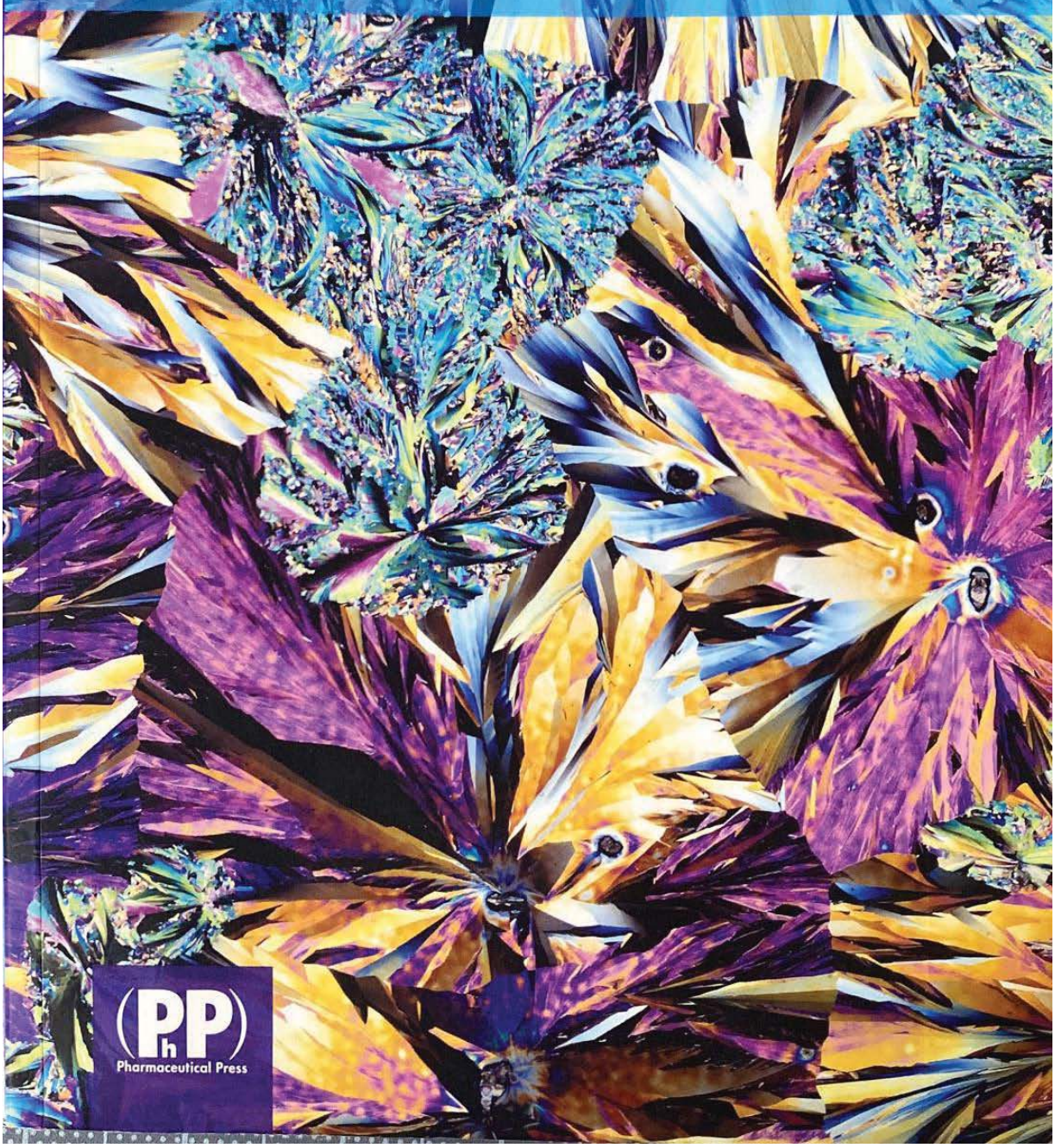
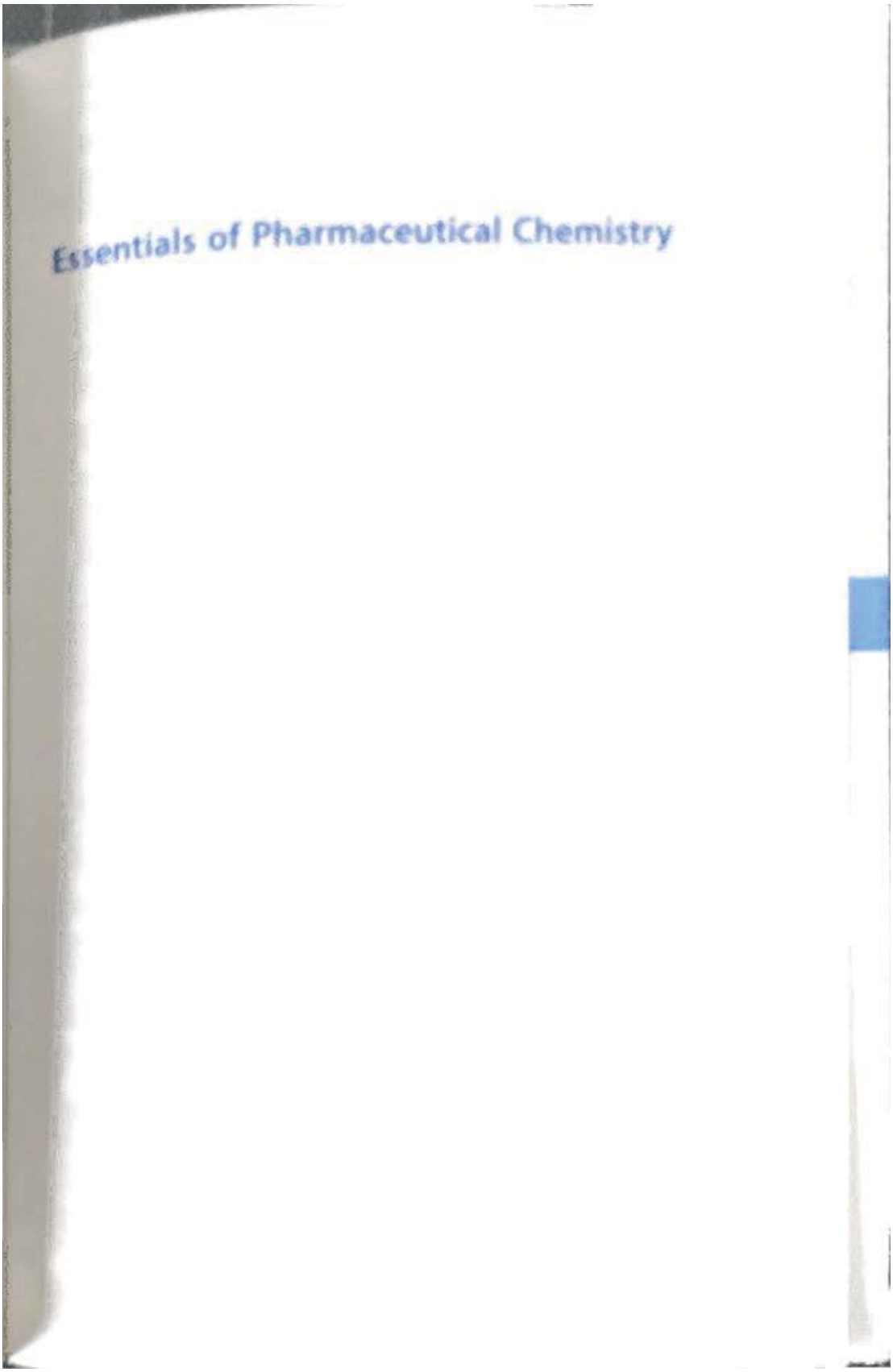
Essentials of Pharmaceutical Chemistry

Fourth edition

Donald Cairns



Pharmaceutical Press



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Essentials of Pharmaceutical Chemistry

FOURTH EDITION

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Dedication

For Elaine, Andrew and Mairi

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Preface to the fourth edition

In 2007 I wrote in the Preface to the third edition that the science and practice of pharmacy were undergoing a period of change. Now, as I write the Preface to the fourth edition of *Essentials of Pharmaceutical Chemistry*, it seems that the profession is still changing. The General Pharmaceutical Council has replaced the Royal Pharmaceutical Society as the regulator for pharmacy, the number of schools of pharmacy in the UK continues to rise and there are plans to integrate the current four year MPharm degree into a five year integrated model incorporating two six month periods in practice. This new edition of EPC (as one of my students calls the book) has been prepared against this changing background. I have tried to incorporate suggestions from users and reviewers and have updated every chapter for this edition and included new chapters, *Chromatographic methods of analysis* and *Medicinal Chemistry: the Science of Rational Drug Design*.

