resonance was measured for solutions in Me_2CO-d_6 and Me_2SO-d_6. Two similar peaks at a separation of 0.125 ppm were recorded for the aromatic protons at room temperature in Me_2CO-d_6. At the same temperature, in Me_2SO-d_6 a broad single peak ($\Delta\nu_{1/2}$ = 2 Hz) was observed for the phenyl protons. Elevation of temperature caused this singlet to split in two, with increasing separation. This was taken to indicate phenyl anisotropy, not the presence of two conformers. This conclusion is supported by the ^{13}C NMR spectra of phenytoin in Me_2SO-d_6. Various types of carbon could be distinguished, but only a single peak was observed at the aromatic range, at 110 ppm. This is in line with a single spatial conformation in phenytoin: the anisotropy of the phenyls (observed in the ^1H NMR) is due to a long-range contribution to the shielding by the two anisotropic carbonyl groups; this contribution is negligible for the ^{13}C chemical shift.[25] Thus, both the theoretical calculations for the isolated molecule and the NMR spectrum of solvated phenytoin indicate that the drug has a single conformation, with the two phenyls rotated significantly with respect to each other.

Conclusion

In summary, the theoretical computation of free cannabidiol and phenytoin indicates that in these compounds the angle between the two rings is close to, but rotated with respect to, the crystal. It is of interest that the changes in both molecules are in the same direction and of similar magnitude. NMR measurements of the solvated molecules support the theoretical prediction.

The data above indicate a close relationship between cannabidiol and phenytoin as regards the spatial relation of the two rings; hence, they are in line with the stereochemical requirements suggested for anticonvulsant drug action. This encompasses also the second requirement, namely, on the similar orientations and positions of the two electron-donating groups: in cannabidiol, the distance between the two groups is 4.77 Å;[9-11] in phenytoin, it is 4.56 Å.[4]

It is of some interest to point out that while the hashish-type activity of THC increases sharply when the pentyl side chain is replaced by 1,2-dimethylheptyl (for example, in compound V), no difference in anticonvulsant activity is observed when a similar change is made in the cannabidiol molecule (for example, in compound VI).[27] This absence of enhancement of anticonvulsant activity is to be expected if the molecular basis of action of cannabidiol (as anticonvulsant) and of THC (as psychotropic agent) are different.

Experimental Section

Cannabidiol was isolated from hashish.[28] Phenytoin was the product of Parke-Davis & Co. and was used without further purification. Me_2SO-d_6 (99.5%) and Me_2CO-d_6 (99.8%) were the product of Merck.

^1H and ^{13}C NMR were recorded on a Brucker WP-60 equipped with a FT attachment, operating at 60 MHz for ^1H and 15.08 MHz for ^{13}C NMR. The temperature was maintained within 1 °C by a variable-temperature control instrument. The ^{13}C NMR spectrum is the result of 130 000 scans with decoupling.

Acknowledgment. We thank the National Institute on Drug Abuse for generous support and Dr. O. Kennard, Cambridge, U.K., for helpful correspondence.

(25) G. C. Levy and G. L. Nelson, "^{13}C NMR for Organic Chemistry", Wiley-Interscience, New York, 1972, p 24.
(26) Reference 1, p 120.
(27) R. Mechoulam and E. A. Carlini, unpublished observations.
(28) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **93**, 217 (1971).

Book Reviews

Heparin: Structure, Cellular Functions, and Clinical Applications. Edited by N. M. McDuffie. Academic Press, New York. 1979. xxi + 387 pp. 16 × 23.5 cm. $19.50.

The International Symposium on Heparin which was held in Saskatoon, Saskatchewan, Canada, in July 1977 is the basis of this book. The book is a compilation of 23 papers presented at this symposium. The major reasons for the symposium were to honor renowned heparin researcher Professor Louis B. Jaques and to enumerate the recent heparin research findings from around the world.

The book is organized into four sections, containing 22 papers and concluding remarks by Professor Jaques on "40 Years of Heparin Research—Past and Future". The four sections are "Structure", "Structure and Pharmacodynamics", "Cellular Function", and "Clinical Application".

