

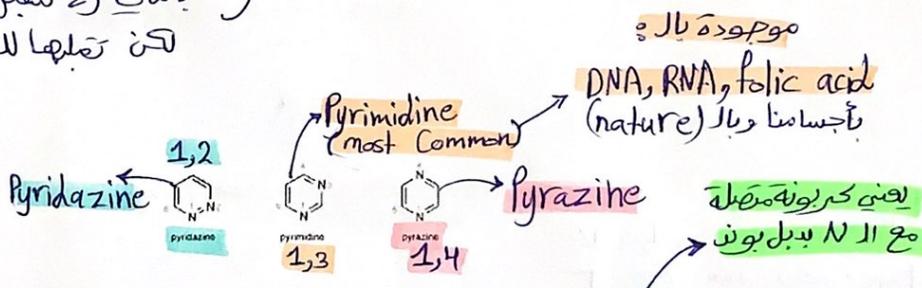
Typical Reactivity of the Diazines: Pyridazine, Pyrimidine and Pyrazine

طبقات مساوية
2N ←
unsaturated

تحدث هذا الشاير عن حلقات مساوية فيها 2 hetero atom

ليس بقدر اضيف E⁺ فقط
على وحدة من الـ N ؟
لأنها سحبت الـ e⁻ بانجذابها
بالتالي ردت تقبلتها تأخذ E⁺
لكن تقبلها لا E⁺ أقل من
الـ pyridine

شرح الآخر
طرح بالسلايد



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. (electron poor والحلقة تبصر أكثر)

صعب اضيف E⁺ (لأنه الـ N يسحب كل الـ e⁻)

increased electron deficiency at carbon makes the diazines more easily attacked by nucleophiles than pyridine. (Diazine) ← بتعلقوا مع Nu⁻ (وجود 2N على الحلقة deficient أكثر)

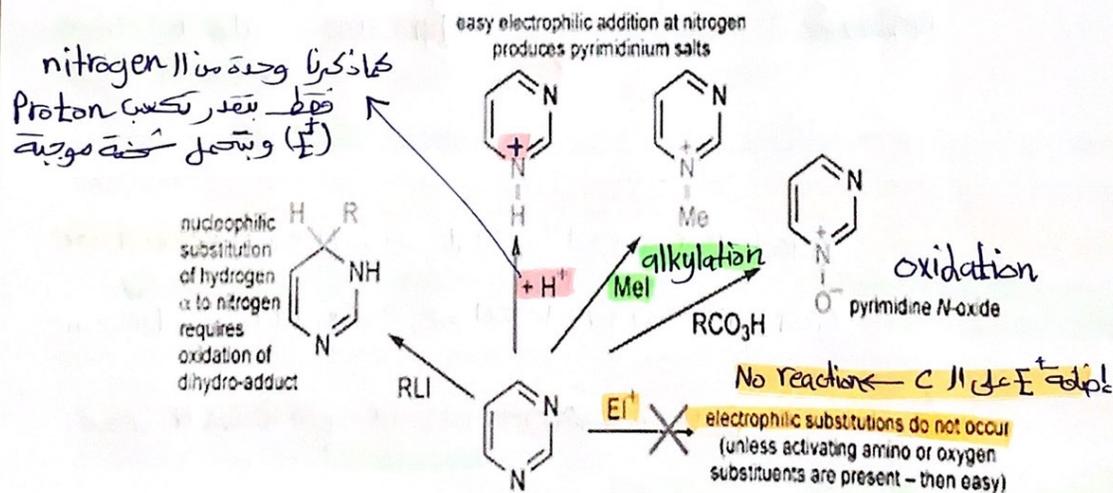
The availability of nitrogen lone pair(s) is also reduced: each of the diazines is appreciably less basic than pyridine, reflecting the destabilising influence of the second nitrogen on the N - protonation. (بعض وجود N إضافية لكنهما ما زادت القاعدية (رأيتها مش مهم))

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.

