

Organic Medicinal Chemistry

A Historical Introduction



Image: National Library of Medicine

3100 BC – Medicines described in Chinese book of herbs (Pentsao), some of which contain constituents of modern medicines (Ma huang – ephedra sinica)

1550 BC – Compilation of 811 Egyptian formulae for fighting disease (Ebers Papyrus, 1862)

150 – Writings of Galen (Greece) assert imbalance of four humours cause disease – herbs with opposing qualities should cure disease (*contraria contrariis curantur*)

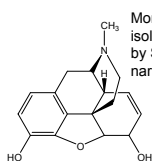
1470 – *Liber de Proprietatibus Rerum*, one of earliest herbals written by Bartholomeus Anglicus and published in Basle

1498 – first pharmacopoeia, *Nuovo Receptario Composito*, compiled by College of Physicians in Venice

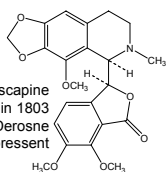
1493-1541 – Swiss physician Paracelsus urged alchemists to seek the *arcanum*, healing essence within effective pharmaceutical preparations (300 years passed before first active principle was successfully extracted from a plant)

1785 – role of oxygen in respiration elucidated by Lavoisier, administered for emergency resuscitation

1805 – morphine extracted from poppy by Sertürner (not widely recognized until 1817, when he reported dose of 100 mg gave symptoms of severe opium poisoning to himself and three companions) – second plant alkaloid reported in the literature (first in 1803)

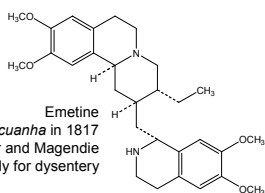


Morphine
isolated from opium in 1805
by Sertürner
narcotic, cough suppressant



Noscapine
isolated from opium in 1803
by Derosne
cough suppressant

Early Alkaloids



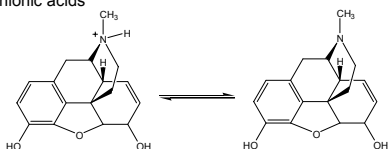
Emetine
isolated from *ipecacuanha* in 1817
by Pelletier and Magendie
emetic, specific remedy for dysentery

Chemical Properties I – Acidity/Basicity

- Observations in the early 1800's
 - These compounds neutralized free acid
 - These compounds precipitate from aqueous alkaline solutions
 - These compounds react with acids to form readily crystallizable salts
- Use your chemical knowledge and the structures to rationalize these observations

Morphine Acid/Base Properties

- The N in morphine is a tertiary amine ($pK_a \sim 9$)
 - The protonated form:
 - neutralizes acids by donating a proton to them
 - is highly water soluble
 - forms crystalline salts with anionic acids
 - The neutral form:
 - is present at high pH
 - is not very water soluble



Relative Acid Strength

Acid		Approximate pK_a	Conjugate Base	
Strongest Acid	HNO_3	< -12		NO_3^-
	HF	-10		F^-
	HCl	-9		Cl^-
	$C_6H_5O_3H$	-6.5		$C_6H_5O_3^-$
	$(CH_3)_3COH$	-3.8		$(CH_3)_3CO^-$
	$(CH_3)_2C=OH$	-2.9		$(CH_3)_2C=O$
	CH_3OH	-2.5		CH_2OH^-
	HNO_2	-1.4		NO_2^-
	CF_3CO_2H	0.18		$CF_3CO_2^-$
	HF	3.2		F^-
	CH_3CO_2H	4.75		$CH_3CO_2^-$
	CH_3COCH_2COOH	9.0		$CH_3COCH_2COO^-$
	C_6H_5OH	9.9		$C_6H_5O^-$
	HCO_2H	10.2		CO_2^-
	$CH_3NH_2^+$	10.6		CH_3NH_2
	CH_3NH_2	16		$CH_2NH_2^-$
	$(CH_3)_2COH$	18		$(CH_3)_2CO^-$
	CH_3COCH_3	19.2		$CH_2COCH_3^-$
	$HC\equiv CH$	25		$HC\equiv C^-$
	H_2	35		H^-
	NH_3	38		NH_2^-
	$CH_2=CH_2$	44		$CH_2=CH^-$
Weakest Acid	CH_4	50		CH_3^-
				Strongest Base

1810 – *Organon der rationellen Heilkunde* published by Hahneman on his unproven principle *similia similibus curantur* (like cures like, homeopathy) opposing Gellen's theory. Therapeutic doses had to be minute as illness renders patient highly sensitive to drug.

