

Unit 2: Alkaloids, Flavonoids and Steroids

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2.1 Alkaloids: introduction and classification

Alkaloids are naturally occurring nitrogen containing compounds, mostly of plant origin, that are basic and usually physiologically potent. The classic definition carries standard exceptions worth quoting in an exam: colchicine is barely basic, some alkaloids come from animals, fungi and microbes (ergot, Unit 1's venom peptides aside), and the nitrogen of piperine sits in an amide. Most alkaloids are biosynthesised from amino acids, and that fact organises the whole family.

Class (by precursor)	Ring skeleton	Examples from this course
Ornithine and lysine derived	Tropane, pyrrolizidine, quinolizidine	Hyoscyamine and atropine, cocaine (tropane)
Phenylalanine and tyrosine derived	Benzylisoquinoline, phenanthrene, aporphine	Morphine, codeine, tubocurarine, papaverine, emetine, berberine
Tryptophan derived	Indole, beta-carboline, quinoline (via strictosidine)	Reserpine, ergot alkaloids, strychnine, quinine, vinca alkaloids
Histidine derived	Imidazole	Pilocarpine
Purine and pseudoalkaloids	Xanthine, steroid and terpene skeletons with nitrogen added late	Caffeine, solasodine, aconitine

An older chemical classification simply names the heterocyclic ring present (pyrrole, pyridine, isoquinoline, indole, imidazole, purine). Both schemes survive because both answer real questions: the ring scheme helps analysis and synthesis, the precursor scheme explains why related structures occur together in a plant. Alkaloids occur in the plant largely as salts of plant acids (oxalic, tannic, citric) or bound to tannins, concentrated in particular organs: bark, root, seed or latex depending on species.

2.2 Isolation and purification of alkaloids

Alkaloid isolation is applied acid-base chemistry. The free base is soluble in organic solvents and poorly soluble in water; the salt reverses both. The working sequence:

ALKALOID SEPARATION BY ACID-BASE SWITCHING

Powdered plant material	
Extract with dilute acid or with alcohol, then acidify	(alkaloids dissolve as salts)
Filter, concentrate	
Basify with ammonia or sodium carbonate	(free bases liberated)
Extract into chloroform, dichloromethane or ether	(alkaloid bases move organic; tannins and salts stay aqueous)
Wash, dry, evaporate	
Separate the mixture	(fractional crystallisation of salts, column and preparative chromatography, counter current distribution)
Pure alkaloid	(constant melting point, single spot on TLC, spectral identity)

Purification details examiners favour: salts differ in solubility (picrates, oxalates, tartrates crystallise well), so a salt is often made to be recrystallised and then broken back to the base; vacuum distillation serves the few liquid alkaloids such as nicotine and coniine; and modern practice follows every fraction by TLC and increasingly by LC-MS, which is bioassay guided fractionation (Unit 1) with better eyes. Identity is fixed by melting point, mixed melting point with an authentic sample, and the spectra of Unit 5.

2.3 Molecular modification and biological activity of alkaloids

Because alkaloid skeletons are potent and complex, modification usually means semi-synthesis: keep the skeleton, edit its edges. The morphine series (Unit 1) showed methylation, acetylation and N-substitution producing a whole pharmacopoeia from one skeleton. General principles:

- **Quaternary salts** (as in tubocurarine) stay out of the brain and act peripherally; tertiary bases cross membranes and reach the CNS. Basicity and charge are distribution switches.
- **N-demethylation** often gives more polar, differently active metabolites (nortropane and normorphine series); N-alkyl size tunes agonist to antagonist character at opioid receptors.
- **Ester hydrolysis and exchange** changes duration: cocaine's benzoyl ester is its activity, and its hydrolysis products are inactive, which is also why local anaesthetic design copied its pharmacophore synthetically (procaine, lignocaine) discarding the tropane ring entirely.
- **Stereochemistry is decisive**: the alkaloid families are heavily stereogenic, and one epimer may be drug and the other near inert (section 2.5 and 2.9).
- Activity targets cluster: neurotransmitter receptors (nicotine, morphine), transporters (cocaine, reserpine), enzymes (physostigmine at acetylcholinesterase) and structural proteins (colchicine and the vinca alkaloids at tubulin). A potent alkaloid almost always has a protein it was evolved to hit.

