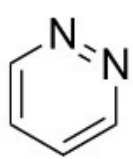
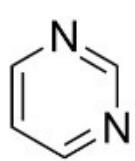
Typical Reactivity of the Diazines: Pyridazine, Pyrimidine and Pyrazine

Q18. Which of the following accurately depicts the chemical structure of pyridine?

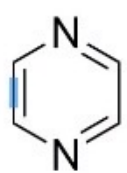
A) 6-membered aromatic ring with one Nitrogen
B) 5-membered aromatic ring with one Nitrogen
C) 6-membered aromatic ring with two Nitrogens
D) 5-membered aromatic ring with two Nitrogens



pyridazine

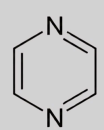


pyrimidine

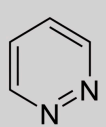


Pyrazine

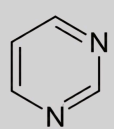
Q27. Identify the following diazines:



pyrazine



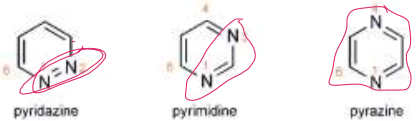
pyridazine

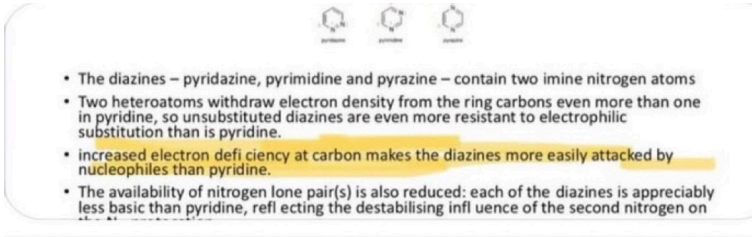


pyrimidine

Q21. Which diazine has the highest basicity?

A. Pyridazine
B. Pyrimidine
C. Pyrazine
D. Triazine





- 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.
- increased electron defi ciency at carbon makes the diazines more easily attacked by nucleophiles than pyridine.
- The availability of nitrogen lone pair(s) is also reduced: each of the diazines is appreciably less basic than pyridine, refl ecting the destabilising infl uence of the second nitrogen on the N - protocation.
- 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.

Electrophilic ترتيب سهولة Substitution

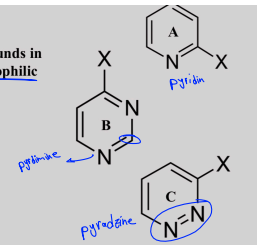
Benzene > Pyridine > Diazines

الترتيب (من الأقوى في Nucleophilic للأضعف) NAS:

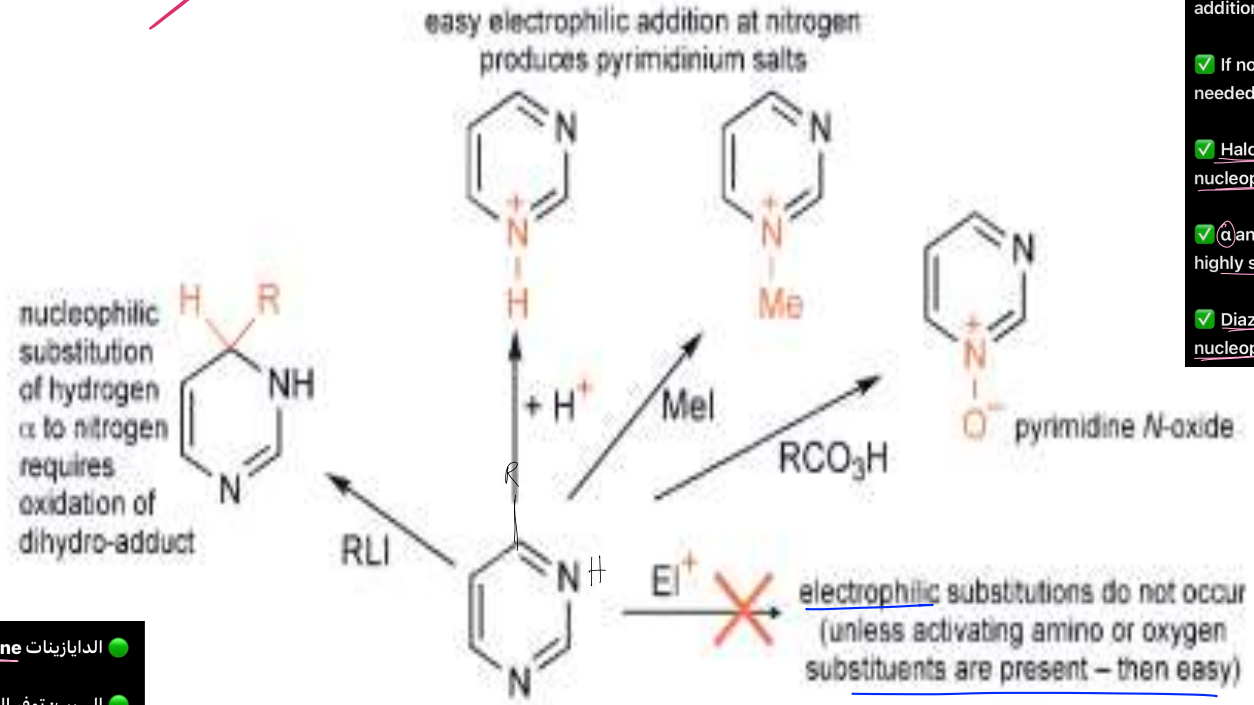
Pyrazine > Pyrimidine > Pyridazine > Pyridine

