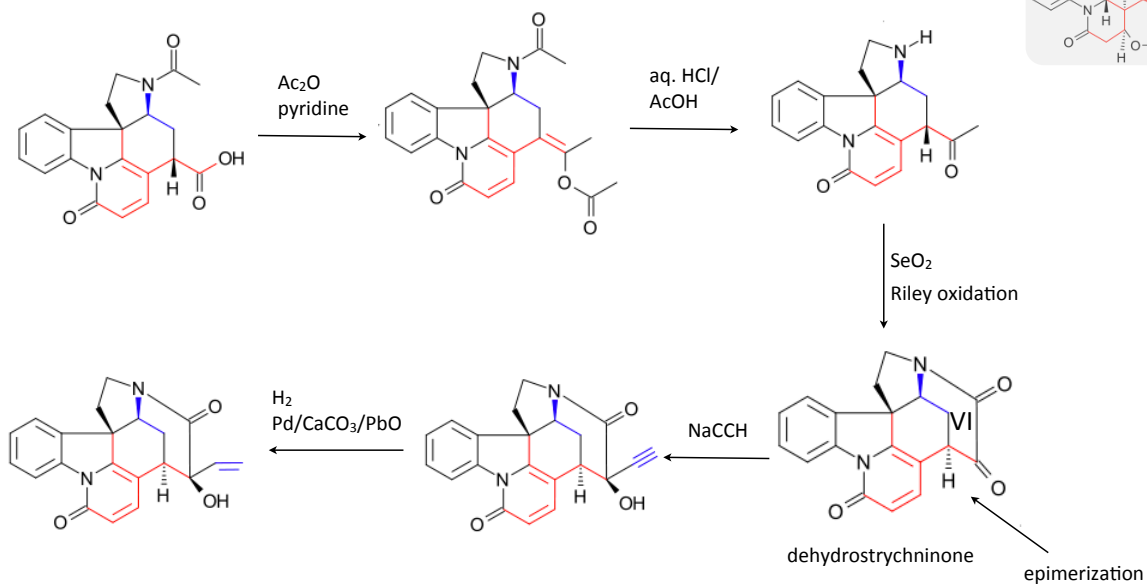
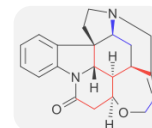


## strychnine



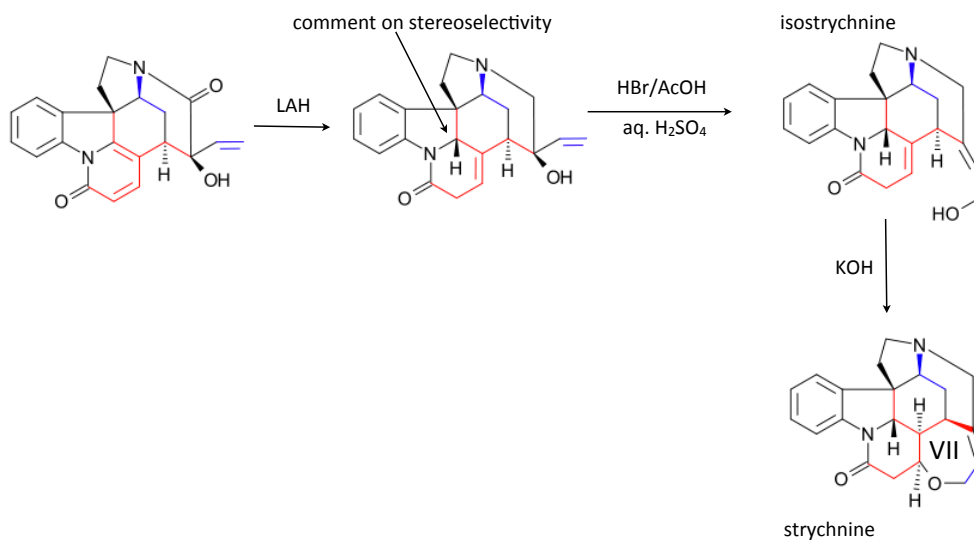
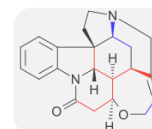
this intermediate could be resolved by quinine,  
and was available via degradation of natural strychnine

# strychnine



59

# strychnine



Avogadro  
introduce reaxys

work mechanisms if time permits