

The
ORGANIC
CHEMISTRY
of DRUG
DESIGN and
DRUG ACTION

•
• Richard B. Silverman

AQUESTIVETHERAPEUTICS, INC. EXHIBIT 1020

The Organic Chemistry of Drug Design and Drug Action

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ACADEMIC PRESS, INC.

A Division of Harcourt Brace & Company

San Diego New York Boston London Sydney Tokyo Toronto

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1020

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Academic Press, Inc.

1250 Sixth Avenue, San Diego, California 92101-4311

United Kingdom Edition published by

Academic Press Limited

24-28 Oval Road, London NW1 7DX

Library of Congress Cataloging-in-Publication Data

Silverman, Richard B.

The organic chemistry of drug design and drug action / Richard B. Silverman.

p. cm.

Includes index.

ISBN 0-12-643730-0 (hardcover)

1. Pharmaceutical chemistry. 2. Bioorganic chemistry.

3. Molecular pharmacology. 4. Drugs--Design. I. Title.

[DNLM: 1. Chemistry, Organic. 2. Chemistry, Pharmaceutical.

3. Drug Design. 4. Pharmacokinetics. QV 744 S587o]

RS403.S55 1992

615'.19--dc20

DNLM/DLC

for Library of Congress

91-47041
CIP

To Mom and the memory of Dad,
for their warmth, their humor, their ethics, their inspiration,
but mostly for their genes.

Prodrugs and Drug Delivery Systems

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I. Enzyme Activation of Drugs

The term *prodrug*, which was used initially by Albert,¹ refers to a pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation. A prodrug also can be activated by a nonenzymatic process such as hydrolysis, but in this case the compounds usually are inherently unstable and may cause stability problems. The prodrug-to-drug conversion can occur before absorption, during absorption, after absorption, or at a specific site in the body. In the ideal case a prodrug is converted to the drug as soon as the desired goal for designing the prodrug has been achieved. It should be noted that although the compounds discussed in this chapter are illustrative of the approaches taken for the design of prodrugs, many of them have not been approved for medical use.

A. Utility of Prodrugs

There are numerous reasons why one may wish to utilize a prodrug strategy in drug design. Specific examples of each of these categories are given in Section II,A,2.

1. Solubility

Consider an active drug that is insufficiently soluble in water so that it cannot be injected in a small dose. A water-soluble group could be attached which could be metabolically released after drug administration.

2. Absorption and Distribution

If the drug is not absorbed and transported to the target site in sufficient concentration, it can be made more water soluble or lipid soluble, depending on the desired site of action. Once absorption has occurred or when the drug is at the appropriate site of action, the water- or lipid-soluble group is removed enzymatically.

3. Site Specificity

Specificity for a particular organ or tissue can be made if there are high concentrations of or uniqueness of enzymes present at that site which can cleave the appropriate appendages from the prodrug and unmask the drug.

4. Instability

A drug may be rapidly metabolized and rendered inactive prior to when it reaches the site of action. The structure may be modified to block that metabolism until the drug is at the desired site.

5. Prolonged Release

It may be desirable to have a steady low concentration of a drug released over a long period of time. The drug may be altered so that it is metabolically converted to the active form slowly.

6. Toxicity

A drug may be toxic in its active form and would have a greater therapeutic index if it were administered in a nontoxic, inactive form that was converted to the active form only at the site of action.

7. Poor Patient Acceptability

An active drug may have an unpleasant taste or odor, produce gastric irritation, or cause pain when administered (e.g., when injected). The structure of the drug can be modified to alleviate these problems, but once administered, the altered drug can be metabolized to the active drug.

8. Formulation Problems

If the drug is a volatile liquid, it would be more desirable to prepare it in a solid form so that it could be formulated as a tablet. An inactive solid derivative could be prepared which would be converted in the body to the active drug.

B. Types of Prodrugs

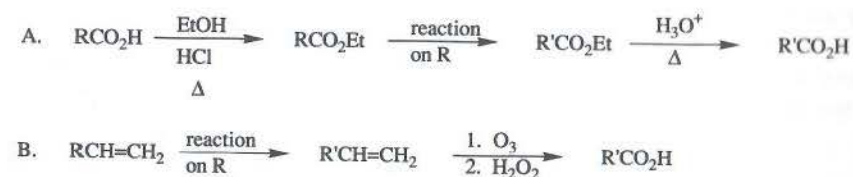
There are several classifications of prodrugs. Some prodrugs are not designed as such; the biotransformations are fortuitous, and it is discovered after isolation and testing of the metabolites that activation of the drug had occurred. In most cases a specific modification in a drug has been made on the basis of known metabolic transformations. It is expected that after administration it will be appropriately metabolized to the active form. This has been termed *drug latention* to signify the rational design approach rather than serendipity.² The term drug latention has been refined even further by Wermuth³ into two classes which he called carrier-linked prodrugs and bioprecursors.

A *carrier-linked prodrug* is a compound that contains an active drug linked to a carrier group that can be removed enzymatically, such as an ester which is hydrolyzed to an active carboxylic acid-containing drug. The bond to the carrier group must be labile enough to allow the active drug to be released efficiently *in vivo*, and the carrier group must be nontoxic and biologically inactive when detached from the drug. Carrier-linked prodrugs can be subdivided even further into bipartate, tripartate, and mutual prodrugs. A *bipartate prodrug* is a prodrug comprised of one carrier attached to the drug. When a carrier is connected to a linker arm which is connected to the drug, the term *tripartate prodrug* is used. A *mutual prodrug* consists of two, usually synergistic, drugs attached to each other (one drug is the carrier for the other and vice versa).

