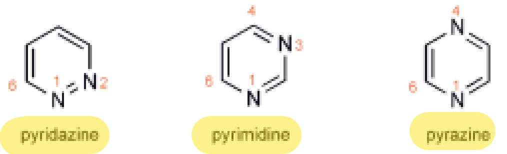
Typical Reactivity of the Diazines: Pyridazine, Pyrimidine and Pyrazine



2 atom N
six-member

- The diazines – pyridazine, pyrimidine and pyrazine – contain two imine nitrogen atoms
- Two heteroatoms withdraw electron density from the ring carbons even more than one in pyridine, so unsubstituted diazines are even more resistant to electrophilic substitution than is pyridine.

  يسحب e من الحلقة → بجعل الحلقة +ve جزئيًا → electrophil → not react with electrophil
- increased electron deficiency at carbon makes the diazines more easily attacked by nucleophiles than pyridine.

  → electrophil → attacked by nucleophil
- The availability of nitrogen lone pair(s) is also reduced: each of the diazines is appreciably less basic than pyridine, reflecting the destabilising influence of the second nitrogen on the N - protocation.

  → why?! because of electron repulsion (تنافر) and reduced stability of the protonated form
- Nevertheless, diazines will form salts and will react with alkyl halides and with peracids to give N - alkyl quaternary salts and N - oxides, respectively.
- Generally speaking, such electrophilic additions take place at one nitrogen only, because the presence of the positive charge in the products renders the second nitrogen extremely unreactive towards a second electrophilic addition.

لأنه لما تتفاعل إلكتروفيل مع ذرة نيتروجين بيتكون شحنة موجبة وتتنافر مع أي إلكتروفيل (+ve) بيحاول يرتبط مع N الثانية

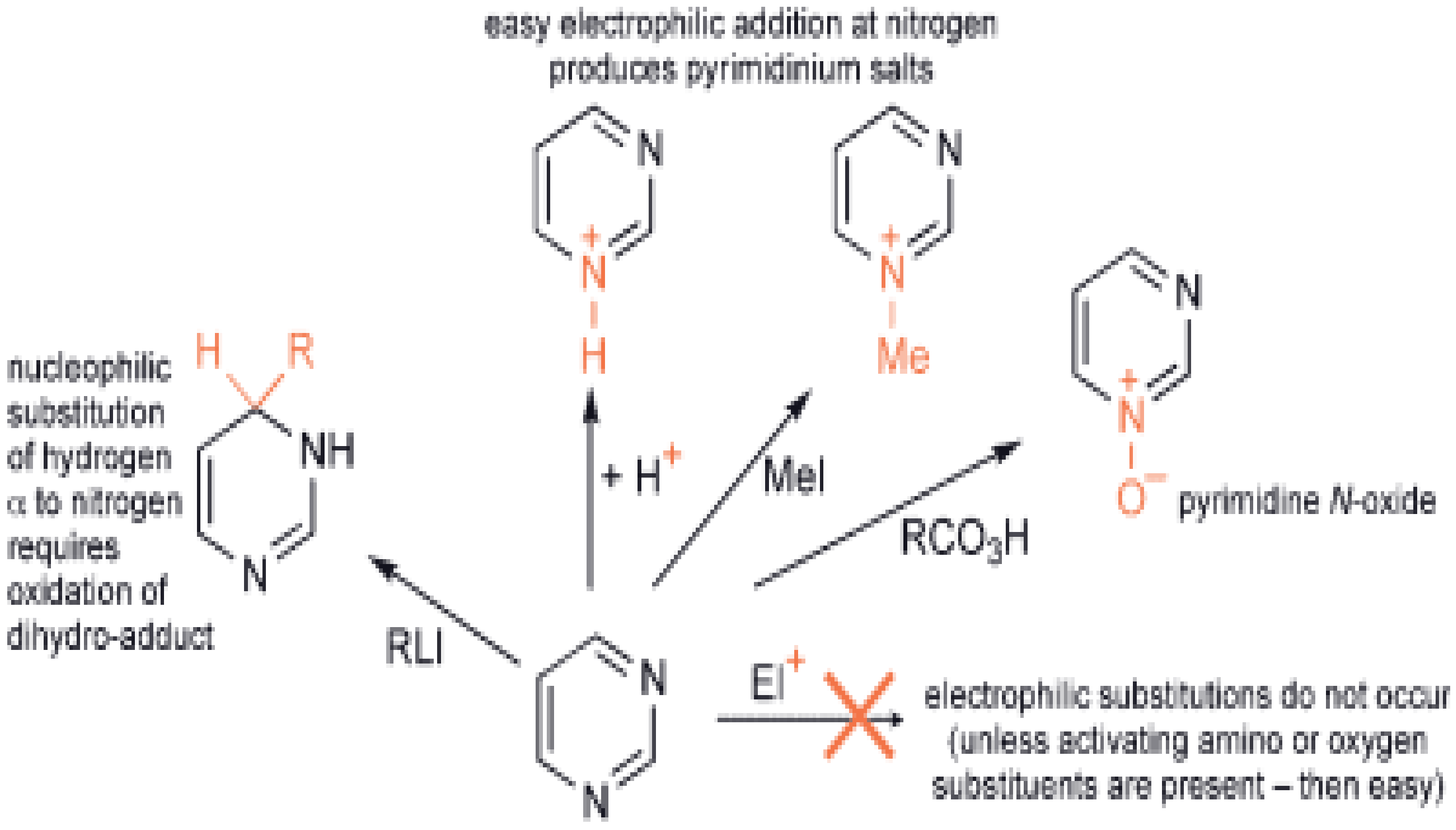
إذا ما عنا هاليد نحتاج لعملية الأكسدة لاكمال الاستبدال بشكل كامل

لأنه بسحب الإلكترونات من الحلقة لذلك يصبح موجب جزئيًا ← electrophil ← يتفاعل مع nucleophil

- A very characteristic feature of the chemistry of diazines, which is associated with their strongly electron - poor nature, is that they add nucleophilic reagents easily. Without halide to be displaced, such adducts require an oxidation to complete an overall substitution. However, halo - diazines, where the halide is α or γ to a nitrogen, undergo very easy nucleophilic displacements, the intermediates being particularly well stabilised.