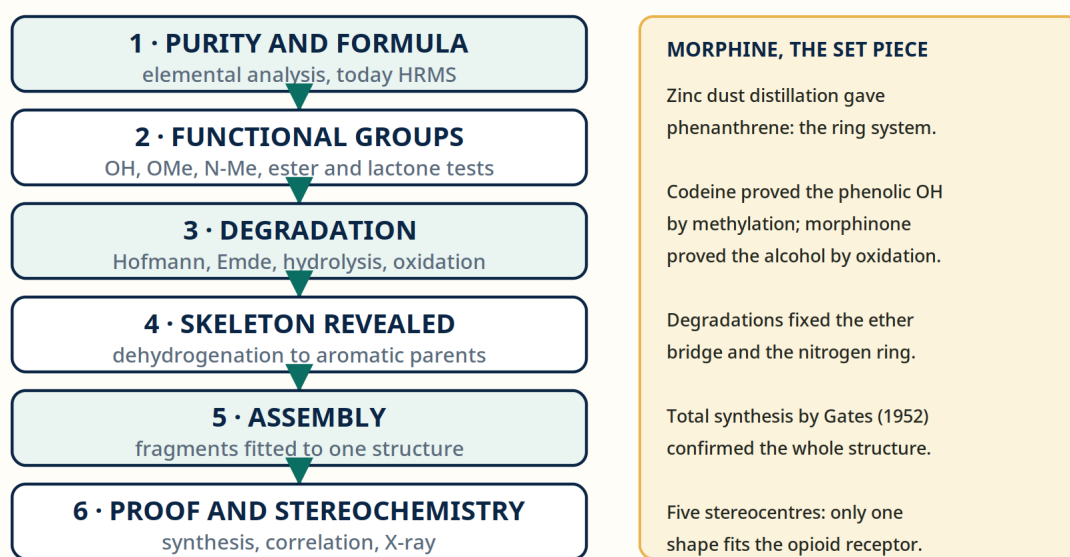
2.4 General methods of structural determination

The classical proof of an alkaloid's structure, the method this unit's five case studies used, ran in a fixed order:

- 1 **Purity and formula**: elemental analysis and molecular weight fix the molecular formula; today HRMS does both in one measurement.

- 2 **Functional group inventory:** tests and spectra for hydroxyl, phenol, methoxyl (Zeisel), N-methyl (Herzig-Meyer), methylenedioxy, olefinic bonds, ester and lactone groups; the degree of unsaturation from the formula tells how many rings and multiple bonds must be accounted for.
- 3 **Skeleton by degradation:** controlled reactions that break the molecule at informative points: Hofmann exhaustive methylation opens nitrogen rings and counts ring attachments to nitrogen; Emde and von Braun degradations cut C-N bonds differently; zinc dust distillation, sulfur or selenium dehydrogenation strips hydrogens to reveal an aromatic parent hydrocarbon (a phenanthrene from the morphine series, a carbazole or beta-carboline from indole alkaloids); oxidation with permanganate or chromic acid cuts side chains to identifiable acids; hydrolysis separates esters, glycosides and amides into known halves.
- 4 **Assembly:** the fragments are fitted into one structure consistent with every degradation and with the biosynthetic logic of the family.
- 5 **Proof by synthesis:** total synthesis of the proposed structure, identical in all properties (including spectra and optical rotation) with the natural compound, was the classical gold standard; Gates's morphine synthesis confirmed the morphine structure in this way.
- 6 **Stereochemistry:** relative configuration from chemical interconversions and coupling behaviour, absolute configuration by correlation with compounds of known configuration and, in the modern era, by X-ray crystallography of salts.

