3

Physicochemical properties of drugs

As has been stated before, most of the drugs used in medicine behave in solution as weak acids, weak bases, or sometimes as both weak acids and weak bases. In this chapter we will explore the reasons why drugs behave as acids or bases and what effects ionisation has on the properties of the drug, and develop strategies to separate mixtures of drugs on the basis of changes in their solubility in various solvents.

The most important thing to realise about acidic and basic drugs is that values of pK_a and pK_b quoted in the literature tell you *absolutely nothing* about whether the drug in question is an acid or a base. The pK_a and pK_b values give information about the strength of acids and bases; they tell you the pH at which 50% of the drug is ionised, but they do not tell you whether a drug behaves as an acid or a base in solution. Amines, for example, are basic and have pK_a values of approximately 9, while phenols are acidic and typically have pK_a values of around 10. *The only sure way to know whether a drug is acidic or basic is to learn the functional groups that confer acidity and basicity on a molecule.* This should be done even if it means learning the names of the functional groups the way you learned multiplication tables at primary school. There are only a few to learn and the important examples are listed below along with some common drugs.

Carboxylic acids

According to the Brønsted–Lowry definition, an acid is a substance that ionises to donate protons to its surroundings. In aqueous solution this is represented as

$$\mathbf{HA + H_2O \rightleftharpoons H_3O^+ + A^-} \tag{3.1}$$

where HA is the acid; water accepts the proton and acts as a base; H_3O^+ is a solvated proton, sometimes called the conjugate acid of the base; and A^- is the anion of the acid. The equilibrium constant for this reaction is the

acidity constant K_a and is expressed mathematically as

$$K_a = \frac{[H_3O^+][A^-]}{HA} \tag{3.2}$$

(taking $[H_2O]$ to be effectively constant for dilute solutions).

From Eq. (3.2) it can be seen that, since K_a is a simple ratio, the higher the numerical value of K_a the stronger will be the acid. As stated in Chapter 1, however, the strength of most acids (and bases) is expressed by the term pK_a, where

$$pK_a = -\log K_a \tag{3.3}$$

Since pK_a is the negative logarithm of K_a, it follows that the *lower* the value of pK_a the *stronger* will be the acid and that on a log scale a difference of one unit in pK_a reflects a tenfold difference in acid strength.

The most commonly occurring functional group conferring acidity on drug molecules is the carboxyl group, which ionises as shown in Fig. 3.1. The anion formed by ionisation of the acid is stabilised by the process of *resonance*. Neither of the two conventional structures ([a] and [b]) of the carboxylate anion shown in Fig. 3.2 is correct. A double bond in C=O is much shorter than a C–O single bond (due to sideways repulsion of the electrons in the bond), yet when the carbon–oxygen bond lengths of the carboxylate anion are measured (e.g. by X-ray diffraction) they are found to be precisely the same length: shorter than a single bond and longer than a double bond. It would also be wrong to say that the actual structure of the carboxylate anion is a single structure rapidly interchanging between [a] and [b]. Structures [a] and [b] represent extremes of the actual structure. It is better to say the actual structure of the anion is a single, symmetrical structure intermediate between [a] and [b] in which the charge is delocalised (distributed) around the carboxylate group. This effect is called *resonance* and is invoked when not all of the observed properties of a compound can be explained or represented by conventional structures. The carboxylate anion is said to be a *resonance hybrid* and [a] and [b] are *canonical forms* that contribute to it. The resonance hybrid is generally a more stable structure than either of the canonical forms, which means it is more likely to exist, which is another way of saying the carboxylic acid is more likely to ionise, which in turn, means it is a stronger acid. It is considered chemical 'good practice' to write the formula of a carboxylic acid as R-COOH since the two oxygen atoms are non-equivalent (one is sp^2 hybridised in a carbonyl group while the other is sp^3 hybridised attached to hydrogen). The anion of a carboxylic acid is written as $R\text{-}CO_2^-$ because the two oxygen atoms are now equivalent due to resonance.

The effect of resonance may be seen when the acidity of a simple carboxylic acid such as acetic acid is compared with the acidity of an alcohol
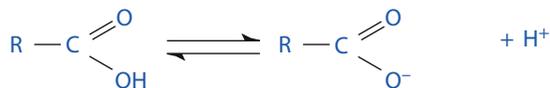
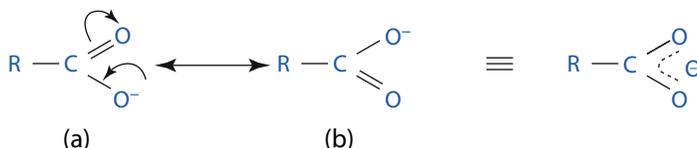**Figure 3.1.** The ionisation of a carboxylic acid.

Figure 3.2. Resonance stabilisation of the carboxylate anion.

such as ethanol. Both compounds can ionise to liberate a proton, but while the anion formed on ionisation of acetic acid is resonance-stabilised, the ethoxide anion formed on ionisation of ethanol is not so stabilised and the negative charge resides wholly on the oxygen atom (Fig. 3.3).
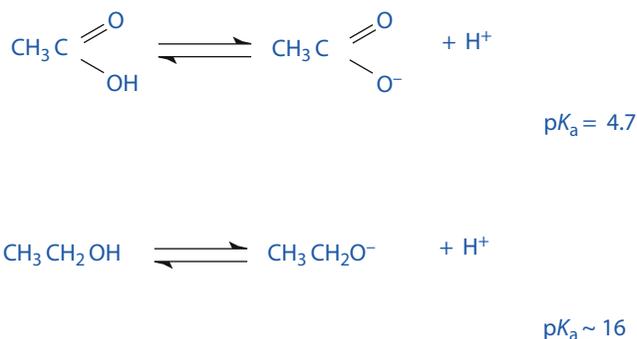

$pK_a = 4.7$

$pK_a \sim 16$

Figure 3.3. The ionisations of acetic acid and ethanol.

The pK_a of acetic acid is 4.7 while the pK_a of ethanol is approximately 16. This means that acetic acid is almost a hundred thousand million (or 10^{11}) times more acidic than ethanol. Alcohols are much weaker acids than water and in biological systems are considered to be neutral. To bring about the ionisation of an alcohol requires the use of a very strong base such as metallic sodium.