عملية إضافة الهالوجين تكون على الموقع α, γ بالنسبة لـ N

- In line with their susceptibility to nucleophilic addition, diazines also undergo substitution by nucleophilic radicals, in acid solution, with ease.



easy electrophilic addition at nitrogen produces pyrimidinium salts

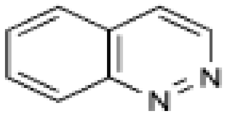
nucleophilic substitution of hydrogen α to nitrogen requires oxidation of dihydro-adduct

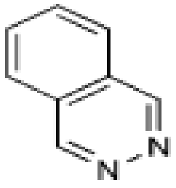
pyrimidine *N*-oxide

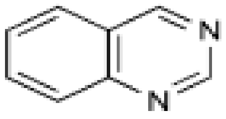
electrophilic substitutions do not occur (unless activating amino or oxygen substituents are present – then easy)

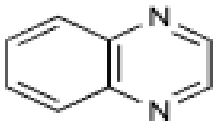
Typical reactions of a diazine illustrated with pyrimidine

حفظ الاسم والشكل


cinnoline


phthalazine


quinazoline

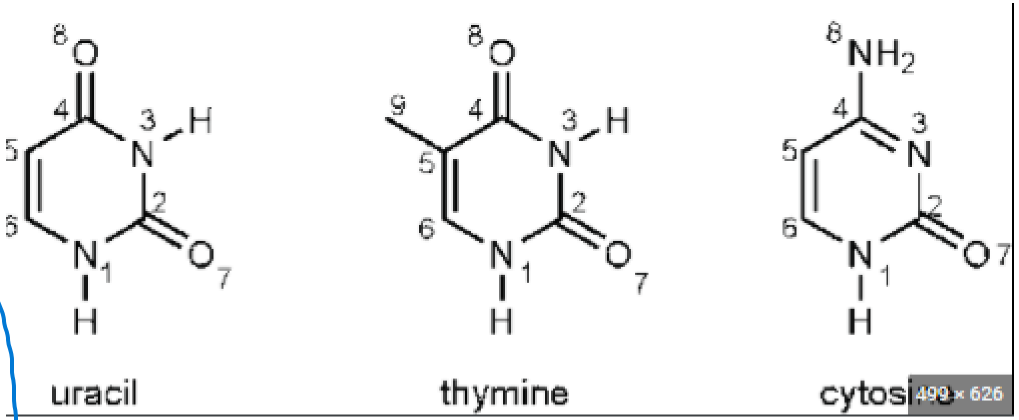

quinoxaline

- The three diazines, pyridazine, 1 pyrimidine, 2 and pyrazine 3 are stable, colourless compounds that are soluble in water.
- The three parent heterocycles, unlike pyridine, are expensive and not readily available and so are seldom used as starting materials for the synthesis of their derivatives.

مركبات diazine غالية على عكس بيريدين (رخيص) لذلك
نادرا نستخدم لإنتاج مواد أخري

- There are only four ways in which a benzene ring can be fused to a diazine: cinnoline, phthalazine, quinazoline and quinoxaline are the bicyclic systems thus generated.

لأنه ذرتين النيتروجين جنب بعض
وبساهموا في زيادة قطبية المركب
فهذا يزيد درجة الغليان للمركب



حفظ الشكل
والاسم

One striking aspect of the physical properties of the diazine trio is the high boiling point of pyridazine (207 ° C), 80 – 90 ° C higher than that of pyrimidine (123 ° C), pyrazine (118 ° C), or indeed other azines, including 1,3,5 - triazine, all of which also boil in the range 114 – 124 ° C.

The high boiling point of pyridazine is attributed to the polarisability of the N – N unit, which results in extensive dipolar association in the liquid.

The most important naturally occuring diazines are the pyrimidine bases uracil, thymine and cytosine, which are constituents of the nucleic acids

Reactions with Electrophilic Reagents

- Addition at Nitrogen
- 14.1.1.1 Protonation
- The diazines, pyridazine (p KaH 2.3), pyrimidine (1.3), and pyrazine (0.65) are essentially mono - basic substances, and considerably weaker, as bases, than pyridine (5.2). This reduction in basicity is believed to be largely a consequence of destabilisation of the mono - protonated cations due to a combination of inductive and mesomeric withdrawal by the second nitrogen atom

أكثر من البيريدين

موجب الشحنة

بس نيتروجينة وحدة بتتفاعل

سحب ودفع الالكترونات
عبر الحلقة

رنين ← انتقال
الإلكترونات عبر
عبر الروابط المزدوجة

في (pyridazine) بكون في في قوة تنافر بين lone pair على ذرتي النيتروجين لذلك عند إضافة H^+ بتقلل عنا هذا التنافر لذلك بتكون هذه العملية سريعة في هذا المركب لذلك هو أقوى قاعدة بينهم

- Secondary effects, however, determine the order of basicity for the three systems: repulsion between the lone pairs on the two adjacent nitrogen atoms in pyridazine means that protonation occurs more readily than if inductive effects, only, were operating. المؤثرة