1826 – Mass production of pharmaceutical natural product – Pelletier's factory processed 150,000 kg of cinchona bark annually to produce 3600 kg of quinine sulphate (an antimalarial compound)

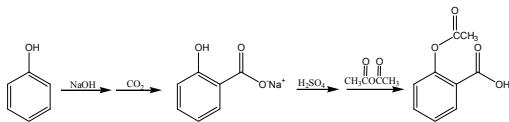
1878 – Concept of a biological receptor formulated by British pharmacologist John Langley studying effects of atropine and pilocarpine on cat salivary flow

1886 – First alkaloid synthesis, coniine (from Hemlock)

1897 – Ehrlich described sidechain theory: germicidal capability of a molecule depends on its structure, particularly its sidechains, which can bind to disease-causing organisms

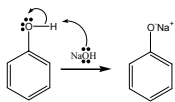
1898 – First mass-produced synthetic drug, Aspirin (Bayer, 1898). Compound first reported in 1853, and could not be patented, process was patented and name was proprietary. First mass mailing of pharmaceutical information (30,000 doctors)

The Bayer Process



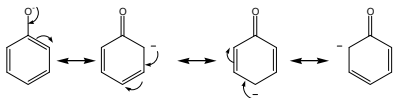
What chemical intermediates are not drawn and what mechanisms are occurring?

Bayer Process – Step 1

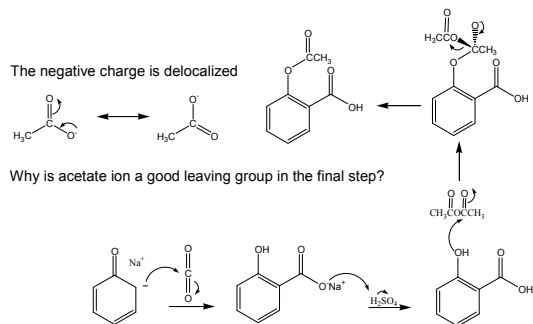


Why is NaOH a strong enough base to remove a proton from this alcohol?

The conjugate base of phenol is resonance-stabilized, phenol is therefore a stronger acid than a typical aliphatic alcohol



Bayer Process – Continued



1940 – DNA ligands leading to cell death are first cancer chemotherapeutics

1950 – First protein structure solved

1963 – Merrifield method of solid-phase peptide synthesis reported, later adapted for combinatorial synthesis (mid-1980's)

1965 – Receptor families and selectivity of agents for family members reported

1979 – First report of computing interactions between a drug and its biological target (ethidium and derivative with DNA fragment)

1989 – High throughput screening allows rapid evaluation of compounds (interleukin-1)

2001 – Drug 'likeness' used as an *in silico* screening strategy

Visualizing Chemical Structures

- Static Images (available in many places on the WWW, in your text, etc)
- Molecular Models
 - Hand held (build it yourself)
 - Computer generated
 - MOE (Molecular Operating Environment)
 - Launch MOE
 - Build Aspirin using the functions available in the Builder
 - Use the 'Using the Mouse' section of the online help to:
 - » rotate the structure
 - » zoom into the structure
 - Spartan

Finding Relevant Literature

- SciFinder Scholar (searches Chemical Abstracts from the early 1900's)
- Medline (1965 present), linked from library home page (exlibris.memphis.edu)
- Science Citation Index (paper copies in main library) allows you to trace from an old reference to newer literature
- Protein DataBank (<http://www.rcsb.org>)
- GenBank (<http://www.ncbi.nlm.nih.gov/Entrez/>)

Class Activity

- Make a preliminary selection of a disease for the class project
- Try to find agents used to treat that disease that have been reported in the literature
- Note in particular:
 - Structures of current therapeutics
 - Mechanism of action (biological target)
 - Is structural information available for biological target?