باختصار: ميتراد الـ Diazines ← صعب جداً اضيف E⁺ وسهل جداً اضيف Nu⁻
وأيضاً إذا كان عندي halide على ring وضعت substitution الـ halide ممكن تفضل في المركب.

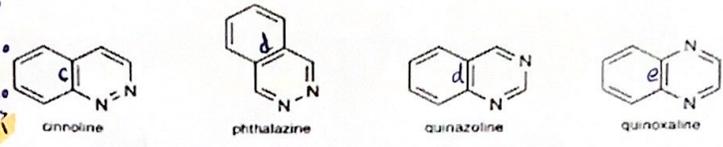
- A very characteristic feature of the chemistry of (diazines), which is associated with their (strongly electron - poor nature) is that they add nucleophilic reagents easily. Without halide to be displaced, such adducts require an oxidation to complete an overall substitution. However, halo - diazines,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



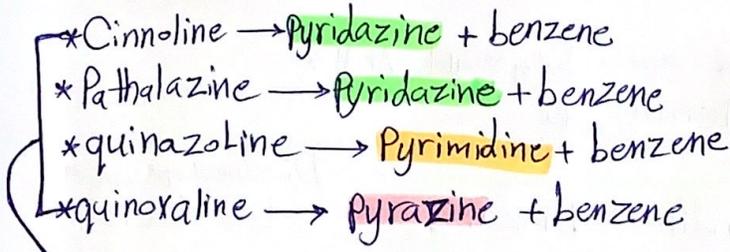
Typical reactions of a diazine illustrated with pyrimidine

note: E⁺ يقبل على
 وحدة من ال N فقط وما يقبل على
 ال Second (N)
 Nu⁻ ← يقبل على ال Ring

• ما يتأكسوا
• ما يتغير لونها
• ما يتأثر بالأكسدة
• ما يتفكك مع
• أشياء حرة

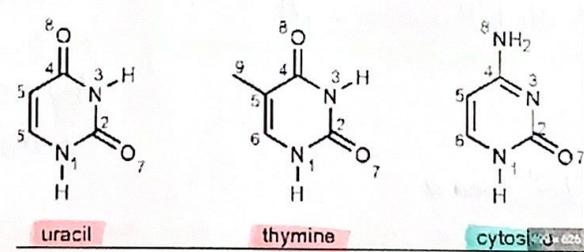


- The three diazines, pyridazine, 1 pyrimidine, 2 and pyrazine 3 are stable, colourless compounds that are soluble in water.
- The three parent heterocycles, unlike pyridine, are expensive and not readily available and so are seldom used as starting materials for the synthesis of their derivatives. *نادر*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



لما أربط حلقه بنزينه
 ← Diazine
 (Common names)

Found in nature for drugs



General formula for Diazines
 $C_4H_4N_2$
 لأن يتكافؤ بالأمثلة
 الفيزيائية

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. *لأنه ال 2N ال جنب بعضهم مباشرة ← highly polarizable والروابط قوية بينهم*

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

building blocks of DNA

anti-metabolite anti-cancer & anti-viral

يوجد في معظم الأدوية

Reactions with Electrophilic Reagents

- Addition at Nitrogen (only one)

فقط 1 نيتروجين
only 1 N

- 14.1.1.1 Protonation

- The diazines, pyridazine (pKaH 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

resonating effect ←

Proton لا يقبله N الثاني *
← quaternary

Imidazole > Pyridine > Diazines
(Basisty) الرتبة حسب القاعدية

Diazines ليست القاعدية
Less basic?
وجود N الثانية
التي تسحب e-
by mesomeric effect
+ Inductive effect

* تفسير اختلاف القاعدية بين Diazines

- 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.