Classical Structure Proof of an Alkaloid



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Figure: The six steps of a classical alkaloid structure proof, with morphine as the worked historical example.

Modern spectroscopy (Unit 5) now obtains in days what degradation took years to win, but examiners still teach the classical logic because it is the clearest training in structural reasoning: every reaction is an experiment whose result the proposed structure must explain.

2.5 Ephedrine: structure and stereochemistry

Ephedrine, the principal alkaloid of *Ephedra* species (ma huang in Chinese medicine), is a phenylpropanolamine, C₁₀H₁₅NO: a benzene ring bearing a three carbon chain with a hydroxyl on the benzylic carbon (C-1) and a methylamino group on C-2. It is a **protoalkaloid**: the nitrogen is not in a ring. Structurally it is the plant world's close copy of adrenaline, missing only the catechol hydroxyls, which is why it acts as a mixed sympathomimetic, releasing noradrenaline and stimulating adrenergic receptors directly, and why removing the ring hydroxyls makes it orally active and longer acting than adrenaline itself.

Elucidation logic. Oxidation gave benzoic acid, fixing a monosubstituted benzene with an oxidisable side chain. The formula and functional tests accounted for one secondary alcohol and one secondary amine. Degradation and synthesis from benzaldehyde based routes confirmed the chain as $\text{Ph-CHOH-CH(NHMe)-CH}_3$.

Stereochemistry is the examinable core. Two stereocentres (C-1 and C-2) give four stereoisomers: the natural product is (1R,2S)-ephedrine, levorotatory; its C-1 epimer, (1S,2S), is **pseudoephedrine**, a different drug (a milder nasal decongestant) despite the identical constitution. The pair teach the permanent lesson that diastereomers are different substances with different pharmacology, and that a natural product structure is not fully stated until configuration is stated.

2.6 Morphine: structural elucidation and stereochemistry

Morphine's proof (Gulland and Robinson, 1923 to 25, confirmed by Gates's total synthesis, 1952) remains the classical set piece.

The evidence trail:

- **Formula and groups:** $\text{C}_{17}\text{H}_{19}\text{NO}_3$; one phenolic hydroxyl (soluble in alkali, gives colour reactions, methylates to codeine), one secondary alcoholic hydroxyl (oxidises to the ketone morphinone), one inert ether oxygen, one tertiary N-methyl base. Codeine is morphine's 3-methyl ether, and heroin its diacetyl derivative (Unit 1), relations proved by hydrolysis back to morphine.
- **The phenanthrene skeleton:** exhaustive methylation and degradation gave trimethylamine and nitrogen free fragments; zinc dust distillation of the alkaloid gave **phenanthrene** itself, proving the three fused ring carbocyclic system.
- **Locating the oxygen bridge and the nitrogen ring:** a long campaign of degradations (the morphine to apomorphine rearrangement under acid, Hofmann degradations of codeine derivatives to compounds such as morphenol, a phenanthrene bearing the ether oxygen) fixed the dihydrofuran bridge across the ring junction and the ethanamine bridge that makes the piperidine ring.
- **The double bond:** uptake of one molar equivalent of hydrogen and the behaviour on oxidation placed one olefinic bond in the third ring, allylic to the alcohol.

Stereochemistry. Morphine has five stereogenic centres (C-5, C-6, C-9, C-13, C-14) and a rigid, T-shaped three dimensional structure; the absolute configuration was established by correlation and confirmed by synthesis, and synthetic efforts that produced the mirror skeleton produced inactive material: the opioid receptor accepts one shape only. For the spectral re-examination of morphine see Unit 5, section 5.4.