A *bioprecursor* is a compound that is metabolized by molecular modification into a new compound which is the active principle or which can be metabolized further to the active drug. For example, if the drug contains a carboxylic acid group, the bioprecursor may be a primary amine which is metabolized by oxidation to the aldehyde which is further metabolized to the carboxylic acid drug (see Section IV,B,1,e of Chapter 7). Unlike a carrier-linked prodrug, which is the active drug linked to a carrier that generally is released by a hydrolytic reaction, a bioprecursor contains a different structure that cannot be converted to the active drug by simple cleavage of a group from the prodrug.

The concept of prodrugs can be analogized to the use of protecting groups in organic synthesis.⁴ If, for example, you wanted to carry out a reaction on a compound that contained a carboxylic acid group, it may be necessary first to protect the carboxylic acid as, say, an ester, so that the acidic proton of the

carboxylic acid does not interfere with the desired reaction. After the desired synthetic transformation is completed, the carboxylic acid analog could be unmasked by deprotection, that is, hydrolysis of the ester (Scheme 8.1A). This is analogous to a carrier-linked prodrug; an ester functionality can be used to give the drug more desirable properties until it reaches the appropriate biological site where it is "deprotected." Another type of protecting group in organic synthesis is one which has no resemblance to the desired functional group. For example, a terminal alkene can be oxidized with ozone to an aldehyde,⁵ and the aldehyde can be oxidized to a carboxylic acid with hydrogen peroxide (Scheme 8.1B). As in the case of a bioprecursor, a drastic structural change is required to unmask the desired group. Oxidation is a common metabolic biotransformation for bioprecursors.



Scheme 8.1. Protecting group analogy for a prodrug.

When designing a prodrug, you should keep in mind that a particular metabolic transformation may be species specific (see Chapter 7). Therefore, a prodrug designed on the basis of rat metabolism studies may not necessarily be effective in humans.

II. Mechanisms of Prodrug Activation

A. Carrier-Linked Prodrugs

The most common reaction for activation of carrier-linked prodrugs is hydrolysis. First, we consider the general functional groups involved, then specific examples for different types of prodrugs will be given.

1. Carrier Linkages for Various Functional Groups

a. Alcohols and Carboxylic Acids. There are several reasons why the most common prodrug form for drugs containing alcohol or carboxylic acid functional groups is an ester. First, esterases are ubiquitous, so metabolic regeneration of the drug is a facile process. Also, it is possible to prepare ester derivatives with virtually any degree of hydrophilicity or lipophilicity. Finally, a variety of stabilities of esters can be obtained by appropriate manipu-

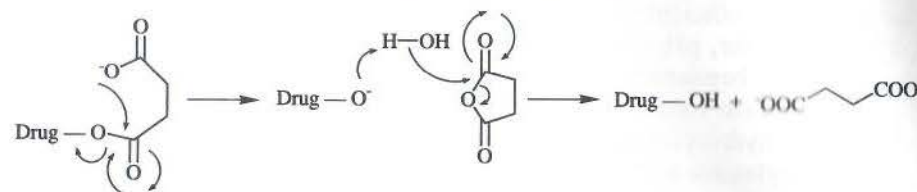
lation of electronic and steric factors. Therefore, a multitude of ester prodrugs can be prepared to accommodate a wide variety of problems that require the prodrug approach.

Alcohol-containing drugs can be acylated with aliphatic or aromatic carboxylic acids to decrease water solubility (increase lipophilicity) or with carboxylic acids containing amino or additional carboxylate groups to increase water solubility (Table 8.1).⁶ Conversion to phosphate or sulfate esters also increases water solubility. By using these approaches a wide range of solubilities can be achieved that will affect the absorption and distribution properties of the drug. These derivatives also can have an important effect on the dosage form, that is, whether used in tablet form or in aqueous solution. One problem with the use of this prodrug approach is that in some cases the esters are not very good substrates for the endogenous esterases, sulfatases, or phosphatases, and they may not be hydrolyzed at a rapid enough rate. When that occurs, however, a different ester can be tried. Another approach to accelerate the hydrolysis rate could be to attach electron-withdrawing groups (if a

Table 8.1 Ester Analogs of Alcohols as Prodrugs

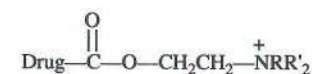
Drug—OH $\longrightarrow$ Drug—OX	
X	Effect on water solubility
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} - \text{R} \end{array}$	(R = aliphatic or aromatic) decreases
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} - \text{CH}_2\text{N}^+\text{Me}_2 \\ \\ \text{H} \end{array}$	increases ($\text{pK}_a \sim 8$)
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} - \text{CH}_2\text{CH}_2\text{COO}^- \end{array}$	increases ($\text{pK}_a \sim 5$)
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C} - \text{C}_6\text{H}_4\text{NH}^+ \end{array}$	increases ($\text{pK}_a \sim 4$)
PO_3^-	increases ($\text{pK}_a \sim 2$ and ~ 6)
$\begin{array}{c} \text{O} \\ \parallel \\ \text{CCH}_2\text{SO}_3^- \end{array}$	increases ($\text{pK}_a \sim 1$)

base hydrolysis mechanism is relevant) or electron-donating groups (if an acid hydrolysis mechanism is important)⁷ to the carboxylate side of the ester. Succinate esters can be used to accelerate the rate of hydrolysis by intramolecular catalysis (Scheme 8.2). If the ester is too reactive, substituents can be appended that cause steric hindrance to hydrolysis. Alcohol-containing drugs also can be converted to the corresponding acetals or ketals for rapid hydrolysis in the acidic medium of the gastrointestinal tract.