Q33. Arrange the following compounds in decreasing reactivity toward nucleophilic substitution:

A. C > B > A
B. B > C > A
C. A > C > B
D. C > A > B



- 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

ما يجب حفظه

✅ Diazines are strongly electron-poor.

✅ They undergo nucleophilic addition easily.

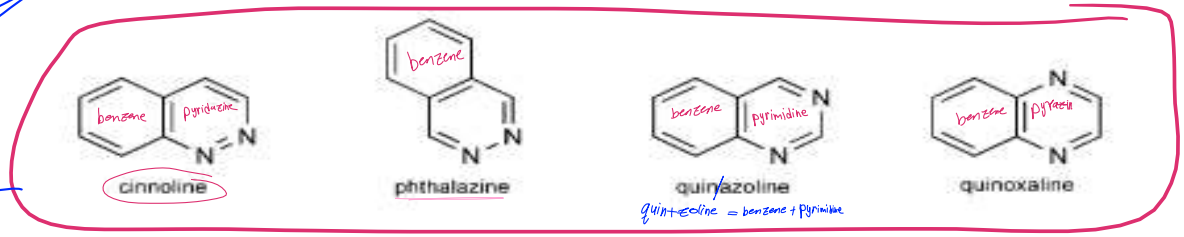
✅ If no halide is present → oxidation is needed to restore aromaticity.

✅ Halo-diazines undergo very easy nucleophilic substitution.

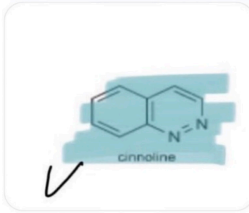
✅ α and γ halo substituents give highly stabilized intermediates.

✅ Diazines can also react with nucleophilic radicals.

- الدايازينات **less basic than pyridine**
- السبب: توفر الـ lone pair أقل
- وجود النيتروجين الثاني يقلل استقرار الـ N-protocation
- يمكنها تكوين **salts**
- تتفاعل مع alkyl halides → **N-alkyl quaternary salts**
- تتفاعل مع peracids → **N-oxides**
- غالباً التفاعل يحدث على نيتروجين واحد فقط



وأي واحد بحتوي 2 كأنه المهم هاد كان الجواب



- 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.
- 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.

pyrimidine

pyrazine

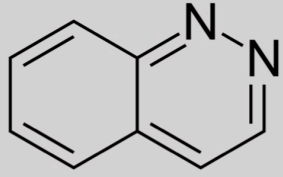
Which of the following is a bicyclic system generated by fusing a benzene ring to a diazine?

pyridazole

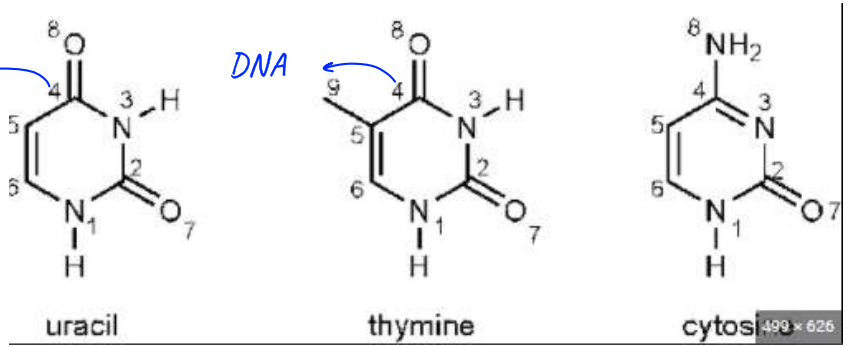
A) Cinnoline
B) Pyridine
C) Imidazole
D) Pyrimidine

Correct Answer: A) Cinnoline

Q10. Identify the following structure:



A. Quinazoline
B. Quinoxaline
C. Phthalazine
D. Cinnoline



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

Q9. Which of the following is a component of DNA and RNA?