2.7 The ergot alkaloids

Ergot is the dark sclerotium of the fungus *Claviceps purpurea* growing on rye and other grasses; its alkaloids explained both the historical poisonings of ergotism and a rich pharmacology. All share **lysergic acid**, a tetracyclic ergoline structure built from tryptophan, with an indole ring fused into a four ring system bearing a carboxyl group whose substituent divides the family:

- **Peptide ergot alkaloids:** ergotamine, ergocristine and relatives, in which lysergic acid is joined to a tripeptide; complex, poorly soluble, vasoconstrictor.
- **Simple amide:** ergometrine (ergonovine), lysergic acid joined to alaninol; water soluble, the oxytocic used against postpartum haemorrhage.
- **Clavines:** smaller relatives such as agroclavine, intermediates on the biosynthetic path.

Elucidation proceeded by hydrolysis: every member yields lysergic acid (or its C-8 epimer, isolysergic acid, an easy isomerisation that complicated early work and is itself an exam favourite), plus ammonia and, for the peptide series, identifiable amino acids and pyruvic acid from the unusual tripeptide. Pharmacology follows the family chemistry: partial agonism at serotonin, adrenergic and dopamine receptors in different proportions, hence uses from migraine (ergotamine) to prolactin suppression by the semi-synthetic bromocriptine, and hence also the toxicity that pushed practice towards the synthetic triptans. The semi-synthetic lysergic acid diethylamide (LSD) is the famous cautionary member of the series.

2.8 Emetine

Emetine is the principal alkaloid of ipecacuanha, the root of *Carapichea ipecacuanha* (long named *Cephaelis ipecacuanha*), accompanied by cephaeline, its phenolic relative. Emetine is a bis-isoquinoline alkaloid: two 6,7-dimethoxy tetrahydroisoquinoline units linked through a substituted ethyl bridge, with four methoxyl groups, one secondary and one tertiary nitrogen, and four stereogenic centres whose configuration was settled by degradation to known fragments and final synthesis.

Elucidation headlines: methoxyl estimation fixed four OMe groups; oxidation and Hofmann type degradations split the molecule into isoquinoline fragments, from which the two halves and their junction were reconstructed. Pharmacologically emetine inhibits protein synthesis by blocking ribosomal translocation in both parasite and host: historically the drug of choice for invasive amoebiasis and, in syrup of ipecac, an emetic; both uses have retreated before safer agents (metronidazole for amoebiasis), making emetine a clean case of a natural drug retired by its own therapeutic index rather than by loss of activity.

2.9 Reserpine

Reserpine, from the root of *Rauwolfia serpentina* (sarpagandha, used in Ayurvedic practice for agitation and hypertension), is a complex indole alkaloid of the yohimbane family, built from tryptamine and the monoterpene secologanin. Its structure carries an indole fused pentacyclic system with a methoxycarbonyl group and a 3,4,5-trimethoxybenzoyl ester on the E ring: hydrolysis therefore yields reserpic acid, methanol and trimethoxybenzoic acid, the first degradation result from which the assembly was worked out. The molecule has six stereogenic centres, and the configuration at C-3, set by the biosynthetic coupling, is critical: its epimer, isoreserpine, is inactive, another stereochemistry decides activity case for the file beside ephedrine.

Reserpine irreversibly blocks the vesicular monoamine transporters (VMAT) that load noradrenaline, dopamine and serotonin into storage vesicles; the transmitters are then destroyed by monoamine oxidase, sympathetic tone falls, and blood pressure falls with it. It was among the first effective antihypertensives, and its mood lowering side effect, depression in a significant minority of patients, both limited its use and historically seeded the monoamine hypothesis of depression. It survives today mainly as a pharmacological tool and a teaching structure.

2.10 Flavonoids: introduction, isolation and purification

Flavonoids are the yellow and coloured polyphenols of the plant world: a C₆-C₃-C₆ skeleton in which two benzene rings (A and B) are joined by a three carbon unit that usually closes into an oxygen heterocycle (the C ring). They are biosynthesised from the shikimate pathway (the B ring and the three carbons, via a cinnamate) condensed with three acetate units (the A ring). The oxidation level and substitution of the C ring define the classes:

Class	C ring character	Examples
Flavones	2,3 double bond, 4-keto, no 3-OH	Apigenin, luteolin