Scheme 8.2. Intramolecular hydrolysis of succinate esters.

Carboxylic acid-containing drugs also can be esterified; the reactivity of the derivatized drug can be adjusted by appropriate structural manipulations. If a slower rate of ester hydrolysis is desired, long-chain aliphatic or sterically hindered esters can be used. If hydrolysis is too slow, addition of electron-withdrawing groups on the alcohol part of the ester can increase the rate. The pK_a of a carboxylic acid can be raised by conversion to a choline ester (8.1, $\text{R} = \text{R}' = \text{Me}$; $\text{pK}_a \sim 7$) or an amino ester (8.1, $\text{R} = \text{H}$, $\text{R}' = \text{H}$ or Me ; $\text{pK}_a \sim 9$).



8.1

b. Amines. N-Acylation of amines to give amide prodrugs is not commonly used, in general, because of the stability of amides toward metabolic hydrolysis. Activated amides, generally of low basicity amines, or amides of amino acids are more susceptible to enzymatic cleavage (Table 8.2). Although

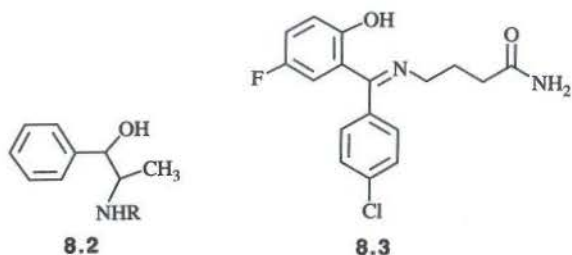
Table 8.2 Prodrug Analogs of Amines

Drug—NH ₂ $\longrightarrow$ Drug—NHX	
X	
$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CR} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CCHNH}_3^+ \\ \\ \text{R} \end{array}$
$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{O}^-\text{Ph} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CH}_2\text{NHCAr} \end{array}$
$=\text{CHAr}$	$=\text{NAr}$

carbamates in general are too stable, phenyl carbamates (RNHCO_2Ph) are rapidly cleaved by plasma enzymes,⁸ and, therefore, they can be used as prodrugs.

The pK_a values of amines can be lowered by approximately 3 units by conversion to their *N*-Mannich bases (Table 8.2, $\text{X} = \text{CH}_2\text{NHCOAr}$). This lowers the basicity of the amine so that at physiological pH few of the prodrug molecules are protonated, thereby increasing its lipophilicity. For example, the partition coefficient (see Chapter 2, Section II,E,2,b) between octanol and phosphate buffer, pH 7.4, for the *N*-Mannich base (8.2, $\text{R} = \text{CH}_2\text{NHCOPh}$) derived from benzamide and the decongestant phenylpropanolamine (8.2, $\text{R} = \text{H}$) is almost 100 times greater than that for the parent amine.⁹ However, the rate of hydrolysis of *N*-Mannich bases depends on the amide carrier group; salicylamide and succinimide are more susceptible to hydrolysis than is benzamide.¹⁰

Another approach for lowering the pK_a values of amines and, thereby, making them more lipophilic, is to convert them to imines (*Schiff bases*); however, imines often are too labile in aqueous solution. The anticonvulsant agent progabide (8.3) is a prodrug form of γ -aminobutyric acid, an important inhibitory neurotransmitter (see Chapter 5, Section V,C,3,a). The lipophilicity of 8.3 allows the compound to cross the blood-brain barrier; once inside the brain it is hydrolyzed to γ -aminobutyric acid.¹¹

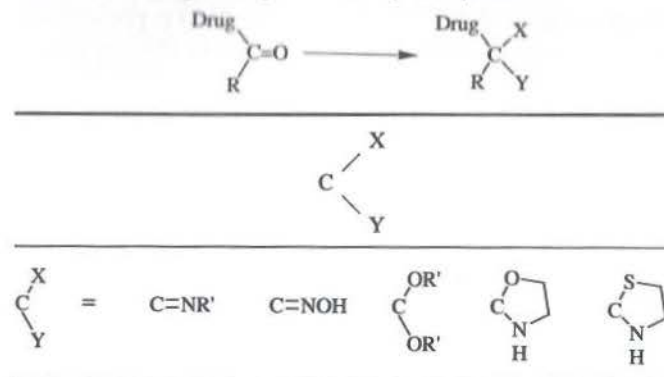


c. Carbonyl Compounds. The most important prodrug forms of aldehydes and ketones are Schiff bases, oximes, acetals (ketals), enol esters, oxazolidines, and thiazolidines (Table 8.3). A more complete review of bioreversible derivatives of the functional groups was written by Bundgaard.⁶

