

112–114°, ultraviolet maxima, 218 (4.11) and 303  $m\mu$  (4.25), infrared maximum ( $\text{CHCl}_3$ ) 1593  $\text{cm.}^{-1}$ . *Anal.* Found: C, 46.22; H, 6.03; N, 4.33; O, 5.13; I, 38.13.

An ether suspension of XI was treated with an excess of isobutylolithium and the resulting enol ether was hydrolyzed with hydrochloric acid to give an 8% yield<sup>7</sup> of the racemic ketone VII, m.p. 44–45°, picrate m.p. 161–162°, identical (infrared spectrum, t.l.c.) with the lyconotine degradation product.<sup>8</sup> Lithium aluminum hydride reduction of the synthetic ketone VII in

(7) Yields up to 35% were obtained in alkylations of XI with less bulky lithium compounds and Grignard reagents.

(8) No isomeric isobutyl ketone was found in the reaction mixture. Thus, both the alkylation and the enol ether hydrolysis are stereospecific.

ether gave a quantitative yield of the racemic alcohol VI, m.p. 134–135°, identical (infrared and n.m.r. spectra, t.l.c.) with the degradation product VI.

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## BOOK REVIEWS

**Medicinal Chemistry.** Volume VI. Edited by E. E. CAMPAIGNE, Professor of Chemistry, Indiana University, and W. H. HARTUNG, Professor of Pharmaceutical Chemistry, Medical College of Virginia. John Wiley and Sons, Inc., 605 Third Ave., New York 16, N. Y. 1963. x + 356 pp. 15.5 × 23.5 cm. Price, \$10.00.

The sixth volume of this serial publication contains three chapters: "Non-barbiturate Hypnotics" by Keith W. Wheeler, "Spinal Cord Depressant Drugs Derived from Polyhydroxy Alcohols" by Edward J. Pribyl, and "X-ray Contrast Media" by James O. Hoppe. It represents a continuing effort on the part of the Division of Medicinal Chemistry of the American Chemical Society to "provide comprehensive and systemic 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." This latest volume meets the objectives quoted from the preface to the series. The wisdom of the approach—the classic one of molecular modification—was amply demonstrated to lead to superior drugs during a 2-day symposium of the Division in New York last September. Nevertheless, one can not visualize how the approach will lead directly to truly novel chemical types of medicaments. For such creativity, the medicinal chemist must either continue to depend upon serendipity or look to a better understanding of biological phenomena upon which to build rationales.

The 245-page chapter by Wheeler represents a completion of the tabulation of hypnotics which began with the single chapter Volume IV on "Barbituric Acid Hypnotics" by Wilbur J. Doran. Dr. Wheeler has brought order out of confusion for the reader in regard to the difference between sedatives, hypnotics, and anesthetics. He has sensibly decided for the purposes of the review to treat all such substances as central nervous system depressants but to center attention for comparative purposes upon hypnotic activity. He defines a hypnotic as a drug which causes loss of the righting reflex in animals. A hypnotic dose has been reached when an animal placed on its back can no longer right itself.

Author Wheeler has done about all that could be expected of him in view of the aims of the series of volumes. His labors will save the interested investigator much time and effort. Many well-known hypnotics, such as chloral hydrate, ethchlorvynol, ethinamate, glutethimide, and paraldehyde are listed. Of course, tables of hundreds of unsuccessful candidates, some of which may not have been adequately evaluated, fill the main part of the chapter.

Buried in Tables 15 and 16 is the infamous thalidomide (Contergan). Chemically known as  $\alpha$ -(N-phthalimido)glutarimide, it should have been listed also in Table 2, "Other Clinically Tested Non-barbiturate Hypnotics." Thalidomide was synthesized in 1953 and introduced in Germany as a hypnotic in 1956. The author covers the literature through 1960. Although the unfortunate cases of phocomelia, or deformities of the limbs in infants, were not fully recognized as being associated with use of the drug by pregnant women until 1961, a strong case for addition

in proof of such important facts might have been made since the volume was only recently printed.

No drug may prove to have had so much influence upon the pharmaceutical industry as might be seen in future practices of the Federal Drug Administration, yet, ironically, thalidomide was never released for sale in this country. It is difficult to see how regulations short of stopping the flow of all new drugs could have prevented the thalidomide tragedy, since animal tests do not reveal its cruel side effects. Yet the drug dramatically rescued Kefauver legislation from the trash can and placed it into stringent new regulations which may cut the flow of new medicaments to a trickle. Thalidomide remains as an ideal hypnotic except for use in pregnant women. But it will not become available because of the obvious risk in keeping it in the medicine cabinet.

