MEDICINAL CHEMISTRY

CAMPAIGNE
HARTUNG
Editors

Volume VI

Medicinal Chemistry

VOLUME VI

A SERIES OF REVIEWS PREPARED
UNDER THE AUSPICES OF THE
DIVISION OF MEDICINAL CHEMISTRY
OF THE AMERICAN CHEMICAL SOCIETY

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WALTER HENRY HARTUNG

1895–1961

In Memoriam

Walter Henry Hartung was born in Welcome, Minnesota, on January 4, 1895. He died unexpectedly at the age of sixty-six on September 29, 1961, and was buried in Welcome. Between these events is a period, all too brief for his devoted family and his many associates, during which he established a record of a full life ideally balanced by the many things he set himself to do and the many other things he refused to leave undone.

His formal education first at the University of Minnesota (B.A., 1918) and subsequently at the University of Wisconsin (Ph.D., organic chemistry, 1926) was interrupted by a tour of duty in France as a member of the United States Marine Corps during World War I. His professional career began in 1926 when he joined the staff of Sharp and Dohme as a research chemist. He served as a visiting lecturer at Temple University during his industrial employment in keeping with his desire, frequently expressed, to have a professional progeny. After ten fruitful years of industrial research, he undertook full-time academic employment in 1936 as Professor and Head of the Department of Pharmaceutical Chemistry at the School of Pharmacy, University of Maryland. He served in the same capacity during the years 1948 to 1956 at the School of Pharmacy, University of North Carolina; and from 1956 until his death at the Medical College of Virginia. Walter Hartung's professional progeny, more than eighteen students who received the master's degree under his direction and forty-eight who received the doctor's degree, attest to the great productivity of their prolific and inspiring teacher.

Equally compelling evidence of Walter Hartung's productivity are his numerous patents and publications in the scientific literature, including the textbook, *The Chemistry of Organic Medicinal Products*, now in its fourth edition. This book was written originally in collaboration with Glenn L. Jenkins and later with Kenneth E. Hamlin, Jr., and John B. Data also. Herein are recorded his outstanding contributions in synthetic organic medicinal chemistry and his fundamental investigations of the correlations of molecular structures and biological activities. Although his interests encompassed the entire spectrum of organic medicinal agents, he is best known for his pioneer work on

sympathomimetic amines, tropine derivatives, amino acids and related compounds, peptides, and hydrogenation catalysis. In recognition of his work on amino alcohols and amino acids, he was awarded the Ebert Prize by the American Pharmaceutical Association.

Walter Hartung was keenly aware of the importance of professional and scientific societies, and he was active in those to which he belonged. He carefully instilled this interest in all who were privileged to be his students. He was a fellow of the American Institute of Chemists, the American Association for the Advancement of Science, and the New York Academy of Science. He was a past chairman of the Maryland Section of the American Chemical Society and the Division of Medicinal Chemistry. He was editor of Volume V of the "Medicinal Chemistry" series of the Division of Medicinal Chemistry, and he was working on manuscripts for the present volume at the time of his death. His other affiliations included the Franklin Institute, the American Pharmaceutical Association, Sigma Xi, Phi Lambda Upsilon, Alpha Chi Sigma, Phi Delta Chi, and Rho Chi.

The greater dimensions in breadth and depth that characterized Walter Hartung's teachings stemmed from his sincere sense of responsibility to society and to his country and, most of all, from his deep religious convictions. He once reminded a grateful student who was stressing the material aspects of various job opportunities, "You must remember that man does not live by bread alone." The vitality of this inspiring teacher, sustained not by bread alone, endures in his progeny and is his greatest legacy.

GEORGE P. HAGER

Minneapolis
May 24, 1962

Preface to the Series

Chemists and pharmacologists concerned with the synthesis and evaluation of new compounds have long realized the need for a publication that would provide comprehensive and systematic summaries of available data on the biological properties of substances already studied. The correlation of structure and activity in such summaries stimulates the visualization of new molecular structures and leads to the synthesis and testing of new compounds.

The Division of Medicinal Chemistry of the American Chemical Society, at its business meeting in Chicago on September 11, 1946, decided to initiate plans for a series of books that would present reviews in the field of medicinal chemistry. This project was to be under the general supervision of an editorial board chosen from the membership of the division and in harmony with the rules of the national society.

