

Unit 3: Terpenoids and Vitamins

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3.1 Terpenoids: classification and isolation

The **terpenoids** (isoprenoids) are the largest family of natural products, built from five carbon isoprene units (C₅H₈) joined, with very few exceptions, head to tail. Carbon count therefore classifies the entire family at sight:

Class	Isoprene units	Carbons	Examples from this unit
Hemiterpenoids	1	C ₅	Isoprene itself, prenol
Monoterpenoids	2	C ₁₀	Citral, menthol, camphor
Sesquiterpenoids	3	C ₁₅	Artemisinin (Unit 1), farnesol
Diterpenoids	4	C ₂₀	Retinol, phytol, taxol (paclitaxel)
Sesterterpenoids	5	C ₂₅	A small marine and insect family
Triterpenoids	6	C ₃₀	Squalene, ginsenosides, sterol precursors
Tetraterpenoids	8	C ₄₀	Carotenoids, beta carotene
Polyterpenoids	Many	Long chains	Rubber, dolichols

Terpenoid Classes by Carbon Count



Count the carbons and divide by five: the class is the isoprene count.

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Figure: Terpenoid classification is carbon counting: each class is a whole number of C₅ isoprene units.

Biosynthetically the C₅ units are isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP), made by the mevalonate pathway in animals, fungi and plant cytosol, and by the methylerythritol phosphate (MEP) pathway in most bacteria and plant plastids; chain elongation and cyclisation by terpene synthases generate the family, and squalene (section 3.5) is the junction to the steroids.

Isolation. The volatile mono and sesquiterpenoids of essential oils are obtained by steam distillation or expression of the plant material, then separated by fractional distillation under reduced pressure and by chromatography; sensitive members demand low temperatures and protection from air, because terpenes

oxidise and polymerise readily (old turpentine is the household example). The higher, non volatile terpenoids are solvent extracted and purified by column chromatography and crystallisation in the usual way of section 2.2.

3.2 The isoprene rule and general methods of structural elucidation

Wallach's isoprene rule observes that terpene skeletons can be dissected into isoprene units; **Ruzicka's biogenetic isoprene rule** goes further and proposes that all terpenoids arise from a few acyclic precursors (geraniol for C₁₀, farnesol for C₁₅, geranylgeraniol for C₂₀, squalene for C₃₀) by cyclisation, rearrangement and oxidation, so a proposed structure must be a plausible child of its acyclic parent. The rule is both a proof tool and a biosynthesis map: menthol and camphor must both be constructible from a geraniol chain folded two different ways, and they are.

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TWO FOLDINGS OF ONE CHAIN: GERANIOL TO MENTHOL AND CAMPHOR
Acyclic start: geraniol (C10, head to tail isoprene units)
|
Fold and ring close between C-1 and C-6
|--- menthol line: keep the single ring, reduce and
|    set three stereocentres (p-menthane skeleton)
|
|--- camphor line: second closure builds the bridged
|    bornane skeleton, oxidise one carbon to the ketone
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General elucidation methods follow the Unit 2 logic with terpene specific tools: formula and unsaturation account; catalytic hydrogenation counts double bonds; ozonolysis and oxidative cleavage cut at double bonds and identify the carbonyl fragments, mapping the chain; dehydrogenation (sulfur, selenium, palladium) converts cyclic terpenes to known aromatic compounds (p-cymene from many monoterpenes), exposing the carbon skeleton; functional group chemistry and spectra complete the proof, and synthesis or X-ray analysis confirms. Where the molecule is an oil that will not crystallise, solid derivatives (semicarbazones of carbonyls, esters of alcohols) were the classical handles, a trick that recurs in the camphor and citral proofs below.

3.3 Monoterpenoids: citral, menthol and camphor

Citral is the lemon scented aldehyde of lemongrass and lemon peel oils, in fact a pair of geometric isomers: geranial (citral a, E) and neral (citral b, Z), an acyclic monoterpene, 3,7-dimethylocta-2,6-dienal. The proof pattern: formula C₁₀H₁₆O, aldehyde reactions and ready semicarbazone formation; oxidation and ozonolysis fragments (acetone from the isopropylidene end, levulinic acid derivatives from the chain) placed the two double bonds and the methyl branches exactly as the isoprene dissection predicts. Citral is also an industrial intermediate: its cyclisation chemistry underlies ionone and vitamin A synthesis.