2. Examples of Carrier-Linked Bipartate Prodrugs

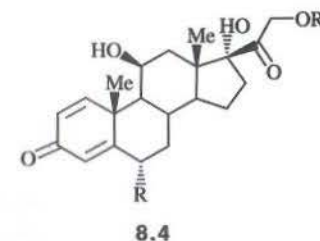
a. Prodrugs for Increased Water Solubility. Prednisolone (8.4; $\text{R} = \text{R}' = \text{H}$) and methylprednisolone (8.4; $\text{R} = \text{CH}_3$, $\text{R}' = \text{H}$) are poorly water-soluble corticosteroid drugs. In order to permit aqueous injection or ophthalmic delivery of these drugs, they must be converted to water-soluble forms

Table 8.3 Prodrug Analogs of Carbonyl Compounds



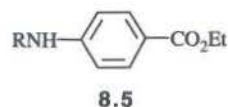
such as one of the ionic esters described in Section II,A,1,a. However, there are two considerations in the choice of a solubilizing group: the ester must be stable enough in aqueous solution so that a ready-to-inject solution has a reasonably long shelf life (greater than 2 years; half-life about 13 years), but it must be hydrolyzed *in vivo* with a reasonably short half-life after administration (less than 10 min). For this optimal situation to occur the *in vivo/in vitro* lability ratio would have to be on the order of 10^6 . This is possible when the biotransformation is enzyme catalyzed.

The water-soluble prodrug form of methylprednisolone that is in medical use is methylprednisolone sodium succinate (8.4, $\text{R} = \text{CH}_3$, $\text{R}' = \text{COCH}_2\text{CH}_2\text{CO}_2\text{Na}$). However, the *in vitro* stability is low; consequently, it is distributed as a lyophilized (freeze-dried) powder that must be reconstituted with water and then used within 48 hr. The lyophilization process adds to the cost of the drug and makes its use less convenient. On the basis of physical-organic chemical rationalizations, a series of more stable water-soluble methylprednisolone esters was synthesized, and several of the analogs were shown to have shelf lives in solution of greater than 2 years at room temperature.¹² Ester hydrolysis studies of these compounds in human and monkey serum indicated that derivatives having an anionic solubilizing moiety such as carboxylate or sulfonate are poorly or not hydrolyzed, but compounds with a

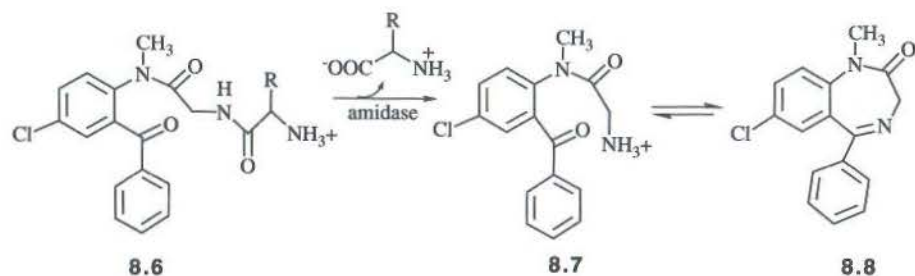


cationic (tertiary amino) solubilizing moiety are hydrolyzed rapidly by serum esterases.¹³ Prednisolone phosphate (**8.4**; R = H, R' = PO₃Na₂) is prescribed as a water-soluble prodrug for prednisolone that is activated *in vivo* by phosphatases.

The local anesthetic benzocaine (**8.5**, R = H) has been converted to water-soluble amide prodrug forms with various amino acids (**8.5**, R = ⁺NH₃-CHR'CO); amidase-catalyzed hydrolysis in human serum occurs rapidly.¹⁴



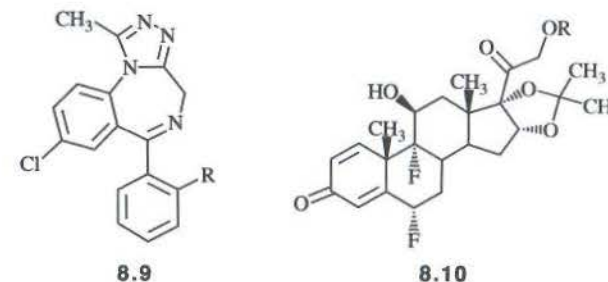
Another prodrug approach is to design acyclic derivatives that are enzymatically hydrolyzed to a product that spontaneously cyclizes to the desired drug. The benzodiazepine tranquilizer diazepam (**8.8**, Scheme 8.3) is very sparingly water soluble, but the open chain amino ketone coupled to an amino acid or peptide is a stable, freely water-soluble prodrug (**8.6**); *in vivo* peptidases hydrolyze the peptide bond, and the resulting 2-aminoacetamidobenzophenone analog (**8.7**) spontaneously cyclizes to give the benzodiazepine.^{15,16} The rate of *in vivo* hydrolysis of the peptide bond depends on which L-amino acid is attached; peptides derived from Phe and Lys are cleaved much faster than those from Gly and Glu. The rate of cyclization depends on the substituents in the phenyl ring and on the amide nitrogen. Although the cyclization of **8.7** to **8.8** occurs with a half-life of 73 sec, that for the corresponding N-desmethyl analog is 15 min. As an example of how effective this approach is for increasing the water solubility, the benzodiazepine triazolam (**8.9**, R = Cl) has a solubility of 0.015 mg/ml at 25° C, but the corresponding open-chain glycylaminobenzophenone derivative (HCl salt) has a solubility of 109 mg/ml.¹⁷ A similar prodrug approach was taken for the benzodiazepine alprazolam (**8.9**, R = H).¹⁸



