

Unit 4: Heterocyclic Chemistry

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4.1 Why heterocycles dominate drug structures

Most drug molecules contain at least one heterocyclic ring: a ring carrying nitrogen, oxygen or sulfur in place of one or more carbons. Heteroatoms give a ring hydrogen bond donors and acceptors, tunable basicity, and dipole moments that fit enzyme and receptor pockets, all inside a rigid, defined shape. This unit takes the named syntheses of the five membered, six membered and fused systems of the syllabus and follows each into the drugs built on that nucleus, because in the examination the reaction and the drug list are asked together.

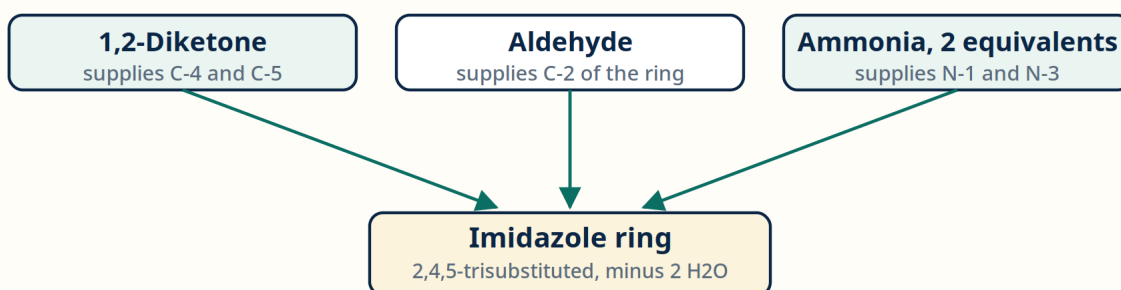
4.2 Debus-Radziszewski imidazole synthesis

The reaction: a 1,2-diketone, an aldehyde and excess ammonia (usually as ammonium acetate in acetic acid) condense to give a 2,4,5-trisubstituted imidazole.

Mechanism in words: ammonia condenses with the aldehyde and with one carbonyl of the diketone to give imine and alpha-imino ketone intermediates; these join so that the two nitrogen atoms and the three carbon fragments assemble into the five membered ring skeleton, and loss of two molecules of water aromatises it to the imidazole. The aldehyde carbon becomes C-2 of the ring (the carbon between the two nitrogens), the diketone supplies C-4 and C-5. The classical example is benzil, benzaldehyde and ammonia giving 2,4,5-triphenylimidazole (lophine).

Drug connection: the imidazole ring is the antifungal nucleus of theazole drugs. In **ketoconazole**, **miconazole**, **clotrimazole** and **terconazole** an imidazole nitrogen coordinates the haem iron of the fungal enzyme lanosterol 14 alpha-demethylase, blocking ergosterol synthesis; commercial routes build the substituted imidazole ring early and attach side chains by N-alkylation. **Metronidazole** is a nitroimidazole: 2-methyl-5-nitroimidazole, made by nitration of 2-methylimidazole, is N-hydroxyethylated with ethylene oxide or 2-chloroethanol; its nitro group is reduced inside anaerobic organisms to cytotoxic intermediates.

Debus-Radziszewski Imidazole Synthesis: Atom Map



Example: benzil plus benzaldehyde plus ammonia gives lophine, 2,4,5-triphenylimidazole.

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Figure: Where every imidazole atom comes from in the Debus-Radziszewski synthesis.

4.3 Knorr pyrazole synthesis

The reaction: a 1,3-dicarbonyl compound condenses with hydrazine or a substituted hydrazine to give a pyrazole. One nitrogen of hydrazine attacks the more reactive carbonyl, the second nitrogen closes onto the other carbonyl, and two dehydrations aromatise the ring; the two nitrogens end adjacent, which is the defining feature of pyrazole against imidazole.

Drug connection: with phenylhydrazine and ethyl acetoacetate the product is the pyrazolone **antipyrine** (phenazone) after N-methylation, and further elaboration gives **metamizole sodium** (dipyrone), the water soluble sulfonated analogue; both are classical analgesic antipyretics. The anti-inflammatory **celecoxib** carries a 1,5-diaryl pyrazole built by condensing a trifluoromethyl 1,3-diketone equivalent with a sulfonamide bearing phenylhydrazine, so the Knorr regiochemistry, which aryl group lands at C-3 and which at C-5, is a real industrial question in that drug.

4.4 Knorr pyrrole synthesis

The KBH copy adds the **Knorr pyrrole synthesis**: an alpha-amino ketone or alpha-amino beta-keto ester (made by nitrosation of a beta-keto ester and reduction) condenses with a second active methylene compound; the amine attacks the partner's carbonyl, cyclisation and dehydration give a polysubstituted pyrrole. It is the standard route to heavily substituted pyrroles and contrasts with the Paal-Knorr synthesis (1,4-diketone plus ammonia) that students often confuse with it: Knorr joins two fragments, Paal-Knorr closes one.

4.5 Pinner pyrimidine synthesis

The reaction: an amidine condenses with a 1,3-dicarbonyl compound (or its enol ether equivalent) under basic conditions to give a pyrimidine. The two amidine nitrogens become N-1 and N-3 of the ring and the amidine carbon becomes C-2; the dicarbonyl supplies C-4, C-5 and C-6. Regiochemistry with unsymmetrical partners is controlled by using enol ethers or enaminones with one defined electrophilic end.