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

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

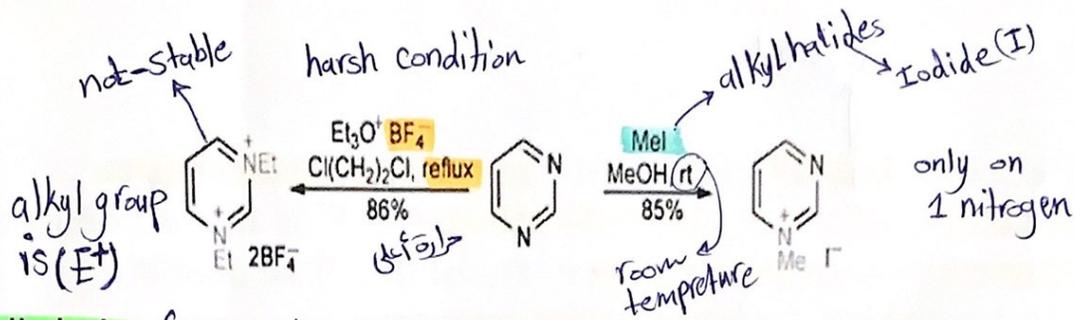
لو أضفنا E+ إلى Diazine في N واحدة

Protonation لا يقبله E+ في N واحدة

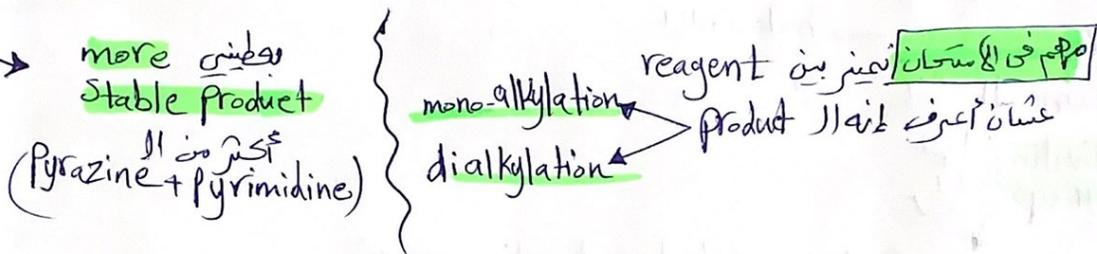
← 2N مستوحاة من + ← diprotonated

في وسط شديد الحموضة

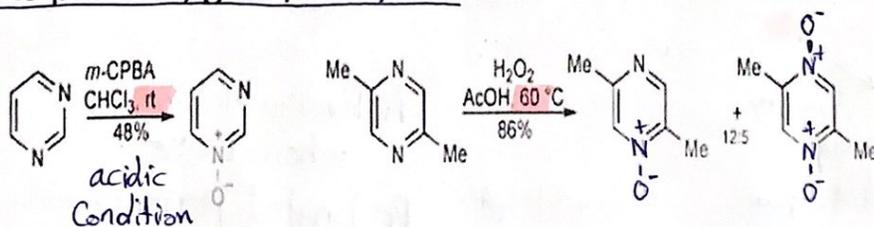
highly acidic condition



- Alkylation (Protonation) methyl Iodide
- 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 (trialkoxonium tetrafluoroborates) 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



- Oxidation All three systems react with (peracids), (giving N - oxides), but care must be taken with pyrimidines due to the relative (instability) of the products under the acidic conditions.
 - Pyrazines form N,N' - (dioxides the (most easily),
 - but pyridazine requires forcing conditions,
 - and pyrimidines, apart from some examples in which further activation is present, give poor yields
- To make nitrogen oxidize (Quaternary nitrogen)
- النتيجة
- unstable at acidic condition