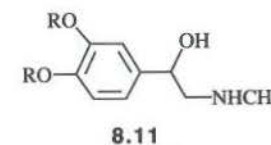
Scheme 8.3. Benzodiazepine prodrug activation.

b. Prodrugs for Improved Absorption and Distribution. The skin is designed to maintain the body fluids and prevent absorption of xenobiotics into

the general circulation. Consequently, drugs applied to the skin are poorly absorbed.¹⁹ Even steroids have low dermal permeability, particularly if they contain hydroxyl groups which can interact with the skin or binding sites in the keratin. Corticosteroids for the topical treatment of inflammatory, allergic, and pruritic skin conditions can be made more suitable for topical absorption by esterification or acetonidation. For example, both fluocinolone acetonide (**8.10**, R = H) and fluocinonide (**8.10**, R = COCH₃) are prodrugs used for inflammatory and pruritic manifestations. Once absorbed through the skin an esterase releases the drug.



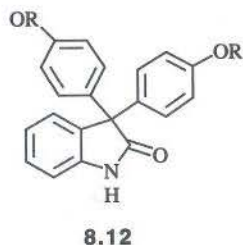
Dipivaloylphenylephrine (dipivefrin; **8.11**, R = Me₃CCO), a prodrug for the antiglaucoma drug epinephrine (**8.11**, R = H), is better able to penetrate the cornea than is epinephrine. The cornea and aqueous humor have significant esterase activity.²⁰



c. Prodrugs for Site Specificity. The targeting of drugs for a specific site in the body by conversion to a prodrug is plausible when the physicochemical properties of the parent drug and prodrug are optimal for the target site. It should be kept in mind, however, that when the lipophilicity of a drug is increased, it will improve passive transport of the drug nonspecifically to all tissues.

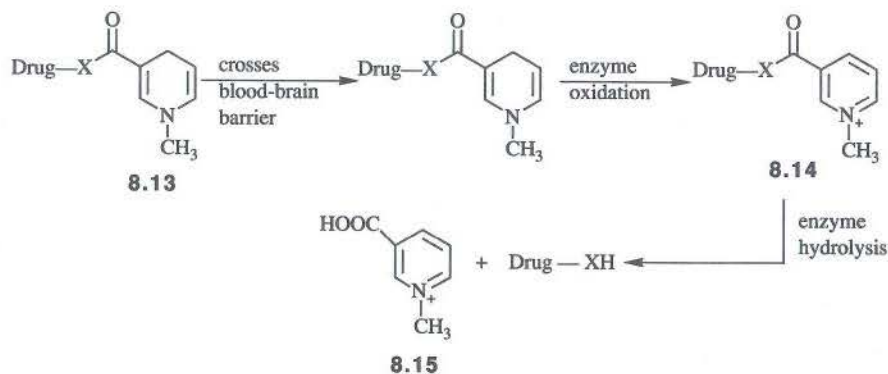
Oxyphenisatin (**8.12**, R = H) is a bowel sterilant that is active only when administered rectally. However, when the hydroxyl groups are acetylated (**8.12**, R = Ac), the prodrug can be administered orally, and it is hydrolyzed at the site of action in the intestines to oxyphenisatin.

One important membrane that often is targeted for drug delivery is the blood-brain barrier, a unique lipidlike protective barrier that prevents hydrophilic compounds from entering the brain unless they are actively transported.²¹ The blood-brain barrier also contains active enzyme systems to

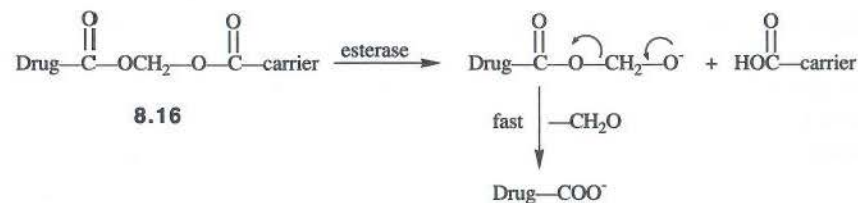


protect the central nervous system even further. Consequently, molecular size and lipophilicity are often necessary, not sufficient, criteria for gaining entry into the brain.²² Also, once the drug has entered the brain, it must be modified so that it does not escape.

Bodor and co-workers have devised a reversible redox drug delivery system for getting drugs into the central nervous system and then, once in, preventing their efflux.^{22,23} The approach is based on the attachment of a hydrophilic drug to a lipophilic carrier (a dihydropyridine, **8.13**) thereby making the bipartite prodrug overall lipophilic (Scheme 8.4). Once inside the brain, the lipophilic carrier is converted enzymatically to a highly hydrophilic species (**8.14**), which is then enzymatically hydrolyzed back to the drug and *N*-methylnicotinic acid (**8.15**) which is eliminated from the brain. The XH group on the drug is an amino, hydroxyl, or carboxyl group. When it is a carboxylic acid, the linkage is an acyloxymethyl ester (**8.16**), which decomposes by the reaction shown in Scheme 8.5. The oxidation of the dihydropyridine (**8.13**) to the pyridinium ion (**8.14**) (half-life generally 20–50 min) prevents the drug from escaping out of the brain because it becomes charged. This drives the equilibrium of the lipophilic precursor (**8.13**) throughout all of the tissues of the body to favor the brain. Any oxidation occurring outside of the brain produces a hydrophilic species that can be rapidly eliminated from the body (see Chapter 7). The released oxidized carrier (**8.15**) is relatively non-



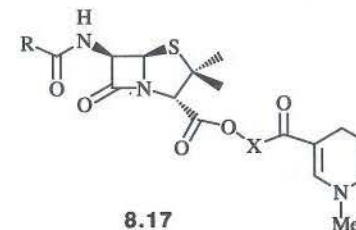
Scheme 8.4. Redox drug delivery system.