As with previous editions, I am very grateful for the help, advice, comments and encouragement from colleagues, reviewers and the many students of pharmacy and pharmaceutical science who are forced to use this book as part of their studies. I hope they find this new edition useful and, perhaps, experience some of the wonder and enjoyment I felt when I was introduced to the chemistry of drugs and medicines more than 30 years ago. If I was being honest with myself, that's still the way I feel about the subject today.

Donald Cairns
Aberdeen
June 2011

Acknowledgements

This book could not have been completed without the help of a great many people. I am very grateful to my colleagues, past and present for their advice and encouragement and particularly, for allowing me to assimilate their good practice (with or without their knowledge). This book would be poorer without their efforts. Special thanks must go to Paul Hambleton who read and commented on my first drafts and who not only allowed me to use a great many of his examination questions but also provided most of the answers!

I am grateful to Louise McIndoe, Christina de Bono and all the staff at the Pharmaceutical Press for keeping me on track when diversions threatened and giving helpful advice about indexes, content pages, etc.

Finally, I must thank my wife, Elaine, who looked after the weans while I bashed the keyboard upstairs.

About the author

Donald Cairns obtained a Bachelor of Science degree in pharmacy from the University of Strathclyde in 1980 and after a pre-registration year spent in hospital pharmacy, he returned to Strathclyde to undertake a PhD on the synthesis and properties of benzylimidazolines. Following a year as a post-doctoral research fellow in the department of pharmacy at Sunderland Polytechnic (now the University of Sunderland), Dr Cairns moved to Leicester Polytechnic (now De Montfort University) where he held a five-year lectureship in pharmacy. In 1992 Dr Cairns was appointed senior lecturer in medicinal chemistry in Sunderland School of Pharmacy and in 2003 moved to a post of Associate Head of the School of Pharmacy at The Robert Gordon University in Aberdeen. In 2006, he was promoted to Professor of Pharmaceutical and Medicinal Chemistry at RGU and in 2010 was appointed Acting Head of the School of Pharmacy and Life Sciences.

Professor Cairns has served as external examiner at Strathclyde, Liverpool, Aberdeen and Belfast Schools of Pharmacy and has authored over 70 peer reviewed research papers.

His research interests include the design and synthesis of selective anticancer agents, the molecular modelling of drug–DNA interactions and the design of prodrugs for the treatment of nephropathic cystinosis.

Donald Cairns is a member of the General Pharmaceutical Council, the Royal Pharmaceutical Society, the Association of Pharmaceutical Scientists and in 2008 was made a Fellow of the Royal Society of Chemistry. In 2006 he was appointed to the British Pharmacopoeia Commission and serves on an Expert Advisory Group of the Commission on Human Medicines.

To travel hopefully is a better thing than to arrive, and the true success is to labour.

Robert Louis Stevenson, 1850–1894

9 Stability of drugs and medicines

Drugs sometimes have quite complicated chemical structures and are, by definition, biologically active compounds. It should not, therefore, come as a surprise that these reactive molecules undergo chemical reactions that result in their decomposition and deterioration, and that these processes begin as soon as the drug is synthesised or the medicine is formulated. Decomposition reactions of this type lead to, at best, drugs and medicines that are less active than intended (i.e. of low *efficacy*); in the worst-case scenario, decomposition can lead to drugs that are actually toxic to the patient. This is clearly bad news to all except lawyers, so the processes of decomposition and deterioration must be understood in order to minimise the risk to patients.

There are almost as many ways in which drugs can decompose as there are drugs in the *British Pharmacopoeia*, but most instability can be accounted for by the processes of *oxidation* and *hydrolysis*.

Oxidation

Oxidation is the process whereby an atom increases the number of bonds it has to oxygen, decreases the number of bonds it has to hydrogen, or loses electrons. The deterioration of drugs by oxidation requires the presence of molecular oxygen and proceeds under mild conditions. Elemental molecular oxygen, or O_2, possesses a diradical (unpaired triplet) electronic configuration in the ground state and is said to be *paramagnetic* (a species with all its electrons paired is called *diagmagnetic*). The structure of oxygen can be represented as $^{\bullet}O{=}O^{\bullet}$ or $O{=}O$ depending on whether the molecular orbital or valence bond theory is employed. The important fact for drug stability is that the radical species possesses two unpaired electrons, which can initiate chain reactions resulting in the breakdown of drug molecules, particularly if the reaction occurs in the presence of catalysts such as light, heat, some metal ions and peroxides. The types of drug that are affected include phenols (such as morphine), catecholamines (e.g. adrenaline (epinephrine)

and noradrenaline (norepinephrine)) as well as polyunsaturated compounds such as oils, fats and fat-soluble vitamins (e.g. vitamins A and E).

Autoxidation

Radical chain reactions of this type are called *autoxidation* reactions and can be quite complicated. All, however, proceed via a number of discrete steps, namely *initiation*, *propagation* and *termination*.

Initiation

Initiation involves homolytic fission of a covalent bond in the drug molecule to produce free radicals (Fig. 9.1). The energy source for this process often comes from light, either ultraviolet or visible, falling onto the sample. Light of these wavelengths is sufficiently energetic to bring about cleavage of the pair of electrons in a covalent bond to yield two radicals.

Stage 1 Chain initiation: involves homolytic fission to produce free radicals (Fig. 9.1).

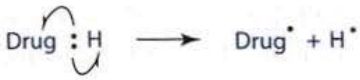


Figure 9.1. The mechanism of initiation.

Propagation

Propagation is the main part of the chemical reaction, in which free radicals react together to produce more and more reacting species (Fig. 9.2). In the case of oxidation, this involves the production of peroxides and hydroperoxides. These hydroperoxides may then undergo further decomposition to give a range of low-molecular-weight aldehydes and ketones. Carbonyl compounds of this type usually have characteristically unpleasant smells, which allows their presence to be detected, literally by following one's nose. They can arise not only from the decomposition of drugs but also from the autoxidation of fats, oils and foodstuffs as well as the perishing of rubber and the hardening of paints.

Stage 2 Chain propagation: free radicals are consumed and generated (Fig. 9.2).

Termination

Reactive free radicals join together to form covalent bonds. This effectively ends the chain reaction process and produces stable compounds (Fig. 9.3).

Stage 3 Chain termination: reactive free radicals are consumed but not generated.

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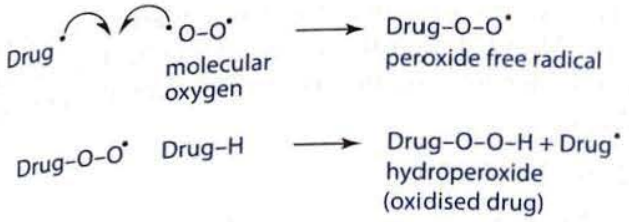


Figure 9.2. The mechanism of propagation.

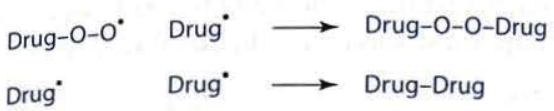


Figure 9.3. The mechanism of termination.

Stability of free radicals

It is useful to be able to look at the structure of a drug molecule and be able to predict which sites, if any, in the molecule are susceptible to oxidative deterioration. To do this we must have an understanding of the ease of formation and the stability of free radical species.

The most common bond in a drug molecule to be broken during an autoxidation process is a covalent bond between hydrogen and another atom, usually carbon. It follows, therefore, that the more easily this bond undergoes homolysis, the more susceptible the drug will be to autoxidation (Fig. 9.4).



Figure 9.4. Autoxidation of carbon–hydrogen bonds.

