Kapitel 3: Heteroalicyclen, Heteroaromaten

▷ Gliederung

- Aromatische und nichtaromatische Heterocyclen: Nomenklatur – Strukturen
- **Nichtaromatische** Heterocyclen: Elektronenstruktur, Ringspannung, Konformation, Stereochemie, Acidität
- **Nichtaromatische** Heterocyclen: Synthese und Reaktionen
- **Heteroaromaten**: Elektronenstruktur, Aromatizität
- **Heteroaromaten**: Synthese und Reaktionen
- **Heteroaromaten**: Substanzklassen
- **Ausgewählte Topics**: Heterocyclische Verbindungen in „life science“ und Materialwissenschaften

Bibliographie

- D. T. Davies, Aromatische Heterocyclen, Basistexte Chemie, Vol. 1, VCH, Weinheim, **1995**.
- A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, Heterocycles in Life and Society - An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine and Agriculture, John Wiley & Sons, Chichester, **1997**.
- T. Eicher, S. Hauptmann, Chemie der Heterocyclen, Georg Thieme Verlag, Stuttgart, **1994**.

Nomenklatur: Hantzsch-Widman

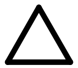
X=O; Oxa-
X=S; Thia-
X=Se; Selena-
X=NR; Aza-
X=PR; Phospha
X=SiR_2; Sila-

Ringgrösse	ungesättigt	gesättigt
3	iren (irin)	iran (iridin)
4	et	etan (etidin)
5	ol	olan (olidin)
6	in	an (inan)
7	epin	epan
8	ocin	ocan
9	onin	onan
10	ecin	ecan

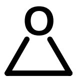
(in Klammer: stickstoffhaltige Verbindungen)

Nomenklatur

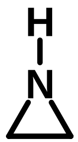
- Trivialnamen
- Substitutionsnomenklatur
- Hantzsch-Widman-Nomenklatur



Cyclopropan

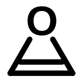


Oxacyclopropan
Oxiran
Ethylenoxid

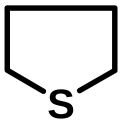


Azacyclopropan
Aziridin
Ethylenimin

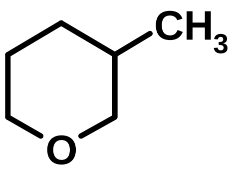
Thiacyclopropan
Thiiran



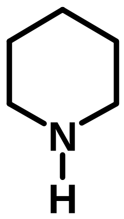
Oxiren



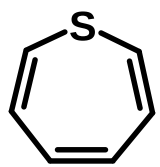
Thiacyclopentan
Tetrahydrothiophen
Thiolan



3-Methyloxacyclohexan
3-Methyltetrahydropyran

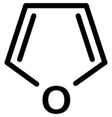


Azacyclohexan
Piperidin

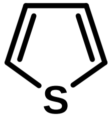


Thiepin

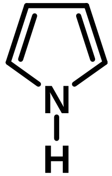
Heteroaromaten - Einige Basisstrukturen



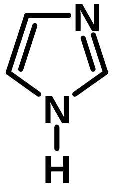
Furan



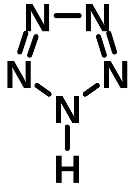
Thiophen



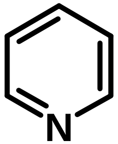
Pyrrol



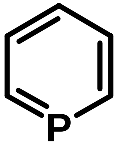
Imidazol



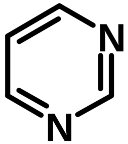
Pentazol



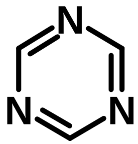
Pyridin



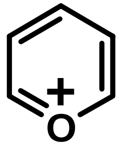
Phosphabenzol
(Phosphabenzen)