Class	C ring character	Examples
Flavonols	Flavone plus 3-OH	Quercetin, kaempferol, myricetin
Flavanones	No 2,3 double bond, 4-keto	Naringenin, hesperetin
Flavanols (catechins)	No 4-keto, 3-OH	Catechin, epicatechin
Anthocyanidins	Flavylium cation, coloured	Cyanidin, delphinidin
Isoflavones	B ring at C-3 instead of C-2	Genistein, daidzein

Flavonoid Classes from One Skeleton

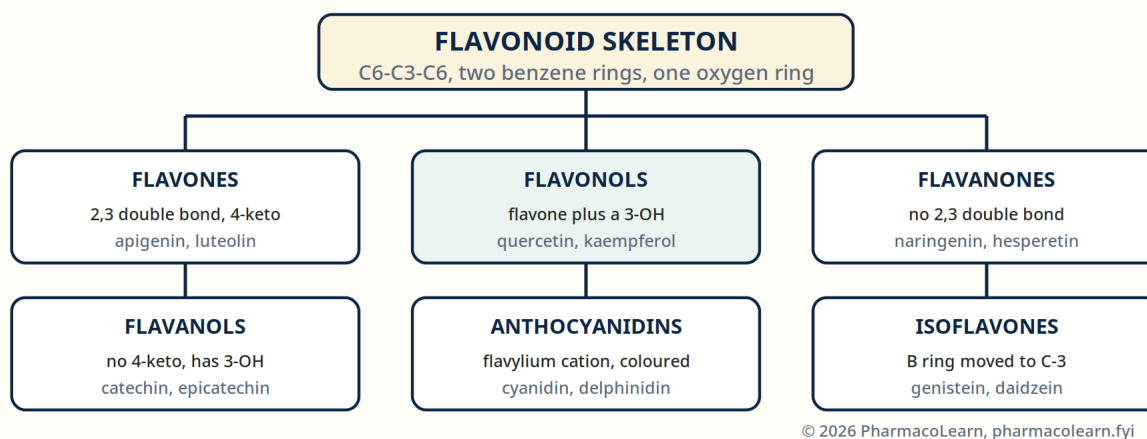


Figure: The flavonoid classes differ only in the oxidation pattern of the central oxygen ring built on the C6-C3-C6 skeleton.

In the plant they occur as **glycosides** (O-glycosides at the 3 or 7 hydroxyl usually; the aglycone is the sugar free part). Isolation: extract with aqueous alcohol or methanol, concentrate, clarify with lead acetate solution (which precipitates interfering tannins and acids, carefully, since it can carry flavonoids too), and separate by column, paper or preparative thin layer chromatography; glycosides are crystallised from alcohol, and hydrolysis with dilute acid releases the aglycone plus identifiable sugars. Flavonoids give diagnostic colour reactions used throughout their classical chemistry: the **Shinoda test** (magnesium and hydrochloric acid, pink to red for most classes), colour with ferric chloride, yellow solutions in alkali that intensify on standing, and fluorescence changes on chromatograms sprayed with aluminium chloride.

2.11 Structural determination of flavonoids and the structural elucidation of quercetin

The classical flavonoid proof combines spectroscopy with controlled destruction:

- **UV spectroscopy with shift reagents** was the great classical fingerprint: Band II (240 to 285 nm, A ring) and Band I (300 to 400 nm, B ring and cinnamoyl system) move in diagnostic directions with sodium methoxide (free 4 prime hydroxyl), sodium acetate (free 7 hydroxyl), aluminium chloride, stable to acid if a 5-hydroxyl or ortho dihydroxyl system is present. Methylation analysis (methylate, hydrolyse, identify which hydroxyls were free) locates glycosylation.
- **Alkaline degradation:** fusion or strong alkali splits a flavonoid at the C ring into an A ring fragment (usually a phloroglucinol or resorcinol derivative) and a B ring fragment (a benzoic or cinnamic acid), identifying the hydroxylation pattern of each ring separately.
- **Hydrolysis and sugar analysis** identify glycosides; NMR and MS (Unit 5) complete the modern proof.