A. Pyridazine
B. Pyrimidine
C. Pyrazine
D. Imidazole

Q13. The most important naturally occurring diazines are:

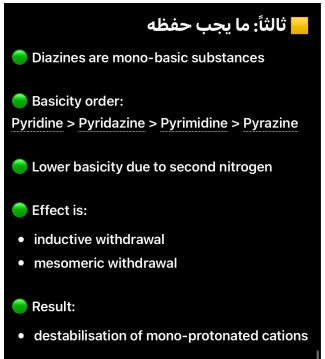
A. Quinoline, Isoquinoline, Cinnoline
B. Uracil, Thymine, Cytosine
C. Pyrrole, Furan, Thiophene
D. Imidazole, Triazole, Tetrazole

🧾 جدول الفرق بين Diazines (مختصر حسب السلايد)

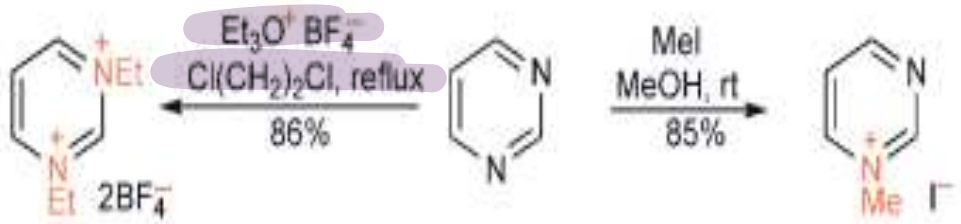
الخاصية	Pyridazine (1,2)	Pyrimidine (1,3)	Pyrazine (1,4)
🟢 عدد N	2 (متجاورين)	2	2
🟢 الاستقرار/اللون	stable, colourless	stable, colourless	stable, colourless
🟢 الذوبان	soluble in water	soluble in water	soluble in water
🟢 الإلكترونات	more electron-poor (strong dipole effect)	electron-poor	electron-poor
🟢 electrophilic substitution	more resistant than pyridine	resistant	resistant
🟢 nucleophilic attack	easier than pyridine	easier	easier
🟢 basicity	less basic than pyridine	less basic	less basic
🟢 boiling point	**207°C (high)**	123°C	118°C

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



- 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 diffi cult and has only been observed in very strongly acidic media



(2) • Alkylation

- 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

Which of the following reagents is required to achieve dialkylation of diazines to form di-quaternary salts?

A) Simple alkyl halides
B) Trialkyloxonium tetrafluoroborates
C) Aqueous NaOH solution
D) Lithium aluminum hydride

Correct Answer: B) Trialkyloxonium tetrafluoroborates

🎯 الترتيب النهائي للحفظ:

Pyrazine > Pyridazine > Pyrimidine

(من الأسهل إلى الأصعب في الأكسدة)

Which of the following diazine systems forms N,N'-dioxides the most easily upon oxidation with peracids?

A) Pyrimidines
B) Pyridazines
C) Pyrazines
D) Pyridines

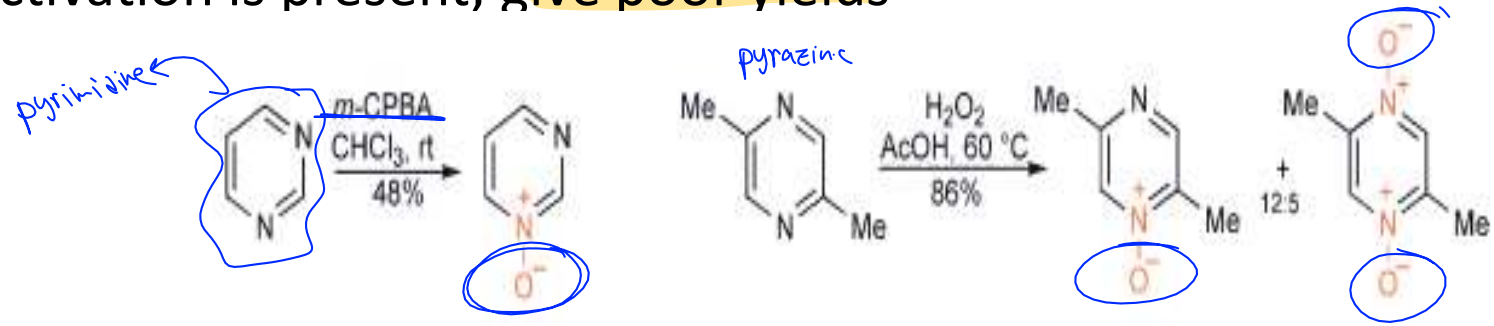
Correct Answer: C) Pyrazines

3

- **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

Q2. Which diazine forms N,N′-dioxides most easily?