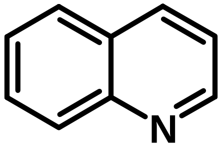
Pyrimidin



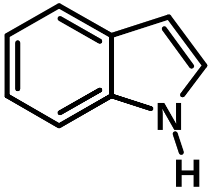
1,3,5-Triazin



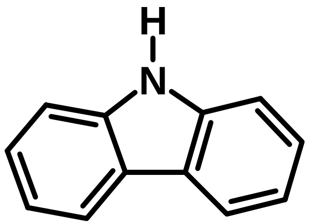
Pyrylium-Ion



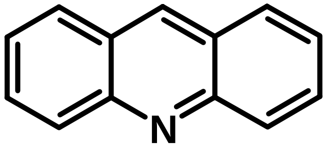
Chinolin



Benzo[b]pyrrol
Indol

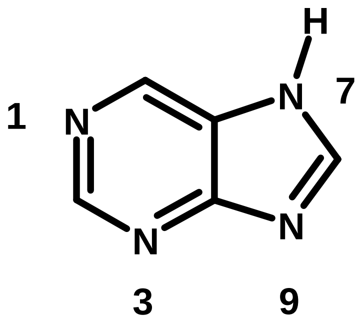


Carbazol
Dibenzopyrrol

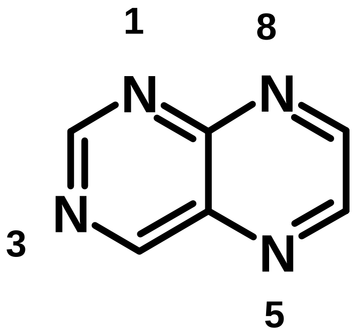


Acridin
Benzo[b]chinolin
Dibenzo[b,e]pyridin

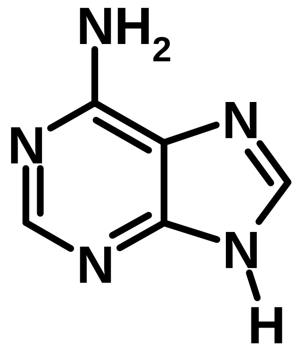
Heteroaromaten: Basisstrukturen



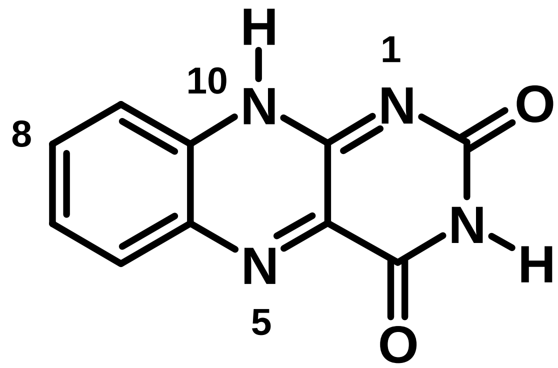
Purin
(7H-Purin)



Pteridin



Adenin



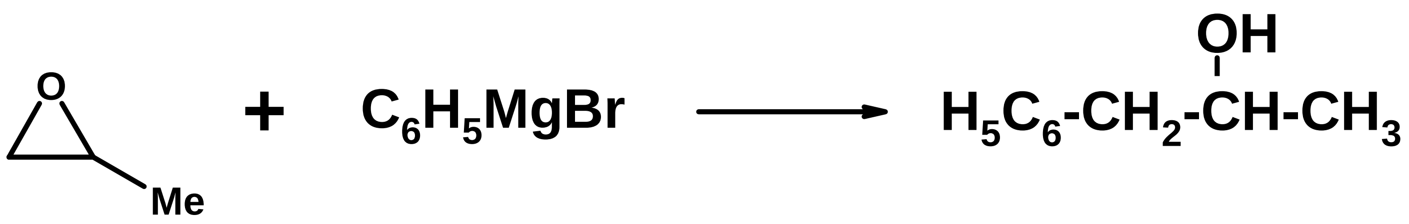
Isoalloxazin (Flavin)

Elektronenstruktur und Spannungsenergie

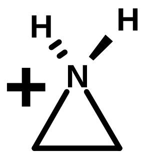
- Dreiringverbindungen besitzen eine strukturtypische Elektronen-konfiguration mit vergleichsweise hohem p-Charakter der endocyclischen Bindungen und höherem s-Charakter der exocyclischen Bindungen (Walsh-Modell, Bananenbindung). Diese Modelle erklären die physikalischen und chemischen Eigenschaften: Basizität von Aziridin, Ionisationspotential von Aziridin, H-Brückenbindung zu Oxiran, spektroskopische Eigenschaften.

Spannungsenergie und Reaktivität

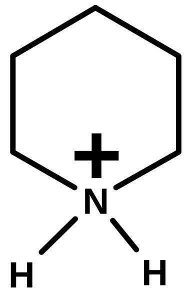
25 kcal/mol | 13 kcal/mol | 14 kcal/mol | 9 kcal/mol



Acidität und Struktur: pK_a-Werte



pk_a = 8.04



pk_a = 11.12

Wieso ist protoniertes Aziridin stärker acid als protoniertes Piperidin?

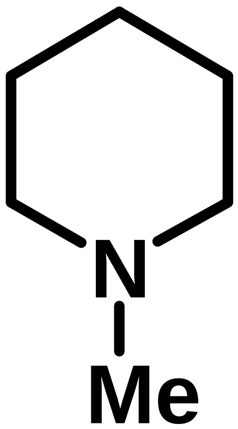
Welchen Wert hat der pk_a der protonierten Form von Morpholin?