The breaking of a bond in this way generates two radicals, each with an unpaired electron. (Note the curved half-arrows in the reaction mechanism. These signify the movement of *one* electron, as opposed to the full arrow found in most reaction schemes, which implies the movement of *two* electrons.) Although almost all free radicals are unstable and react to gain an extra electron to complete a full octet of electrons in their outer electron shell, some radicals are *relatively* more stable than others, and hence will be more likely to form and persist. In general, the more substituted a radical is (with alkyl groups) the more stable it will be, and the more likely it will be to take part in chemical reactions. A rank order can be drawn up that lists the relative stabilities of free radicals; a highly substituted tertiary (3°)

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radical is considerably more stable than a secondary (2°) or a primary (1°) one. The least stable alkyl radical is the methyl radical, which has no alkyl substituents and, therefore, no mechanism whereby the unpaired electron can be stabilised:

$$3^\circ > 2^\circ > 1^\circ > CH_3^\bullet$$

Radicals in which the lone electron can be distributed around the molecule by resonance effects are particularly stable and occur in a number of oxidative reaction mechanisms. Examples of comparatively stable radicals of this type are the benzyl free radical and free radicals containing the allyl (or propenyl) group. These species can be stabilised, as shown in Fig. 9.5.

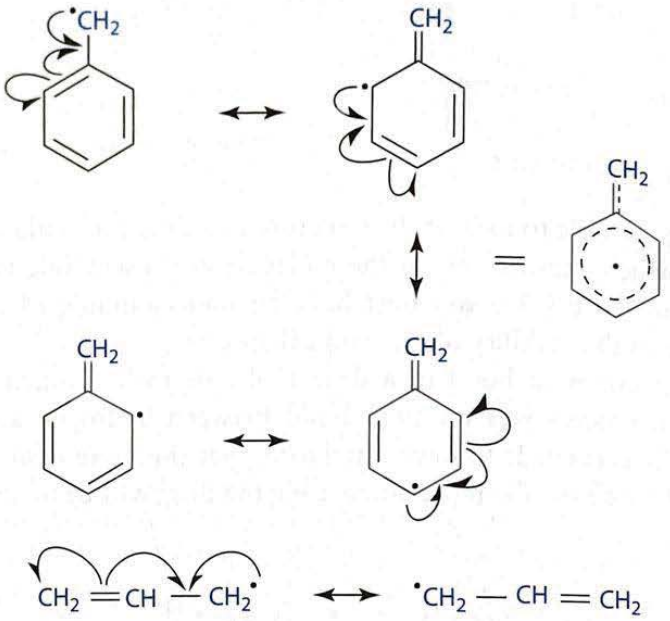


Figure 9.5. The stability of allyl and benzyl radicals.

Drugs that are susceptible to oxidation of carbon–hydrogen bonds include ethers (which oxidise to form highly explosive peroxides), aliphatic amines (which oxidise at the α-hydrogen atom) and aldehydes (which are easily oxidised to carboxylic acids and peroxy acids). Examples of these reactions are shown in Fig. 9.6.

Other bonds that oxidise easily are the oxygen–hydrogen bond found in phenols and the nitrogen–hydrogen bonds found in aromatic amines (Fig. 9.7).

In the case of oxidation of phenols, the reaction can very quickly give a complex mixture of products. This is because the phenoxy radical formed on abstraction of the hydrogen radical, $H^\bullet$ can give rise to carbon–carbon, carbon–oxygen and oxygen–oxygen coupling reactions.

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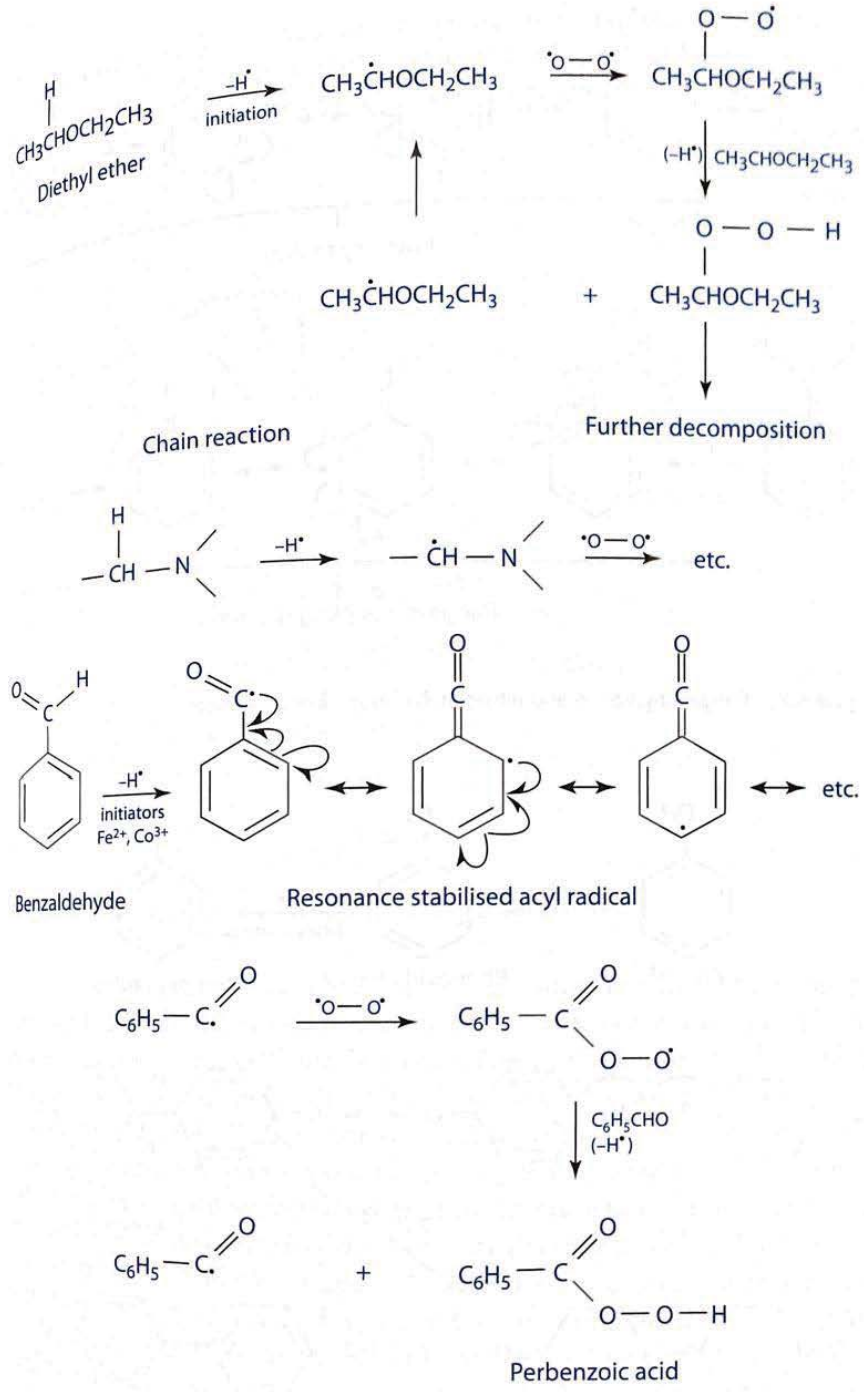


Figure 9.6. Carbon–hydrogen bond cleavage in ethers, amines and aldehydes.

The pH at which the phenol is stored is also important since a phenoxide ion, formed at high pH, can easily be oxidised to the phenoxy radical (Fig. 9.8).

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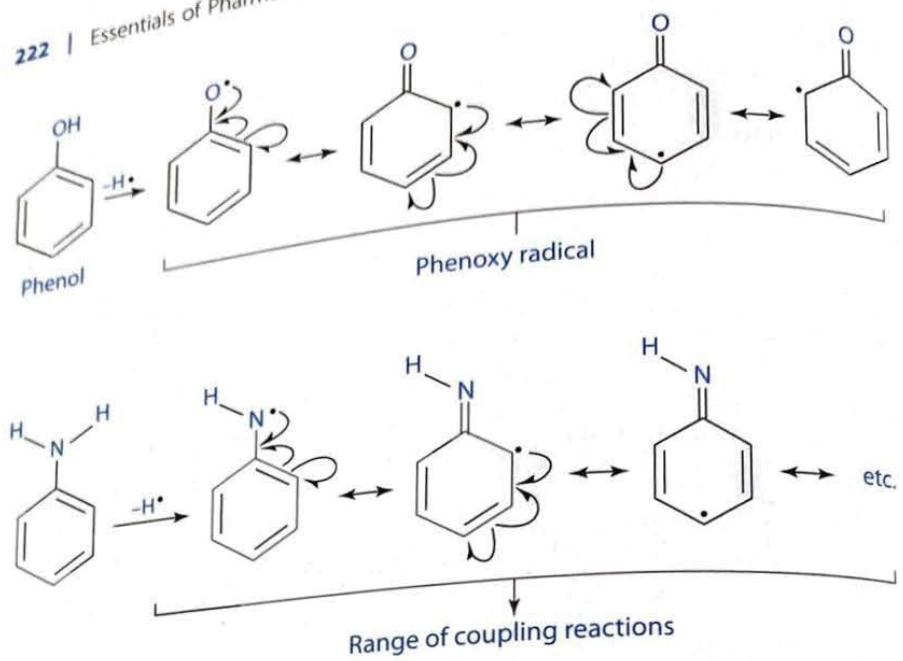


Figure 9.7. Oxygen–hydrogen and nitrogen–hydrogen bond cleavage.