A. Pyridazine
B. Pyrimidine
C. Pyrazine
D. Cinnoline

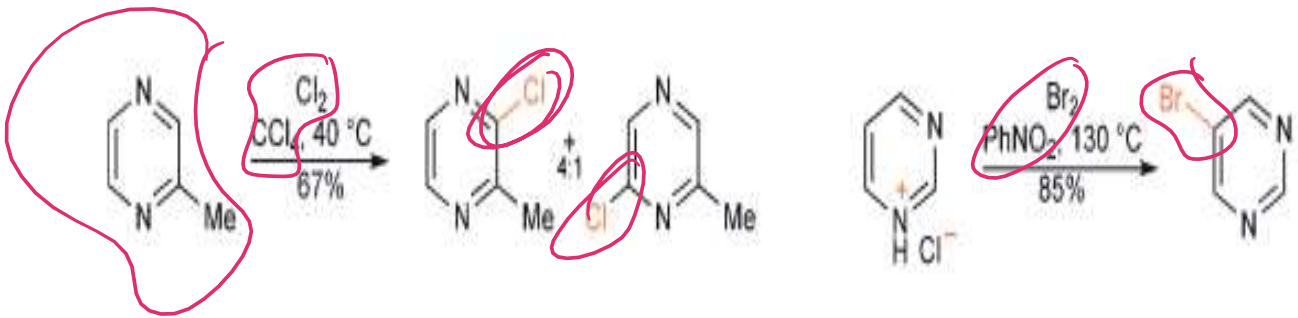


- Substitution at Carbon Recalling the resistance of pyridines to electrophilic substitution, it is not surprising to fi nd that introduction of a second azomethine nitrogen, in any of the three possible orientations, greatly increases this resistance:
- no nitration or sulfonation of a diazine or simple 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

4

- Halogenation

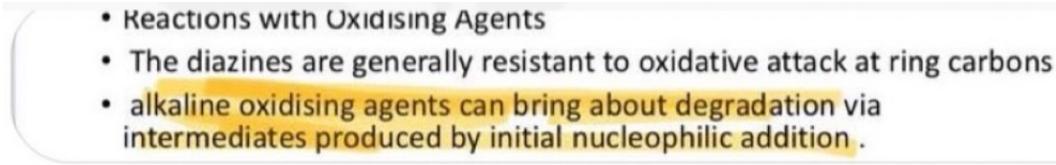
- Chlorination of 2 - methylpyrazine occurs under such mild conditions that it is almost certain that an addition/elimination sequence is involved, rather than a classical aromatic electrophilic substitution. Halogenation of pyrimidines may well also involve such processe



Degradation via intermediates produced by initial nucleophilic addition can be brought about by which type of oxidising agents?