Stereochemie - Stereoisomerisierung

✍ Analysieren Sie die konformative Eigenschaften von N-Methylpiperidin.

Zeichnen Sie die beiden Konformationen der Sesselform.

Für die Isomerisierung gibt es zwei Mechanismen. Welche?



Synthese nichtaromatischer Heterocyclen (Heteroalicyclen)

- Cyclisierung von ω-Halogenalkoholen bzw. ω-Halogenalkylaminen (Verdünnungsprinzip)
- Kronenethersynthese (Templatsynthese)
- [2+1]-Cycloaddition: Epoxidierung
- [2+2]-Cycloaddition: Paterno-Büchi Reaktion (Photochemie)
- [3+2]-Cycloaddition: Styrol und Phenylazid→Diphenyltriazolin (1,3-dipolare Cycloaddition)

Reaktionen nichtaromatischer Heterocyclen

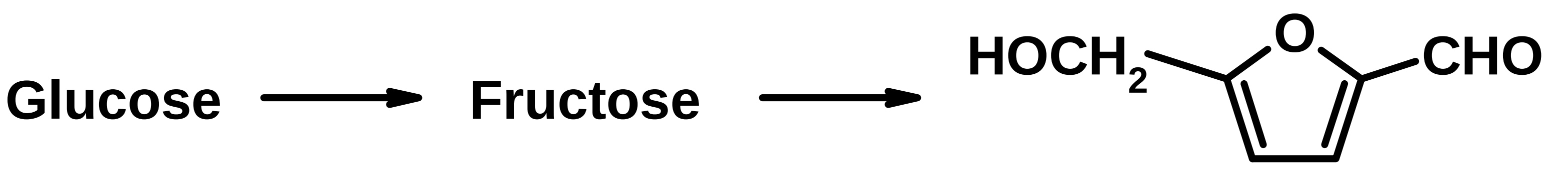
- Ringöffnung von Dreiring und Vierringverbindungen: Addition eines Nucleophils; Katalyse. (Ringspannung, S_N-Typ Reaktion)
- Carbonylumpolung: 1,3-Dithian-Chemie (Carbanionchemie)
- Tetrahydropyranyl-Schutzgruppe für Alkohole (Enoletherchemie)

Heteroaromaten: Furan, Thiophen, Pyrrol, Pyridin
Elektronenstruktur und molekulare Struktur

* Molekülorbitalmodell
* Mesomeriestabilisierung (Aromatizität): Benzol>Pyridin>Thiophen>Pyrrol>Furan
* Elektronendichteverteilung: elektronenreiche (z.B. Pyrrol) und elektronenarme Heterocyclen (z.B. Pyridin) – Analogie zu substitutierten Benzolen (Anilin bzw. Nitrobenzol)
* Basizität heterocyclischer Verbindungen (pK_a der konjugierten Säuren): Pyrrol (-3.8); Pyrimidin (1.0); Pyridin (5.2); Imidazol (6.8); Pyrrolidin (11.1)
  Vergleich Anilinium pK_a: 4.6
* N-H Acidität (pK_a): Pyrrol (~17); Pyrrolidin (~36)

Heteroaromaten: Furan, Thiophen, Pyrrol
Ausgewählte Synthesen

* Paal-Knorr-Synthese: 2,5-Dimethylfuran
* 1,3-Dipolare Cycloaddition: 1,5-Dialkyltetrazol aus Nitril und Azid
* 5-Hydroxymethylfurfural aus Hexose (Glucose, Fructose) durch Reaktion in Wasser mit Schwefelsäure als Katalysator