After plans for the new publication had matured so that a definite proposal could be made, including discussion with prospective publishers, the board of directors of the American Chemical Society was asked for permission to proceed with the publication under the specific auspices of the Division of Medicinal Chemistry and the general guidance of the committee on publications of the society. Approval was granted by the board on April 19, 1948. It is a pleasure to express our indebtedness to the directors of the society for this expression of confidence and to Mr. Alden H. Emery, Dr. W. A. Hamor, and Mr. Arthur B. Hanson of the American Chemical Society, who have been most cooperative in advice on matters of general policy and contractual arrangements.

A chief objective of MEDICINAL CHEMISTRY is to include in each chapter references to all the compounds that have been tested for a particular type of pharmacological activity. Where it is necessary to limit one chapter to a segment of the field because of lack of space, a division is made, based on a chemical classification. It is expected that the additional areas will be treated in later volumes. The compounds are presented mostly in tabular form according to chemical groups or series. Associated with this comprehensive survey of compounds are discussions of the relationships between chemical structure

and pharmacological action. Many references are given to groups of compounds, particularly in the patent literature, which have been claimed to have pharmacological activity even if data to sustain this statement have not been published. Each chapter also contains brief discussions of methods of synthesis and pharmacological test procedures which aid the reader in judging the status of work in a given area. It is not feasible, within the space limitations, to give a comprehensive treatment of organic or analytical chemistry problems or, on the other hand, of the detailed pharmacology of single compounds. The interests of the chemist and pharmacologist, who are searching for new and useful molecular structures, seem best served by concentration on the comparison of the "screening" results. These preliminary data are employed in making decisions as to what compounds receive intensive study.

Those concerned with this publication will be pleased to have suggestions with regard to improvements for future volumes and comments on subject matter suitable for review. Suggestions from the members of the Division of Medicinal Chemistry are particularly solicited because this is a publication of their division.

Contents

CHAPTER 1

NON-BARBITURATE HYPNOTICS

KEITH W. WHEELER
The Wm. S. Merrell Co., Division of Richardson-Merrell Inc., Cincinnati 15, Ohio

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SCOPE OF THIS REVIEW

An attempt has been made in this review to tabulate all compounds which have been prepared for study as hypnotics, tested as hypnotics, or

in which hypnotic activity was observed in the course of other studies, for the period 1907–1960. The barbituric acids and their close derivatives have been excluded, since they are the subject of Volume IV of this series of reviews.

The literature was searched by means of *Chemical Abstracts* for the years 1907 through 1960, the main terms searched being *anesthetics*, *hypnotics*, *narcotics*, *sedatives*, and *soporifics*. In addition, individual issues of some thirty or more of the journals most likely to contain the desired information were scanned as they appeared during 1959 and 1960, in order to make the coverage of the literature published through 1960 as complete as possible. No attempt was made to cover systematically the literature before 1907, although some earlier references are included.

When available, pharmacological data are reported for each compound, either as the presence or the absence of hypnotic activity. Compounds are included that are stated to have been prepared for testing as hypnotics, even though the results of such testing were not found. The patent literature is included, references being given to groups of compounds reported as having hypnotic activity, but without supporting data.

The definition of what is included as a "hypnotic" is discussed in the section on pharmacology, page 4.

Each compound is listed in one or more of the tables, which have been arranged into several large groups, based on a rather broad chemical classification. Each table contains compounds of closely related type, arranged systematically according to structure.

HISTORICAL DEVELOPMENT

The first use of sedatives and hypnotics is lost in antiquity, since the induction of sleep is often the end result, even if not the desired effect, of the use of alcoholic beverages or of opium.

The first rational use of drugs to depress the central nervous system to the point of producing sleep dates from around the middle of the 19th century. Inorganic bromides were first used by Laycock in 1853 in the treatment of epilepsy. Their later use as sedatives has been very largely supplanted by the use of less toxic agents. Liebrich first reported the hypnotic property of chloral hydrate in 1869, and it is still a widely used agent. Paraldehyde was introduced in 1882, but its unpleasant taste and the odor it imparts to the breath have prevented its wide use. Ethyl carbamate, or urethan, was first reported in 1885 to cause rapid and deep hypnosis in dogs. It is still sometimes used as an anesthetic for experimental animals but is not of value in man. Several other carbamate esters have since been introduced with modest success in the field of hypnotics.