The 44-page chapter on spinal cord depressants by Pribyl covers polyhydroxy alcohols and derivatives based upon the prototype mephenesin. In contrast to curariform agents which relax skeletal musculature by acting peripherally, mephenesin-like compounds act by depression of the spinal cord. Such drugs have afforded the greatest relief of spastic conditions. The search continues for compounds that might show greater specificity or longer duration of effect. Most of the tabulated substances were evaluated pharmacologically by measurement of the degree of depression of the central nervous system. Thus, structure-activity correlations are discussed in terms of relative depressant or paralyzing effects. Obviously, complete estimate of the value of a compound can not rest upon that basis. Such factors as acute toxicity, side effects, absorption, and solubility play important roles in final judgments.

Meprobamate (2-methyl-2-propyl-1,3-propanediol dicarbamate, Miltown or Equanil) referred to popularly as the tired businessman's tranquilizer and relaxant, of course, falls within the scope of the chapter, even though it is not, as mephenesin, used therapeutically as a valuable substitute for curare for relaxation of musculature in surgical procedures.

The author has failed at times to adhere to the accepted practice of lower case for nonproprietary drug names and capitalization for trade or proprietary names. For example, Myanesin is incorrectly represented in lower case on p. 247, while Metrazol, a proprietary name, is inconsistently represented (pp. 249, 253, 256, and 258).

Unlike the authors of the first and third chapters who refer the reader to the literature for chemical preparative procedures, Dr. Pribyl thoughtfully outlines more than three pages of general methods of preparation. After all, the title of the volume does include the word chemistry.

Although the author has appropriately covered his topic in accord with the title of the chapter, the reader may regret the omission of remaining chemical types of centrally acting skeletal muscle relaxants, e.g., the benzoxazolinones represented by chlorzoxazone, especially since the group is a small one.

Sixty pages, with five references extending into the year 1961, cover the topic "X-ray Contrast Media," a rather specialized area of medicinal chemistry. While the usual objective of drug

design is pharmacodynamic or chemotherapeutic activity, the goal in searching for diagnostic radiopaques is biological inertness. Iodine is the radiopaque element of choice because it forms inexpensive, stable carbon compounds. Despite the large doses needed, several agents have been found to meet the requirements of low toxicity, high radiopacity, selective localization, and complete elimination.

The subject matter of the chapter illustrates the futility of establishing permanent generalizations based upon structure or solubility and utility. Barium sulfate because of water insolubility is well established as a contrast medium for gastrointestinal roentgenography, but water insolubility is not a requisite for gastrointestinal visualization since sodium diatrizoate, a water-soluble iodinated organic compound, has recently been recommended for that purpose. The same organic salt finds excellent utility in intravenous injection for cardiovascular angiography and excretion urography, but the free acid can not be used for injection.

Author Hoppe shows an inclination to discuss the same subject under more than one heading and to use the same heading more than once. Thus, the properties and uses of barium sulfate are mentioned on pp. 319 and 322, and Chemical and Biological Properties fall under General Properties as well as under Structure-Activity Relationships. But no harm results, for as Churchill has declared, one should make his point three times to be understood.

The reader will be disappointed if he expects Volume VI to contain scintillating discourses on up-to-the-minute topics. The chief value of the work lies in its timeless, encyclopedic quality. The future researcher or reader who wishes enlightenment on the three subjects will be saved countless hours by having the volume at hand. In addition to purely informational value, discussions of the authors might afford the reader concepts, approaches, and philosophies applicable to other areas.

The paper, printing, and binding of the well-known publisher meet the usual standard of excellence.

Volume VI of "Medicinal Chemistry" was appropriately dedicated to the memory of the late Walter H. Hartung, who edited Volume V and co-edited Volume VI. Medicinal chemistry, as a field and as a curriculum, owes much to Walter Hartung. He demanded that his graduate students become good chemists—especially competent in organic chemistry—and that they complete courses in basic medical science in order to become medicinal chemists. Indeed, the chief practitioners of medicinal chemistry today carry out organic chemical procedures in the light of biological and physical information. Nevertheless, Volume VI contains a minimum of chemical and maximum of pharmacological considerations. Such coverage becomes acceptable upon recollection that the curricula of most organic chemists now working in medicinal chemistry contained little or no biological science.

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**The Modern Structural Theory of Organic Chemistry.** By LLOYD N. FERGUSON, Chairman, Department of Chemistry, Howard University, Washington, D. C. Prentice-Hall, Inc., Englewood Cliffs, N. J. 1963. 600 pp. 16 × 24 cm. Price, \$13.00.