A number of commonly used drugs are carboxylic acid derivatives. These include aspirin (pK_a 3.5), the anticancer compound methotrexate (pK_a 3.8, 4.8 and 5.6) and the diuretic (previously called frusemide in the UK; pK_a 3.9). The structures of these compounds are shown in Fig. 3.4.
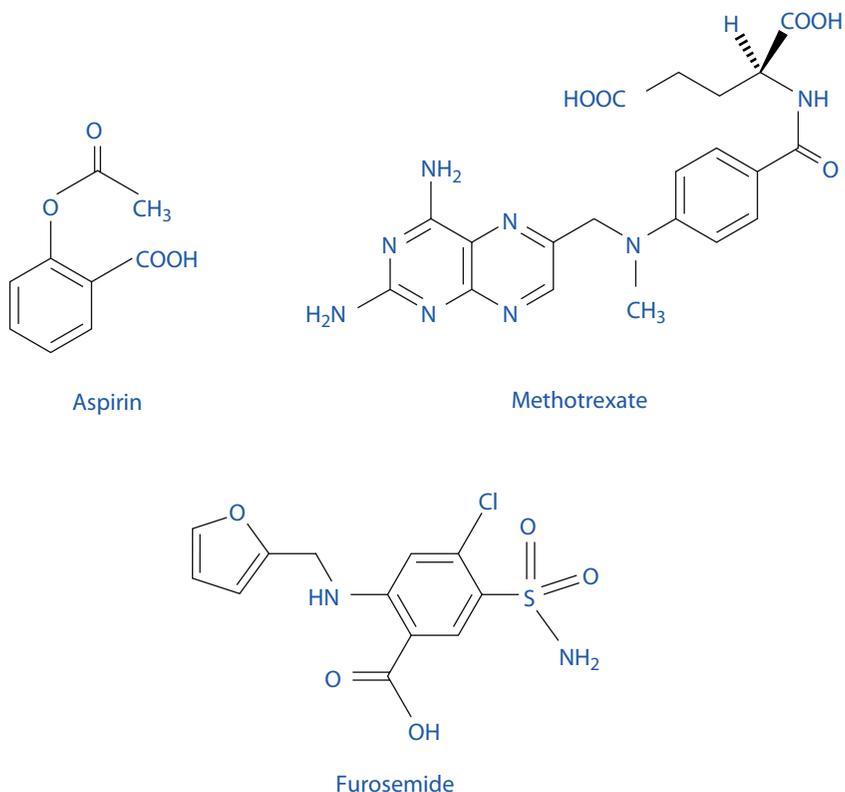

Aspirin

Methotrexate

Furosemide

Figure 3.4.   The structures of aspirin, methotrexate and furosemide.

Knowledge of the pK_a value of a drug and the approximate rule of thumb introduced in Chapter 1 allows a prediction of the extent to which each of these drugs is ionised at the pH of human blood (7.4). For aspirin and furosemide acid with pK_a values of 3.5 and 3.9, the answer is that 99.99% of a given dose of drug will be ionised at the pH of blood or intracellular fluid. For methotrexate, the answer will be slightly less, but still greater than 99%. This strongly suggests that these drugs are pharmacologically active as the anion, and interact with their individual receptors in the ionic form. This conclusion has been reached without considering the detailed three-dimensional structure of each drug's receptor molecule, merely by

applying knowledge of the pK_a and an appreciation of the extent to which drugs ionise in solution. Deductions of this type form the basis of *medicinal chemistry*, the science of rational drug design.

Phenols

Another commonly encountered acidic functional group found in drug molecules is phenol, or hydroxybenzene. Phenols are weak acids that liberate protons to give the phenoxide anion. This anion is resonance-stabilised and four canonical forms may be drawn (Fig. 3.5).
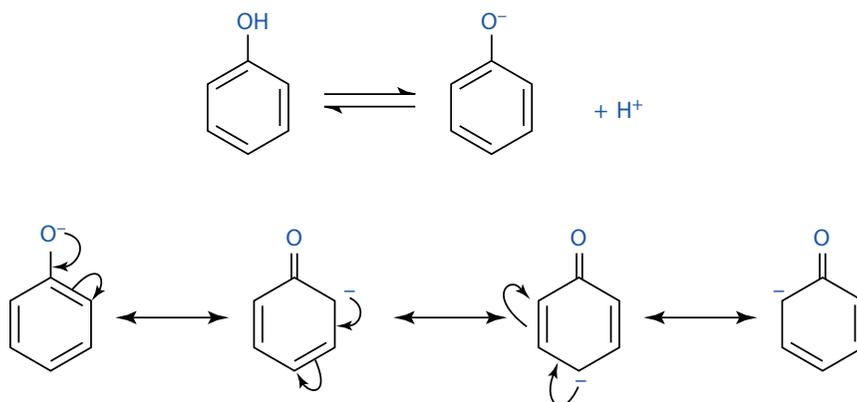

Figure 3.5. Resonance stabilisation of the phenoxide anion.

As with carboxylic acids, the effect of resonance is to distribute the negative charge around the anion, rather than have it concentrated on the oxygen atom. Phenols have pK_a values of approximately 10, which means they are about a million times less acidic than carboxylic acids but are about a million times more acidic than simple alcohols. Phenols are also weaker acids than carbonic acid (H_2CO_3), which means that they do not react with sodium bicarbonate (cf. carboxylic acids) and may be precipitated from solution of the phenoxide by saturation with carbon dioxide.

A number of common drugs contain the phenol functional group. These include paracetamol (pK_a 9.5), morphine (pK_a 9.9) and levothyroxine (thyroxine) (pK_a 10). Since these phenolic drugs are 50% ionised when the pH equals their pK_a, it follows from the 'rule of thumb' introduced in Chapter 1 that they will only ionise to approximately 1% at the pH of blood (7.4) (Fig. 3.6).
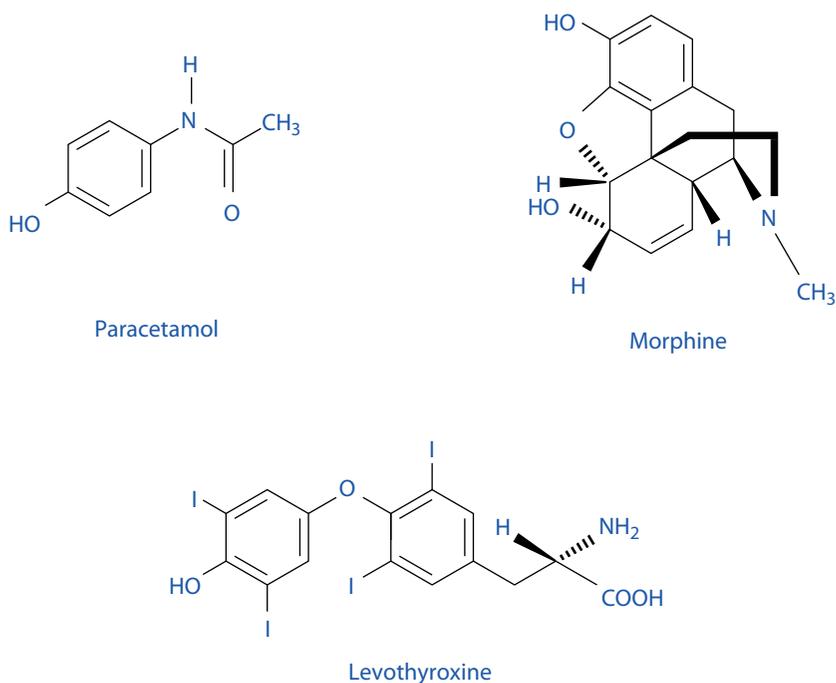
Paracetamol