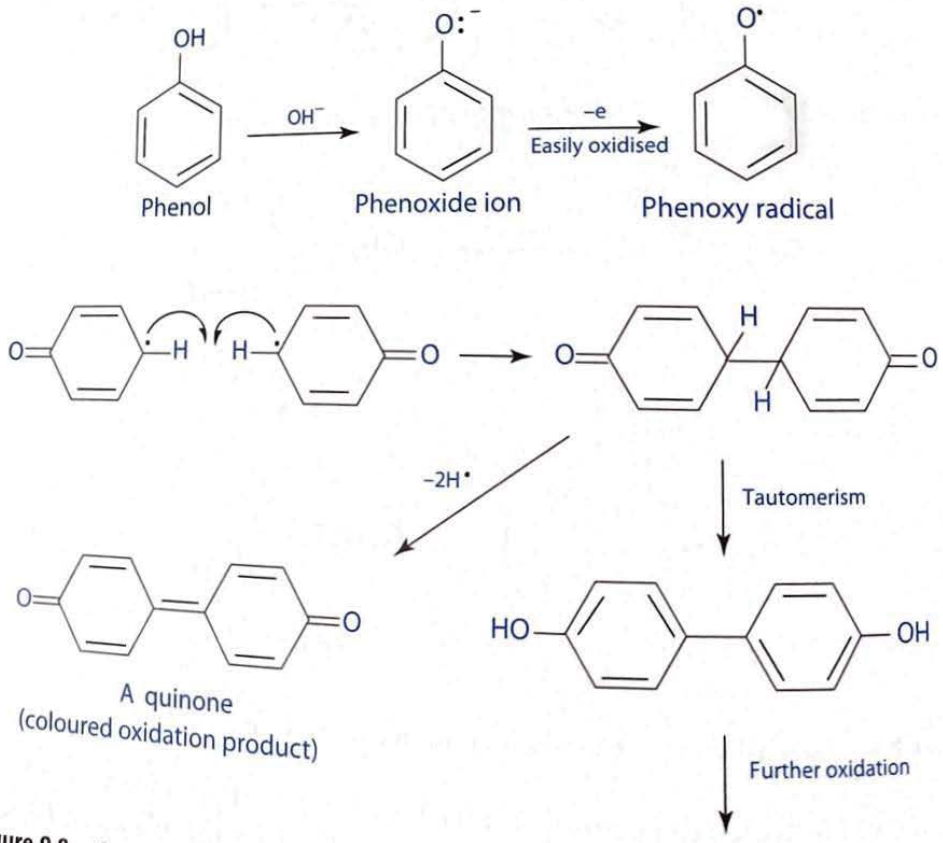


Figure 9.8. Oxidation of the phenoxide ion.

Drugs containing phenolic groups include the analgesics morphine (and related opiates) and paracetamol as well as the bronchodilator salbutamol, widely used in the treatment of acute asthma (Fig. 9.9).

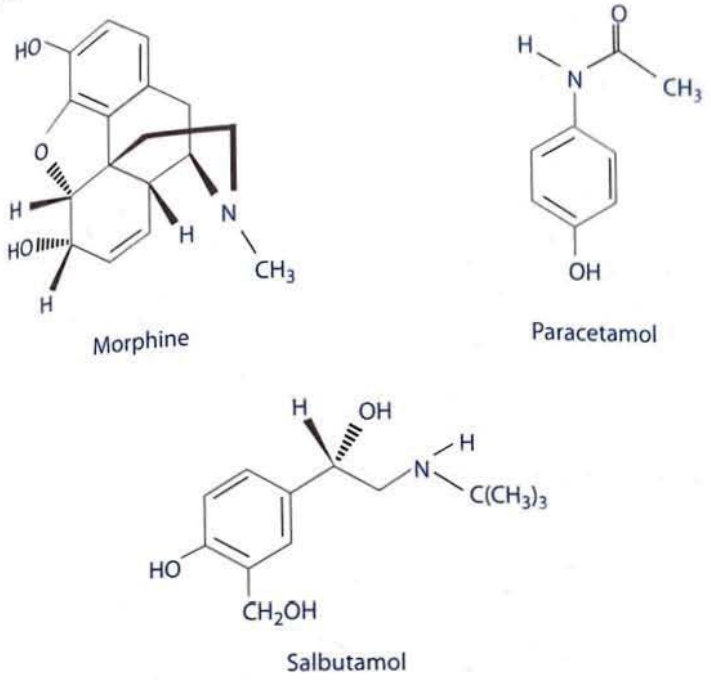


Figure 9.9. The structures of morphine, paracetamol and salbutamol.

Drugs that contain two phenolic groups, such as adrenaline (epinephrine) and other catecholamines such as noradrenaline (norepinephrine) and isoprenaline are particularly susceptible to oxidation and have to be formulated at acidic pH. All of these compounds are white crystalline solids, which darken on exposure to air. Adrenaline forms the red coloured compound adrenochrome on oxidation (Fig. 9.10), which can further polymerise to give black compounds similar in structure to melanin, the natural skin pigment. Injections of adrenaline that develop a pink colour, or that contain crystals of black compound, should not be used for this reason. Adrenaline for injection is formulated as the acid tartrate (Fig. 9.10), which, in aqueous solution, gives a pH of approximately 3. It is called the acid tartrate since only one carboxylic acid group of tartaric acid is used up in salt formation with adrenaline. This leaves the remaining carboxylic group to function as an acid.

Cleavage of the nitrogen–hydrogen bond in aromatic amines occurs in a similar manner to that described for phenols, to give a complex mixture of products due to coupling reactions of the type shown in Fig. 9.11.

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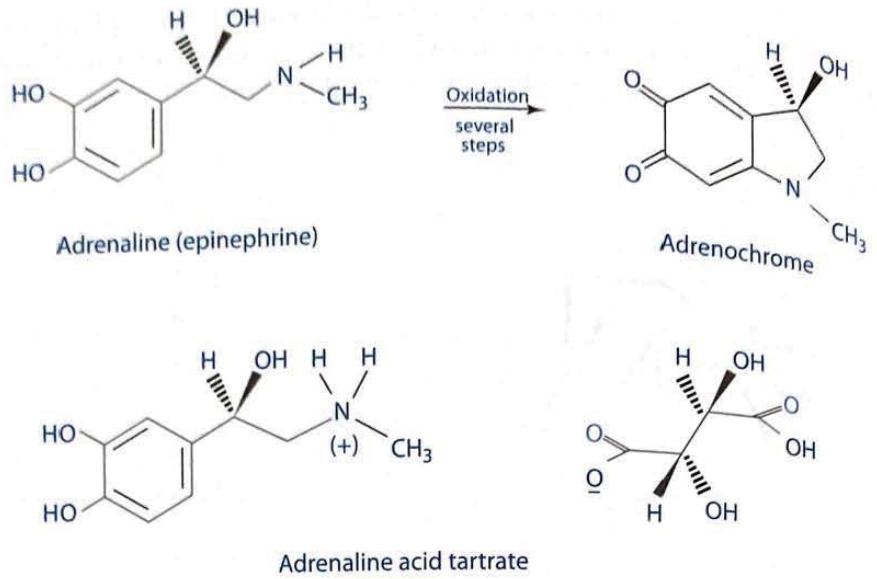


Figure 9.10. Oxidation of adrenaline (epinephrine).