The disulfones of ketone mercaptals, as represented by Sulfonal and Trional, were discovered in 1888 to have a strong hypnotic action. For a time, they were among the most widely used hypnotics. In 1903, diethylbarbituric acid or Veronal® was introduced, and it was the forerunner of the hundreds of related compounds reviewed in Volume IV of this series.

Although research on barbituric acids has dominated the field of hypnotics almost since their introduction, a number of other agents have been successfully marketed and a great deal of work on compounds of other types has been reported. Many acylated amides and ureides were introduced in the early years of the 20th century. Most of these are used only as sedatives, since they seldom are powerful enough to cause sleep at a safe dose. The first hydantoin, the 5-ethyl-5-phenyl analog, was introduced in 1916. The hydantoins have generally found their greatest utility as anticonvulsants.

During recent years much research has been reported on compounds derived from tetrahydropyridine-2,4-dione, piperidine-2,4-dione, and piperidine-2,6-dione. Products such as Noludar® and Doriden® have met with considerable success as hypnotics. Still other chemical classes, such as the acetylenic tertiary alcohols, have given such products as Dormison® and Placidyl®.

In spite of the great variety of chemical structures in which sedative and hypnotic properties have been found, the "ideal" hypnotic still eludes the medicinal chemist. It is hoped that the present review will provide a helpful background for future research which will be done in the field of hypnotic agents.

Numerous earlier reviews have covered various groups of hypnotic structures or time intervals. An excellent review of the field before 1923 is that of Volwiler.[690] Hypnotics based on urea have been reviewed,[600] as have the hydantoins, hydrouracils, and related heterocycles.[543] Other general reviews are those of Renner,[560] Green,[279] Rice,[561] and the Symposium held in 1954.[492]

CHEMISTRY

Because of the great variety of types of chemical structures that have been studied as hypnotics, even a brief résumé of the methods of synthesis of the various types of compounds seems impractical within the confines of this review.

Brief reviews of the synthesis of typical hypnotics of various types appear in the chapters on sedatives and hypnotics in the books by Burger, by Dyson and May, and by Jenkins and Hartung.[102] The reviews

mentioned in the preceding section contain summaries of typical reactions used to prepare hypnotics. The reader is directed to the original articles cited from chemical journals for details of the preparation of specific types of compounds.

PHARMACOLOGICAL SCREENING

Degrees of Central Nervous System Depression

Depression of the central nervous system occurs in a continuous spectrum ranging from very mild sedation or a calming effect through hypnosis, a condition approaching that of normal sleep, to deep surgical anesthesia. Since this is a continuous range, it is difficult to define exactly what is a "sedative," a "hypnotic," or an "anesthetic." Because different investigators have used various criteria for these or other related terms, what one investigator calls a "hypnotic" might be classed as a sedative or possibly as an anesthetic by another worker using other methods and definitions.

For this review, the most commonly used meaning of the term "hypnotic" has been used. That is, a hypnotic is a drug which causes loss of the righting reflex in experimental animals. The righting reflex is the tendency of an animal, when placed on its back, to right itself, and this reflex is abolished when the animal is under the influence of a hypnotic dose of a drug. With many drugs, a small dose will be merely sedative but a larger dose will be hypnotic or even anesthetic. As this is not always true, many sedatives will not cause sleep no matter how large a dose, short of a toxic amount, is given. In other cases, some powerful hypnotics have almost no sedative dose range.

The terms "soporific" and "somnifacient," often used in the earlier literature, are taken to be generally synonymous with "hypnotic." Some investigators have used such terms as hypnotic, sedative, narcotic, and anesthetic very loosely without adequate explanation of their criteria of drug end-point, so that it is often difficult to determine just what degree of CNS depression was actually observed.

The listing of a compound in this review as hypnotic or not is only indicative of the presence or absence of a certain degree of depressant activity. In assessing the potential value of a compound or a series of compounds, other factors such as the toxicity, the therapeutic ratio, or ratio of the effective dose to the toxic dose, the duration of action, and presence of side effects must be considered. Such a consideration is outside the scope of this review, and the reader is referred to the original articles for such information.