A) Acidic
B) Neutral
C) Alkaline
D) None of the above

Correct Answer: C) Alkaline

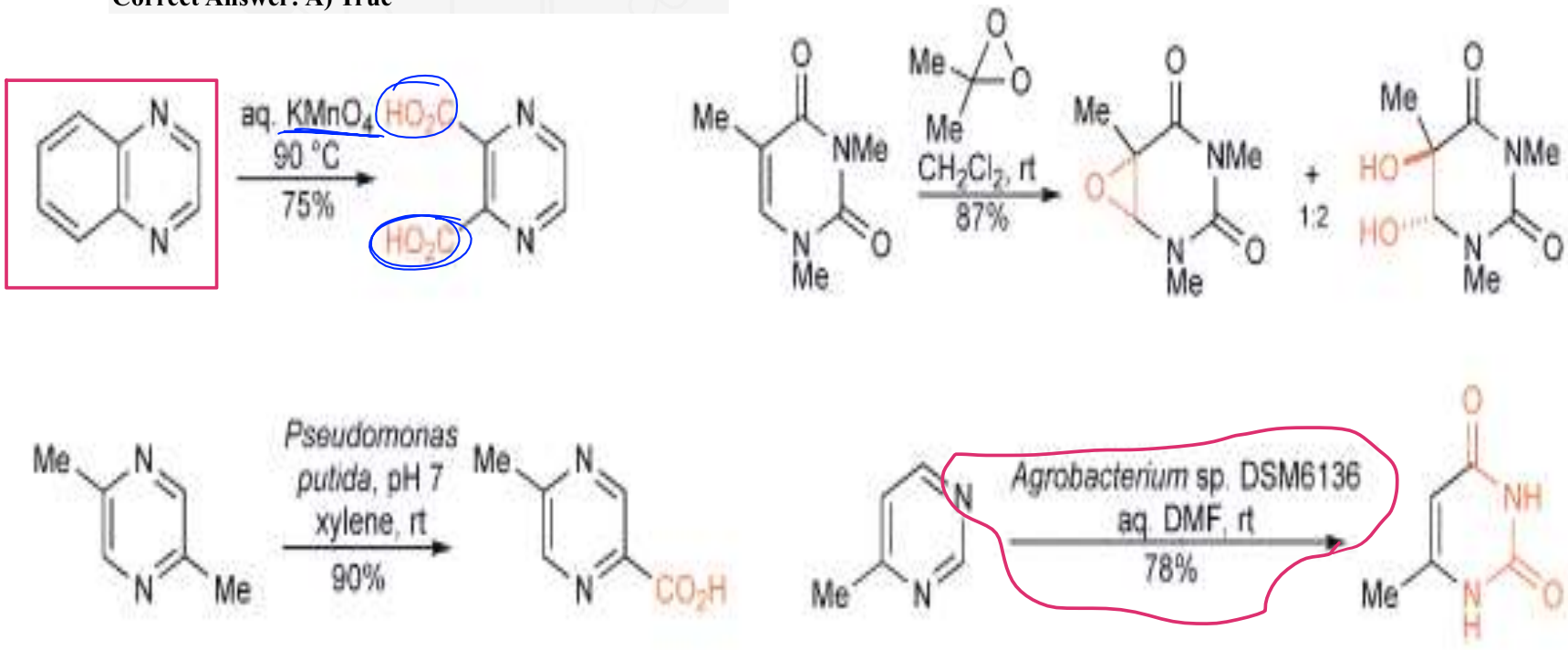


- Reactions with Oxidising Agents
- The diazines are generally resistant to oxidative attack at ring carbons
- alkaline oxidising agents can bring about degradation via intermediates produced by initial nucleophilic addition.
- Alkyl substituents and fused aromatic rings can be oxidised to carboxylic 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

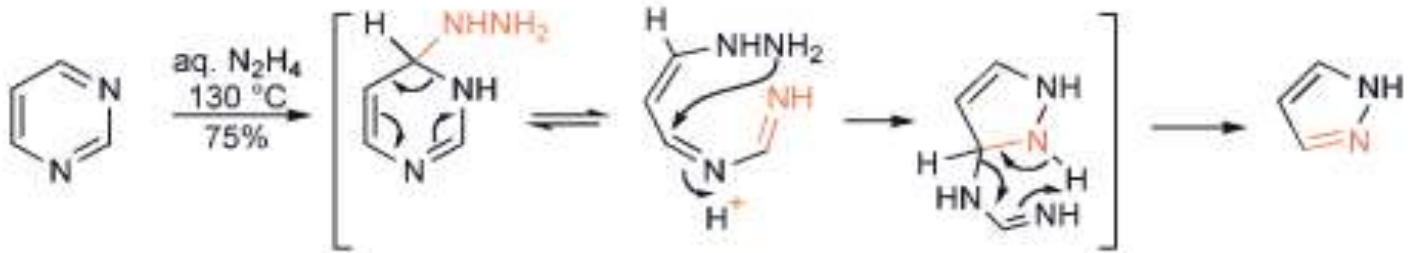
The microbial oxidation of 2,5-dimethylpyrazine to 5-methylpyrazine-2-carboxylic acid requires the use of Pseudomonas putida bacteria.