لا يقبل E^+

- 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

لإزالة الوجوه التي يقبل E^+ → مثل halogenation

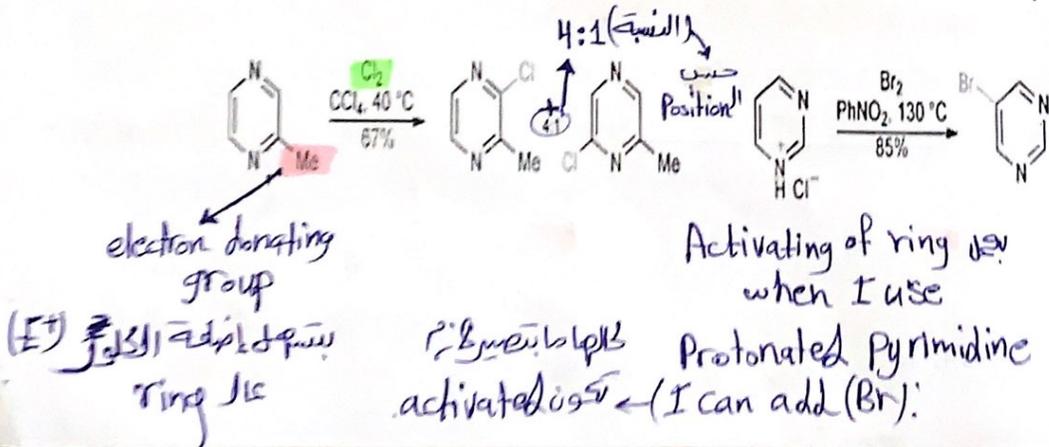
Diazine

(Activating group)

rich of electron (electron donating group)
(Methoxy, methyl)

بالتالي halogenation activation group

- 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 processes



- Reactions with Oxidising Agents (It's hard to oxidation the Carbon)
- 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. *Condition very harsh*
- Alkyl substituents and fused aromatic rings can be oxidised to carboxylic acid residues, leaving the heterocyclic ring untouched. *وہاں تسمیہ (بالاکسید)*
- An oxygen can be introduced into pyrimidines at vacant C - 2 and/or C - 4 positions using various bacteria. *(Microorganism)*
- Dimethyldioxirane converts N,N - dialkylated uracils into 5,6 - diols probably via 5,6 - epoxides

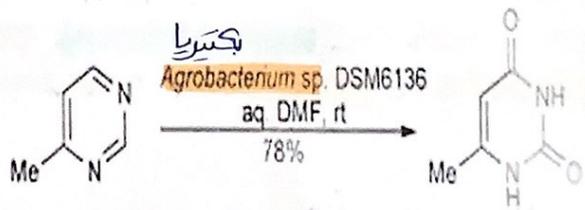
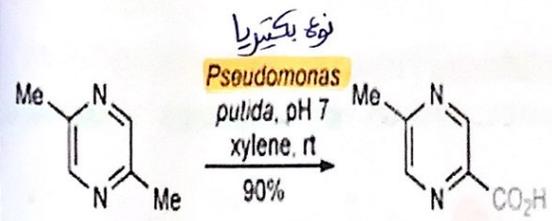
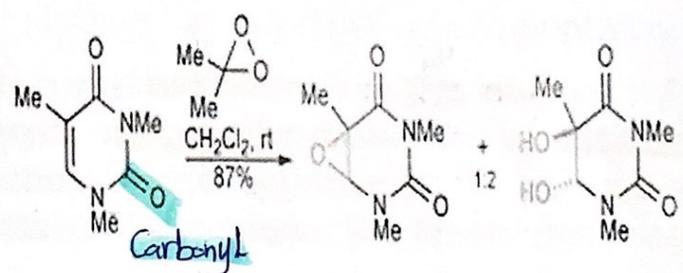
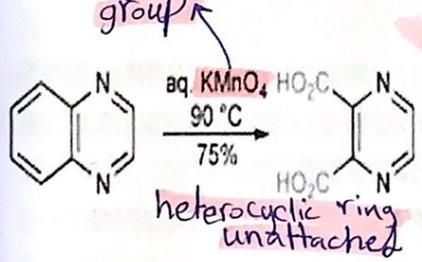
At oxidation of (Cinnoline) under harsh Condition \rightarrow بتکسر الجزیئہ

oxygen is added to my Compound (Simple reagent) *عصب الاستعمال*

والمسبب: التکثیر عندہا لتزیم معین *بصیر (Stereoselectivity)* بتکثیر وبتکثیر سکتھیں