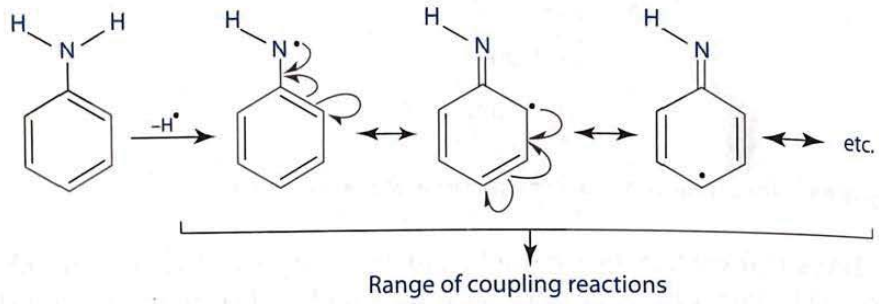


Figure 9.11. Nitrogen–hydrogen bond cleavage in amines.

Prevention of oxidative deterioration

A number of steps can be taken to minimise oxidative decomposition in drugs and medicines. These can be summarised as follows.

Exclusion of oxygen

This is pretty obvious: if oxygen in the air is causing the oxidation, then exclusion of oxygen from the formulation will minimise oxidative deterioration. This is usually achieved by replacing the oxygen with an inert gas atmosphere (e.g. nitrogen or argon). The container should also be well filled with product and closed tightly to minimise the possibility of air getting to the medicine.

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Use of amber or coloured glass containers

Amber glass excludes light of wavelengths <470 nm and so affords some protection to light-sensitive compounds. Special formulations, such as metered dose inhalers used in the treatment of asthma, also offer protection from light and oxygen since the drug is dissolved or suspended in propellant and stored in a sealed aluminium container.

Use of chelating agents

Oxidation reactions can be catalysed by the presence of tiny amounts of metal ions (e.g. 0.05 ppm Cu^{2+} can initiate decomposition of fats) and so stainless steel or glass apparatus should be used wherever possible during manufacture of susceptible compounds. If the presence of metal ions cannot be avoided, then chelating agents, such as disodium edetate, are used to chelate and remove metal ions. Disodium edetate is the disodium salt of ethylenediaminetetraacetic acid (EDTA) and is shown in Fig. 9.12.

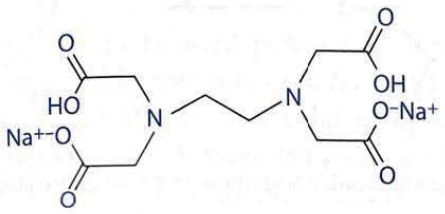


Figure 9.12. The structure of disodium edetate.

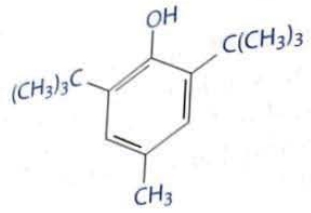
Use of antioxidants

Antioxidants are compounds that undergo oxidation easily to form free radicals but which are then not sufficiently reactive to carry on the decomposition chain reaction. They selflessly sacrifice themselves to preserve the drug or medicine. Most antioxidants are phenols and a few of the most commonly used are shown in Fig. 9.13. Ascorbic acid (vitamin C) also functions as an antioxidant and is added to medicines and foodstuffs for this reason. Food manufacturers enthusiastically label their products as having 'added vitamin C'. What they are not so keen to tell you is that the vitamin is not there for the consumers' benefit but rather as an antioxidant to stop their product decomposing oxidatively (see Fig. 9.14).

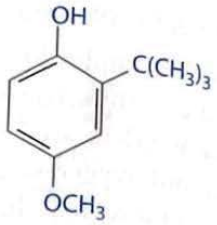
Autoxidation of fats and oils

Fixed oils and fats are naturally occurring products, usually of plant origin, that are used extensively in pharmaceutical formulation. They are very susceptible to oxidative decomposition (a process called *rancidity*) and special precautions must be taken to control their stability and prevent their decomposition. Compounds of this type exist as complex mixtures of structurally

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Butylated hydroxytoluene



Butylated hydroxyanisole

Figure 9.13. The structures of butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA).

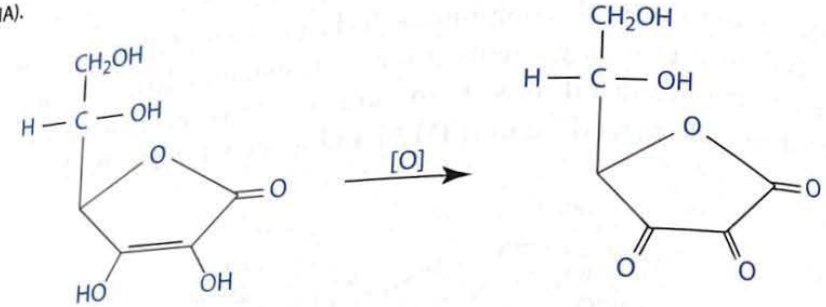


Figure 9.14. The structure of ascorbic acid, showing oxidation to diketone.

similar oils, the composition of which can vary from year to year depending on factors such as climate, time of harvest, and so on. Chemically, fixed oils and fats are esters of the alcohol glycerol (propan-1,2,3-triol) with three molecules of long-chain carboxylic acids, called fatty acids, which may be the same or different depending on the oil (Fig. 9.15).

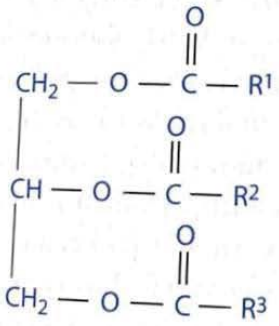


Figure 9.15. The structure of triglycerides.

Compounds of this type are called *triglycerides* and contain several sites within the molecule where autoxidation can occur to cause breakdown of the molecule. This is especially true if the fatty acids are *unsaturated* (i.e. contain at least one carbon–carbon double bond; if the carbon chain contains several double bonds, the oil is said to be *polyunsaturated*).

The stability of oils is very important in pharmaceuticals since non-polar drugs (e.g. contraceptive steroids and neuroleptic tranquillisers) are often formulated in oily injection vehicles for intramuscular or depot injection. Injections of this type can be given, for example, once a month, and the drug exerts its pharmacological effect as it leaches out of the injection site into the bloodstream. Oils used as injection vehicles include arachis oil, from the peanut plant, olive oil, castor oil and ethyl oleate, the ethyl ester of the 18-carbon fatty acid oleic acid (Fig. 9.16).

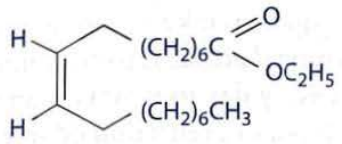


Figure 9.16. The structure of ethyl oleate.

These oils, if they are to be used parenterally, need to be chemically pure and free from microbial contamination. As stated above, plant oils are often complex mixtures of chemically similar compounds and so require special forms of pharmaceutical assay (e.g. determination of their acid and saponification values) as well as physical methods of assay such as determination of density (i.e. weight per millilitre) and measurement of their refractive index. Increasingly, modern instrumental methods of analysis, such as gas chromatography are being used to identify component oils and ensure purity (e.g. the BP assay of Arachis Oil).

Ageing

The effects of oxygen are not limited to the oxidation of small molecules found in drugs and medicines. It is now thought that most of the chemical effects of human ageing are the result of sustained and cumulative oxidative damage on important macromolecules present in our cells (particularly DNA). The old joke to the effect that air is poisonous – everyone who breathes the stuff dies – does have some truth in it. As soon as we are born, the cells in our bodies begin to suffer damage from reactive oxygen species (such as hydroxyl and superoxide radicals).

These reactive species are formed by the breakdown of oxygen present in all our cells and, once formed, can react with essential cell components such as phospholipid membranes, cellular proteins and DNA.

Damage to DNA results in genetic mutations, which can be passed on to subsequent generations of cells. If the oxidative damage is severe, the cell in question will enter a programme of cell death, called *apoptosis*, and effectively commit suicide.

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To counteract these onslaughts by reactive forms of oxygen, the body has evolved a number of elegant defence mechanisms. Repair enzymes can detect damaged DNA bases and repair them *in situ* without disrupting the function of the DNA. Similarly, damaged membrane is repaired to restore cell integrity. These repair enzymes are essentially catalysing an intracellular REDOX process and require a number of essential nutrients such as vitamins C and E to act as antioxidants. The ageing effects of oxidative damage cannot be reversed (yet!) and no amount of expensive cosmetic preparations will stop skin from ageing, but the amount of damage to cells may be reduced by an adequate intake of vitamins and antioxidants in the diet. The most recent nutritional advice is to consume at least five helpings of fresh fruit and vegetables every day to maintain an adequate dietary intake of essential antioxidants. It is a sad reflection on our society that much more time, money and advertising are spent on expensive cosmetic 'remedies' for ageing than are spent ensuring a healthy diet for all in the population.