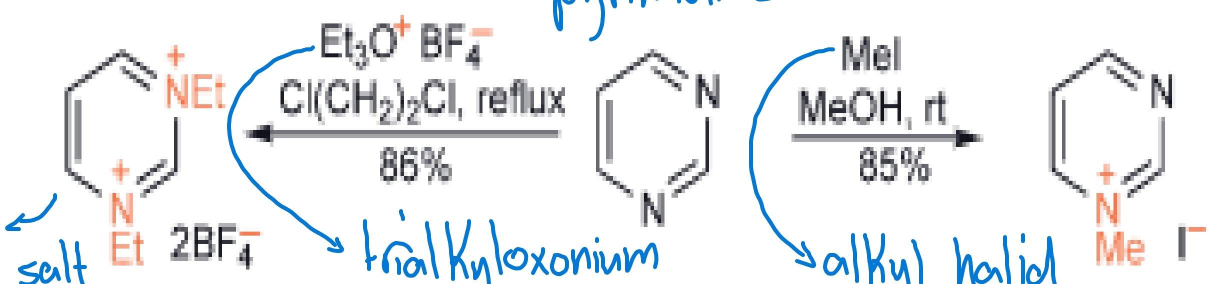
- In the case of pyrazine, mesomeric interaction between the protonated and neutral nitrogen atoms probably destabilises the cation

لأنه بيكسب المركب شحنة موجبة زي ما حكين فوق بيمنع ارتباط النيتروجين الثاني بـ H^+ فهذا يقلل استقرار المركب.

- N,N′ - Diprotonation is very much more difficult and has only been observed in very strongly acidic media

صعب يصير هذا المركب بس مش مستحيل

pyridazi



- Alkylation → add alkyl group

- The diazines react with alkyl halides to give mono - quaternary salts, though somewhat less readily than comparable pyridines. Dialkylation cannot be achieved with simple alkyl halides, however the more reactive trialkyloxonium tetrafl uoroborates do convert all three systems into di - quaternary salts

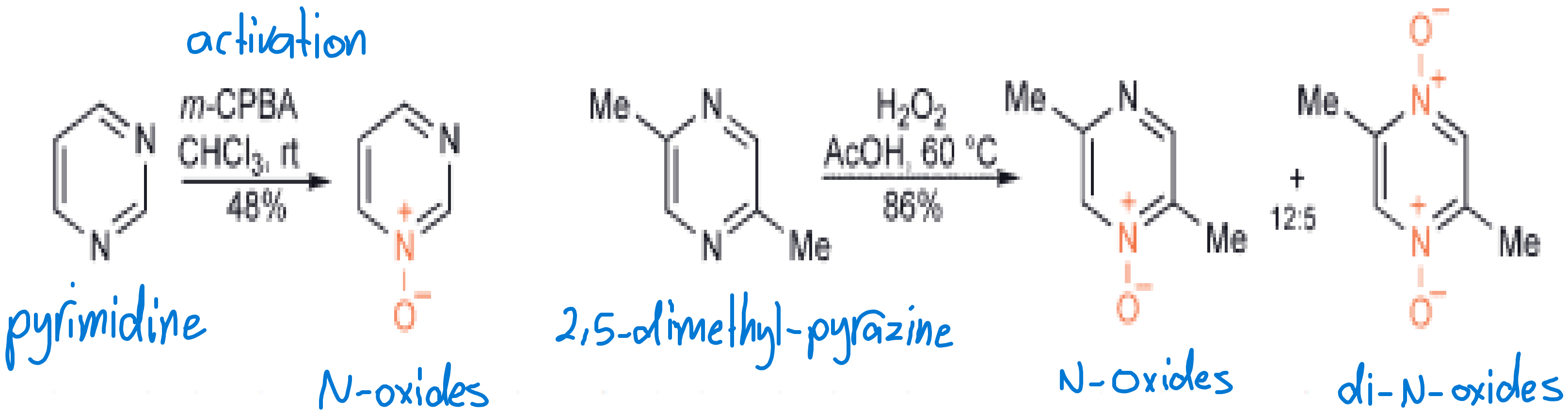
- **Pyridazine** is the most reactive in alkylation reactions and this again has its origin in the lone - pair/lone - pair interaction between the nitrogen atoms

↳ repulsion interaction

عملية الألكلة بتقلل التنافر بينهم عشان هيك بتصير بسرعة

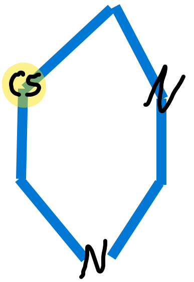
pyrazine
pyridazine + peracid ⟶ N- oxides

- Oxidation All three systems react with peracids, 8 giving N - oxides, but care must be taken with pyrimidines 9 due to the relative instability of the products under the acidic conditions. Pyrazines 10 form N,N′ - dioxides the most easily, but pyridazine 10 requires forcing conditions, and pyrimidines, apart from some examples in which further activation is present, give poor yields



بيحكي أن البيريدين عندها مقاومة بسبب وجود نيتروجين فما بالك بهذا النظام اللي فيه ذرتين نيتروجين
رح يكون أكثر "فقراً" بالالكترونات من البيريدين يعني أكثر مقاومة لتفاعلات الاستبدال الالكتروفيلي

- Substitution at Carbon Recalling the resistance of pyridines to electrophilic substitution, it is not surprising to find that introduction of a second azomethine nitrogen, in any of the three possible orientations, greatly increases this resistance: no nitration or sulfonation of a diazine or simple alkyl - diazine has been reported, though some halogenations are known. It is to be noted that C - 5 in pyrimidine is the only position, in all three diazines, which is not in an α - or γ - relationship to a ring nitrogen, and is therefore equivalent to a β - position in pyridine. Diazines carrying electron - releasing (activating) substituents undergo electrophilic substitution much more easily