Scheme 8.5. Hydrolysis of acyloxymethyl esters.

toxic and easily eliminated from the brain. Although this is a carrier-linked prodrug, it requires enzymatic oxidation to target the drug to the brain. The oxidation reaction is a bioprecursor reaction (see Section II,B,2,c).

An example of this approach is the brain delivery of β -lactam antibiotics for the possible treatment of bacterial meningitis. The difficulty in purging the central nervous system of infections arises from the fact that the cerebrospinal fluid contains less than 0.1% of the number of immunocompetent leukocytes found in the blood and almost no immunoglobulins; consequently, antibody generation to these foreign organisms is not significant. Since the β -lactam antibiotics are hydrophilic, they enter the brain very slowly, but they are actively transported back into the blood. Therefore, they are not as effective in the treatment of brain infections as elsewhere. Bodor and co-workers²⁴ prepared a variety of penicillin prodrugs attached to the dihydropyridine carrier through various linkers (**8.17**) and showed that β -lactam antibiotics could be delivered in high concentrations into the brain.

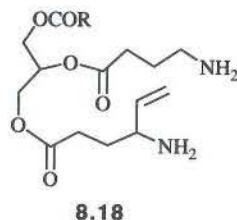


As was discussed in Section V,C,3,a of Chapter 5, increasing the brain concentration of the inhibitory neurotransmitter β -aminobutyric acid (GABA) results in anticonvulsant activity. However, GABA is too polar to cross the blood-brain barrier, so it is not an effective anticonvulsant drug. In order to increase the lipophilicity of GABA, a series of γ -aminobutyric acid and γ -aminobutyric Schiff bases were synthesized.¹¹ Progabide (**8.3**) emerged as an effective lipophilic analog of GABA that crosses the blood-brain barrier, releases GABA inside the brain, and shows anticonvulsant activity.²⁵

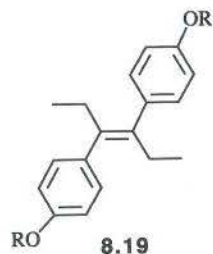
Another related approach for anticonvulsant drug design was the synthesis of a glyceryl lipid (**8.18**, R = linolenoyl) containing one GABA molecule and one vigabatrin molecule, a mechanism-based inactivator of GABA amino-

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transferase and anticonvulsant drug (see Section V,C,3,a of Chapter 5).²⁶ This compound inactivates GABA aminotransferase *in vitro* only if brain esterases are added to cleave the vigabatrin from the glyceryl lipid. It also is 300 times more potent than vigabatrin, *in vivo*, presumably because of its increased ability to enter the brain.

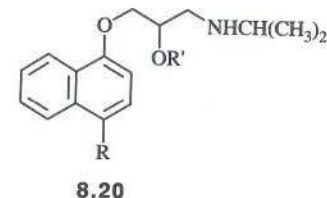


In the above examples, the lipophilicity of the drugs was increased so that they could diffuse through various membranes. Another approach for site-specific drug delivery is to design a prodrug that requires activation by an enzyme found predominantly at the desired site of action. For example, tumor cells contain a higher concentration of phosphatases and amidase than do normal cells. Consequently, a prodrug of a cytotoxic agent could be directed to tumor cells if either of these enzymes were important to the prodrug activation process. Diethylstilbestrol diphosphate (8.19, R = PO₃²⁻) was designed for site-specific delivery of diethylstilbestrol (8.19, R = H) to prostatic carcinoma tissue.^{2,27} In general, though, this tumor-selective approach has not been very successful because the appropriate prodrugs are too polar to reach the enzyme site, the relative enzymatic selectivity is insufficient, and the tumor cell perfusion rate is too poor.

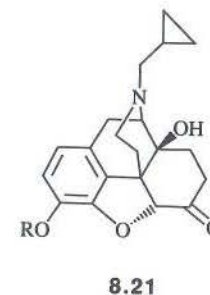


d. Prodrugs for Stability. Some prodrugs protect the drug from the first-pass effect (see Section I of Chapter 7). Propranolol (8.20, R = R' = H) is a widely used antihypertensive drug, but because of first-pass elimination an oral dose has a much lower bioavailability than does an intravenous injection. The major metabolites (see Chapter 7) are propranolol *O*-glucuronide (8.20, R = H, OR' = glucuronide), *p*-hydroxypropranolol (8.20, R = OH, R' = H), and its *O*-glucuronide (8.20, R = OH, OR' = glucuronide). The hemisuccinate ester of propranolol (8.20, R = H, R' = COCH₂CH₂COOH)

was prepared to block glucuronide formation; following oral administration of propranolol hemisuccinate, the plasma levels of propranolol were 8 times greater than when propranolol was used.²⁸



Naltrexone (8.21, R = H), used in the treatment of opioid addiction, is nonaddicting and is well absorbed from the gastrointestinal tract. However, it undergoes extensive first-pass metabolism when given orally. Ester prodrugs, namely, the anthranilate (8.21, R = CO-*o*-NO₂Ph) and the acetylsalicylate (8.21, R = CO-*o*-AcOPh), enhanced the bioavailability 45- and 28-fold, respectively, relative to 8.21 (R = H).²⁹