Menthol is the cooling alcohol of peppermint oil (*Mentha piperita* and related), a saturated cyclic monoterpene alcohol of the p-menthane skeleton (a cyclohexane ring bearing methyl and isopropyl groups para to each other, hydroxyl at C-3 old numbering). Three stereogenic centres give eight stereoisomers, of which natural (minus)-menthol, (1R,2S,5R), is the potent cooling agent acting at the TRPM8 cold receptor; the others are weaker or differently flavoured, ephedrine's lesson (section 2.5) again. Oxidation of menthol gives menthone, the corresponding ketone, and dehydrogenation gives p-cymene, tying the skeleton proof together.

Camphor is the bridged bicyclic ketone of *Cinnamomum camphora*:

1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, the bornane skeleton, a cyclisation of the geraniol chain that builds a bridge and so escapes flat ring chemistry. Its classical proof (Bredt, 1893) rested on oxidation to camphoric acid, a dicarboxylic acid whose own degradations mapped the ring system carbon by carbon;

camphor became one of the earliest structures proved against serious alternatives and later a standard chiral starting material and resolving agent. Its IR carbonyl, unusually high for a ketone because of the strained ring, returns in Unit 5.

3.4 Diterpenoids: retinol, phytol and taxol

Retinol is vitamin A alcohol, treated chemically here and physiologically in section 3.7. A C₂₀ molecule built of four isoprene units ending in a beta-ionone ring, with a conjugated pentaene side chain terminating in a primary alcohol; the all trans form is the natural standard. The conjugated system is its identity (intense UV absorption, the Carr-Price blue colour with antimony trichloride) and its weakness: light, air and heat isomerise and oxidise it, which is why vitamin A preparations are protected and why its aldehyde (retinal) and acid (retinoic acid) partners interconvert in vision and in gene regulation respectively.

Phytol is the acyclic diterpene alcohol, 3,7,11,15-tetramethylhexadec-2-en-1-ol, obtained by hydrolysis of chlorophyll, whose phytyl ester side chain it is. Only one double bond and one alcohol: a deliberately plain molecule whose elucidation (Fischer's school) by stepwise oxidation proved the regular head to tail assembly of four isoprene units and anchored the isoprene rule for the diterpene class. In industry phytol is a starting material for vitamins E and K synthesis.

Taxol (paclitaxel) returns from Unit 1 as the diterpenoid case study: a taxane skeleton of an eight membered ring fused into a strained tricyclic system with an oxetane ring, heavily oxygenated, bearing the N-benzoyl phenylisoserine side chain that its microtubule binding requires. Its elucidation (structure published 1971 by Wani and Wall) used exactly the classical armamentarium: degradation to baccatin fragments, spectroscopy and derivatisation, on milligram quantities of a molecule with eleven stereogenic centres. The supply sequel, semi-synthesis from 10-deacetylbaccatin III, is in section 1.3.

3.5 Triterpenoids: squalene and the ginsenosides

Squalene is the acyclic C₃₀ triterpene hydrocarbon, six isoprene units joined with a centre of symmetry where two farnesyl units meet tail to tail. Isolated first from shark liver oil (*Squalus*), it occurs in olive oil, human sebum and every eukaryote that makes sterols, because it is the sterol precursor: squalene epoxidase and oxidosqualene cyclase fold and cyclise squalene 2,3-epoxide into lanosterol (in animals and fungi) or cycloartenol (in plants), and nineteen further steps trim lanosterol to cholesterol. Structure proof rested on its formula C₃₀H₅₀, six double bonds by hydrogenation, and oxidative fragments consistent with the symmetrical chain; its cyclisation products, predicted by the biogenetic isoprene rule with a chair boat chair folding, were found exactly as predicted, one of the rule's great confirmations.

Ginsenosides are the saponins of ginseng root (*Panax ginseng* and *Panax quinquefolius*): glycosides of triterpene aglycones, chiefly of the dammarane type (protopanaxadiol and protopanaxatriol series), named by their chromatography (Rb1, Rb2, Rc, Rd from the diol series; Re, Rg1 from the triol series). Acid or enzymatic hydrolysis gives the aglycone plus glucose, rhamnose, arabinose and xylose in member specific patterns. They are the chemical basis on which ginseng preparations are standardised, whatever view is taken of the adaptogen claims, and they show the triterpene family wearing the saponin dress of section 2.12: the same foam, haemolysis and sugar chemistry on a dammarane rather than spirostane frame.