Hydrolysis

Hydrolysis, in its widest sense, is the breaking of a chemical bond through the reaction with water. This contrasts with *hydration*, which is the addition of the elements of water to a multiple bond, but with no associated fragmentation of the molecule. A large number of functional groups found in drugs are prone to hydrolysis on storage (Fig. 9.17), but the most commonly encountered are esters and amides.

The hydrolysis of esters and amides occurs as a result of nucleophilic attack on the carbon of the carbonyl group and subsequent cleavage of the carbon–oxygen or carbon–nitrogen single bond. The carbon of the carbonyl group is more positive than expected as a result of the high electronegativity of the adjacent oxygen. The unequal sharing of the bond electrons causes a polarisation of the bond so that the carbon bears a partial positive charge (δ^+), while the oxygen has a partial negative charge (δ^-).

Hydrolysis reactions occur quite slowly, but, in the presence of acid or alkali, the rate of the reaction increases and significant decomposition can occur. It should be remembered that many drugs are amines, which can be rendered water soluble by formation of their hydrochloride salt. Salts of weak bases and strong mineral acids are acidic by partial hydrolysis (see Chapter 1 if this is not familiar) and the hydrogen ion formed by hydrolysis of the salt can catalyse hydrolysis reactions on the drug itself. Similarly, drugs that are salts of weak acids with strong bases are alkaline in solution and the hydroxyl ion produced by partial hydrolysis of the salt can act as a catalyst and bring about decomposition. The mechanisms of acid- and base-catalysed hydrolysis of esters are shown in Figs. 9.18 and 9.19; the mechanisms for hydrolysis of amides are similar.

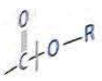
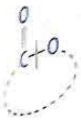
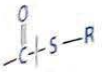
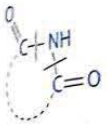
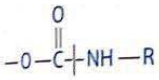
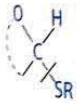
Group	Name	Examples
	ester	ethyl oleate, aspirin, procaine
	cyclic ester	warfarin, nystatin, digoxin, digitoxin
	thioester	spironolactone
	amide	nicotinamide, paracetamol, procainamide
	imide	phenytoin, barbiturates, riboflavin
	cyclic amide (lactam)	penicillins, cephalosporins
	carbamate (urethane)	carbachol, neostigmine, carbimazole
	imine (azomethine or Schiff base)	diazepam, pralidoxime
	acetal	digoxin, aldosterone
	thioacetal	lincomycin, clindamycin
	sulfate ester sulfamate	heparin
	phosphate ester	hydrocortisone sodium phosphate, triclofos sodium

Figure 9.17. Functional groups prone to hydrolysis.

Acid-catalysed hydrolysis

The initial protonation on the carbonyl oxygen produces a resonance stabilised cation; this increases the electrophilicity of the carbonyl group, making it susceptible to attack by the nucleophilic water (Fig. 9.18).

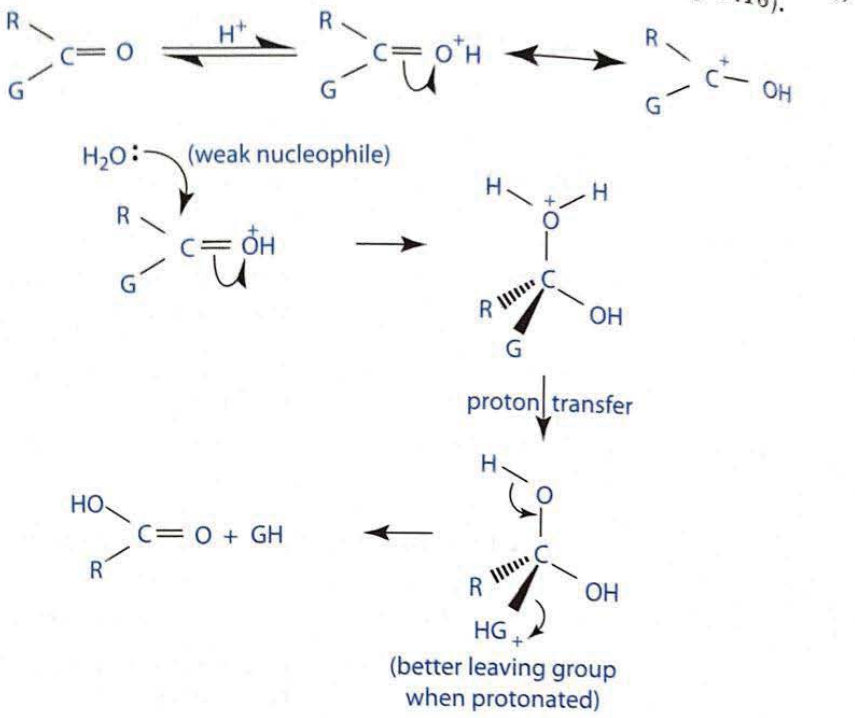


Figure 9.18. The mechanism of acid-catalysed hydrolysis.

Proton transfer from the water to the alcohol converts the latter into a better leaving group (G). Incidentally, this mechanism is the reverse of the mechanism for formation of an ester from an acid and an alcohol under acidic conditions (esterification).

Base-catalysed hydrolysis

The base-catalysed reaction is easier to follow; the nucleophile in this case is the strongly basic hydroxyl ion, which attacks the δ^+ carbon of the carbonyl group directly (Fig. 9.19).

Note that in base-catalysed hydrolysis, the acid formed by hydrolysis instantaneously reacts with the excess of base to form the salt of the acid. The free acid may be obtained, if desired, by acidification of the mixture.

Examples of drugs susceptible to hydrolysis

Fig. 9.17 lists examples of the types of drug containing functional groups prone to decomposition by hydrolysis. There is insufficient space

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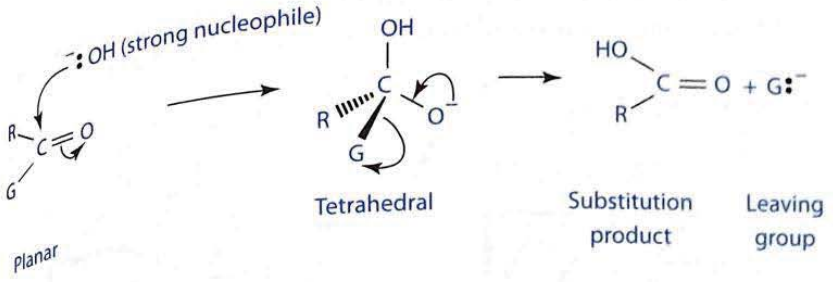


Figure 9.19. The mechanism of base-catalysed hydrolysis.

to consider each drug in detail, but a few important examples will be considered.

Aspirin

Aspirin, the widely used analgesic, is the acetyl ester of salicylic acid and is very susceptible to hydrolysis; moisture in the air is sufficient to bring about significant decomposition. A bottle of aspirin tablets smells of vinegar when opened; this is due to the reaction shown in Fig. 9.20 taking place to liberate salicylic and acetic acids. The rate of decomposition is increased because members of the public often store medicines in a cabinet in the bathroom, the one room in the house that is almost guaranteed to have a hot, steamy atmosphere ideal for hydrolysis reactions.

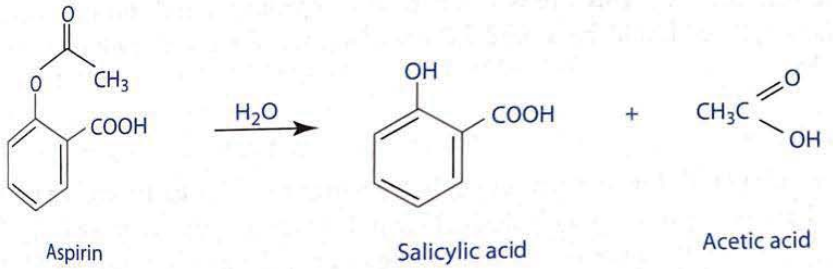


Figure 9.20. The hydrolysis of aspirin.