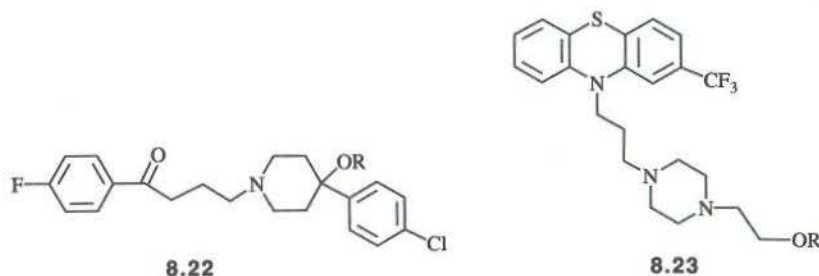


e. Prodrugs for Slow and Prolonged Release. The utility of slow and prolonged release of drugs is severalfold. (1) It reduces the number and frequency of doses required. (2) It eliminates nighttime administration of drugs. (3) Because the drug is taken less frequently, slow, prolonged release minimizes patient noncompliance. (4) When a fast released drug is taken, there is a rapid surge of the drug throughout the body. As metabolism of the drug proceeds, the concentration of the drug diminishes. A slow release drug would eliminate the peaks and valleys of fast released drugs which are a strain on cells. (5) Because a constant lower concentration of the drug is being released, it reduces the possibility of toxic levels of drugs. (6) It reduces gastrointestinal side effects. A common strategy in the design of slow release prodrugs is to make a long chain aliphatic ester because these esters hydrolyze slowly.

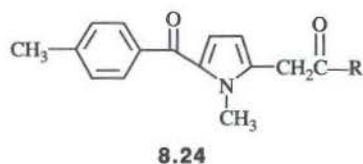
Prolonged release drugs are quite important in the treatment of psychoses because these patients require medication for extended periods of time and often show high patient noncompliance rates. Haloperidol (8.22, R = H) is a potent, orally active central nervous system depressant, sedative, and tran-

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quilizer. However, peak plasma levels are observed between 2 and 6 hr after administration. Haloperidol decanoate [8.22, R = CO(CH₂)₈CH₃], however, is injected intramuscularly as a solution in sesame oil and its antipsychotic activity lasts for about 1 month.³⁰ The antipsychotic fluphenazine (8.23, R = H) also has a short duration of activity (6–8 hr). Fluphenazine enanthate [8.23, R = CO(CH₂)₅CH₃] and fluphenazine decanoate [8.23, R = CO(CH₂)₈CH₃], however, have durations of activity of about a month.³¹



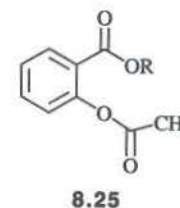
Conversion of the nonsteroidal anti-inflammatory (antiarthritis) drug tolmetin sodium (8.24, R = O⁻ Na⁺) to the corresponding glycine conjugate (8.24, R = NHCH₂COOH) increases the potency and extends the peak concentration of tolmetin from 1 to about 9 hrs because of the slow hydrolysis of the prodrug amide linkage.³²



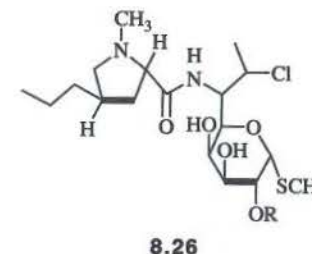
f. Prodrugs to Minimize Toxicity. The prodrugs that were designed for improved absorption (Section II,A,2,b), for site specificity (Section II,A,2,c), for stability (Section II,A,2,d), and for slow release (Section II,A,2,e) also lowered the toxicity of the drug. For example, epinephrine (8.11, R = H) (see Section II,A,2,b), used in the treatment of glaucoma, has a number of ocular and systemic side effects associated with its use. The prodrug dipivaloyl epinephrine (8.11, R = Me₃CCO), has been shown to be more potent than epinephrine in dogs and rabbits and nearly as effective in humans²⁰ with a significantly improved toxicological profile compared with epinephrine.

Another example of the utility of the prodrug approach to lower the toxicity of a drug can be found in the design of aspirin (8.25, R = H) analogs.³³ Side effects associated with the use of aspirin are gastric irritation and bleeding. The gastric irritation and ulcerogenicity associated with aspirin use may result from an accumulation of the acid in the gastric mucosal cells. Esterification of

aspirin (8.25, R = alkyl) and other nonsteroidal anti-inflammatory agents greatly suppresses gastric ulcerogenic activity. However, esterification also renders the acetyl ester of aspirin extremely susceptible to enzymatic hydrolysis (the *t*_{1/2} for deacetylation of aspirin in human plasma is about 2 hrs, but that for deacetylation of aspirin esters is 1–3 min). Esters of certain N,N-disubstituted 2-hydroxyacetamides (8.25, R = CH₂CONR₁R₂) were found to be chemically highly stable but were hydrolyzed very rapidly by pseudocholinesterase (cholinesterase) in plasma³³; therefore, they are well suited as aspirin prodrugs to lower the gastric irritation effects of aspirin.