تکسر طبعاً الجزیئہ *Carboxylic group*

Pure Product *وہاں*

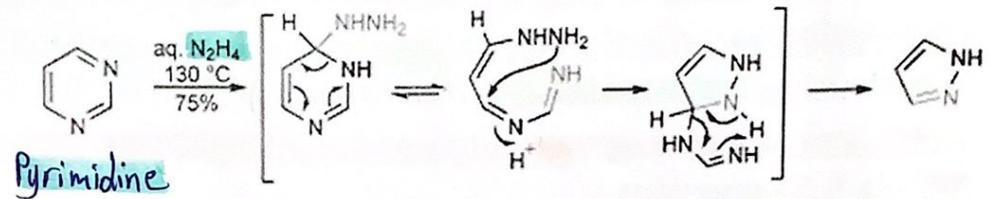


oxidation of the ring isn't easy

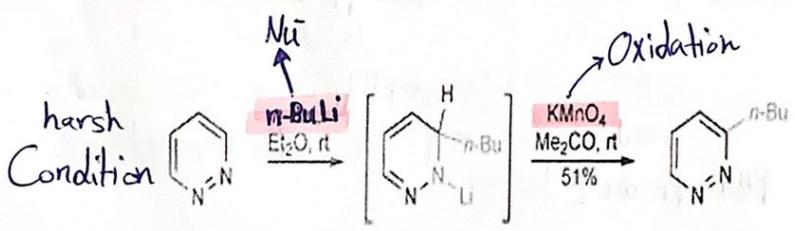
Need high energy + Strong Catalysts

في الـ Pyrimidine
(Nu) مع الـ Lewis
Substituted reaction مع الـ Lo
ring مع الـ كسر الـ ring
5 membered ring

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.



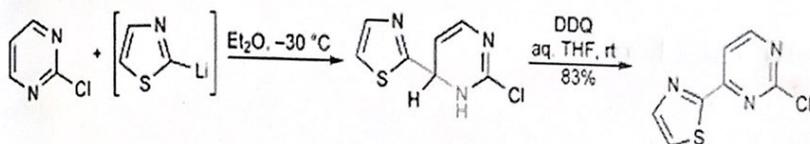
(N2H4) مع Pyrimidine
الـ كسر الـ ring (new hetero cyclic ring)



- 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, and pyridazines at C-3, but Grignard reagents add to pyridazines at C-4

(Li) مع الـ *
(Nu) مع الـ

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



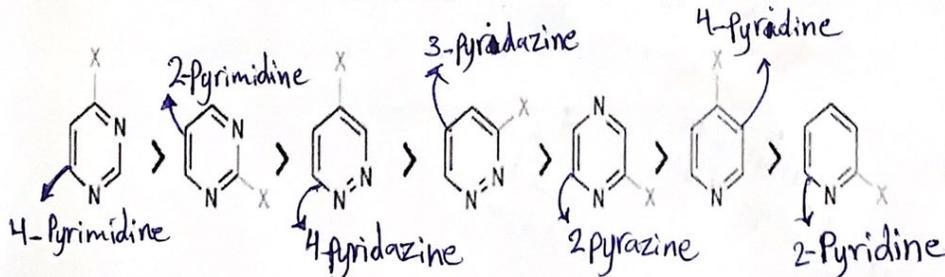
Pyrimidine الكيمياء
 4 ← Position في
 halogenated Pyrimidine

+ Organolithiums Product

Substitution في
 2 ← Position في
 rather than 4

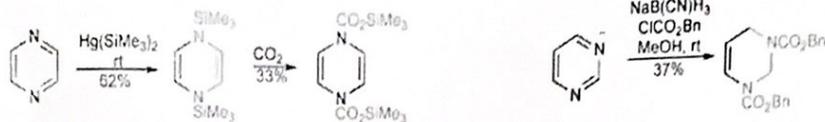
(Substitution في halogen بنقل Nu)

