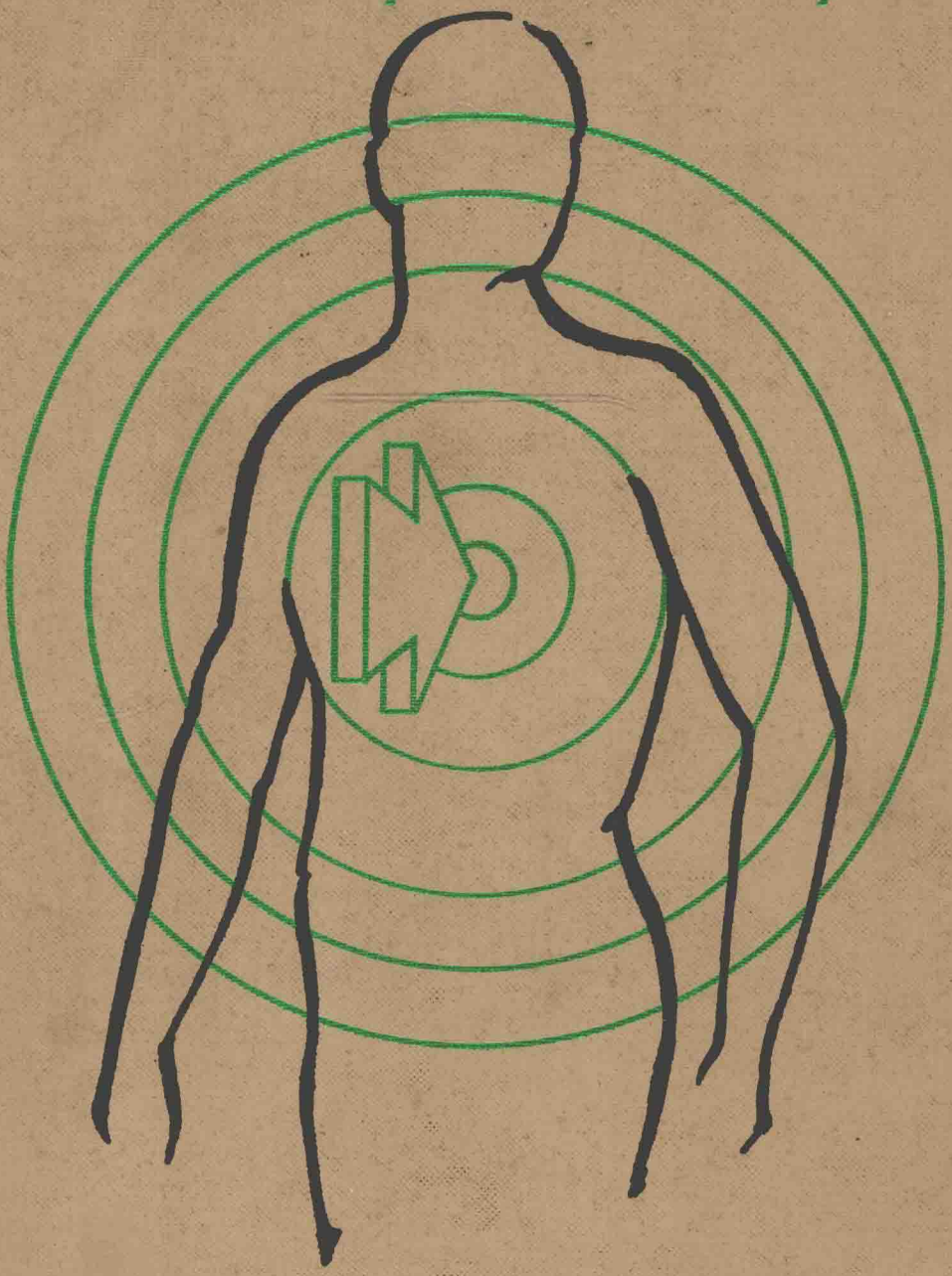
DRUGS

how they act and why



Alex Gringauz

DRUGS

how they act and why

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DRUGS
how they act and why

To my sons,

MARSHALL, DANIEL, and STEVEN,

that they may live in a healthier world

PREFACE

This book began as a course that I developed several years ago for pharmacists who had left formal academic training before many of the drugs now commonly employed by physicians were known and for that matter before the mechanisms by which most medicinal agents exert their action were recognized or understood.