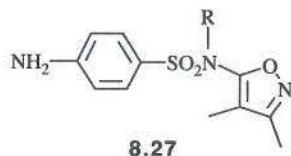


g. Prodrugs to Encourage Patient Acceptance. A fundamental tenet in medicine is that in order for a drug to be effective, the patient has to take it. Painful injections and unpleasant taste or odor are the most common reasons for the lack of patient acceptance of a drug. An excellent example of how a prodrug can increase the potential for patient acceptance is related to the antibacterial drug clindamycin (8.26, R = H). Whereas clindamycin causes pain on injection, the prodrug clindamycin phosphate (8.26, R = PO₃H₂) is well tolerated; hydrolysis of the prodrug *in vivo* occurs with a *t*_{1/2} of approximately 10 min.³⁴ Also, clindamycin has a bitter taste, so it is not well accepted by children who do not take pills. However, it was found that by increasing the chain length of 2-acyl esters of clindamycin the taste improved from bitter (acetate ester) to no bitter taste (palmitate ester).³⁵ Of course, when dealing with young children, it is not sufficient for a drug to be just tasteless; consequently, clindamycin palmitate [8.26, R = CO(CH₂)₁₄CH₃] is sold for pediatric use in a cherry-flavored syrup. Bitter taste results from a compound dissolving in the saliva and interacting with a bitter taste receptor in the mouth. Esterification with long-chain fatty acids makes the drug less water soluble



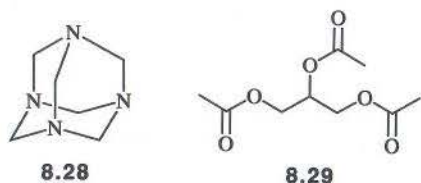
and unable to dissolve in the saliva. It also may alter the interaction of the compound with the taste receptor.

The antibacterial sulfa drug sulfisoxazole (**8.27**, R = H) also is bitter tasting, but sulfisoxazole acetyl (**8.27**, R = COCH₃) is tasteless. For pediatric use this drug is combined with the tasteless prodrug form of erythromycin, namely, erythromycin ethylsuccinate, in a strawberry-banana-flavored suspension (my 6-year-old loves it).



h. Prodrugs to Eliminate Formulation Problems. Formaldehyde (CH₂O) is a flammable, colorless gas with a pungent odor that is used as a disinfectant. Solutions of high concentrations of formaldehyde are toxic. Consequently, it cannot be used directly in medicine. However, the reaction of formaldehyde with ammonia produces a stable adamantane-like solid compound, methenamine (**8.28**). In media of acidic pH, methenamine hydrolyzes to formaldehyde and ammonium ions. Since the pH of urine in the bladder can be made acidic, methenamine is used as a urinary tract antiseptic.³⁶ To prevent hydrolysis of this prodrug in the acidic environment of the stomach, the tablets are enteric coated.

The topical fungistatic prodrug triacetin (**8.29**) owes its activity to acetic acid, the product of skin esterase hydrolysis of triacetin.



3. Macromolecular Drug Carrier Systems

a. General Strategy. Although the prodrug approach has been very fruitful in general, there are three areas that need improvement: site specificity, protection of the drug from biodegradation, and minimization of side effects. Another carrier-linked bipartate prodrug approach that has been utilized to address these shortcomings is *macromolecular drug delivery*. This is a drug carrier system in which the drug is covalently attached to a macromolecule, such as a synthetic polymer, a glycoprotein, a lipoprotein, a lectin, a hor-

mone, albumin, a liposome, DNA, dextran, an antibody, or a cell. Because the absorption and distribution of the drug depend on the physicochemical properties of the macromolecular carrier, not the drug, these parameters can be altered by manipulation of the properties of the carrier. This approach has the potential advantage of targeting drugs for a specific site and improving the therapeutic index by minimizing interactions with nontarget tissues (i.e., lowering the toxicity) as well as reducing premature drug metabolism and excretion. However, it has the disadvantages that the macromolecules may not be well absorbed after oral administration, requiring alternative means of administration, and may be immunogenic. Although polymer conjugates generally cannot pass through membranes, they can gain access to the interior of a cell by *pinocytosis*, the process by which the cell membrane invaginates the particle and then pinches itself off to form an intracellular vesicle which moves into the cell and eventually fuses with lysosomes. Because the breakdown of proteins and other macromolecules is believed to occur in the lysosomes,³⁷ and because this breakdown then liberates the drug, the design of a macromolecular drug carrier system should be a fruitful approach to deliver the drug inside a cell.

An ideal drug carrier (macromolecular or otherwise) must (1) protect the drug until it is at the site of action, (2) localize the drug at the site of action, (3) allow for release of the drug chemically or enzymatically, (4) minimize host toxicity, (5) be biodegradable, biochemically inert, and nonimmunogenic, (6) be easily prepared inexpensively, and (7) be chemically and biochemically stable in its dosage form. Some of the macromolecular drug carrier systems exert their effects while the drug is still attached to the carrier, but these are not prodrugs. Several examples of macromolecular drug carrier systems follow.

b. Synthetic Polymers. Aspirin linked to poly(vinyl alcohol) (**8.30**) was shown to have the same potency as aspirin but was less toxic. Another anti-inflammatory agent, ibuprofen (the carboxylic acid of **8.31**) was attached as a poly(oxyethylene) diester (**8.31**).³⁸ This macromolecular carrier system resulted in a sustained release of ibuprofen, giving prolonged anti-inflammatory activity and a higher plasma half-life relative to the free drug.