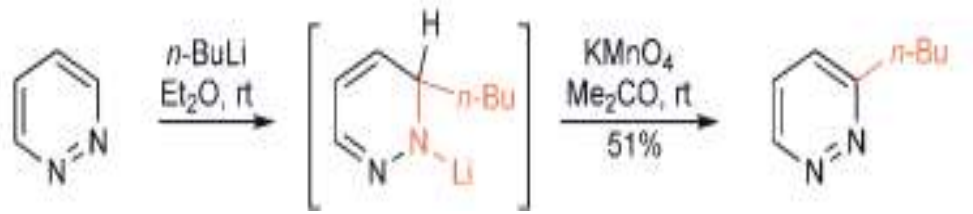
A) True
B) False

Correct Answer: A) True



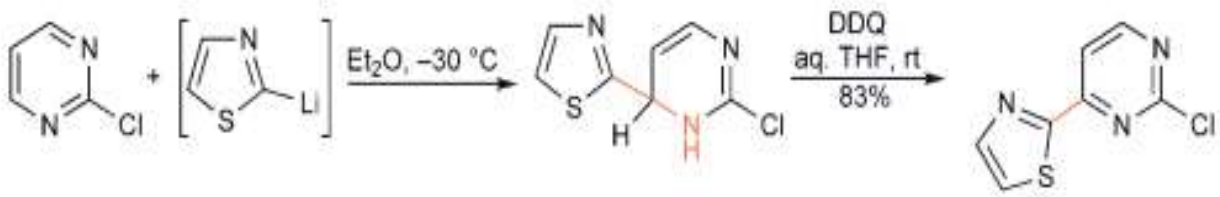
- Reactions with Nucleophilic Reagents The diazines are very susceptible to nucleophilic addition: pyrimidine, for example, is decomposed when heated with aqueous alkali by a process that involves hydroxide addition as a fi rst step. It is converted into pyrazole by reaction with hot hydrazine.



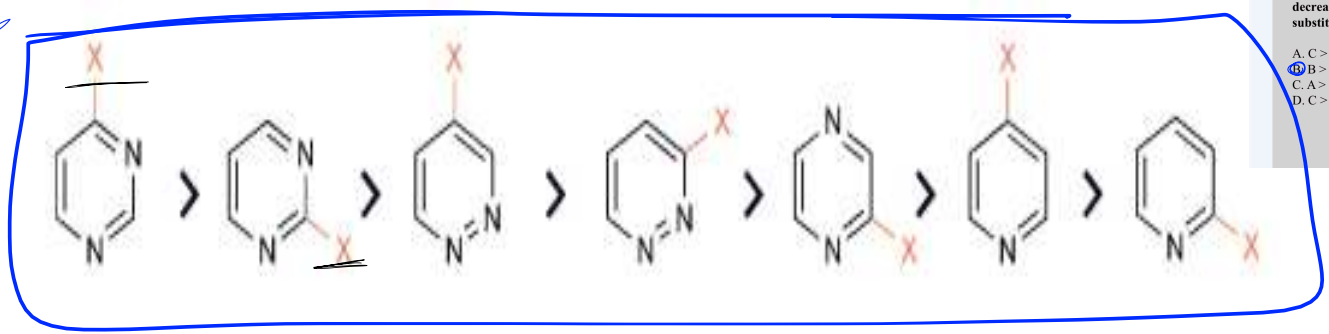


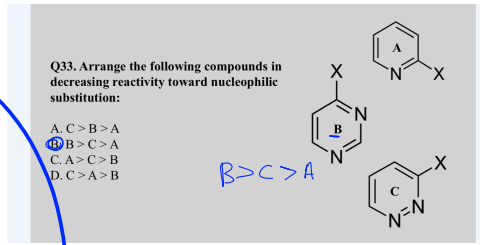
- Nucleophilic Substitution with ‘ Hydride ’ Transfer
- 14.3.1.1 Alkylation and Arylation The diazines readily add alkyl - and aryllithiums, and Grignard reagents, to give dihydro - adducts that can be aromatised by oxidation with reagents such as potassium permanganate or 2,3 - dichloro - 5,6 - dicyano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

- 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



- 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:

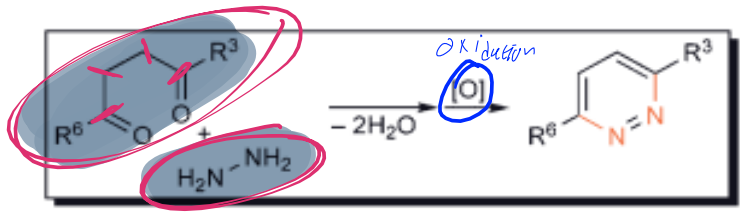




- Reactions with Reducing Agents Due to their lower aromaticity,
- diazines are more easily reduced than pyridines. diazine >>> pyridine (more easily reduced)
- Pyrazine and pyridazine can be reduced to hexahydro - derivatives with sodium in hot ethanol; under these conditions pyridazine has a tendency 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 trifl uoroacetic acid at room temperature, the products thus retaining a guanidine unit