Morphine

Levothyroxine

Figure 3.6. The structures of paracetamol, morphine and levothyroxine.

Warfarin

Warfarin is an anticoagulant that inhibits the clotting action of blood through an action on vitamin K-derived clotting factors. It is commonly prescribed to elderly patients who suffer from deep-vein thrombosis or pulmonary embolism. Warfarin is used in the UK as the sodium salt, which strongly suggests that the drug is acidic, although the presence of the acidic hydrogen may not be immediately apparent. The acidic hydrogen (drawn in bold in Fig. 3.7) is located between two electron-withdrawing carbonyl groups. Upon ionisation, the negative charge can be delocalised onto each of the electronegative oxygen atoms of the dicarbonyl group to yield a resonance-stabilised anion. This enhanced stability of the anion allows warfarin to lose a proton and renders the drug acidic with a pK_a of 5.0. Warfarin in the free acid form is not very soluble in water and is, therefore, always administered (and is official in the *British Pharmacopoeia*) as the sodium salt.
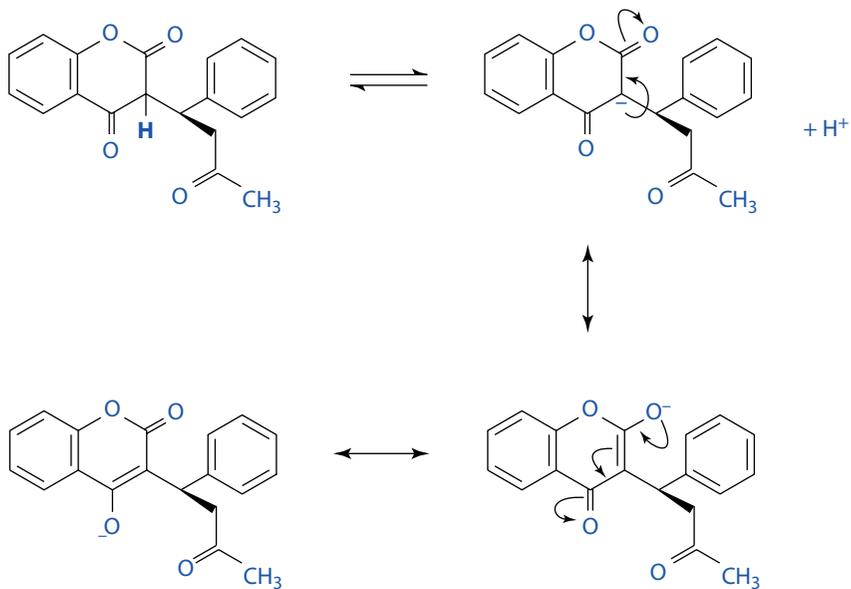
Figure 3.7. The ionisation of warfarin.

Warfarin is an interesting compound in that, in addition to ionising, it exhibits keto–enol *tautomerism*. This means that warfarin exists in two constitutional isomeric forms (tautomers) that are in equilibrium with each other, although one of the forms is usually present to a much higher degree than the other (Fig. 3.8).
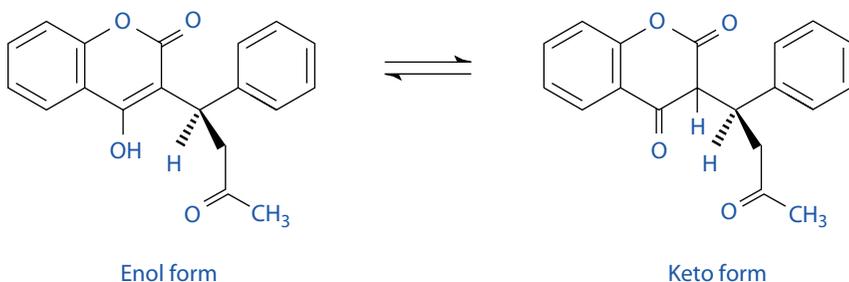

Enol form   Keto form

Figure 3.8. The tautomerism of warfarin.

It is important not to confuse the properties of tautomerism and resonance. They are quite different effects and the differences between them are summarised in Table 3.1. Although the enol form of warfarin is present to a

very small extent, it is acceptable to consider the ionisation of the compound in terms of the enol, and this is shown in Fig. 3.9.

Table 3.1 Comparison of resonance and tautomerism

Resonance forms of a drug[a]	Tautomeric forms of a drug[b]
Same compound	Different compounds
Differ only in position of *electrons*	Differ in position of *atoms* (usually hydrogen)
Each canonical form contributes to a single resonance structure	Each form exists in equilibrium
Canonical forms cannot be isolated	Each tautomer may be isolated

[a] Represented by a double-headed arrow ↔.
[b] Represented by an equilibrium arrow ⇌.
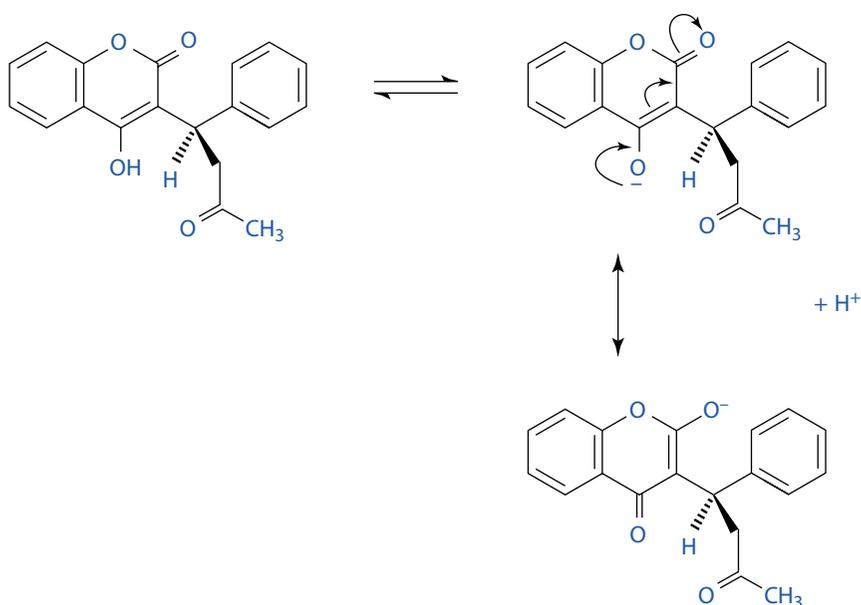
Figure 3.9. The ionisation of the enol form of warfarin.