Drug connection: the pyrimidine ring of the antibacterial **sulfamerazine** is 2-amino-4,6-dimethylpyrimidine, built by Pinner logic from amidine chemistry and then coupled as its amino group with N-acetylsulfanilyl chloride, hydrolysis freeing the sulfanilamide NH. **Trimethoprim** is a 2,4-diaminopyrimidine: its ring is closed by cyclisation with guanidine (the amidine partner) onto a three carbon unit derived from 3,4,5-trimethoxybenzaldehyde, giving the benzyl substituted diaminopyrimidine that inhibits bacterial dihydrofolate reductase. **Triamterene** is a pteridine, a pyrimidine fused to a pyrazine, and belongs to the same diaminopyrimidine family in its binding logic.

4.6 Combes quinoline synthesis

The reaction: an aniline condenses with a 1,3-diketone to give an enaminone (a beta-anilino enone); strong acid (concentrated sulfuric acid classically) then cyclises it by electrophilic attack of the protonated carbonyl carbon onto the ortho position of the aniline ring, and dehydration gives a 2,4-disubstituted quinoline.

Comparison within the family: Skraup builds quinoline from glycerol as the three carbon unit under harsh oxidising conditions and gives the unsubstituted ring; Doebner-Miller (Unit 2) uses an alpha,beta-unsaturated carbonyl partner and gives 2-substituted quinolines; Combes gives the 2,4-pattern directly and predictably, which is why it is the textbook choice for substituted quinolines, with the limitation that meta substituted anilines can cyclise to either ortho position and give mixtures.

Drug connection: the quinoline nucleus carries the antimalarials. **Chloroquine and hydroxychloroquine** are 4-aminoquinolines: the industrial route makes 4,7-dichloroquinoline (by a Gould-Jacobs type cyclisation) and displaces the reactive 4-chloro group with the dialkylamino side chain amine;

hydroxychloroquine differs only in carrying a hydroxyethyl group on the side chain nitrogen. **Quinine**, the original antimalarial, is a quinoline methanol alkaloid from cinchona bark, obtained by extraction rather than total synthesis in commerce, but its quinoline half is the same nucleus this section builds.

4.7 Bernthsen acridine synthesis

The reaction: a diarylamine is heated with a carboxylic acid (or anhydride) and zinc chloride at high temperature; the acid carbon becomes C-9 of the acridine, inserted between the two rings by double electrophilic substitution, giving a 9-substituted acridine.

Drug connection: acridines are flat, DNA intercalating tricyclics. **Quinacrine** (mepacrine) is a 9-aminoacridine antimalarial whose side chain is attached at C-9 through the amino group, a descendant of the Bernthsen construction; **amsacrine** is a 9-anilinoacridine anticancer agent, a topoisomerase II poison. The phenothiazine antipsychotics belong to the neighbouring sulfur bridged family: **promazine**, **chlorpromazine** and **prochlorperazine** are built on phenothiazine, made by heating diphenylamine with sulfur (Bernthsen's thionation), chlorination at C-2 for the chlorinated members, and N-alkylation of the ring nitrogen with the appropriate aminoalkyl chloride side chain, the side chain being the main structural variable among the three drugs.

4.8 Smiles rearrangement

The **Smiles rearrangement** is an intramolecular nucleophilic aromatic substitution: in a system such as a 2-hydroxy or 2-amino diaryl sulfone, base generates the internal nucleophile, which attacks the other ring at the carbon bearing the sulfone, through a spiro Meisenheimer intermediate; the carbon-sulfur bond then breaks, completing a net migration of the aryl group from sulfur to oxygen or nitrogen.

It is examined as the elegant proof that S_NAr (Unit 1) can be made intramolecular, and its synthetic use is to build diaryl ethers and hydroxy sulfones with substitution patterns that direct coupling gives poorly. The Truce-Smiles variant extends the same idea to carbon nucleophiles, where a carbanion displaces a sulfone.

4.9 Traube purine synthesis

The reaction: a 4,5-diaminopyrimidine (carrying the substituents wanted at the future 2 and 6 positions) is heated with formic acid or a formamide equivalent; the 5-amino group is formylated and then cyclises onto the 4-amino group, closing the fused imidazole ring and giving the purine. Where a substituent other than hydrogen is wanted at C-8, the corresponding carboxylic acid or derivative replaces formic acid.

Drug connection: purine is the nucleus of the xanthines and the antimetabolites. **Theophylline** is 1,3-dimethylxanthine (a purine-2,6-dione), classically built by the Traube route from dimethylurea and a malonic unit through the daminouracil, nitrosation, reduction and formic acid closure sequence.

Mercaptopurine (6-mercaptopurine) is made from hypoxanthine by replacing the 6-oxygen with sulfur (phosphorus pentasulfide thiation), and **thioguanine** is its 2-amino analogue; both are cytotoxic antimetabolites whose action depends on the purine ring being accepted by the salvage pathway enzymes.

4.10 The fused and remaining drug nuclei in outline

Two named drug groups of the syllabus sit on fused systems not covered by a single named reaction above, and the examination expects their nuclei recognised:

- **Alprazolam** is a triazolobenzodiazepine: a benzene ring fused to a seven membered diazepine that is itself fused to a triazole. Its synthesis builds the benzodiazepinone framework (from 2-amino-5-chlorobenzophenone chemistry) and annelates the triazole ring at the end, illustrating that fused systems are usually built one ring at a time onto a preformed ring, the strategy generalised in Unit 5.
- The **phenothiazines** (section 4.7) complete the fused list: five membered, six membered and fused nuclei, each reached by a named ring closure from simple precursors, which is the single pattern this whole unit teaches.

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