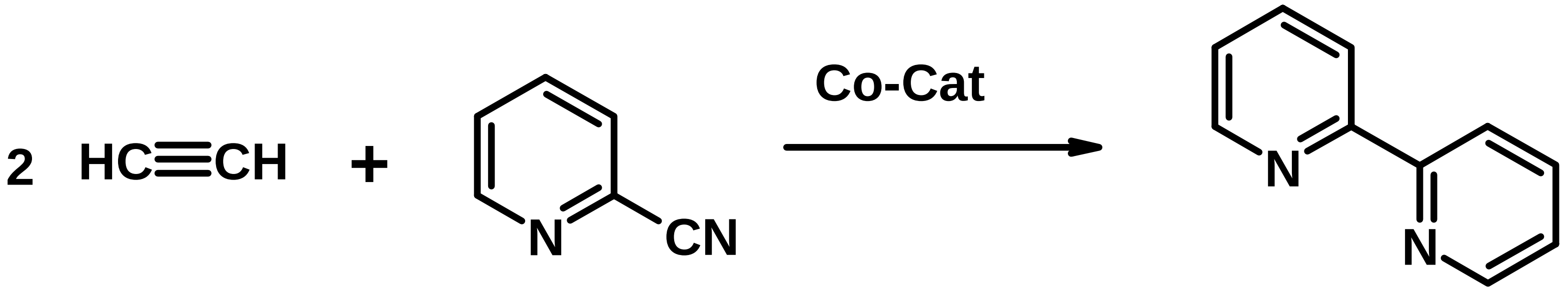
5-Hydroxymethylfurfural

Heteroaromaten: Furan, Thiophen, Pyrrol
Ausgewählte Reaktionen

* Elektrophile Substitution: 2-Nitropyrrol, 3-Nitropyrrol (Nitroniumacetat)
* Porphinsynthese: Pyrrol-2-aldehyd/Ameisensäure
* Ringöffnung: 2,5-Dimethylfuran (H^+/erhitzen)$\rightarrow$2,5-Hexandion
* Diels-Alder Reaktion: Furan reagiert mit Acetylendicarbonsäurediethylester
* Lithiierung von Thiophen: 2-Lithiumthiophen

Heteroaromaten: Pyridine - Ausgewählte Synthesen

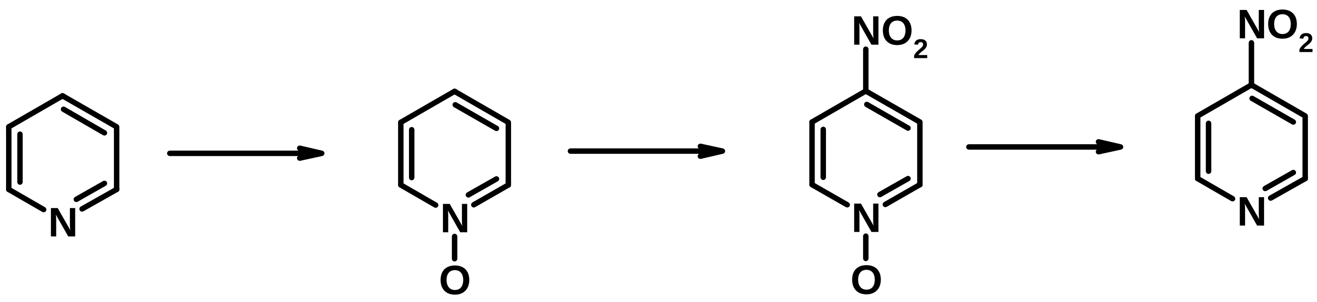
* Hantzsch Synthese substituierter Pyridine, Dreikomponentenreaktion: ß-Oxoester, Aldehyd, Ammoniak
* Übergangsmetallkatalysierte Cyclisierung



2,2'-Pyridin

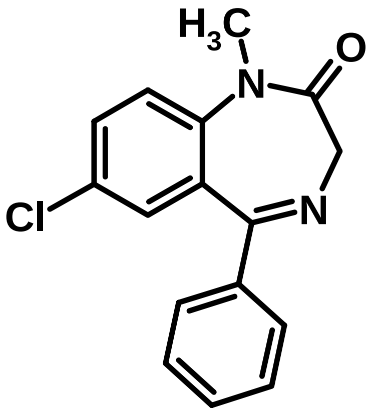
Heteroaromaten: Pyridine - Ausgewählte Reaktionen

* Elektrophile Substitution: Pyridin-3-sulfonsäure
* Pyridin-N-oxid: 4-Nitropyridin

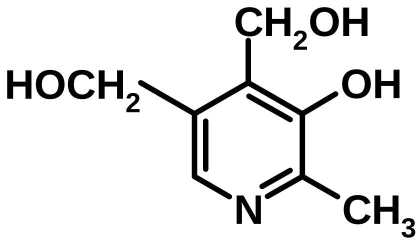


* Nucleophile Substitution: 2-Aminopyridin

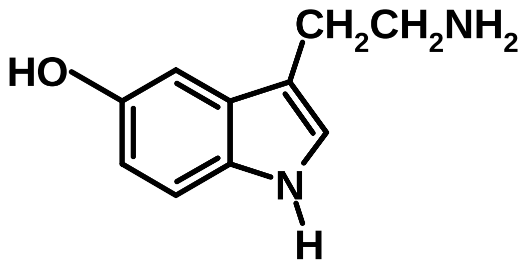
Ausgewählte Topics und Strukturen: Wirkstoffe, Vitamine, Neurotransmitter, Kronenether