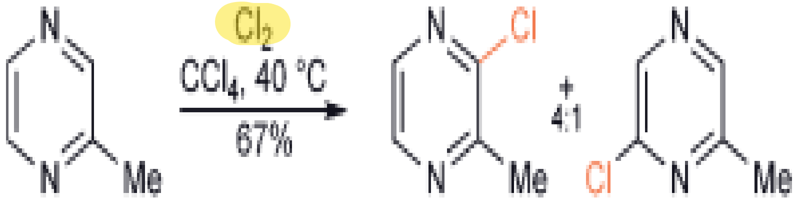


هو الموقع الأكثر قابلية للتفاعل ← B-carbon ←
(يكافئ مع B-carbon في البيريدين)

add Cl and remove H

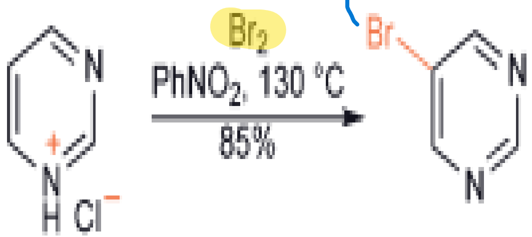
- **Halogenation** Chlorination of 2 - methylpyrazine occurs under such mild conditions that it is almost certain that an addition/elimination sequence is involved, rather than a classical aromatic electrophilic substitution. Halogenation of pyrimidines may well also involve such processe

mild condition



2-methylpyrazine

react at C5 (β-carbon)



pyrimidine

5-bromo-pyrimidine

- Reactions with Oxidising Agents

ما بيعمل أكسدة على الكربون بس على النيتروجين

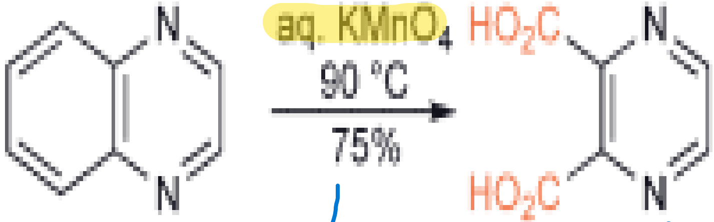
- The diazines are generally resistant to oxidative attack at ring carbons
- alkaline oxidising agents can bring about degradation via intermediates produced by initial nucleophilic addition .

أول شي بصير إضافة نيوكليوفيلية بعدين بصير أكسدة

- Alkyl substituents and fused aromatic rings can be oxidised to carboxylic acid residues, leaving the heterocyclic ring untouched.
- An oxygen can be introduced into pyrimidines at vacant C - 2 and/or C - 4 positions using various bacteria.
- Dimethyldioxirane converts N,N - dialkylated uracils into 5,6 - diols probably via 5,6 - epoxides