The "Structure" section contains seven papers devoted to the structural features of heparin. Examples are "Enzymatic Degradation of Heparin as a Tool for Structural Analysis", "The Metabolism of Macromolecular Heparin", and "Structural Characteristics of Heparins revealed by Electrofocusing". Various chemical and enzymatic methods of structural elucidation are provided. For example, proton magnetic resonance spectra of heparins from different sources are examined and interpreted. Thin-layer chromatography, enzyme studies, and electrophoresis are also described. In this section, the reader will be able to learn the most recent research advances in heparin structural elucidation and recent advances in heparin chemistry. Medicinal chemists, biochemists, molecular biologists, and others interested in heparin's structure and activity will find this section of interest. I believe the reader will find the "Discussion" of these papers particularly stimulating.

In the section entitled "Structure and Pharmacodynamics", six papers describe various aspects of heparin's chemical structure in relation to its absorption, biological effects, interaction with factor VIII, and other substances like fibrinogen. The discussion of the chemistry of heparin binding sites requiring a specific sequence of different disaccharide units in the chapter entitled "Structural Basis for the Biological Effects of Heparin" by U. Lindahl will be of interest to medicinal chemists involved in drug design and synthesis.

The third division of the book entitled "Cellular Function" contains six papers. This section provides recent findings related to the functional role of heparin at the cellular level, comparison of heparin to chondroitin sulfate, hyaluronic acid and glycoproteins of nervous tissue, heparin's involvement in the storage of histamine in mast cells and its relationship to endothelium, and the pharmacological action of small doses of heparin.

The fourth division of the book entitled "Clinical Application" describes "Heparin Therapy in Venous Thrombosis and Pulmonary Embolism: Clinical and Experimental Observation", "Heparin in Inhalation", and "Clinical Use of Heparin and He-

parinoids, Exluding the Treatment of Thromboembolism". The findings reported on heparin therapy in venous and pulmonary embolism will be of interest to many readers. J. Hirsch et al. discuss the shorter half-life of heparin in pulmonary embolism vs. deep venous thrombosis due to increased heparin clearance and the need for larger initial doses of heparin in the treatment of acute pulmonary embolism.

The book concludes with a stimulating review of heparin research by Professor L. B. Jaques entitled "40 Years of Heparin Research--Past and Future". His review, evaluation, and interpretation of the "Chemical Nature of Heparin", "Chemistry of Mucopolysaccharides versus Proteins and Nucleic Acids", "Nomenclature Reform", "Standardization of Heparin", "Heparin and Mast Cells", "Heparin and other Cells", "Nonmast Cell Histamine and Heparin", and "Clinical Uses of Heparin" provides an excellent perspective to past and present research on heparin.

In summary, anyone who is interested in recent heparin research and clinical applications will find this book a rewarding experience.

University of Florida **Richard H. Hammer**

Carbon-Carbon Bond Formation. Volume 1. Techniques and Applications in Organic Synthesis. Edited by R. L. Augustine. Marcel Dekker, New York. 1979. vii + 461 pp. 15.0 × 22.5 cm. $45.00.

This well-produced book is the first volume in a series on carbon-carbon bond-forming reactions. The book consists of three chapters: "Aldol and Related Reactions" (by Z. G. Hajos), "Alkylation and Related Reactions of Ketones and Aldehydes via Metal Enolates" (by D. Caine), and "Alkylations and Acylations of Phosphonium Ylides" (by H. J. Bestmann and R. Zimmermann).

Chapter 1 surveys the aldol reaction. Following a brief introduction and mechanistic considerations, the author dwells on inter- and intramolecular versions of the aldol reaction. A section of the chapter is devoted to alternative methods for circumventing intermolecular aldol reactions. At the end of the chapter, the related reactions such as the Perkin reaction, Claisen reaction, Knoevenagel reaction, etc. are briefly reviewed.