There is a popular misconception that because amines are basic and amines contain a nitrogen atom all drugs that contain nitrogen will be basic. This is not true, as a moment's thought will confirm.

Amides contain nitrogen and are neutral, and quite a few drugs containing nitrogen atoms are actually acidic. Compounds are basic only if

the lone pair of electrons on the nitrogen is available for reaction with protons. In the case of amides, the carbon–nitrogen bond has significant double-bond character due to resonance, as shown in Fig. 3.10. The lone pair of electrons on the nitrogen of some drug molecules can be completely unavailable for reaction with protons. Drugs of this type are so weakly basic that they actually behave as *acids* in solution. This effect can be illustrated by considering the compounds below.
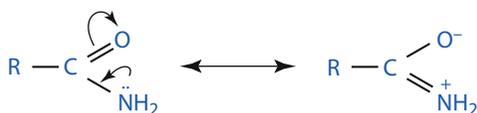

Figure 3.10. Resonance effects of the amide group.

Phenylbutazone

Phenylbutazone is a non-steroidal anti-inflammatory drug (NSAID) that exerts its anti-inflammatory action through inhibition of the enzyme cyclo-oxygenase and inhibition of the production of inflammatory mediators such as prostaglandins. Phenylbutazone, despite containing nitrogen, is a weak acid with a pK_a of 4.4. The acidic hydrogen is on the 4-position of the pyrazolidinedione ring and upon ionisation the negative charge is delocalised onto the adjacent carbonyl groups in a similar manner to that in warfarin (pK_a 5.0) (Fig. 3.11).

Indometacin

Indometacin is another NSAID with a similar mode of action to that of phenylbutazone. Indometacin is acidic due to ionisation of the carboxylic acid group and has a pK_a value of 4.5. The nitrogen atom in indometacin is present as an amide and is essentially neutral (Fig. 3.12).

Barbiturates

Barbiturates are cyclic imides used as hypnotics and (in the case of phenobarbital) as anticonvulsants. They are all derivatives of barbituric acid (which is not pharmacologically active) and differ only in their substituents on the 5-position of the ring. Barbiturates contain nitrogen atoms, but the lone pair on the nitrogen is not available for reaction with protons, so barbiturates are not basic. Instead, they behave as weak acids in solution (diprotic actually, though the second ionisation is very weak); the negative charge formed on
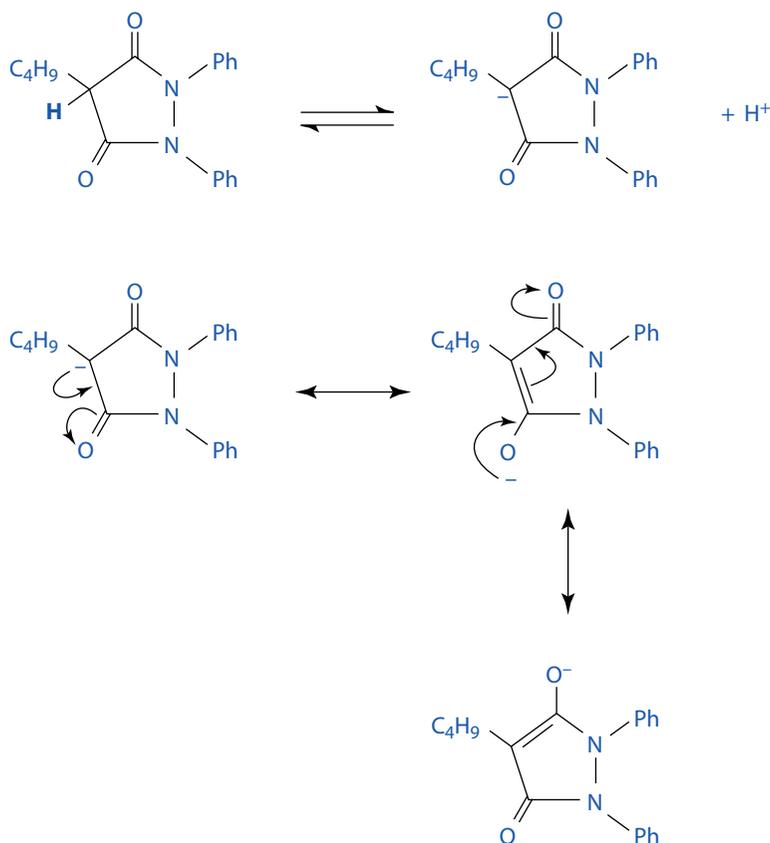
Figure 3.11. The ionisation of phenylbutazone.

ionisation delocalises around the two adjacent carbonyl groups in a manner similar to that in warfarin.

The pK_a values for barbiturates are typically 7–8 for the first ionisation and approximately 11–12 for the second, although the drugs are usually administered in the form of the sodium salt to increase water solubility.

The first ionisation of a barbiturate is shown in Fig. 3.13.