→ pyrimidine with bacteria → add O at C2 or C4 or both

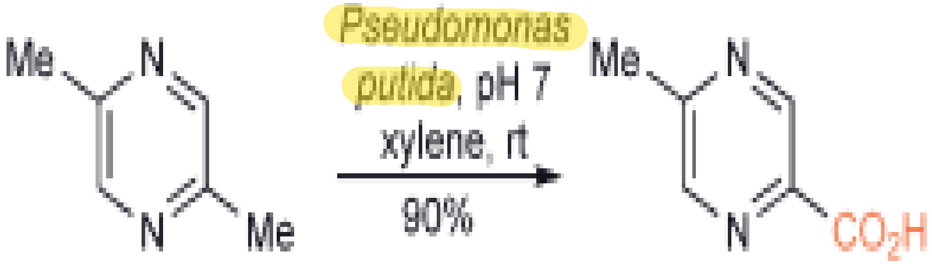
oxidizing agent



quinoxaline

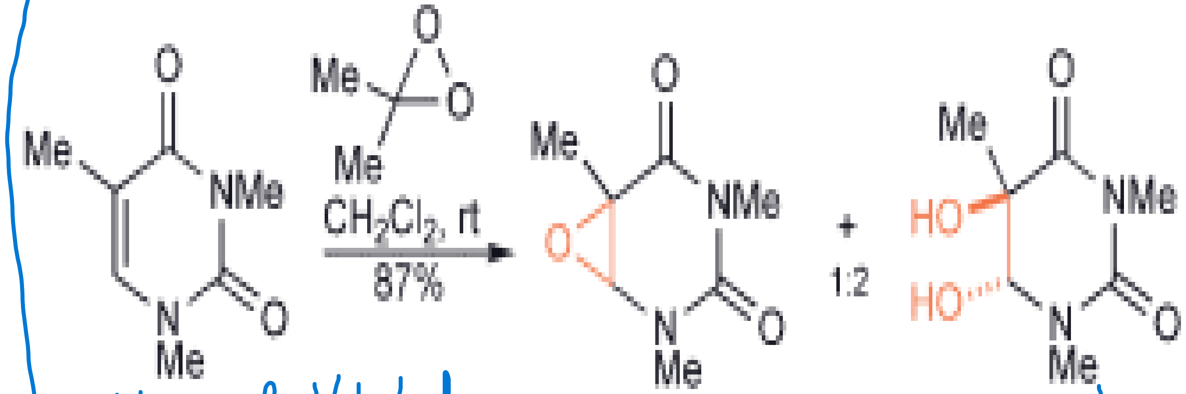
↳ degradation to benzene

carboxylic acid



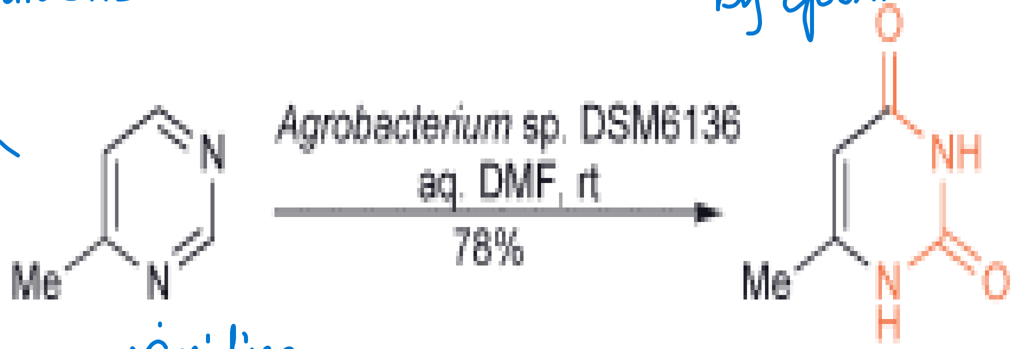
alkyl-pyrazine

carboxylic acid



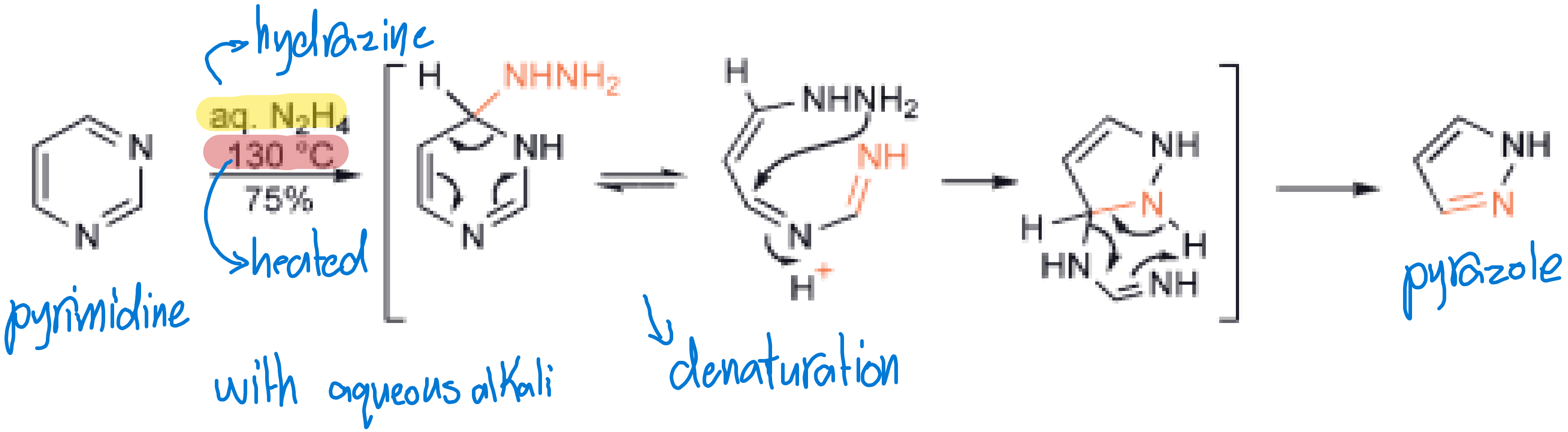
N,N-dialkylated uracils

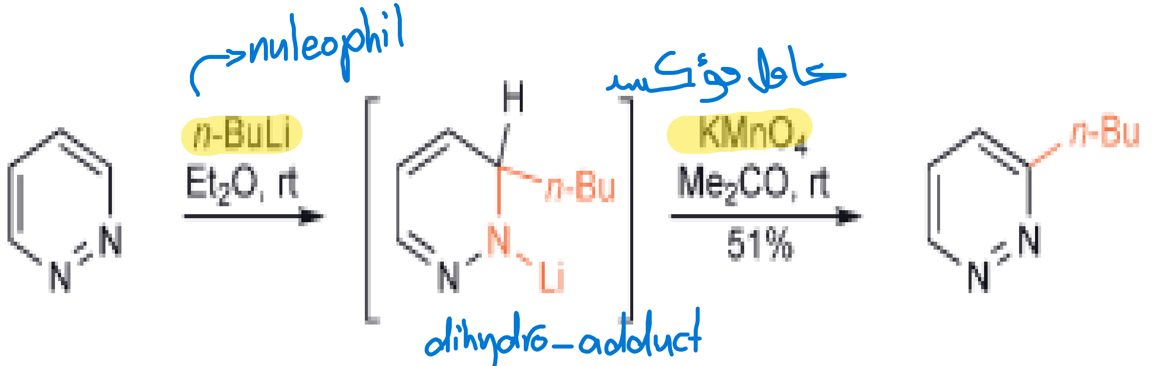
5,6-diol by epoxide



pyrimidine

- Reactions with Nucleophilic Reagents The diazines are very susceptible to nucleophilic addition: pyrimidine, for example, is decomposed when heated with aqueous alkali by a process that involves hydroxide addition as a first step. It is converted into pyrazole by reaction with hot hydrazine.





- Nucleophilic Substitution with ‘ Hydride ’ Transfer 14.3.1.1 Alkylation and Arylation The diazines readily add alkyl - and aryllithiums, and Grignard reagents, to give dihydro - adducts that can be aromatised by oxidation with reagents such as potassium permanganate or 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (DDQ). In reactions with organolithiums, pyrimidines react at C - 4, 13 and pyridazines at C - 3, but Grignard reagents add to pyridazines at C - 4