The idea subsequently developed that a book designed for that course, with proper modification and expansion, would be of value not only to pharmacists but also to physicians, dentists, nurses, and others who deal with or are interested in drugs. The purpose of this volume is to update and increase the reader's fundamental knowledge of how drugs exert their biological effects and ultimate clinical results. Thus biologists and chemists or advanced students in these areas, although not directly involved with therapeutic agents, may also find this book interesting and useful.

Certain assumptions about the reader have been made. It is expected that the reader has a minimal background in organic chemistry and biochemistry. Even so, pertinent aspects of the latter will be reviewed in the first chapter. It is assumed that the reader is at least superficially familiar with the names and basic actions of the most commonly used drugs, for example, that a penicillin is used to treat susceptible infections, that morphine is an analgetic, and that aspirin lowers fever.

After an introduction of the fundamentals of biochemistry, this book discusses certain general characteristics of drug action mechanisms, as well as the chemical and physical factors affecting them. Most of the remainder of the book covers major drug groups primarily from a mechanistic standpoint with clinical pharmacology added where needed to round out the picture. Thus sulfonamides, anticancer drugs, antibiotics, and autonomic drugs are viewed from a biochemical-pharmacological standpoint, as are analgetics and psychopharmacological agents. The last category of drugs covered is a disparate group related only in their utility in the treatment of the various aspects of cardiovascular disease. The last chapter delves into the area of drug interactions, which is both old and new, and explains them on the basis of mechanisms discussed throughout the book. Two appendices give a brief overview of drug metabolism and the effects of drugs on clinical laboratory test results. Both contain tables of examples to illustrate the discussions.

It is hoped that readers will gain or improve upon their understanding of fundamental drug activity and have their intellectual appetite sufficiently whetted to pursue some of the areas presented in greater depth. Toward this end, a suggested reading list will be found in the back of the book to accommodate the motivational momentum for continued study.

Not all categories of drugs are covered since this effort is not meant to be encyclopedic. It is not even claimed that all important drug groups will be discussed. The selection of topics has of necessity been somewhat arbitrary. Thus oral antidiabetics, local anesthetics, most steroids, and general anesthetics, although obviously of great therapeutic significance, will not be dealt with directly. In several chapters tables of drugs and drug products will appear. These are representative of important, widely used, or recently introduced agents but are not intended to be all inclusive.

It is hoped that this book will provide a dual service as a textbook in chemically and pharmacologically oriented courses on drugs and as a personal library acquisition for those no longer in formal academic pursuit but interested in or working with drugs.

Alex Gringauz

CONTENTS

CHAPTER 1

BIOCHEMISTRY

Biochemistry is in some ways the most important area of scientific endeavor. Studies in this field are beginning to give us an insight into life processes at the cellular and molecular level. Biochemistry probably should not be considered a distinct scientific discipline but rather an integrated, interdisciplinary area with its foundations originating in organic chemistry, physical chemistry, and biology and with its tools of investigation coming from physics (ultracentrifuge, chromatograph) and electronics (spectrophotometer, electron microscope).

Any rational understanding of drug activity and any successful design and development of new and better medicinal agents are completely dependent on biochemistry and the extension of biochemical horizons. Disease processes—whether infectious (bacterial, viral) or physiological (mental illness, diabetes)—are biochemical in nature.

Biochemistry deals with chemical processes that occur in living matter ranging from viruses and bacteria to plants and animals. Living matter consists of lifeless molecules, as do inanimate things. The most conspicuous difference, though, is that in the living organism the lifeless molecules are arranged in highly organized and complicated systems that possess intricate structures consisting of a great number of complex molecules. Most of these biomolecules are organic compounds in which carbon is found in a relatively reduced form.

To get some idea of the complexity of life, consider that one of the smallest bacteria, *Escherichia coli,* is estimated to contain 5,000 different organic compounds of which 3,000 are believed to be different proteins and about 1,000 are different nucleic acids. In considering the human organism we are probably dealing with several million different kinds of proteins.

Before we become totally discouraged, however, it should be pointed out that this vast variety of compounds can be simplified when certain facts are considered. We know that the extremely large biomolecules called biopolymers consist of a large number of relatively simple, small molecules that might be considered building blocks. For example, proteins with molecular weights of several hundred thousand consist of chains of up to several hundred amino acids, which are small molecules with precisely known structures. All investigated proteins have been found to contain only 20 different amino acids. Their sequential arrangement varies from one protein to another much as the letters

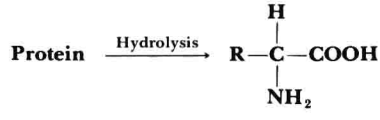
of an alphabet make possible the large number of words (and sentences) in a language simply by changing the order in which they are grouped.