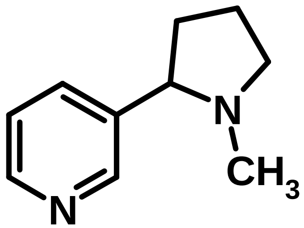
Diazepam
Valium



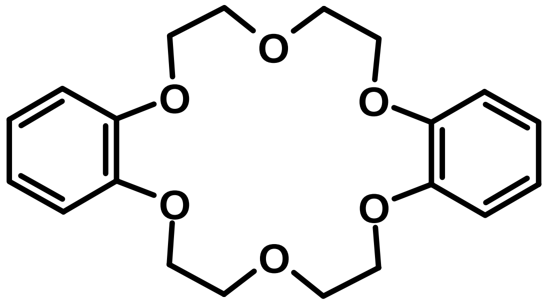
Pyridoxin
Vitamin B_6



Serotonin
(Neurotransmitter)



Nicotin

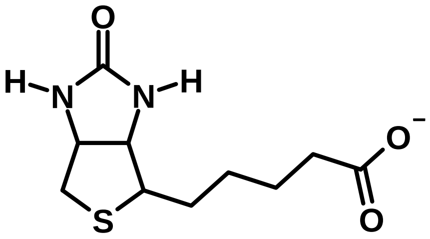


Dibenzo[18]krone-6

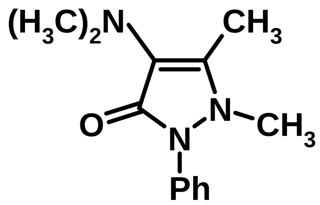
Ausgewählte Topics: Substanzklassen und Anwendungen

* Thiolan/Diazolidinon: Biotin (Vitamin H)
* 5-Pyrazolon (5-Oxo-4,5-dihydropyrazol, Tautomerie), Pyramidon
* Imidazole: Histidin (Aminosäure)
* 1,3-Dithiole: Tetrathiafulvalen (Organische Leiter, Supraleiter)
* Indol (Fischer Indolsynthese), Tryptophan (Aminosäure)
* Benzothiazol: Cyaninfarbstoffe, Luciferin (Glühwürmchen, Chemo- und Biolumineszenz)
* Indolderivate: Indigo (Farbstoff), Spiroindoline (Photochromie)
* Vitamine und Coenzyme
  - Vitamin B_1, Thiaminpyrophosphat
  - Vitamin $B_{6,}$ Pyridoxalphosphat (PLP)
* Pyridiniumverbindungen: Bispyridiniumchlorid (Paraquat, Herbicid); Niacin, Nicotinamid-adenin-dinucleotid (Coenzym)
* 2,4,6-Trichlor-1,3,5-triazin: Farbstoffchemie/Färbeverfahren
* Chinolin (Skraup'sche Chinolin-Synthese), (-)-Chinin (Chinolin-Alkaloide)

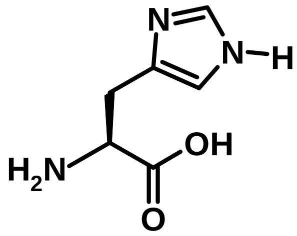
Ausgewählte Topics: Strukturen



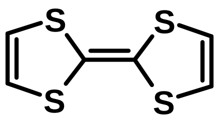
Biotin (vitamin H)



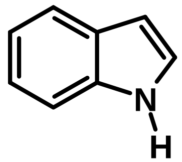
Pyramidon
[1-Phenyl-2,3-dimethyl-
4-dimethyl-amino-
pyrazolon-(5)]



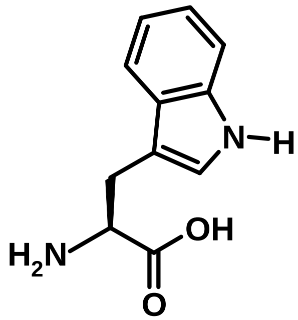
L-Histidin



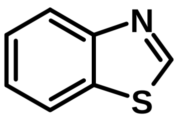
Tetrathiafulvalen
(TTF)