The sulfur analogue of pentobarbital, called thiopental (Fig. 3.14), is widely used in operating theatres for the induction of general anaesthesia. Thiobarbiturates of this type have a much higher partition coefficient than the oxobarbiturates used as hypnotics (see Chapter 2). As a result, thiopental, when administered intravenously to a vein in the back of the hand, can induce unconsciousness in a matter of seconds that lasts for several minutes. This is sufficient time for the anaesthetist to introduce an airway to the patient and commence general anaesthesia.
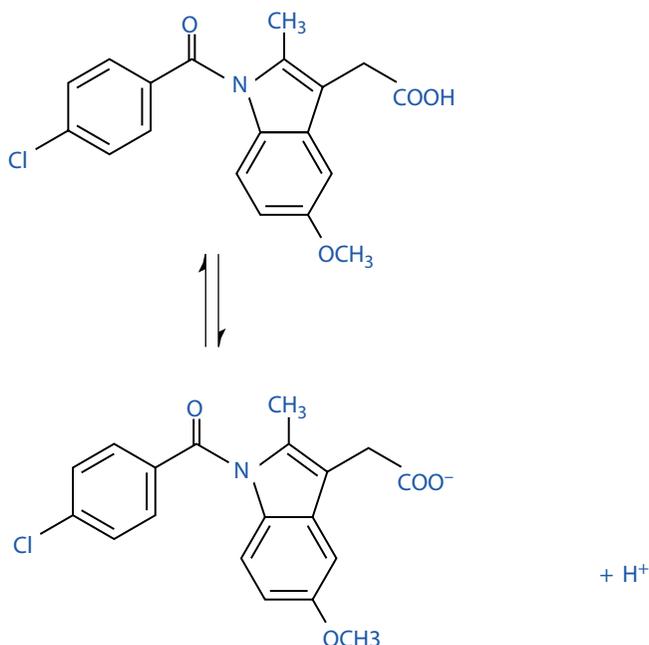
Figure 3.12. The ionisation of indometacin.

Phenytoin

Phenytoin is an anticonvulsant widely used in the treatment of epilepsy. The properties of phenytoin resemble those of barbiturates. It is a cyclic imide with a pK_a of 8.3. The anion is stabilised by resonance of the negative charge onto the oxygens of the carbonyl group and the drug is usually administered as the sodium salt to increase water solubility (Fig. 3.15).

Phenytoin and barbiturates display tautomerism of the imine–imide type, as shown in Fig. 3.16. The predominant tautomer is the imide form, although some older textbooks list the structure of the drug as the minor tautomer.

Sulfonamides

Sulfonamides are a class of antibacterial compounds, all of which contain the sulfonamido group $-SO_2NH$. Although they were widely used in the past, their use has decreased in recent years with the advent of newer antibiotics such as penicillins and cephalosporins. Sulfonamides are all weakly acidic (pK_a approximately 5–8) due to the powerful electron-withdrawing effect of the $-SO_2-$ substituent and stabilisation of the resulting anion by resonance. Sulfonamides are usually administered in the form of the sodium salt to
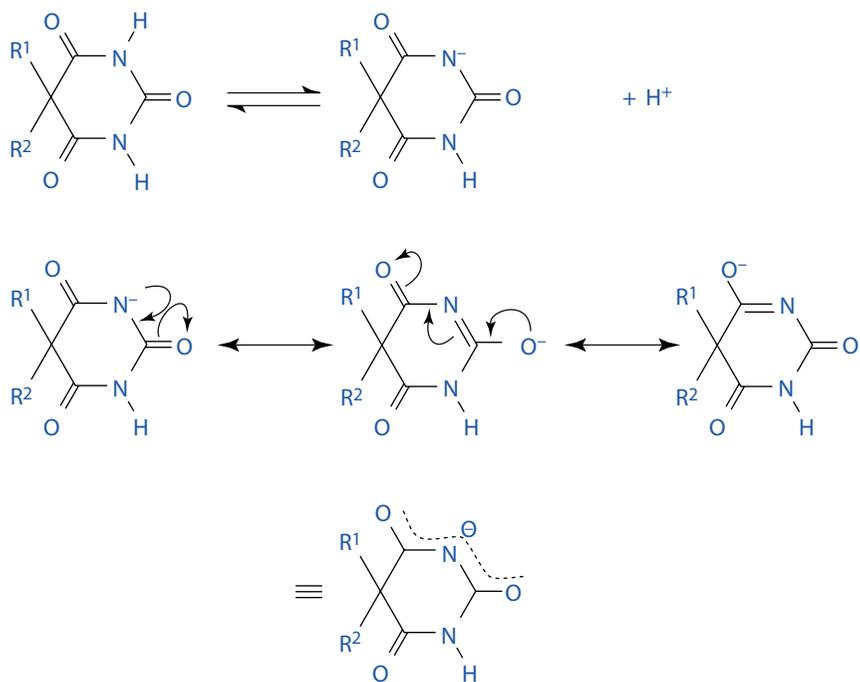
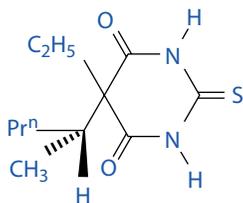**Figure 3.13.** The ionisation of a barbiturate.

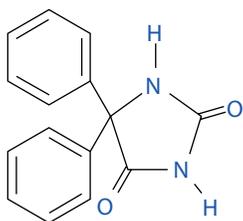**Figure 3.14.** The structure of thiopental.
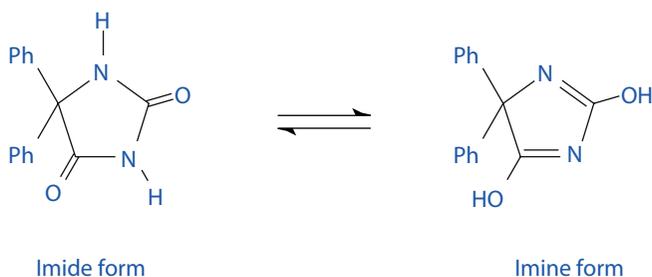

Figure 3.15. The structure of phenytoin.

Figure 3.16. The tautomerism of phenytoin.

increase their water solubility. The ionisation of a typical sulfonamide is shown in Fig. 3.17.
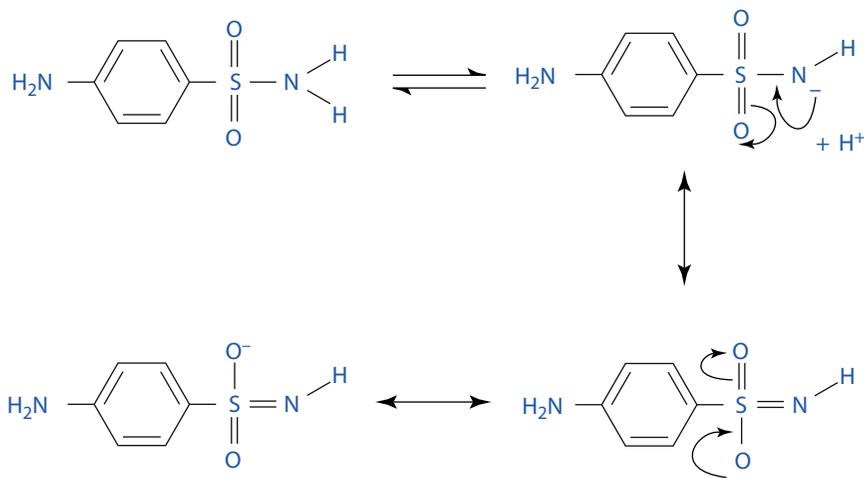

Figure 3.17. The ionisation of a sulfonamide.