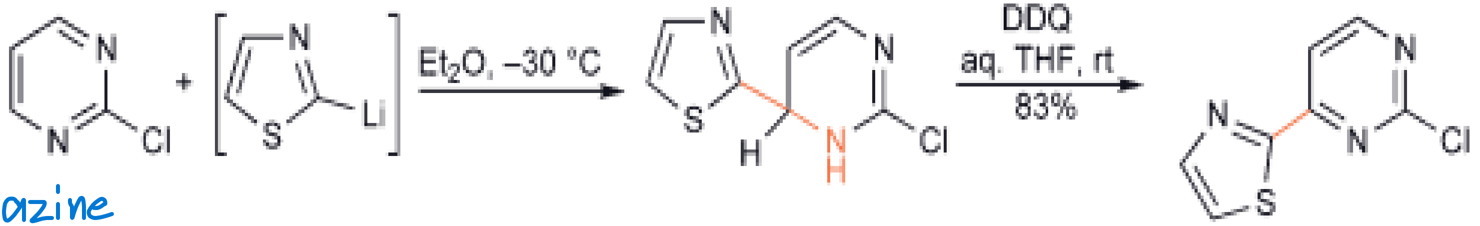
organolithium → pyrimidine at C4

organolithium → pyridazine at C3

grignard reagent → pyridazine at C4

هدول المركبين
بعملو كعامل
مؤكسد

- An important point is that in diazines carrying chlorine or methylthio substituents, attack does not take place at the halogen - or methylthio - bearing carbon; halogen and methylthio - containing products are therefore obtained



diazine
carrying chloride
or maybe
methylthio-substituent

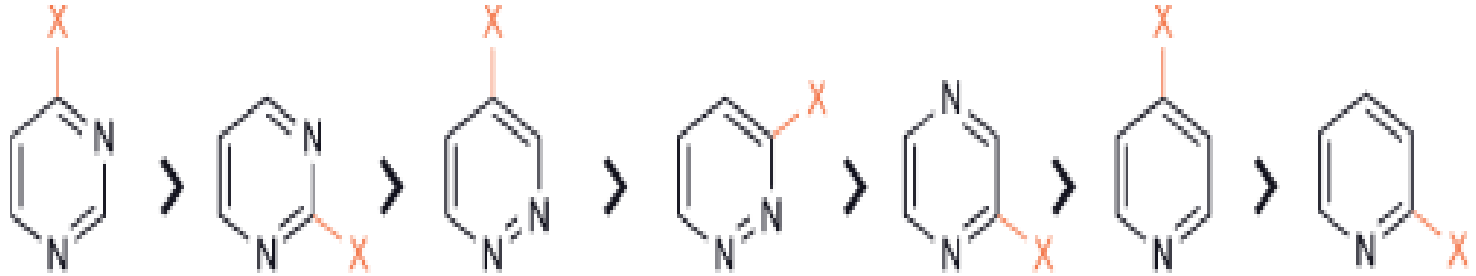
not react with soft nucleophil → نفسو بيتا كربون الي حكيناه فوق

- Nucleophilic Substitution with Displacement of Good Leaving Groups
  All the halo - diazines, apart from 5 - halo - pyrimidines, react readily with ‘ soft ’ nucleophiles, such as amines, thiolates and malonate anions, with substitution of the halide. Even 5 - bromopyrimidine can be brought into reaction with nucleophiles using microwave heating. 27 All cases are more reactive than 2 - halo - pyridines: the relative reactivities can be summarised:

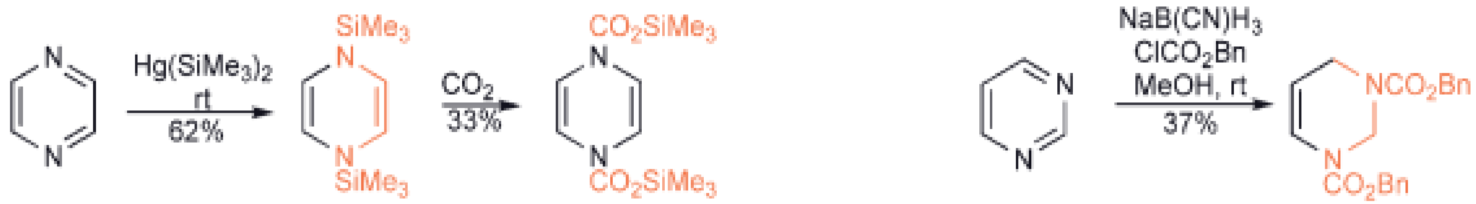
pyrimidine

حفظ

5-halopyrimidine



2-halopyridine



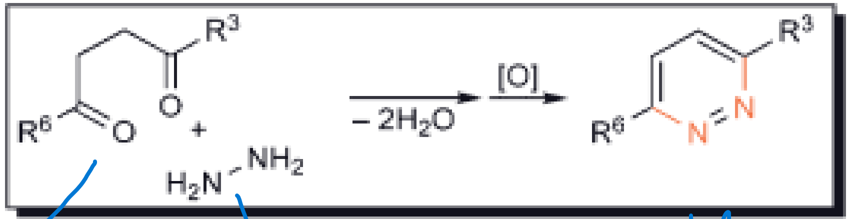
- Reactions with Reducing Agents Due to their lower aromaticity, the diazines are more easily reduced than pyridines. Pyrazine and pyridazine can be reduced to hexahydro - derivatives with sodium in hot ethanol; under these conditions pyridazine has a tendency for subsequent reductive cleavage of the N – N bond.
- Partial reductions of quaternary salts to dihydro - compounds can be achieved with borohydride, but such processes are much less well studied than in pyridinium salt chemistry
- 1,4 - Dihydropyrazines have been produced with either silicon 68 or amide 69 protection at the nitrogen atoms, and all the diazines can be reduced to tetrahydro derivatives with carbamates on nitrogen, which aids in stabilisation and thus allows isolation.
- 2 - Amino - pyrimidines are reduced to 3,4,5,6 - tetrahydro derivatives with triethylsilane in trifluoroacetic acid at room temperature, the products thus retaining a guanidine unit

↳ C-N-C

Synthesis of Diazines

- Pyridazines

- From a 1,4 - Dicarbonyl Compound and a Hydrazine A common method for the synthesis of pyridazines involves a 1,4 - dicarbonyl compound reacting with hydrazine; unless the four - carbon component is unsaturated, a final oxidative step is needed to give an aromatic pyridazine.