REVIEW OF FUNDAMENTALS

Amino acids and proteins

Before studying biopolymers and their functions, it is important to review some of the chemistry of the simpler building blocks from which biopolymers are subsequently synthesized. As previously discussed, all proteins are "built" from a small group of amino acids, which can be considered the monomer units of proteins. (Later the monomers of other classes of biopolymers will be considered.)

When a simple protein is hydrolyzed (by acid, base, or enzymes) the products obtained are α-amino acids, a group of carboxylic acids having the common feature of an amino group ($-NH_2$) on the α-carbon atom.

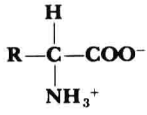


(1-1)

α-Amino acids

The naturally occurring amino acids found in all proteins except glycine occur in an optically active form; that is, when a solution of the substance is placed in the path of plane-polarized light in a polarimeter, the optically active substance will rotate that plane. This rotation occurs because the α-carbon is asymmetrical*; that is, it is bonded to four different groups: the carboxyl group (COOH), the α-amino group (α-NH_2), the H atom, and the R group, which is different for each amino acid. The configuration is designated L, meaning that the orientation of the $-NH_2$ group in space is, from a specific vantage point, to the left. The D configuration, which represents the orientation of the amino group to the right, does not occur in proteins.† The proteins in our bodies consist only of L-amino acids. Thus, if we were fed D-amino acids, they would not be useful to us as a source of nutrition.‡ The structures of the L-amino acids are presented in Table 1-1.

Certain physical properties of amino acids, such as high melting point and low solubility in nonaqueous solvents, suggest that their structure is most likely an inner salt—or *zwitterion*—rather than the uncharged formula often used to represent them.

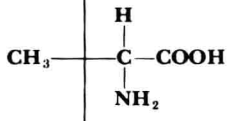
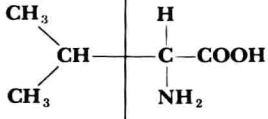
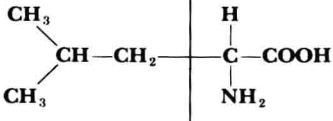
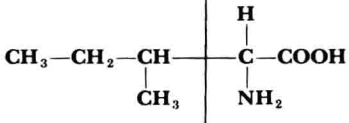
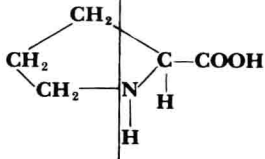
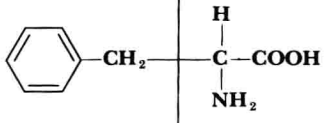
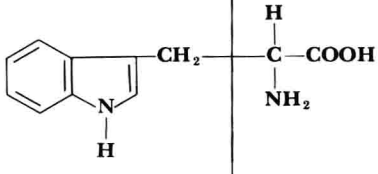
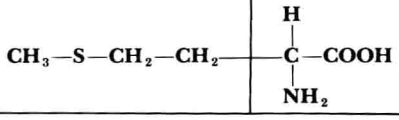


Zwitterion structure

Thus, when an acid is added to a solution of an amino acid, protons (hydrogen

*It would be more correct to say that the α-carbon generates a center of asymmetry.
†D-Amino acids are found in nature in bacterial cell walls and several antibiotics.
‡There are several enzymes in bacteria that can interconvert D- and L-amino acids.

Table 1-1. L-Amino acids—the building blocks of proteins

	R group	Name	Symbol
	Nonpolar R groups, aliphatic or aromatic		
1		Alanine	Ala
2		Valine	Val
3		Leucine	Leu
4		Isoleucine	Ile
5		Proline	Pro
6		Phenylalanine	Phe
7		Tryptophan	Trp
8		Methionine	Met

Continued.