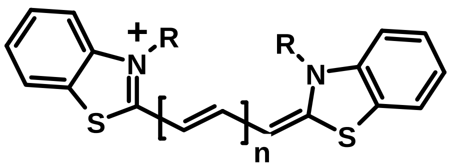
Indol
Benzo[b]pyrrol



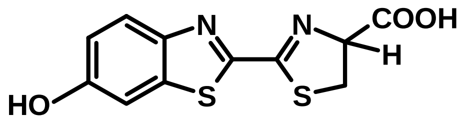
L-Tryptophan



Benzothiazol

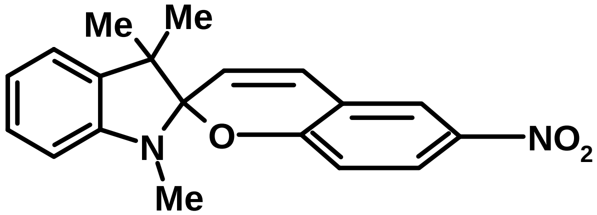


Farbstoff vom Cyanintyp

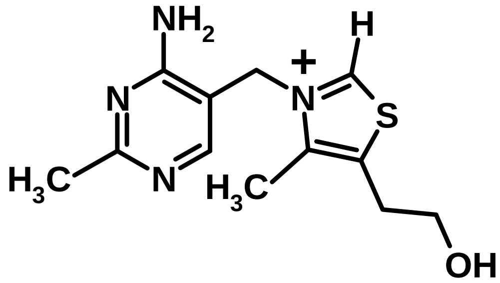


Luciferin
(Leuchtkäfer)

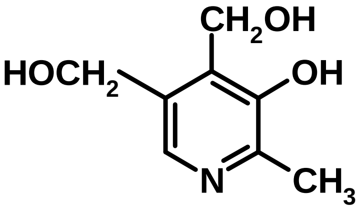
Ausgewählte Topics: Strukturen



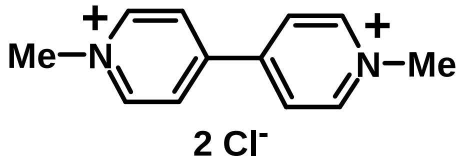
1,3,3-Trimethyl-2,3-dihydro-
indol-2-spiro-2'-(6-nitro-2H-chromen)
(photochromes Spiroindol)



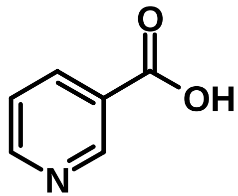
Thiaminpyrophosphat



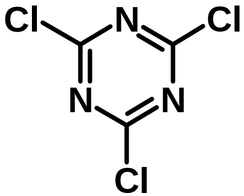
Pyridoxin
Vitamin B_6



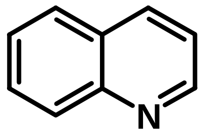
Paraquat
(Herbizid)



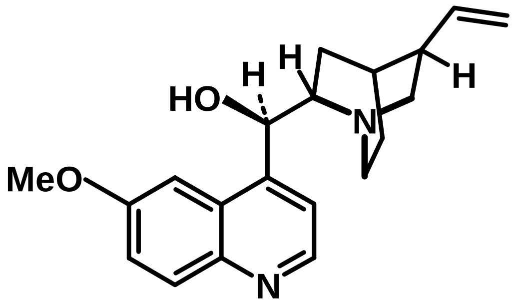
Niacin



2,4,6-Trichlor-
1,3,5-triazin



Chinolin

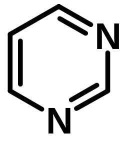


(-)-Chinin

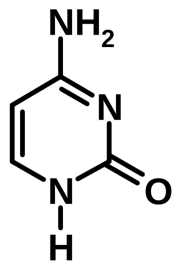
Ausgewählte Topics: Kondensierte π-Heterocyclen und makrocyclische π-Heterocyclen

* Pyrimidin, Cytosin, Uracil, Thymin (DNA-Basen)
* Purin, Adenin, Guanin (DNA-Basen), Coffein
* Isoalloxazin (Flavin), Riboflavin
* 1,3,5,8-Tetraazanaphthalin (Pteridin), Xanthopterin, Folsäure
* Phenothiazin
* Porphyrin, Chlorophyll, Vitamin B_{12}, Phthalocyanin

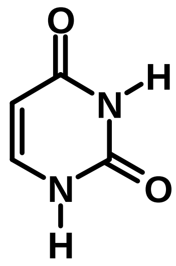
Ausgewählte Topics: Heterocyclische Grundstrukturen von Naturstoffen