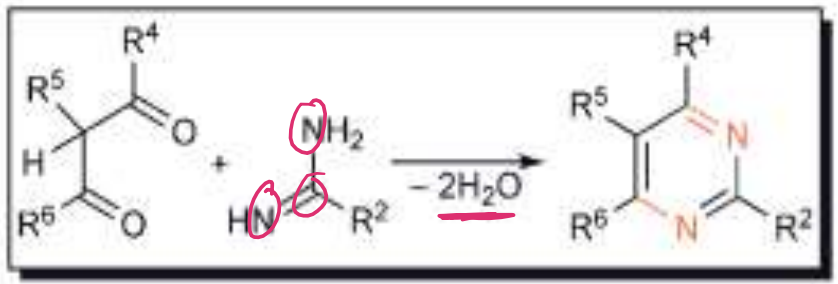
Synthesis of Diazines

- 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 fi nal oxidative step is needed to give an aromatic pyridazine.

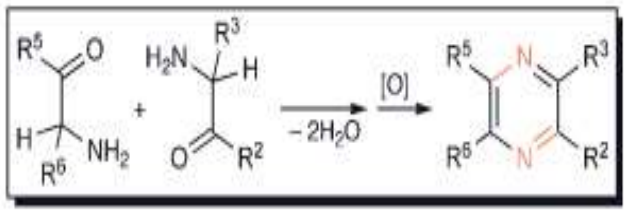


- Pyrimidines

- 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

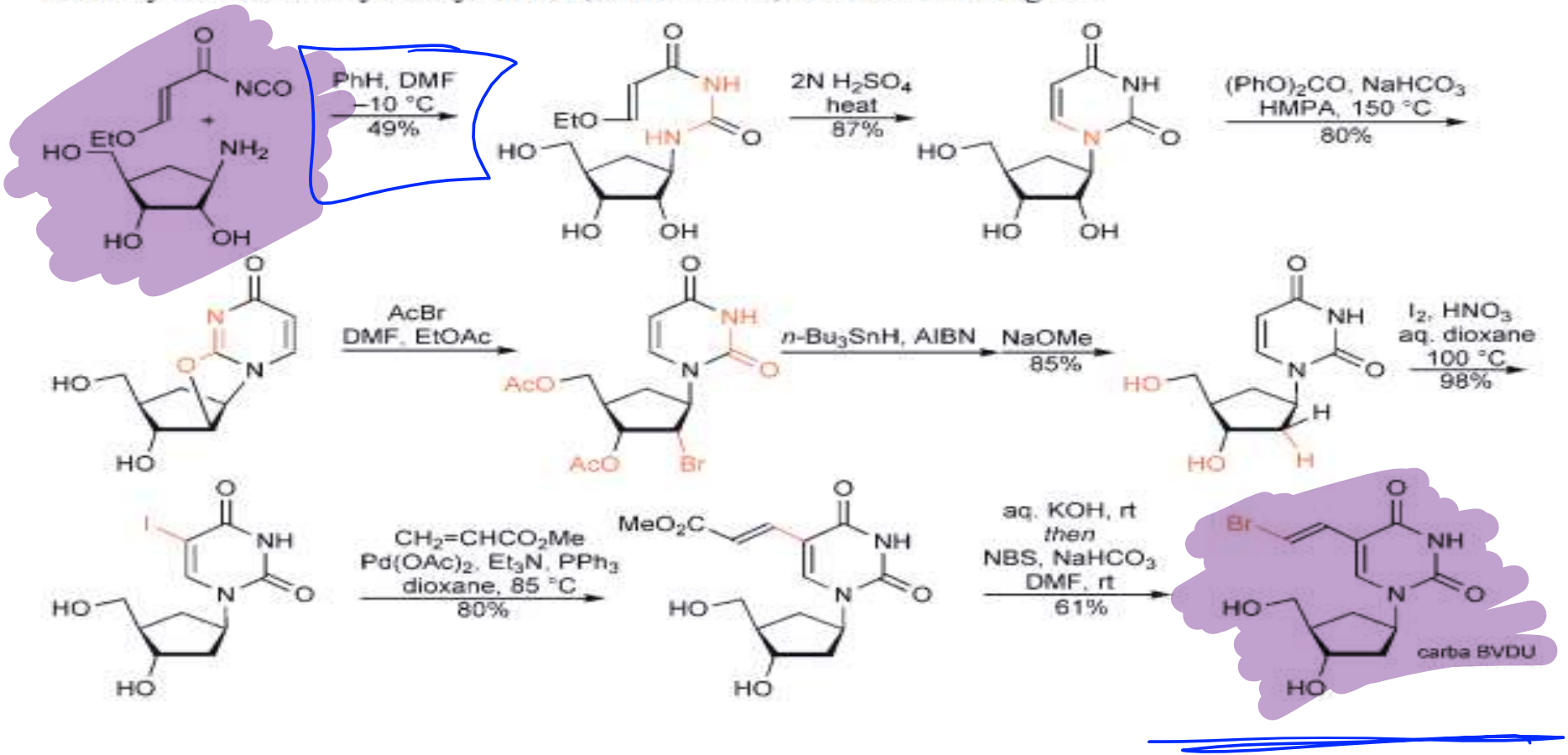


- Pyrazines Pyrazine is not easily made in the laboratory. Commercially, the high temperature cyclodehydrogenation of precursors such as N - hydroxyethylethane - 1,2 - diamine is used.
- From the Self - Condensation of a 2 - Amino - Ketone Symmetrical pyrazines result from the spontaneous self condensation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



14.13.4.2 Carbocyclic bromovinyldeoxyuridine

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



3 Pteridines

Q11. Pteridines are the common name for:

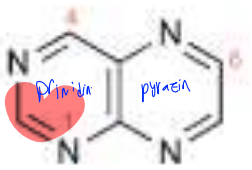
A. Pyrazino[2,3-d]pyrimidines
B. Benzo[b]pyridines
C. Pyrazino[1,2-a]pyridines
D. Pyrido[2,3-b]pyrazines

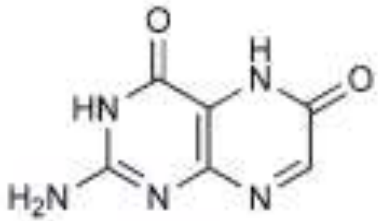
- Pyrazino[2,3 - d]pyrimidines are known as ‘ pteridines ’, 223 because the fi rst examples of the ring system, as natural products, were found in pigments, like xanthopterin (yellow), in the wings of butterfl ies (Lepidoptera).
- The pteridine ring system has subsequently been found in coenzymes that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

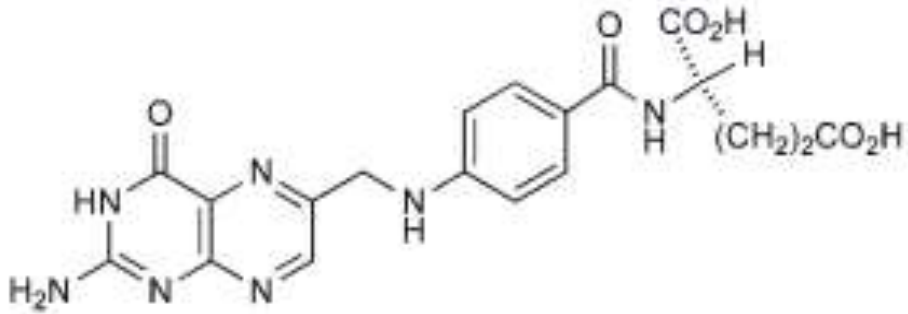
Pyrazino[2,3-d]pyrimidines are commonly known by which name?

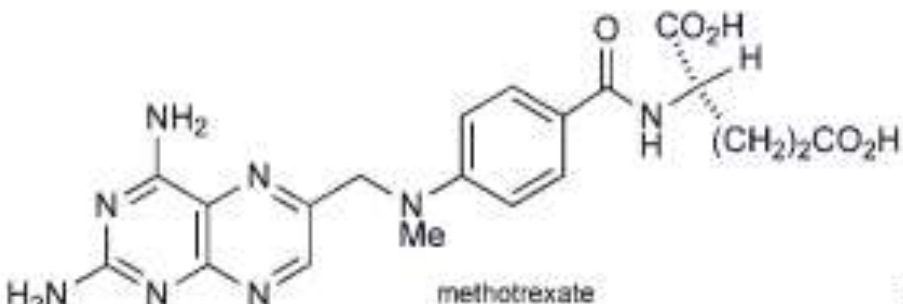
A) Purines
B) Pteridines
C) Pyridines
D) Pyrazines

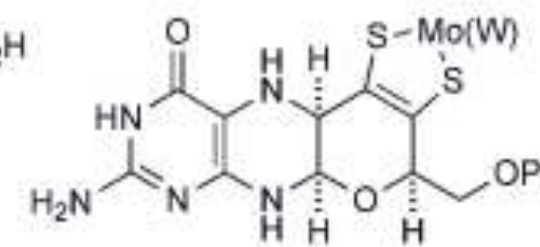
Correct Answer: B) Pteridines











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