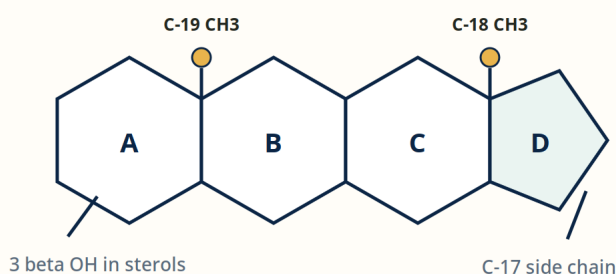
Quercetin worked fully: formula C₁₅H₁₀O₇; five acetyltable hydroxyls (pentaacetate); methylation then degradation gave phloroglucinol from the A ring and protocatechuic acid (3,4-dihydroxybenzoic acid) from the B ring, fixing the B ring diol pattern; alkaline fusion products and the flavonol colour and UV behaviour

(free 3-hydroxyl shown by its aluminium chloride complex and by ready oxidation) place hydroxyls at 3, 5, 7, 3 prime and 4 prime. Quercetin is therefore **3,5,7,3 prime,4 prime-pentahydroxyflavone**, and it occurs in plants chiefly as glycosides: rutin (3-O-rutinoside, from rue and buckwheat), quercitrin (3-O-rhamnoside) and isoquercitrin (3-O-glucoside). Onion, apple, tea and many leafy vegetables supply it in the diet; its antioxidant activity in vitro is strong, its oral bioavailability limited, and examiners expect that measured verdict rather than supplement advertising.

2.12 Steroids: sterols, sapogenins and cardiac glycosides

The **steroid nucleus** is the cyclopentanoperhydrophenanthrene (gonane) system: three six membered rings (A, B, C) fused to a five membered ring (D), carrying angular methyl groups at C-10 and C-13 in most natural members. Everything in the steroid industry is a variation on this frame.

The Steroid Nucleus and How to Read It



READ THE FRAME

beta: above the plane, solid
alpha: below it, dashed

5 alpha series: A/B trans
5 beta series: A/B cis

Oestrane: C18 carbons
Androstane: C19 carbons
Pregnane: C21 carbons
Cholestane: C27 carbons

Sterols, sapogenins, cardiac
glycosides and hormones
[share this gonane frame.](#)

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Figure: The gonane steroid nucleus: rings A to D, the angular methyl groups, and the alpha and beta convention used throughout steroid nomenclature.

Sterols are steroid alcohols with a 3 beta hydroxyl and a side chain at C-17: cholesterol in animals, beta-sitosterol and stigmasterol in plants, ergosterol in fungi (the vitamin D2 precursor, section 2.14). Cholesterol is the biosynthetic parent of every steroid hormone and of the bile acids.

Sapogenins are the aglycones of the saponins, glycosides that froth in water and haemolyse red cells. Steroidal sapogenins such as **diosgenin** (from *Dioscorea* species) carry a spiroketal side chain (the spirostane system). Diosgenin's industrial importance is hard to overstate: the Marker degradation converted it into progesterone and onward to cortisone and the contraceptive steroids, making yam derived diosgenin the feedstock that founded the steroid industry before total synthesis and fermentation routes matured.

Cardiac glycosides join a steroidal aglycone (genin) of the cardenolide type to sugars at the 3-hydroxyl. The genin carries an unsaturated five membered lactone (butenolide) ring at C-17 and a 14 beta hydroxyl; *Digitalis purpurea* gives digitoxin, *Digitalis lanata* gives digoxin (12 beta hydroxy digitoxin) and their relatives. They inhibit the sodium potassium ATPase, raising intracellular calcium in cardiac muscle: positive inotropy for heart failure, at a notoriously narrow therapeutic index the spectral study revisits in Unit 5.