3.6 Carotenoids: beta carotene

The carotenoids are C₄₀ tetraterpenoids: eight isoprene units joined to a long conjugated polyene chain, the conjugation (eleven conjugated double bonds in beta carotene) producing the yellow, orange and red colours of carrots, tomatoes (lycopene) and autumn leaves. **Beta carotene**, C₄₀H₅₆, carries a beta-ionone ring at each end of the chain. Its structure was settled by degradation and by synthesis (Karrer, Nobel

laureate for this and the vitamin work of section 3.7), and its physiology is its chemistry: oxidative cleavage at the central double bond by the intestinal enzyme beta carotene 15,15 prime dioxygenase yields two molecules of retinal, making beta carotene the principal **provitamin A**. The same conjugated system quenches singlet oxygen and radicals, the basis of carotenoid antioxidant discussion, and its intense absorption makes it a food colour (E160a) as well as a nutrient.

3.7 Vitamins: chemistry and physiological significance

The vitamins are organic micronutrients the body cannot make (or cannot make enough of) whose absence produces specific deficiency disease. Eight are in this syllabus; each entry below gives the chemistry first and the physiology as its consequence.

Vitamin	Chemical identity	Physiological significance and deficiency
A (retinol)	Diterpenoid alcohol, conjugated pentaene, beta-ionone ring	Retinal is the visual pigment chromophore; retinoic acid regulates gene expression and epithelial differentiation. Deficiency: night blindness, xerophthalmia, a leading preventable cause of childhood blindness
B1 (thiamine)	Pyrimidine and thiazolium rings joined by a methylene bridge; the thiazolium carbon is the reactive centre	As thiamine pyrophosphate, coenzyme for oxidative decarboxylation (pyruvate and alpha-ketoglutarate dehydrogenases, transketolase). Deficiency: beriberi and Wernicke Korsakoff syndrome
B2 (riboflavin)	Isoalloxazine ring system with a ribityl side chain	Built into FMN and FAD, the redox coenzymes of dehydrogenases and oxidases; the isoalloxazine ring carries the electrons. Deficiency: ariboflavinosis, sore tongue, photophobia, cracked lips
B12 (cobalamin)	A cobalt containing corrin ring, the most complex vitamin; cyanocobalamin is the stable pharmaceutical form	Coenzyme for methionine synthase and methylmalonyl CoA mutase; absorbed only with intrinsic factor. Deficiency: megaloblastic anaemia and, distinctively, demyelinating neurological damage; pernicious anaemia is the absorption failure form
C (ascorbic acid)	A sugar like enediol lactone, a strong reducing agent; oxidises reversibly to dehydroascorbic acid	Cofactor for the hydroxylases of collagen synthesis (prolyl and lysyl hydroxylases) and for catecholamine and carnitine synthesis; antioxidant. Deficiency: scurvy, failed wound healing and bleeding gums
E (tocopherols)	Chromanol ring with a phytyl side chain; alpha tocopherol the most active of the four tocopherols	The principal lipid soluble chain breaking antioxidant of membranes, protecting polyunsaturated fatty acids from peroxidation. Deficiency is rare, seen in fat malabsorption: neuropathy and haemolysis
Folic acid	Pteridine ring plus para-aminobenzoic acid plus glutamate (pteroylglutamic acid)	As tetrahydrofolate, the carrier of one carbon units for purine and thymidylate synthesis, hence DNA synthesis. Deficiency: megaloblastic anaemia and fetal neural tube defects, the basis of periconceptional supplementation
Niacin	Vitamin B3: nicotinic acid and nicotinamide, pyridine derivatives	Built into NAD and NADP, the hydride carrying coenzymes of hundreds of dehydrogenases. Deficiency: pellagra, dermatitis, diarrhoea and dementia

Two structural threads tie the table to the rest of the unit: retinol is this unit's own diterpenoid (section 3.4) viewed as a nutrient, and vitamin E's side chain is phytol's (section 3.4), the chlorophyll tail recycled into an antioxidant. Vitamin D is deliberately not in this table: the syllabus places it with the steroids in Unit 2 (section 2.14) and in the spectral exercises of Unit 5.

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