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. All cases are more reactive than 2 - halo - pyridines: the relative reactivities can be summarised:



note:
 Pyridine
 2N poor reactivity
 diazines
 2N poor more poor in electron

Poor electrophiles (Nu) ← أقوى (مع E+ كبر)



- Reactions with Reducing Agents Due to their lower aromaticity,
- diazines are more easily reduced than pyridines. & Benzene
- 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.) → (N-N) بين Bond كسر الى كسرتين

Full reduction
Na⁺

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 → Partially reduction

- 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

note: قبل ما نعمل reduction لازم نحقق الشروط باستخدام Protecting group

قروبات يضيفها الجزء اللي بيبرد
أحده من دخول التفاعل وبيبرد
ما يتدخله التفاعل بفسدهم.

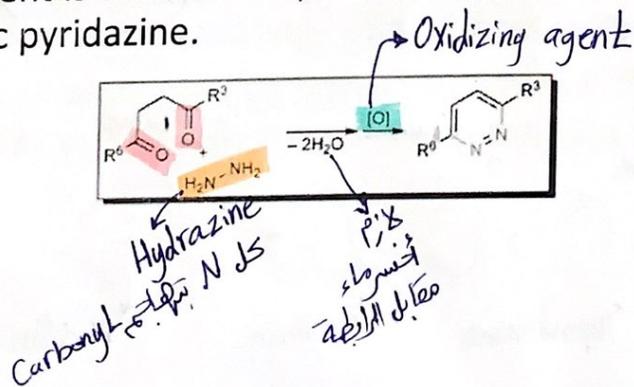
سؤال ممكن يجي
Can we reduced (a Diazine)?
True الجواب
easy

التخليق Synthesis of Diazines

Pyridazines

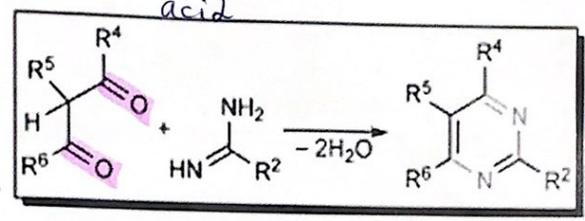
فيه 2N جبروفين

- From a 1,4 - Dicarboxyl 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.



Pyrimidines

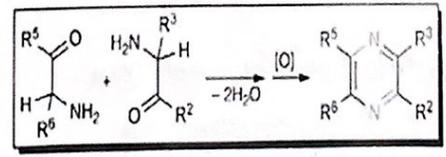
- From a 1,3 - Dicarbonyl Compound and an N - C - N Fragment The most general pyrimidine ring synthesis involves the combination of a 1,3 - dicarbonyl component with an N - C - N fragment such as a (urea, an amidine or a guanidine) \rightarrow Diamino
 (amino acid) \rightarrow Diamino
 (amino acid) \rightarrow Diamino