Diamorphine

Diamorphine (or heroin) is the diacetyl derivative of morphine and, like morphine, is used as a narcotic analgesic (Fig. 9.21). The two acetyl groups are important for two reasons. First, they render the molecule more lipophilic (increasing the partition coefficient), which means that diamorphine is absorbed into the central nervous system more rapidly than is morphine; this in turn, results in a faster onset of action than for morphine (and, sadly, makes the compound a favourite with addicts). The second

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aspect of the two acetyl groups is that they are susceptible to hydrolysis, to yield morphine and two molecules of acetic acid (Fig. 9.21).

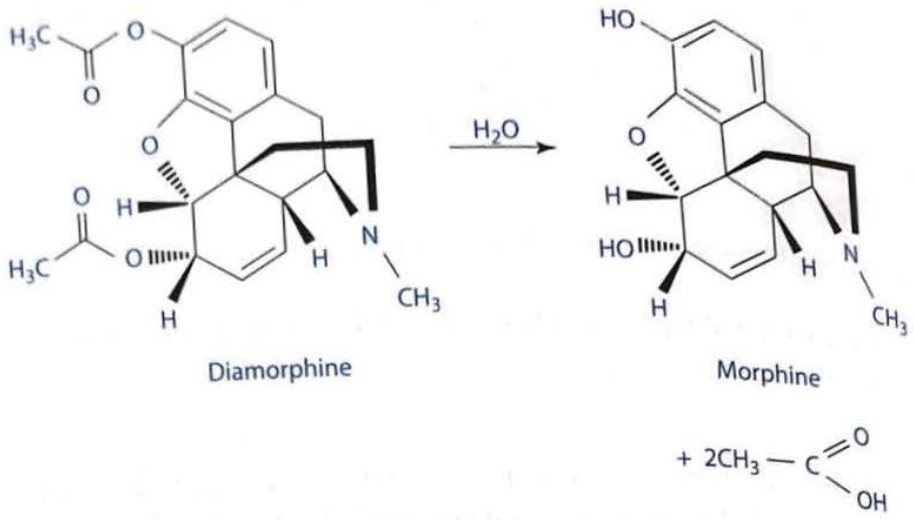


Figure 9.21. The structure and hydrolysis of diamorphine.

Diamorphine injection is prepared by dissolving the contents of a sealed container in Water for Injections BP immediately prior to use. The instability of the ester groups precludes sterilisation of the injection by autoclaving.

A close inspection of the structure of diamorphine will show that the molecule also contains 'benzylic' hydrogen atoms, on the CH_2 adjacent to the benzene ring. This site is susceptible to oxidation and, for this reason, diamorphine should be stored in a well-closed container protected from light.

Penicillin

Penicillin (and, for that matter cephalosporin) antibiotics are cyclic amides and are very prone to hydrolysis. Normal amide bonds are more resistant to hydrolysis than are esters, but in penicillins, the amide is cyclised into a four-membered β-lactam ring. The bond angles in this ring are close to 90°, in contrast to an open-chain amide in which the bond angle is 120° (sp^2 hybridised carbon). This unnatural bond angle in the β-lactam ring means that the ring is very easily opened by nucleophiles, particularly water.

The effect is compounded by the geometry of the fused bicyclic ring system. The β-lactam and thiazolidine rings of penicillin do not lie in the same plane (in fact, they lie almost perpendicular to each other), so resonance effects within the cyclic amide are prevented, which leaves the carbonyl carbon atom much more δ^+ than expected and hence more liable to nucleophilic attack. The structures of a penicillin (ampicillin) and the decomposition product, penicilloic acid, are shown in Fig. 9.22.

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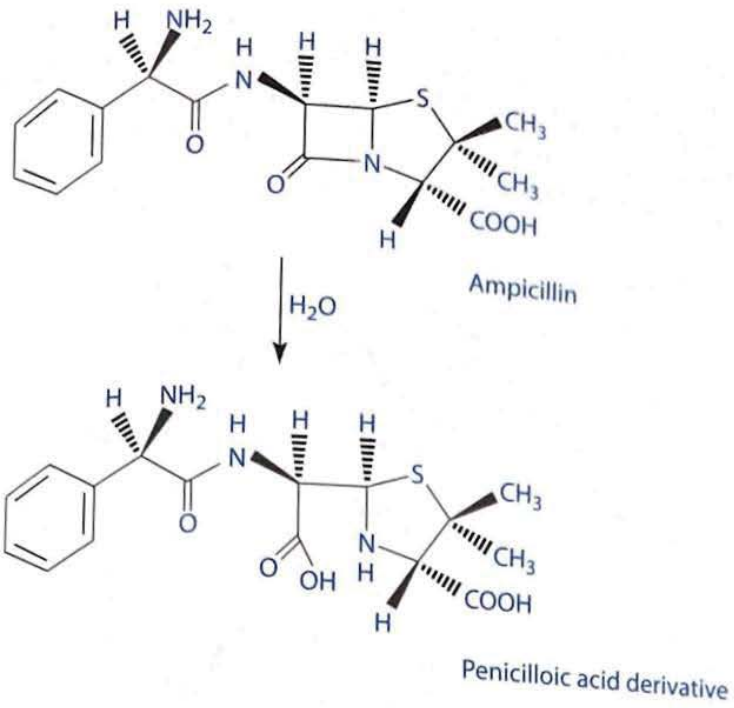


Figure 9.22. The structures of ampicillin and penicilloic acid.

Penicillin and cephalosporin antibiotics are insufficiently stable to be supplied dissolved in aqueous solutions. Instead, they are supplied as a dry powder, which is reconstituted immediately prior to dispensing by the pharmacist. The solution (or, more accurately, suspension) dispensed must be stored in a refrigerator and discarded after 7 days. The ring-opened product (penicilloic acid) is inactive as an antibiotic.

Other mechanisms of degradation

Rarely, some other forms of decomposition may be encountered. These include *hydration* (found in some alkaloids of ergot), *polymerisation* (which can affect solutions of the antibiotic ampicillin) and *dimerisation* reactions (which can be seen as a result of free radical attack on morphine). While these methods of decomposition are important and should be borne in mind, the majority of chemical deterioration can be explained by consideration of the few mechanisms outlined above.

Prodrugs

While the preceding pages have dealt with decomposition of a drug as something to be avoided, it should be borne in mind that occasionally drugs are designed to decompose *in vivo* to release the active moiety. These compounds are called *prodrugs* and are defined as compounds which are

themselves pharmacologically inert but which may break down within the body to release the active molecule. Prodrugs are usually used to overcome problems of poor oral bioavailability (e.g. the angiotensin-converting enzyme inhibitor enalapril is a prodrug designed to hydrolyse *in vivo* to release the active inhibitor enalaprilate; Fig. 9.23).

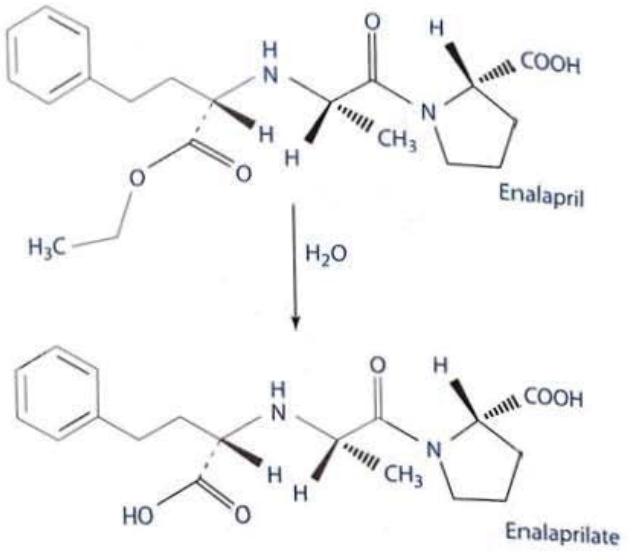


Figure 9.23. Hydrolysis of enalapril to enalaprilate.

Alternatively, prodrugs may be employed when the active compound is excessively toxic. An example of this type of prodrug is the nitrogen mustard anticancer drug cyclophosphamide, which is converted within the body to phosphoramide mustard, a very toxic alkylating agent and acrolein, as shown in Fig. 9.24. Alkylating agents react with nucleophilic centres present within DNA (usually N7 of guanine). If the reaction occurs twice, the nitrogen mustard can cross-link the two strands of DNA and so inhibit DNA replication and tumour cell division.