Methods of Testing for Hypnotic Activity

Hypnotic activity has most often been measured by determining the dose which causes loss of the righting reflex in white mice or in rats after intraperitoneal or oral administration of the compound. The smallest dose which causes the animal, when placed on its back, to lose the ability to right itself, is called the "minimum hypnotic dose" or MHD. That dose which causes loss of the righting reflex in 50% of a group of animals each receiving it is the "hypnotic dose 50" or HD_{50} and is the value used wherever possible in this review. Some investigators have used these terms interchangeably. The duration of the hypnosis and the "lethal dose 50" or LD_{50}, the dose killing 50% of the group of animals receiving it, are the other most important factors in determining whether a particular compound is of potential value or not. Many compounds show hypnotic effects only at or near the lethal dose and so are of no use in humans. The method of Litchfield and Wilcoxon[432] is widely used to determine the confidence limits of the HD_{50} and LD_{50} values.

Many other kinds of experimental animals—rabbits, guinea pigs, dogs, and occasionally cats—have been used, as well as other routes of administration—intravenous, subcutaneous, rectal, and occasionally intramuscular—for the detection of hypnotic action.

Birds, such as finches and pigeons, have also been used[191,335,629] for determining the hypnotic properties of drugs. Fish have been used by a number of investigators to determine hypnotic effects of glycidamides,[56] dioxolanes,[248] various glycols,[423,507,670,671] benzoxazolones,[424–426] and brominated esters.[552] The fish are put into very dilute solutions of the drugs in water, and the compound is said to be hypnotic if it causes the fish to become immobile. Some of these compounds were also tested on dogs, but sufficient data are not available to determine whether the same relative order of activity obtains in fish as in warm-blooded animals. Tadpoles,[171] eel larvae,[259] and Rotifera (*Brachionis calyciflorus*)[475] have been used, but it is doubtful if the results obtained with these organisms are a true indication of hypnotic action in higher animals.

Although the method based on the loss of righting reflex is widely used, it is not without certain deficiencies, and many investigators have tried to devise other, more sophisticated methods for determining the beginning or the end of narcosis, the depth of sleep, or the sedative component of compounds. Wenzel and Lal[702] have described a method in which a mouse is placed in a cell the dimensions of which are such that only a fully conscious animal can climb out. Stimuli are provided by intermittent blasts of air. This method is claimed to give an unmistakable end-point, smaller error, and to provide a more valid value for the drug-induced sleeping time than does the righting reflex method.

Other methods have involved suspending mice by their tails and measuring the decrease in wriggling done by the animals after administration of the drug;[677] or holding the animals supine and measuring the movement of each limb while a low-voltage shock is applied to the animal's back periodically.[218] The latter method is claimed to give a very accurate and consistent record of the onset, depth, and duration of hypnotic effects.

Generally the effects of sedatives and hypnotics are antagonized by stimulants or convulsants, and this fact is the basis for methods[146,616] of determining the relative potency of hypnotic agents by finding the dose of the compound which is just below that necessary to save the life of the animal given one minimum lethal dose of a convulsant such as strychnine.

Since in many cases the differences between sedative, hypnotic, and anesthetic action are largely a matter of degree, much work has been done on methods to distinguish drugs which have primarily one or the other of these actions. One method[656] reported to distinguish anesthetic action from hypnotic action is based on the observation that at least in some hypnotics there is a long-lasting decrease in both the rate and the volume of respiration, whereas in certain anesthetics there is a slight increase in both rate and volume of respiration. The types of drugs studied were so few that it is doubtful if valid generalizations can be drawn on the basis of this study alone.

While no attempt was made here to include methods dealing with sedative action only, three such methods might be mentioned to illustrate ways of detecting mild sedative action. Feurt and La Rocca[234] describe an activity cage for mice in which each movement of the animals actuates electrical contacts which trigger a counter. The combined count for a one-hour period, when compared to the count for a control group, measures sedative activity when no gross change in behavior is apparent. The same thing may be measured using photoelectrical cells whose light beams are broken by the animals in similar cages. Maffii[464] has described a method in which rats are induced into natural sleep by isolating them from outside environmental stimuli. The effect of drugs is then evaluated by noting the decrease in time necessary for the rats to go to sleep again after half-hourly awakening stimulation. Reinhard and Scudi[558] administer drugs orally or intraperitoneally to mice, then 30 minutes or more later give a subhypnotic dose of hexobarbital sodium. The dose of the drug necessary to induce the loss of the righting reflex in 50% of the animals is then determined. This method detects mild depressants and distinguishes from those which prolong a hypnotic dose of a barbiturate by interference with its metabolism.

This entire area of the experimental evaluation of sedative and hypnotic agents has recently been reviewed.[431]