2.13 Steroid nomenclature and stereochemistry

Steroid stereochemistry is described relative to the plane of the ring system. The angular methyls at C-10 and C-13 are taken as **beta** (above the plane, drawn solid), and any substituent is alpha (below, dashed) or beta by comparison. Parent hydrocarbon names encode the framework and the A/B ring junction:

Parent	Feature
Oestrane	18 carbons, no C-10 methyl, aromatic A ring in the hormone series
Androstane	19 carbons, methyls at C-10 and C-13
Pregnane	21 carbons, androstane plus a two carbon side chain at C-17
Cholestane	27 carbons, full cholesterol side chain

Within this frame: 5 alpha steroids have the A/B junction trans (H at C-5 alpha, rings extended and near planar in effect); 5 beta steroids have it cis (epimeric at C-5, the A ring bent under), which distinguishes the bile acid and cardiac glycoside series (5 beta) from the androstane hormone series (5 alpha). Hydroxyls are cited as 3 beta, 11 beta, 17 beta and so on; ketones as oxo positions (androst-3-one); double bonds by locants with the Greek delta in older literature. A structure written as pregn-4-ene-3,20-dione is, by these rules alone, already nearly drawn: that is progesterone.

2.14 Sex hormones, contraceptive agents, adrenocorticoids and vitamin D

Testosterone is androst-4-en-17 beta-ol-3-one, the principal androgen, made in the testes from cholesterol through pregnenolone and dehydroepiandrosterone; its 5 alpha reduced metabolite dihydrotestosterone is the more potent androgen in prostate and skin. Oral testosterone is destroyed by first pass oxidation of the 17 beta hydroxyl, so the clinic uses 17 esters by injection or 17 alpha alkylated analogs (hepatotoxic, hence disfavoured).

Oestradiol (estradiol) is oestra-1,3,5(10)-triene-3,17 beta-diol: the A ring is aromatic, the C-10 methyl is absent (lost during aromatisation of an androgen precursor), and the phenolic 3-hydroxyl is its binding handle. **Progesterone**, pregn-4-ene-3,20-dione, is the natural progestogen of the corpus luteum and placenta, preparing and maintaining the endometrium; it is orally weak, which is why contraception was built from analogs.

Contraceptive agents. The combined oral contraceptive pairs an estrogen, **ethinylestradiol** (17 alpha ethinyl estradiol, the ethinyl group blocking 17 oxidation and so conferring oral activity), with a progestin: 19-nor steroids such as **norethisterone** and **levonorgestrel** (from the testosterone frame with the C-10 methyl removed and a 17 alpha ethinyl added) or later pregnane and spironolactone derived progestins such as drospirenone. The mechanism is endocrine feedback: suppression of the midcycle LH surge, so ovulation does not occur, with cervical mucus and endometrial effects in support. The whole family tree (sterol to diosgenin to progesterone to norethisterone) is the steroid industry's founding story, told in section 2.12.

Cortisone is the adrenal glucocorticoid frame: pregn-4-ene-17,21-diol-3,11,20-trione, its active form in tissue being the 11 beta alcohol cortisol (hydrocortisone), to which cortisone is reduced and back. The 11 oxygen function, so hard won in the early syntheses (the famous routes from bile acids and diosgenin existed largely to install it), is the glucocorticoid signature; modifications such as the 1,2 double bond (prednisone, prednisolone) and 9 alpha fluorine (dexamethasone, with a 16 methyl) raised anti-inflammatory potency stepwise.

Vitamin D belongs in this unit because it is a **secosteroid**: in skin, ultraviolet light opens the B ring of 7-dehydrocholesterol to give previtamin D3, which thermally isomerises to cholecalciferol (vitamin D3); ergosterol from fungi and yeast gives ergocalciferol (D2) the same way. Two hydroxylations, liver to

calcidiol (25-OH) and kidney to calcitriol (1,25-(OH)₂), convert it into a hormone regulating calcium and phosphate. Its chemistry is revisited spectroscopically in Unit 5 and nutritionally in Unit 3.

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