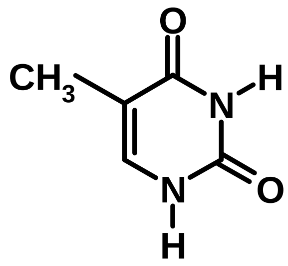
Pyrimidin



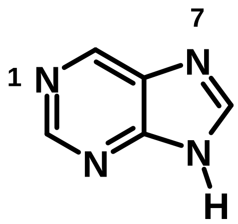
Cytosin



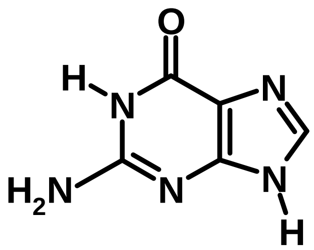
Uracil



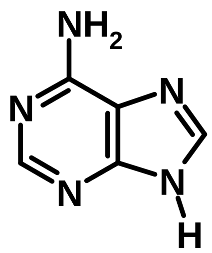
Thymin



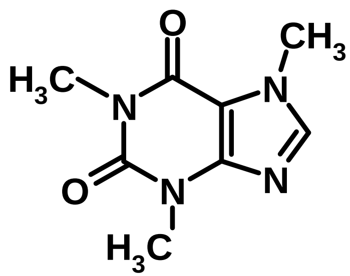
9H-Purin



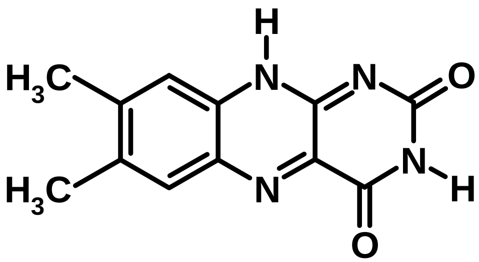
Guanin



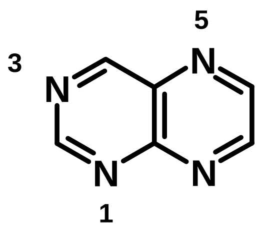
Adenin



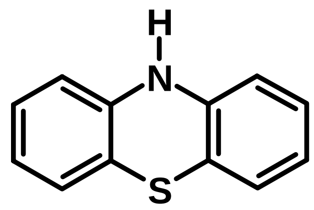
Coffein



7,8-Dimethylisoalloxazin

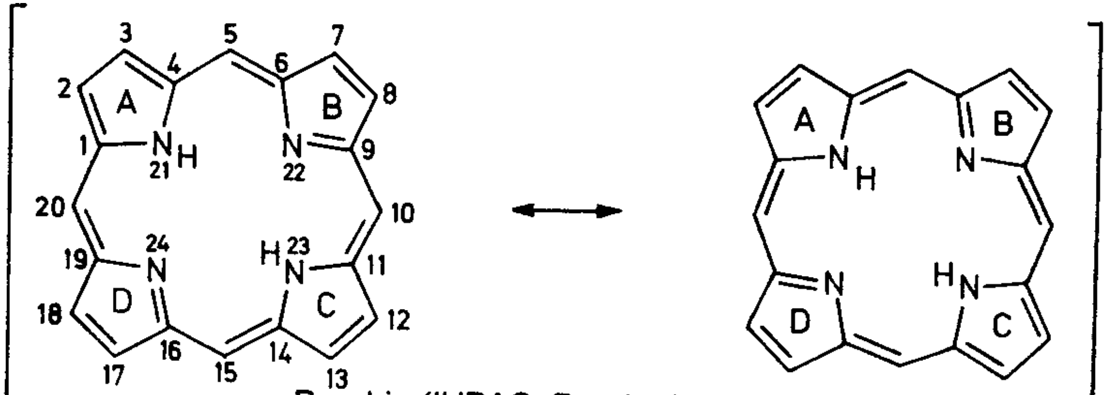


Pteridin

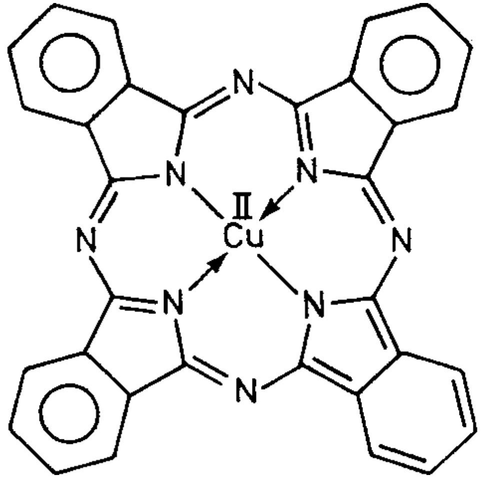


Phenothiazin

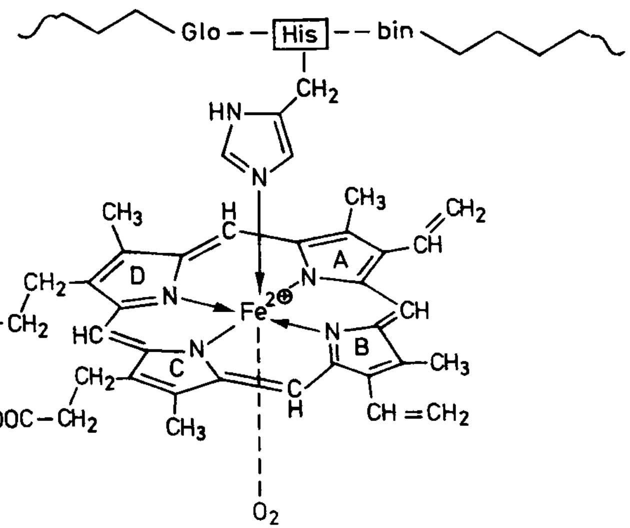
Ausgewählte Topics: Macrocyclische Heteroaromaten