Table 1-1. L-Amino acids—the building blocks of proteins—cont'd

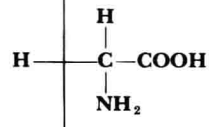
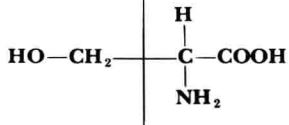
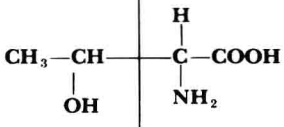
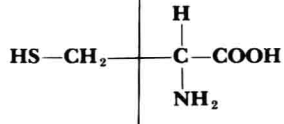
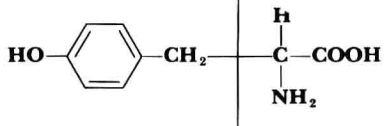
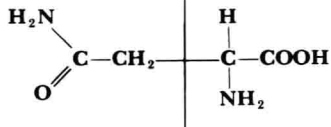
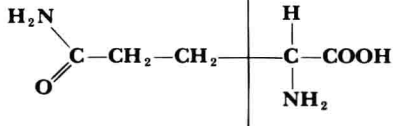
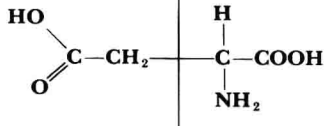
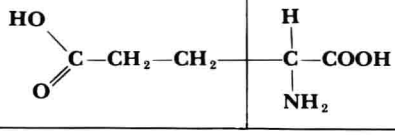
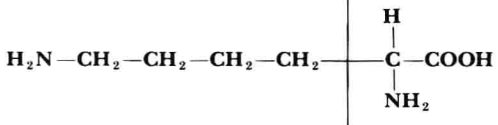
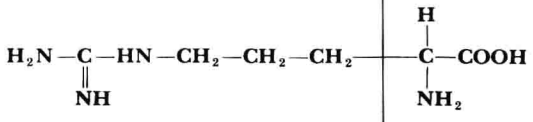
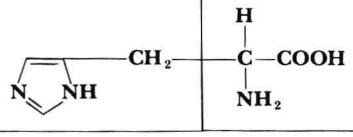
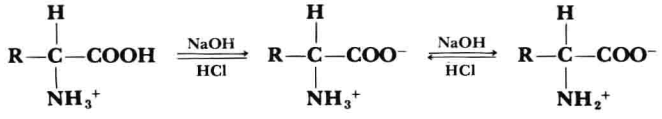
	R group	Name	Symbol
	Polar but uncharged R groups		
9		Glycine	Gly
10		Serine	Ser
11		Threonine	Thr
12		Cysteine	Cys
13		Tyrosine	Tyr
14		Asparagine	Asn
15		Glutamine	Gln
	Acidic R groups		
16		Aspartic acid	Asp
17		Glutamic acid	Glu

Table 1-1. L-Amino acids—the building blocks of proteins—cont'd

	R group	Name	Symbol
Basic R groups			
18		Lysine	Lys
19		Arginine	Arg
20		Histidine	His

ions) are added to the carboxylate anion, COO^-. Addition of base removes a proton from the amino group.



(1-2)

I I II III

In an acid solution form I is the dominant form and the amino acid is positively charged. When placed in an electrical field* it will migrate towards the cathode, the negative pole. The rate of such a migration will depend on the magnitude of the charge.† In an alkaline solution the carboxyl groups will carry a negative charge as in form III so that migration will occur towards the anode, the positive pole. A net charge of zero as in form II indicates that the amino acid has a zwitterion structure and no migration occurs. The pH at which the zwitterion occurs is the *isoelectric point,* which is different for each amino acid.

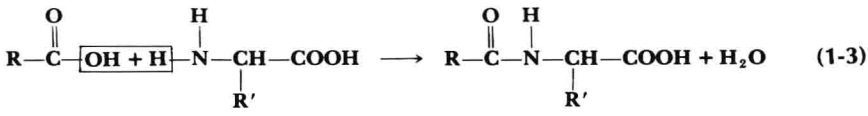
One of the important characteristics of amino acids is their ability to join together via an amide linkage,‡ which forms by the action of the amino group of one amino acid upon the carboxyl group of a second amino acid. In the process§ a molecule of water is eliminated. The product formed is called a

*As is done, for example, in order to separate the various amino acids after the hydrolysis of a protein.

†Lysine will carry a double positive charge, therefore moving faster in an electrical field than alanine.

‡Such an amide coupling in biochemistry is called a *peptide bond* and will be referred to as such hereafter.

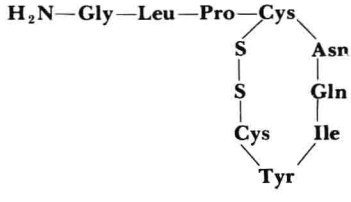
§In the laboratory such a synthesis cannot be accomplished in this simple manner; it involves a somewhat more complicated procedure to prevent by-products.