Basic drugs

The Brønsted–Lowry definition of a base is an acceptor of protons. Pharmaceutical and biological sciences are concerned mainly with the behaviour of drugs in aqueous systems. Under these conditions, drugs will behave as bases only if they contain *a nitrogen atom with a lone pair of electrons available for reaction with protons*. The major class of compound to work in this way is the amines. An amine in aqueous solution will react with water to release hydroxide ions (OH^-), as shown in Eq. (3.4).

$$R_3N + H_2O \rightleftharpoons R_3NH^+ + OH^- \tag{3.4}$$

Water donates the proton and functions as an acid in this reaction. The equilibrium constant for this reaction is defined as K_b and the greater the value of K_b the stronger will be the base.

$$K_b = \frac{[R_3NH^+][OH^-]}{[R_3N]} \tag{3.5}$$

However, as was discussed in Chapter 1, most of the pharmaceutical literature refers to the strength of bases in terms of the pK_a of the conjugate acid of the base (R_3NH^+ above). In this case, *the higher the value of pK_a the stronger is the base*.

Basic drugs are usually administered as their water-soluble salts (generally the hydrochloride). Care must be taken not to co-administer anything that will raise the pH of the hydrochloride salt solution in case precipitation of the less water-soluble free base occurs.

The key point to remember about basicity of amines is the availability of the lone pair of electrons on the nitrogen atom. If the lone pair is involved in interactions elsewhere in the molecule, then the amine will not be basic. This can be illustrated by consideration of the basicity of the local anaesthetic procaine (Fig. 3.18). The nitrogen of the diethylamino moiety is present in a tertiary amine. The lone pair of electrons is concentrated on the nitrogen atom and is available to accept a proton. This means the aliphatic nitrogen can ionise at the pH of human plasma (pH 7.4) to form the mono-cation of procaine. Conversely, the lone pair of electrons on the amino group attached to the benzene ring is less available for reaction with protons due to delocalisation into the ring. This delocalisation increases the electron density of the *ortho-* and *para*-carbon atoms and means that the Ar–NH_2 group does not ionise at the pH of blood.
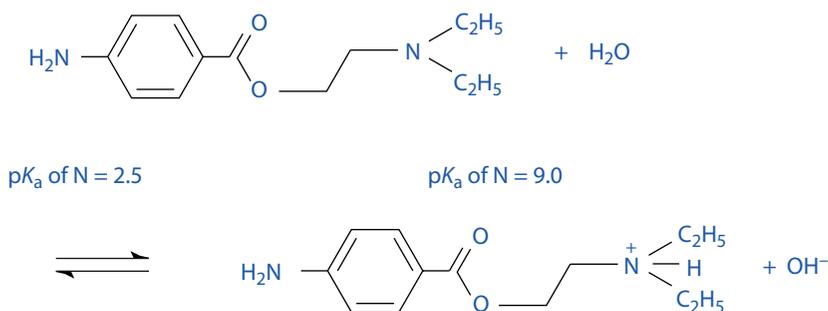

Figure 3.18. The ionisation of procaine.

Basicity of heterocyclic compounds

Many drugs and biologically active compounds contain nitrogen in a hetero-cyclic ring. While a full discussion of their basicity is beyond the scope of this book, a brief summary of factors influencing basicity will be considered.

In *aliphatic heterocyclic compounds*, the nitrogen atom is part of a saturated heterocyclic ring and the lone pair of electrons is available for reaction with protons (e.g. piperidine, Fig. 3.19). Compounds of this type are similar in base strength to their open-chain aliphatic counterparts, with typical pK_a values of 8–9.

In *aromatic heterocyclic compounds* lone pairs on the nitrogen atoms are involved in interaction with electrons of the aromatic ring. In pyrrole (Fig. 3.19), the lone pair contributes to the aromatic sextet and is not available for reaction with protons. As a result, pyrrole is a very weak base with a pK_a value so low that it is a negative number.

The six-membered nitrogen heterocycle pyridine (Fig. 3.19) is also a weak base. In the case of pyridine, however, only one electron from the nitrogen contributes to the aromatic sextet. This leaves an unshared pair of electrons, which can accept a proton, and so pyridine is measurably basic, with a pK_a value of 5.2. This value is similar to that found in aromatic amines such as aniline (aminobenzene).
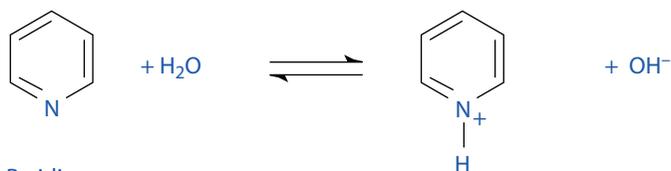
Separation of mixtures

It is often the case that pharmaceutical and/or chemical procedures give rise to mixtures of chemicals. These could arise as a result of incomplete chemical reaction, as in the case of side-reactions and by-products, or when drugs have to be isolated from complex mixtures of chemicals (e.g. isolation of a drug metabolite from a blood or urine sample). Knowledge of the acidity and basicity of drugs is essential if efficient separation is to be achieved. When a drug molecule ionises, the solubility profile of the compound changes dramatically. Free acids and bases when they are unionised tend to dissolve well in non-polar organic solvents such as diethyl ether, chloroform or ethyl acetate. Upon ionisation, the acid will form an anion and the base will form a conjugate acid. These will both be more soluble in aqueous solvents such as water or buffer. This means that acidic drugs are soluble in organic solvents at low pH (when they are primarily unionised) and soluble in polar solvents at high pH. Bases, conversely, are soluble in organic solvents when the pH is high (and the base is unionised) and are water soluble at low values of pH.
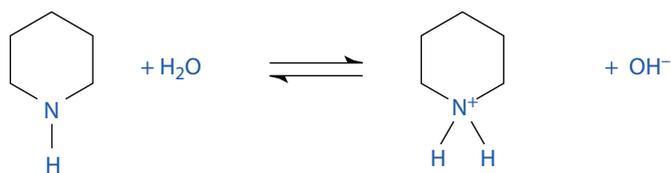
Piperidine
$pK_a = 11.2$
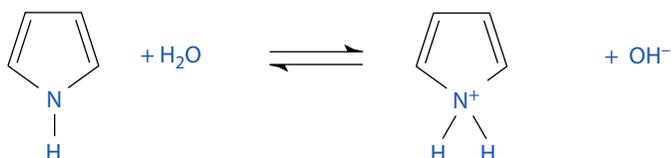
Pyrrole
$pK_a = -0.27$

Pyridine
$pK_a = 5.2$

Figure 3.19. The ionisation of some nitrogen-containing heterocyclics.