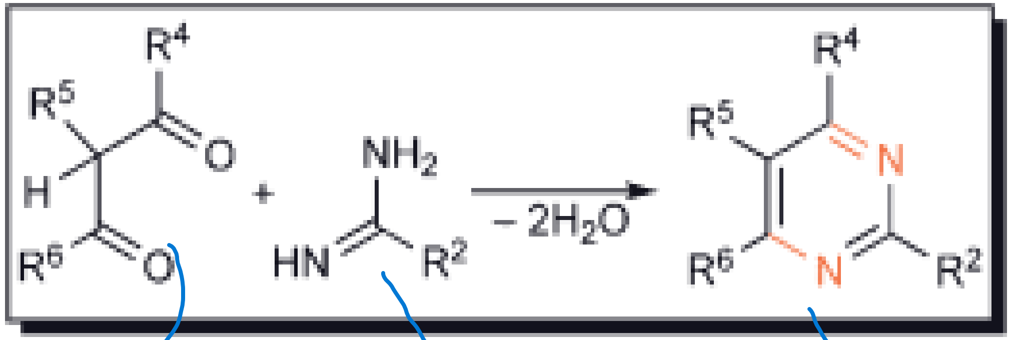


1,4-dicarbonyl compound

hydrazine

pyridazine

- Pyrimidines
- From a 1,3 - Dicarbonyl Compound and an N – C – N Fragment The most general pyrimidine ring synthesis involves the combination of a 1,3 - dicarbonyl component with an N – C – N fragment such as a urea, an amidine or a guanidine

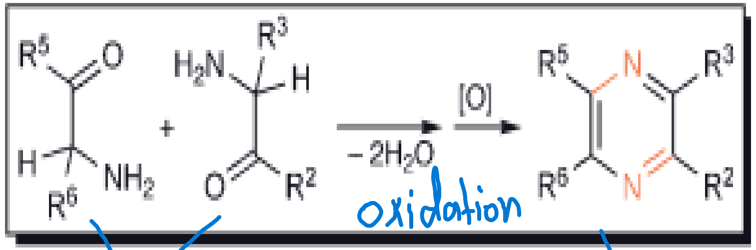


1, 3-dicarbonyl compound

N-C-N

pyrimidine

- Pyrazines Pyrazine is not easily made in the laboratory. Commercially, the high temperature cyclodehydrogenation of precursors such as N - hydroxyethylethane - 1,2 - diamine is used.
- From the Self - Condensation of a 2 - Amino - Ketone Symmetrical pyrazines result from the spontaneous self condensation of two mole equivalents of a 2 - amino - ketone, or 2 - amino - aldehyde, followed by an oxidation



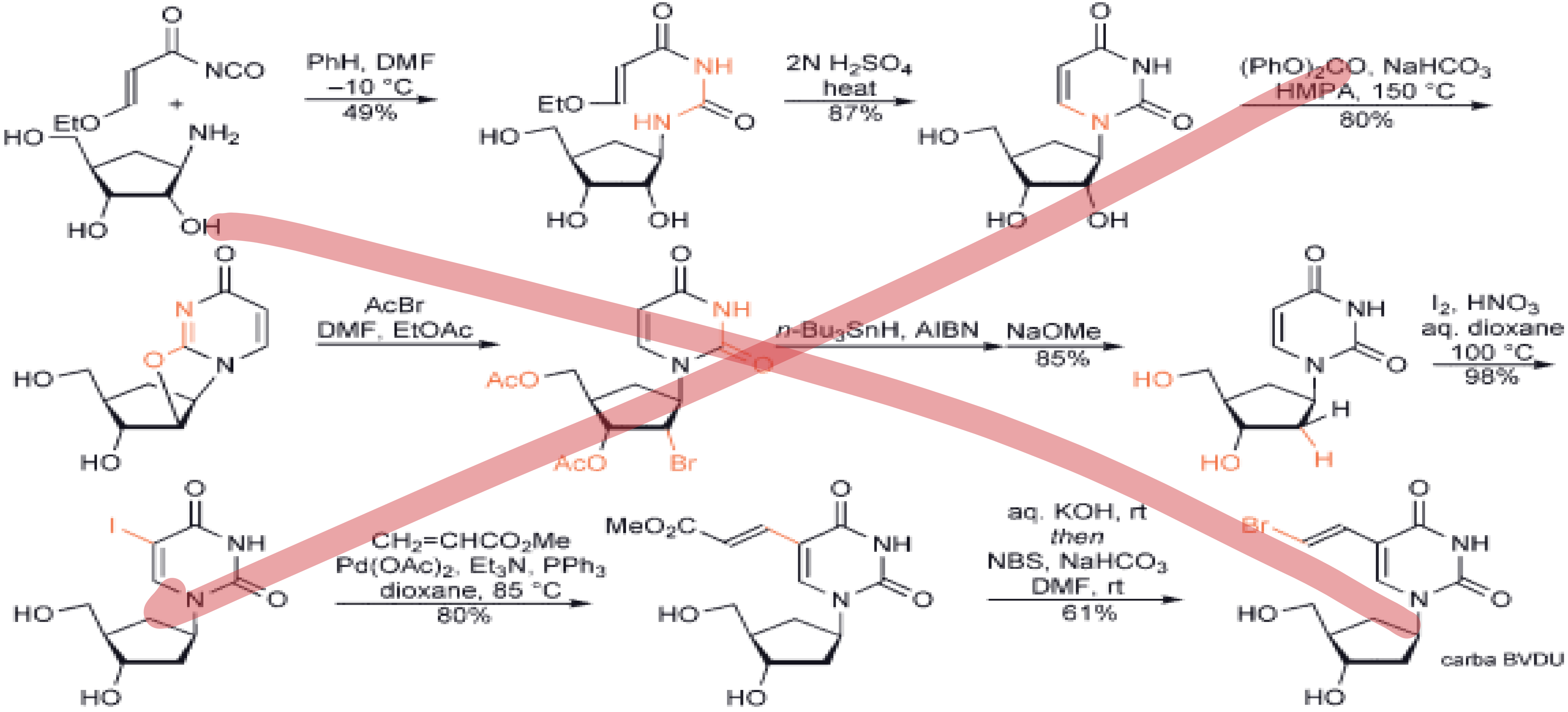
oxidation

amino Ketone

symmitrical compound (pyrazine)