Prodrugs may also be employed in a rare disease called nephropathic cystinosis. This condition is characterised by the accumulation of very high levels of the amino acid cystine in the lysosomes of cells. The cystine crystallises from solution, causing multiple organ damage; if untreated, patients can expect to die from kidney failure by age 15. Treatment of cystinosis is by administration of the aminothiol cysteamine (mercaptamine). Unfortunately, this drug possesses an unpleasant taste and smell and irritates the gut when administered orally. Work is currently underway in our laboratories to design and synthesise novel prodrug forms of cysteamine that will be odourless, tasteless and orally active (Fig. 9.25).

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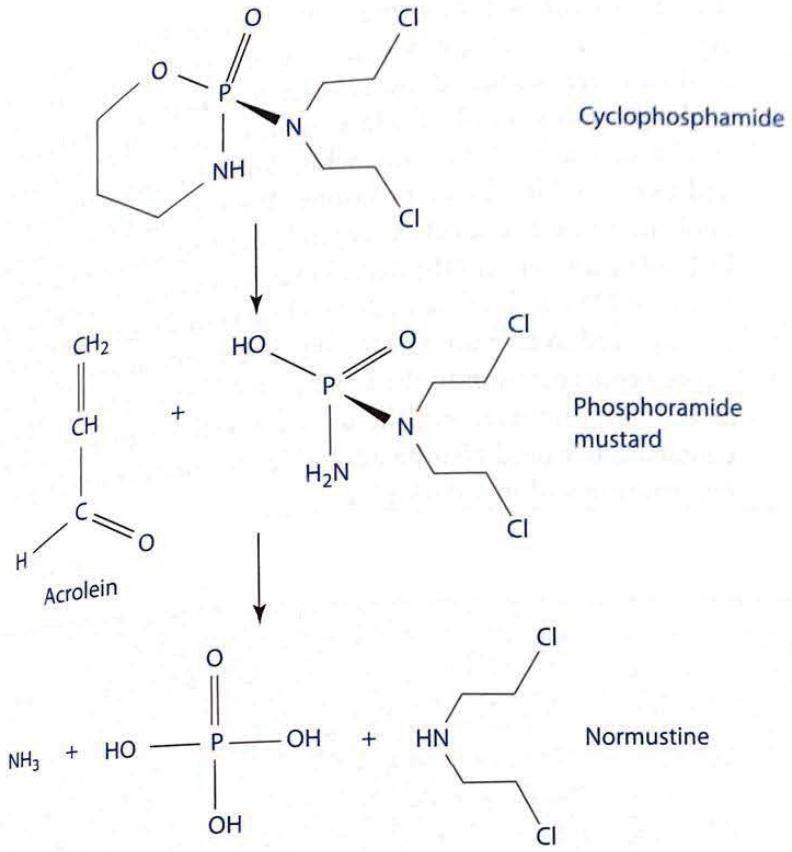


Figure 9.24. Metabolic activation of cyclophosphamide.

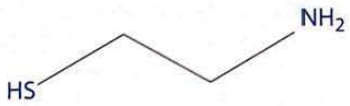


Figure 9.25. The structure of cysteamine (mercaptamine).

Tutorial examples

Q *1 Predict which of the following fatty acids will undergo oxidation most easily, and explain what precautions should be employed to minimise the oxidation:*

$CH_3(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_6COOH$ *(oleic acid)*

$CH_3(CH_2)_3CH_2CH{=}CHCH_2CH{=}CHCH_2(CH_2)_6COOH$ *(linoleic acid)*

$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2(CH_2)_6COOH$ *(linolenic acid)*

A 1 Compounds that contain allylic and benzylic centres are especially prone to autoxidation, since the radicals formed on oxidation are stabilised by resonance. Oleic acid contains two allylic positions; linoleic acid contains two allylic positions and one 'double allylic' position, while linolenic contains two allylic and two 'double allylic' positions. We would, therefore, expect linolenic to be the most susceptible acid to oxidation, followed by linoleic and oleic. (The actual relative rates of autoxidation are linolenic (25) > linoleic (12) > oleic (1).) Precautions that can be employed to minimise oxidative deterioration are reducing the oxygen concentration in the container, for example, by the use of an inert atmosphere, and the use of a well-closed and well-filled container. It would also be advisable to store the product at low temperature and in a dark place.

Q *2 The BP monograph for Chloramphenicol Eye Drops contains a limit test for 2-amino-1-(4-nitrophenyl)propane-1,3-diol (Fig. 9.26).*

(a) Explain why this limit test is included, and show how the diol could be formed.

(b) Both chloramphenicol and the diol absorb ultraviolet light at the same λ_{max}. Outline the principles of a stability-indicating test that could be used to measure the amount of diol in the eye drops.

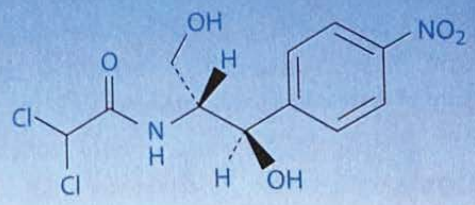


Figure 9.26. The structure of chloramphenicol.

A 2 (a) Chloramphenicol possesses an amide bond that can undergo hydrolysis to give 2-amino-1-(4-nitrophenyl) propane-1,3-diol, which is inactive as an antibiotic. The limit test is included in the BP monograph to control the level of diol in the eye drops.
(b) Since both compounds have the same chromophore, they will absorb ultraviolet radiation of the same wavelength. They must,

therefore, be separated from each other and measured individually, otherwise an ultraviolet assay will be unable to determine the extent of deterioration. This separation may easily be accomplished by addition of dilute hydrochloric acid solution to the eye drops. The diol is basic and will ionise to form the hydrochloride salt. Extraction with an organic solvent removes the neutral chloramphenicol, leaving the salt in the aqueous phase, which can easily be measured spectrophotometrically. A chromatographic technique, such as high performance liquid chromatography (HPLC), would also allow determination of the diol in the presence of chloramphenicol. Here the separation is achieved on an HPLC column and each compound enters the ultraviolet detector individually.

Problems

Q9.1 Novobiocin (Fig. 9.27) is an antibiotic, formerly used in the treatment of infections caused by Gram-positive organisms.

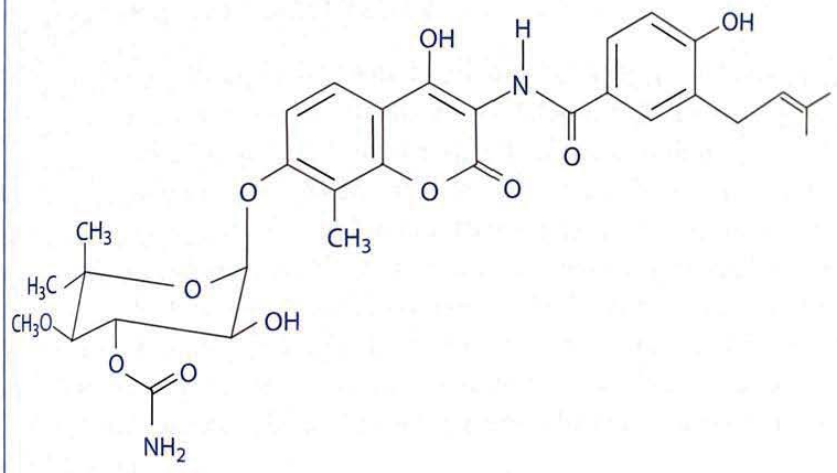


Figure 9.27. The structure of novobiocin.

(a) Identify and name the functional groups that are likely to undergo oxidation on storage.

(b) Identify and name the functional groups that are susceptible to hydrolysis.

(c) What conditions would you recommend for the storage of novobiocin?

(d) When novobiocin was mixed with 5% Dextrose Injection, the solution became cloudy. Account for this observation.

Q9.2 Explain each of the following observations. Your answer should include appropriate chemical formulae.

(a) Penicillin suspensions are supplied as dried granules and are reconstituted by the pharmacist immediately prior to use.

(b) Solutions of adrenaline (epinephrine) become pink on exposure to sunlight.

(c) Samples of aspirin tablets invariably smell of vinegar.

(d) The vasoconstrictor peptide angiotensin II has a very short half-life within the body.

(Answers to problems can be found on pp. 289–292.)