Solubility differences of this type allow the separation of some quite complex mixtures to be carried out easily and quickly in the laboratory. All that is needed is a pair of immiscible solvents, a separating funnel and an understanding of the effects of pH on the solubility of drugs. An example of this type of separation is shown below.
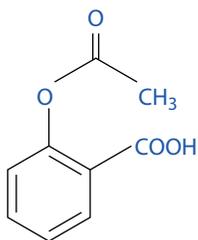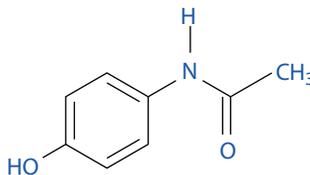
Tutorial examples

Q *1 An 'over-the-counter' analgesic called APC Tablets contains aspirin, paracetamol and codeine. An extract of these tablets was dissolved in toluene (methylbenzene) and filtered to remove insoluble solids. Devise a separation scheme to isolate all three drugs in a pure form.*
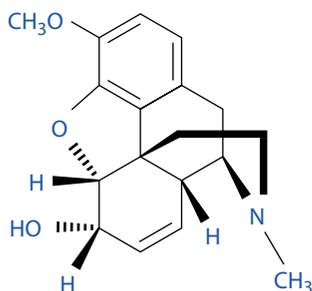
A 1 The structures and pK_a values of the three drugs are shown in Fig. 3.20.

Aspirin pK_a = 3.5   Paracetamol pK_a = 9.5

Codeine pK_a = 8.2

Figure 3.20. The structures and pK_a values of aspirin, paracetamol and codeine.

Aspirin and paracetamol are both acidic compounds, while codeine is a weak base. If a student cannot correctly identify whether the drugs in question are acids or bases, the whole question becomes impossible to solve and misery will surely follow. There is no easy way to do this other than to learn (parrot fashion if necessary) the functional groups that cause a drug to function as an acid or a base.

All three drugs will be soluble in toluene in their unionised form. The separation strategy is to ionise the drugs sequentially and remove them in the aqueous phase, whereupon back-extraction into an organic solvent will yield the (hopefully) pure compounds.

Addition of dilute hydrochloric acid will ionise the codeine and form codeine hydrochloride. This salt will be water soluble and will partition into the aqueous (lower) phase. Removal of the aqueous phase and addition of fresh organic solvent and a strong base (such as sodium hydroxide) will liberate codeine base in the organic phase. Evaporation of the volatile solvent yields pure codeine.

Aspirin is a carboxylic acid derivative, while paracetamol is a substituted phenol. Addition of a strong base (e.g. sodium hydroxide) would result in ionisation of both acids (and some hydrolysis of the aspirin). To separate the acids successfully, a discriminating base must, therefore, be used, which is formed from an acid intermediate in strength between carboxylic acids and phenols. Such an acid is carbonic acid (H_2CO_3), and addition of sodium bicarbonate solution will result in ionisation of the aspirin as the sodium salt. This salt will be water soluble and may be removed in the lower phase. Addition of fresh organic solvent and dilute hydrochloric acid solution will yield aspirin as free acid.

The remaining drug, paracetamol, may be isolated by simple evaporation of the toluene or extracted into aqueous solvent by addition of a strong base such as sodium hydroxide solution. The separation is shown schematically in Fig. 3.21.
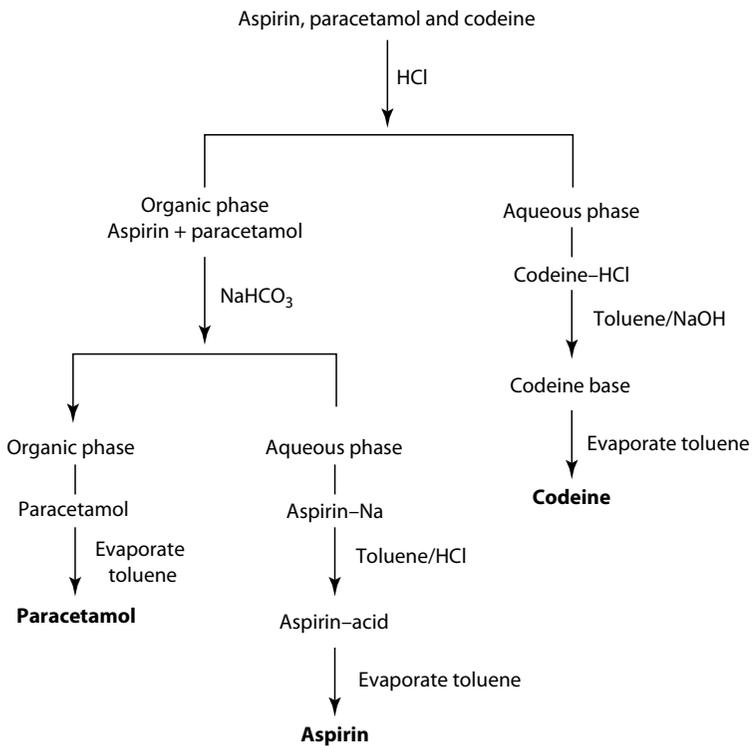
Figure 3.21. A separation scheme for a mixture of aspirin, paracetamol and codeine.

Q 2 *The structures of sulfanilamide and sulfacetamide are shown in Fig. 3.22. Explain why both drugs behave as acids in solution and predict which compound will be the stronger acid.*
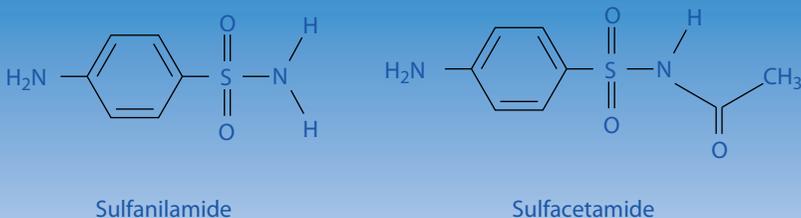
Figure 3.22. The structure of sulfanilamide and sulfacetamide.