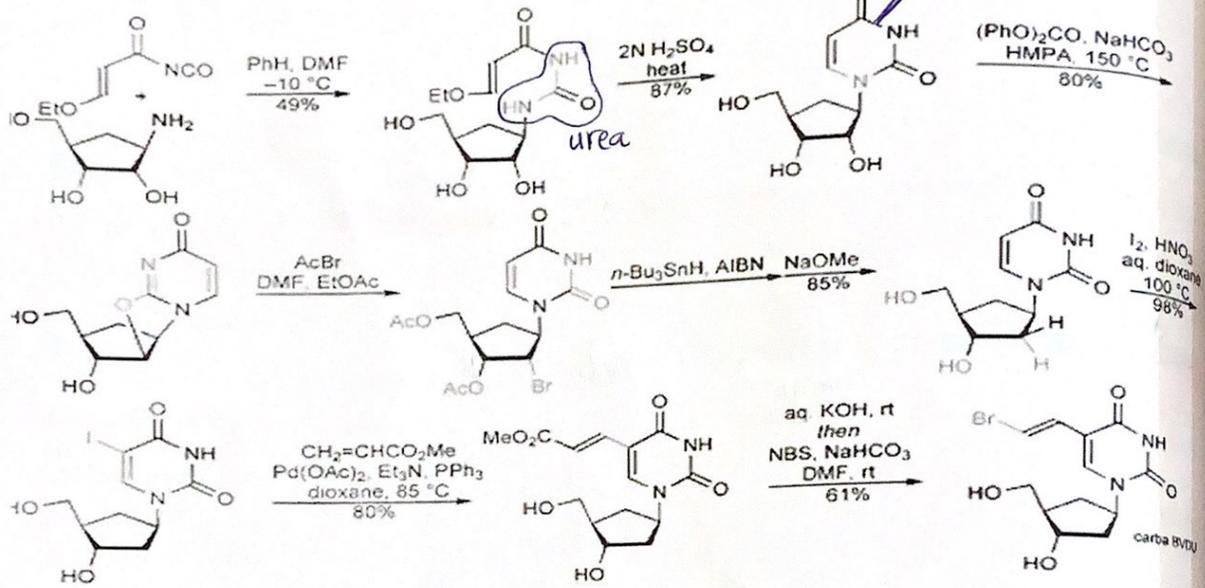
أمعيب واحد

- 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

كل N تتفاعل مع Carbonyl
 ثم يتأكسد المركب



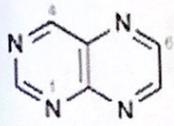
4.13.4.2 Carboyclic bromovinyldeoxyuridine (CarbaBVDU) is an anti-viral agent.²²¹ Pyrimidine



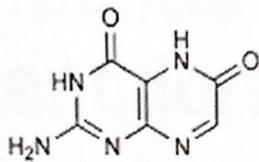
Pteridines (~~Pyrazine~~ + Pyrimidine)

- 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). ← بالبداية
- The pteridine ring system has subsequently been found in coenzymes that use tetrahydrofolic acid (derived from the vitamin folic acid), and in the cofactor of the oxomolybdoenzymes 224 and comparable tungsten enzymes.

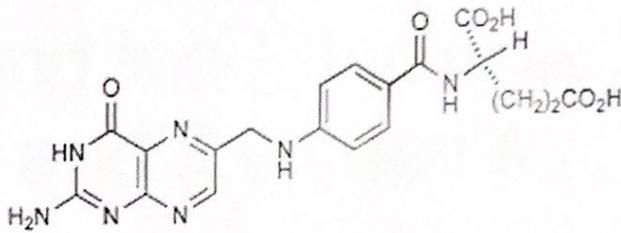
وعن الوقت اكتشفوا انه موجود في
 Co-enzyme لا المسؤول عن تصنيع
 building Block ← (Folic acid) → build
 وهو ضروري لنمو خلايا الانسان والحيوان



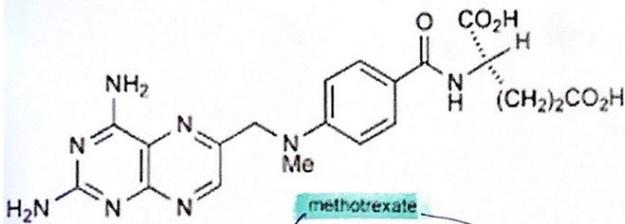
pteridine



xanthopterin

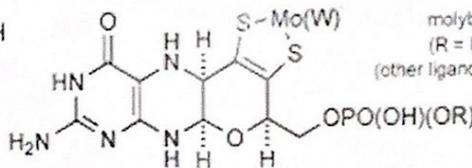


folic acid



methotrexate

methotrexate
anti-metabolic drug
(anti cancer)



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

folic acid 11 only
Carbonyl $\text{H} \leftarrow \text{O} \leftarrow \text{S}$
amino group $\text{H} \leftarrow \text{N} \leftarrow \text{S}$

Tertiary amine $\text{C} \leftarrow \text{N} \leftarrow \text{S}$
rather than secondary amine