This book is capable of providing a senior or first year graduate student with an excellent qualitative introduction to that segment of physical organic chemistry having to do with structures of molecules in the normal state. Although some attention is devoted to the subject of reaction mechanisms, this area of study is not emphasized.

Most of the chapters in the book serve more as an introduction to a given subject than as a rigorous treatment of it. For example, the chapter on absorption spectra gives an interesting and lucid discussion of ultraviolet, visible, infrared, and nuclear magnetic resonance spectra, but the research worker who makes use of spectra in the elucidation of structures of molecules will have to study more advanced texts in order to make efficient use of his spectral data. However, this book represents a good starting point for such study, and the numerous references given therein will guide the reader to more rigorous treatments.

Certain topics are covered in greater depth in this book than in any other essentially qualitative text that the reviewer has read.

For example, the discussions of charge-transfer complexes and inclusion compounds are especially commendable.

There are five chapters in the book covering the broad topics of "Chemical Bonds," "Electronegativity and Electric Dipole Moments," "Intramolecular Forces," "Charge Distributions and Molecular Properties," and "Absorption Spectra." The references provided in each of these chapters are reasonably up-to-date and well selected. In fact, the majority of books and research articles cited were published in the period of 1950-1962.

The book is remarkably free of typographical errors, and the drawings, tables, and structural formulas are clear and visually appealing. The questions provided throughout the book are, for the most part, pertinent and thought-provoking. The student who makes a determined effort to answer these questions will certainly derive a more complete understanding of the contents of the book.

Throughout the book, much attention is given to the use of physical methods in the investigation of structure, conformational effects, kinetics, and equilibria. Such discussions should prove helpful to the reader when he faces similar problems in his own research efforts.

Inasmuch as most teachers of physical organic chemistry give preference to the subject of reaction mechanisms, it is unlikely that there will be numerous adoptions of this book as a class text. However, the reviewer hopes that many seniors and graduate students will study it carefully as they prepare themselves for a productive career in chemical research.

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**Metall- $\pi$ -Komplexe mit di- und oligoolefinischen Liganden.** By Professor Dr. ERNST OTTO FISCHER und Dr. HELMUT WERNER, Anorganisch-Chemisches Institut der Universität München. Verlag Chemie, G.m.b.h., Weinheim/Bergstr., Postfach 149, Germany. 1963. 142 pp. 15 × 32 cm. Price, DM 19.

This monograph is a survey of the enormous and ever-increasing field of transition metal complexes with olefinic systems. The book begins with a brief historical survey of the development of the field, and contains an interesting extract showing Liebig's scepticism of Zeise's preparation of the first ethylene complex of platinum(II), his now-famous salt  $K[C_2H_4PtCl_2]$ . A brief survey of theoretical treatments of olefin-metal bonding follows, and a comparison is made between the relative  $\sigma$ - and  $\pi$ -bonding abilities of CO and olefins on the basis of dipole moment and infrared data. After a review of general methods of preparing olefin complexes, we have the last and longest section of the book: a survey of the complexes formed with various transition metals by a series of cyclic olefins, starting with cyclobutadiene and substituted cyclobutadienes and increasing in complexity to 1,5,9-cyclododecatriene, acenaphthylene, and dipentene. The complexes formed by noncyclic conjugated and noncyclic nonconjugated diolefins and triolefins conclude the work; monoolefin complexes are arbitrarily excluded. Infrared, n.m.r., and (where available) X-ray structural data on the complexes are tabulated, and 252 references are given (not alphabetically). There is a subject index, but no author index.

The problems of organizing the material in this field are immense, but this reviewer nevertheless feels that greater effort could be made to compare and evaluate all the results listed. Thus, the recently discovered complexes of  $\pi$ -allyl ligands, which can be regarded as donating three  $\pi$ -electrons to a metal, are evidently intermediate in character between olefin complexes and aromatic complexes. These receive no coherent treatment in the book, although they are mentioned in various places throughout. Surely a separate section on unsymmetrically delocalized  $\pi$ -complexes could have been written. The bonding in cyclobutadiene-metal complexes can be readily compared with that in  $\pi$ -cyclopentadienyl and  $\pi$ -arene complexes, but this is not done. In general, the theoretical treatment given does not go beyond the Dewar-Chatto ideas for monoolefin complexes, which are in any case excluded from the experimental section. The possibility of regarding conjugated diene complexes, such as (butadiene)Fe(CO)<sub>2</sub> and cyclopentadiene complexes, as Diels-Alder adducts, with  $\sigma$ - and  $\pi$ -bonding from the olefin to the metal, is not discussed. The authors mention in the introduction that the expansion in the chemistry of metal-olefins has had repercussions in other fields, but there is no mention of the possible im-