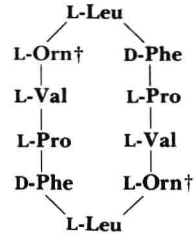
(1-3)

dipeptide. A third amino acid can be linked to the dipeptide through its amino or carboxyl group to form a tripeptide. Chains containing a large number of amino acids linked by peptide bonds are referred to as *polypeptides.* When the molecular weight of such a polypeptide reaches several thousand, the polypeptide is known as a protein.*

The amino acid sequence, as well as other structural features, of several biologically active polypeptides is completely known. These may be important hormones or antibiotics. Examples of these are shown.



Oxytocin



Gramicidin S

Oxytocin is a hormone that is isolated from the posterior lobe of the pituitary gland and is used in obstetrics to induce labor. Gramicidin S is an antibiotic. Note that the phenylalanine is in D configuration not found in a true protein.

Proteins have various functions. They function as structural support as in cartilage and muscle and are involved in such biochemical reactions as the carrying of oxygen (hemoglobin) and the metabolism of glucose (insulin). However, the most important, widely distributed function of proteins is the catalysis of almost all biochemically important reactions. Proteins able to act as biocatalysts are the enzymes, which will be discussed later in this chapter.

The actual sequence of amino acids occurring in a protein chain is referred to as the *primary structure.* The actual three-dimensional appearance of the biomolecule is dictated by the primary structure and by the nature of the R groups of the various amino acid residues and their relative positions in the chain. For example, the first eight amino acids given in Table 1-1 have nonpolar aliphatic or aromatic side chains, which are essentially hydrophobic (*hydro,* water; *phobic,* hating) and therefore repelled by the aqueous environment. Thus when a large protein molecule folds into its characteristic shape (that is, tertiary structure) these R groups will tend to be next to each other and away from polar groups and the aqueous exterior. Such coordination between nonpolar groups of amino acid residues in a polypeptide chain is referred to as *hydrophobic interaction.*

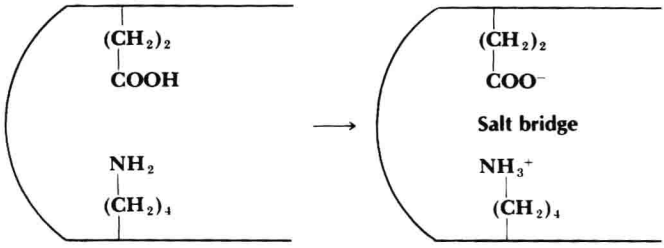
---

*Strictly speaking the designation "protein" would apply only if all the amino acids were of the L configuration.

†Ornithine is an amino acid derived from arginine.

Amino acids with polar but uncharged side groups such as phenolic or alcoholic hydroxyl groups (Table 1-1) confer *hydrophilic* (water-loving) properties to the molecule or to the immediate neighborhood of the protein chain of which it is part. These groups have the ability to *hydrogen bond** to water *or* other polar groups elsewhere in the chain, thus also contributing to the ultimate three-dimensional structure of the biopolymer.

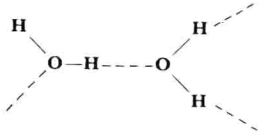
Table 1-1 also lists amino acids with side chains that are acidic and basic. These amino acids are invariably charged entities in the biological pH and therefore capable of interacting as only ionic species in a water environment could, that is, by forming ionic bonds or salt bridges.



It is apparent that a glutamic acid and lysine residue spaced appropriately in a protein chain will interact ionically to help stabilize coiling in a strand. We can now begin to visualize how such factors as amino acid sequence (that is, primary structure), hydrogen bonding, ionic bonding, and hydrophobic interactions contribute to the so-called *secondary structure* of proteins.

Only one, but very significant secondary structural feature will be discussed, namely the spiral coiling, or *α-helix,* found in many proteins with nonstructural functions. The α-helix is believed to be caused by the hydrogen bonding between the carbonyl oxygen of one peptide bond and a hydrogen atom of another peptide bond at the appropriate distance "down" the chain.

*Hydrogen bonding is a relatively weak inter- or intramolecular force occurring between H atoms and electronegative elements such as oxygen, nitrogen, sulfur, and the halogens, especially fluorine and chlorine. In water, for example, the hydrogen bond acting as a type of bridge extends from a hydrogen in one molecule to the oxygen of a different molecule.



The strength of such an interaction is only about 3 to 5 kcal/mole. (A covalent bond is about 90 to 100 kcal/mole.) However, in contributing to the overall stability and structure of molecules, especially organic compounds, the hydrogen bond is, of course, the weakest link in the chain and therefore the most important.