A 2 Both drugs are sulfonamides and ionise with the release of a proton. The anion formed is stabilised by resonance as discussed previously. The pK_a value for sulfanilamide is 10.4, while the pK_a of sulfacetamide is 5.4. Clearly, since the value of pK_a is lower, sulfacetamide is a much stronger acid than sulfanilamide (five units difference on a log scale is 100 000 times stronger). This difference in acidity is caused by the presence of a carbonyl group adjacent to the sulfonamido hydrogen. This allows additional resonance to take place in sulfacetamide. Upon ionisation, the negative charge on the anion can delocalise onto the carbonyl oxygen as shown in Fig. 3.23. This delocalisation further stabilises the anion and is in addition to the normal resonance present in the sulfonamido group.
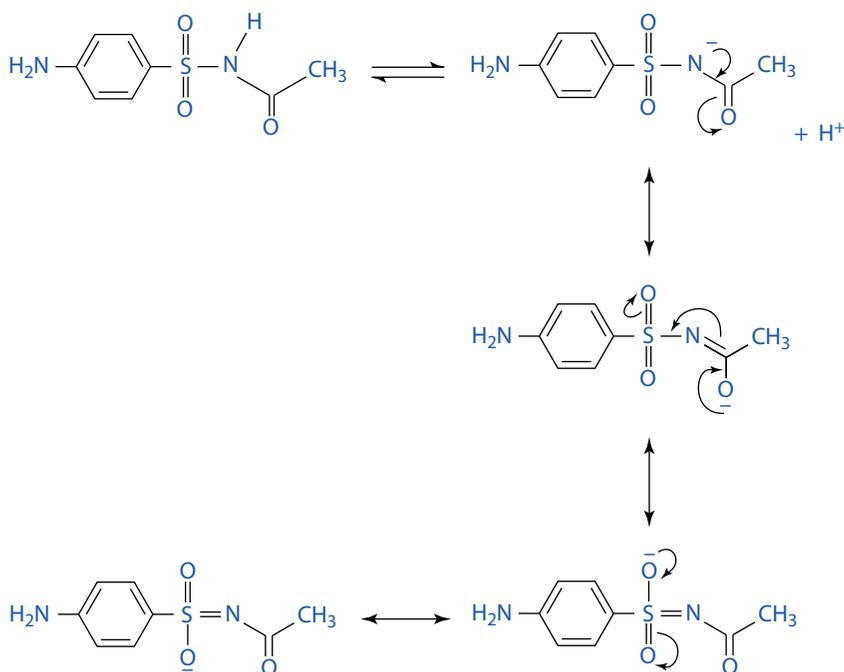

Figure 3.23. Resonance effects in sulfacetamide.

Problems

Q3.1 Co-trimoxazole tablets contain sulfamethoxazole and trimetho-
prim and are used in the treatment of chest and urinary tract
infections. Classify sulfamethoxazole and trimethoprim as acidic,
basic or neutral and hence describe how you could separate a
mixture of the two drugs in the laboratory using simple glassware
and reagents. See Fig. 3.24.
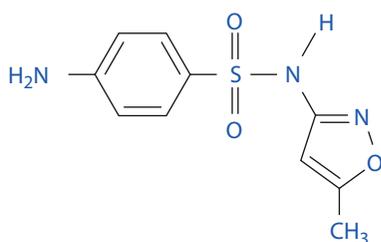
Sulfamethoxazole
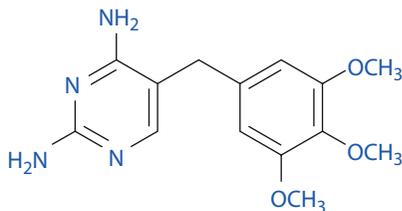
Trimethoprim

Figure 3.24. The structures of sulfamethoxazole and trimethoprim.

Q3.2 Refer to the structures numbered 1 to 6 in Fig. 3.25. In each case
select the form of the drug that predominates in human plasma
at pH 7.4:

(a) mono-cation
(b) di-cation
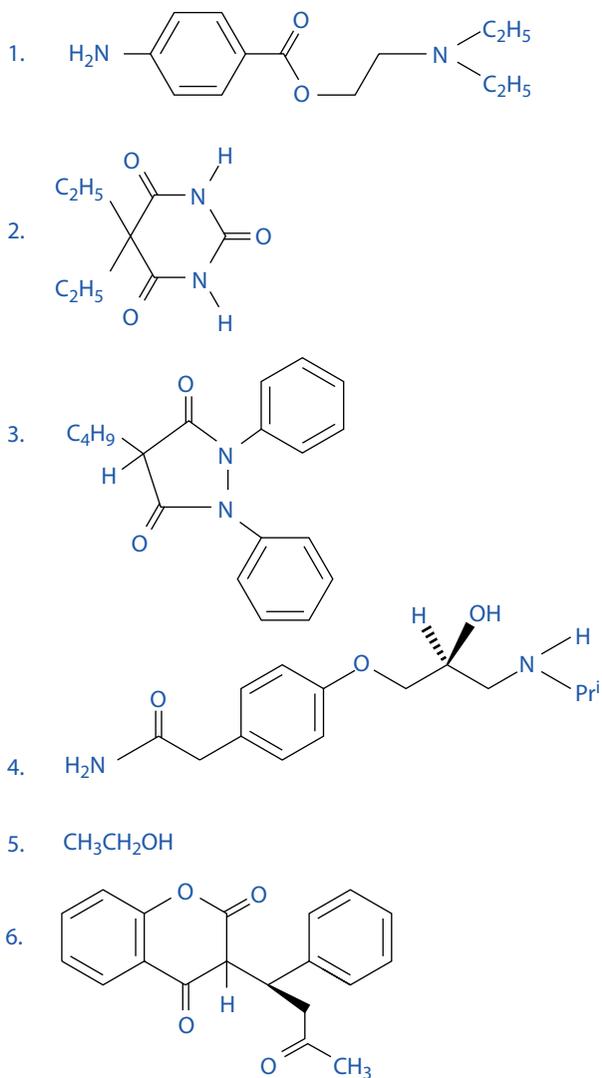(c) mono-anion
(d) di-anion
(e) neutral molecule.

Figure 3.25. Structures of drugs.

Q3.3 The structure of nicotine is shown in Fig. 3.26. Classify nicotine as acidic, basic or neutral; draw the structure of the form of nicotine that will predominate at plasma pH and suggest the form of nicotine that is active pharmacologically.
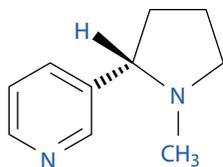

Figure 3.26. The structure of nicotine.

(Answers to problems can be found on pp. 281–283.)