14.13.4.2 Carbocyclic bromovinyldeoxyuridine

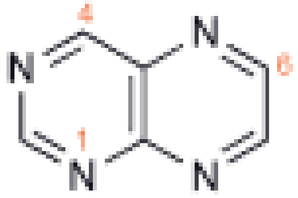
Carbocyclic bromovinyldeoxyuridine (CarbaBVDU) is an anti-viral agent.[221]



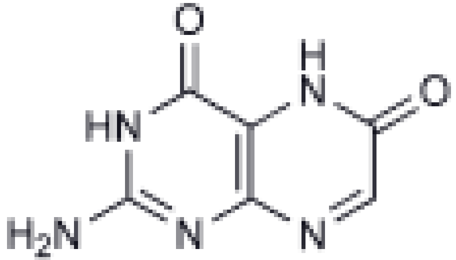
Pteridines

- Pyrazino[2,3 - d]pyrimidines are known as ‘ pteridines ’, 223 because the first examples of the ring system, as natural products, were found in pigments, like xanthopterin (yellow), in the wings of butterflies (Lepidoptera). صبغة
- The pteridine ring system has subsequently been found in 1 coenzymes that use tetrahydrofolic acid (derived from the vitamin folic acid), and 2 in the cofactor of the oxomolybdoenzymes 224 and 3 comparable tungsten enzymes.

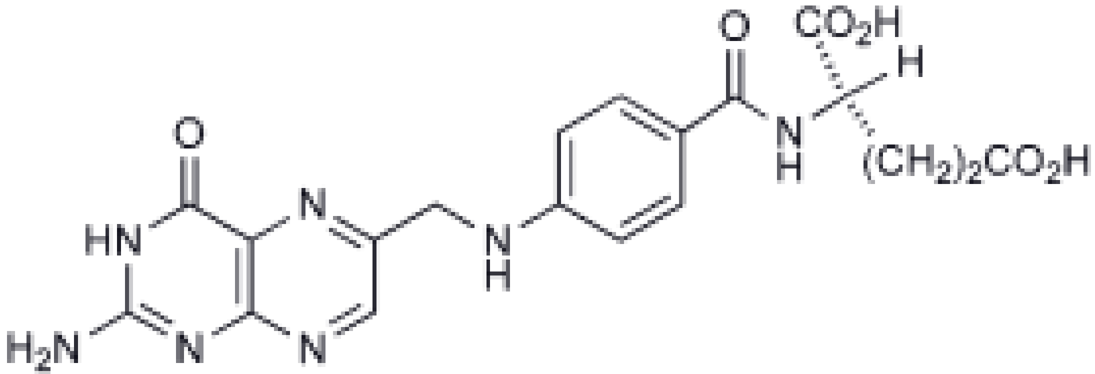
حفظ التركيب والإسم



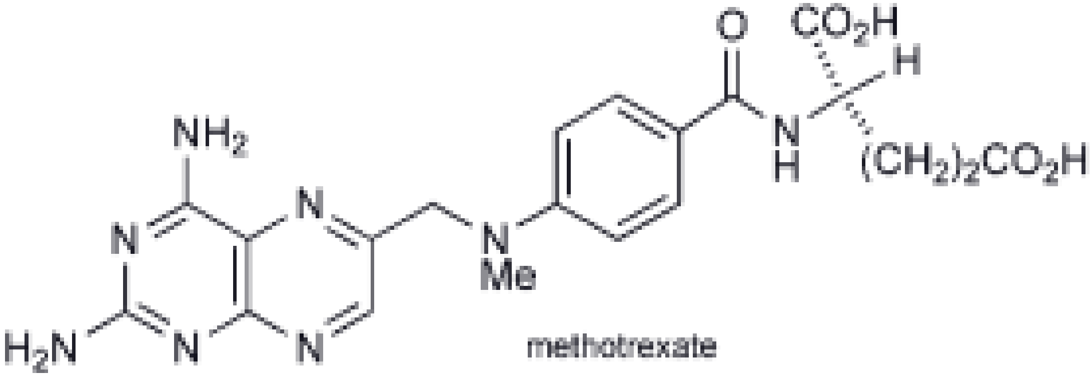
pteridine



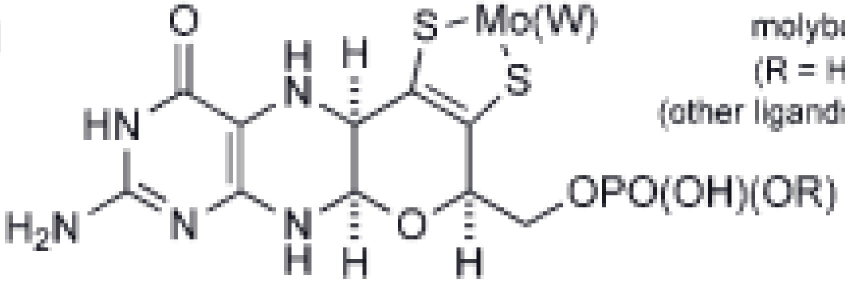
xanthopterin



folic acid



methotrexate



molybdenum cofactor
(R = H or nucleoside)
(other ligands on metal not shown)