Porphin (IUPAC: Porphyrin)



Kupfer-Phthalocyanin:
tiefblau, λ_{max} = 678 nm;
logε = 5,3



Hämoglobin

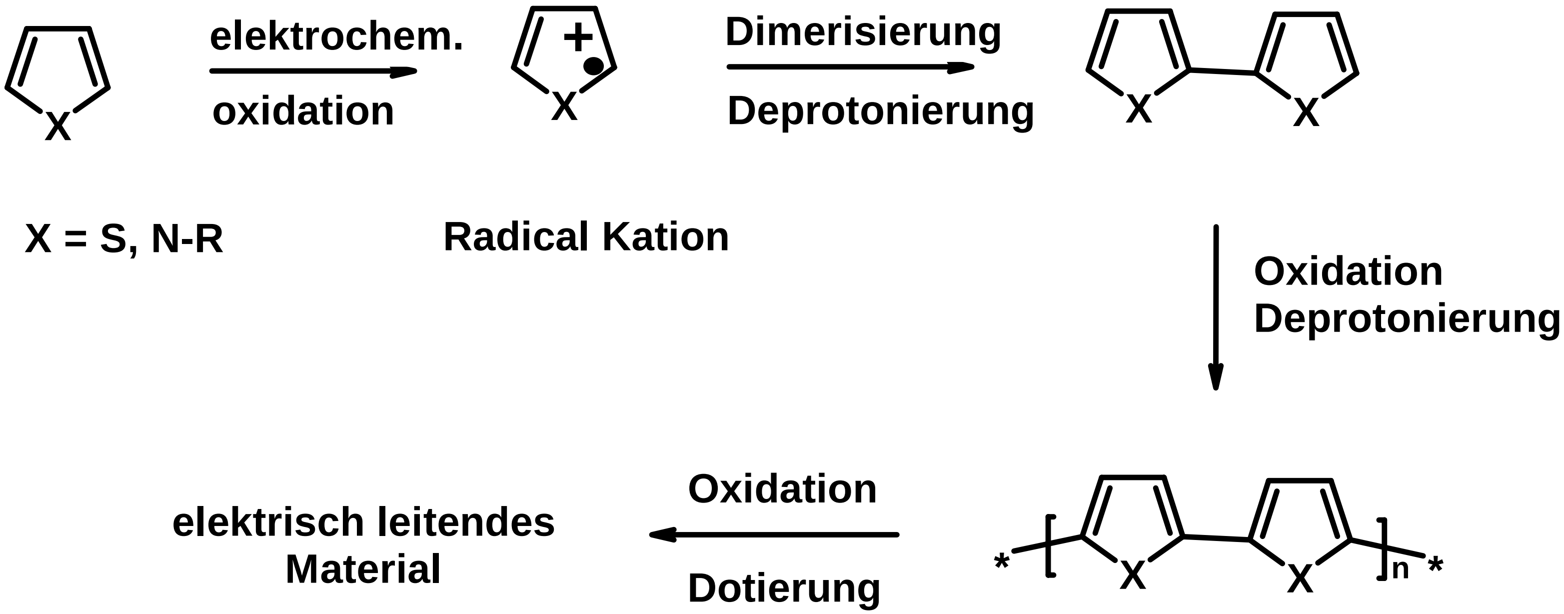
Heterocyclen in ‚life science‘ und Materialwissenschaften: Stoffsammlung

- Naturstoffe
- Herbicide, Fungicide, Insektizide
- Alkaloide
- Schmerzmittel
- Vitamine
- Hormone
- Antibiotika
- Arzneimittel
- Porphyrine

- Farbstoffe, Fluoreszenzfarbstoffe
- Kronenether, Cryptanden
- Elektrisch leitende Materialien (Polythiophen)
- Tetrathiafulvalen (Elektronendonor)
- N,N‘-Bipyridinium chlorid (Paraquat) (Herbicid, Elektronenakzeptor)

Organische Materialien: Elektrisch leitende Polymere

* Polypyrrol und Polythiophen



» M. Rehahn, *Chemie in unserer Zeit* **2003**, *37*, 18-30.