Chapter 2, which fills half of the book, gives an indepth analysis of the alkylation of metal enolates. The author has provided a thorough compilation of literature references. Numerous examples are cited, many in tabular form. As with the previous chapter, valuable experimental information is provided for the student of organic chemistry. One minor criticism stems from a duplication of data in Chapters 1 and 2. For example, much of the information found in the section on "Kinetic Enolate Salts of Ketones With Aldehyde Acceptors" in Chapter 1 (page 24) reappears in Chapter 2 on page 264 under the title "Directed Aldol Condensations via Preformed Metal Enolates of Saturated Ketones". Overall this is an outstanding Chapter.

Chapter 3, which contains a general overview of phosphonium ylide chemistry, concentrates primarily on acylation, alkoxycarbonylation, alkylation, cyanylation, and carboxylation.

An author index and subject index, along with chapter/topic indexes, are extremely useful in locating data.

This book constitutes a contribution to synthetic organic chemistry which the organic chemists, in particular, advanced undergraduates and graduate students, will find of great value.

University of Pittsburgh **Paul A. Grieco**

The Chemistry of Heterocyclic Compounds. Volume 25. Indoles. Part 3. Edited by William J. Houlihan. Wiley, New York. 1979. x + 586 pp. 15.5 × 23.5 cm. $70.00.

This book consists of two long review chapters, the first (by Thomas F. Spande) on "Hydroxyindoles, Indole alcohols, and Indolethiols", and the second (by William A. Remers) on "Indole Aldehydes and Ketones". The text, tables, and appendices of this book offer an excellent entry into the literature concerning these compounds. The indoles described in this volume are important as psychoactive agents, as structural components of physiologically active alkaloids, and as biologically active compounds in their own right. Furthermore, the involvement of hydroxyindoles in the melanizing process adds many biologists to the range of scientists who will need information about these compounds.

The treatment of the syntheses, reactions, and properties of these compounds is well organized and succinct. There are more than 1600 original literature references cited, literature being treated through 1977. Many references to patents as well as to papers are given. Tables of constants for many compounds and derivatives are a valuable feature of the chapters, and a table of hydroxyindole color reactions will be valuable to the preparative chemist using thin-layer chromatography. This book is essential for the library and will be found useful as a daily reference by synthetic chemists working in this field.

Northeastern University **P. W. Le Quesne**

Phosphorus: An Outline of Its Chemistry, Biochemistry, and Technology. By D. E. C. Corbridge. Elsevier Scientific, Amsterdam. 1978. x + 455 pp. 25 × 17 cm. $71.25.

According to the introduction, Professor Corbridge's book is intended to deal with "all aspects of phosphorus chemistry: organic, inorganic, biochemical, physical, environmental, and technical". Not surprisingly, it fails to do justice to all of these aspects.

The test is organized according to the elements present in the molecules discussed. Starting with inorganic phosphides, Professor Corbridge proceeds to inorganic phosphates, organophosphorus compounds, compounds of phosphorus and nitrogen, phosphate esters (and biochemistry), phosphorus–sulfur compounds, compounds with phosphorus–phosphorus bonds, and compounds of phosphorus with elements in groups 3 and 4. A final chapter deals with special topics, including free radicals, radiochemistry, physical methods, and stereochemistry of phosphorus compounds (a topic also discussed in earlier chapters). Very brief appendices dealing with the literature of phosphorus chemistry, phosphorus nomenclature, hazards presented by phosphorus compounds, and a list of atomic data for 103 elements (apparently in the wrong book) complete the text.

Reflecting Professor Corbridge's own interests, the topic most adequately treated in this book is structural chemistry, particularly of inorganic phosphorus compounds. This text should be useful to a biochemist or organic chemist desiring a quick introduction to the structural chemistry of phosphorus compounds.

In contrast, Professor Corbridge's treatment of phosphorus reactions is far less satisfactory. While the text includes equations for a vast number of reactions, there seems to be little attempt to emphasize the most synthetically useful or theoretically interesting reactions. There is essentially no discussion of the mechanisms of even the most important reactions. As a result, the reader is presented with a hodgepodge of disconnected data. This effect is exacerbated by the organization of the book, which discusses almost identical reactions—the hydrolysis of phosphonite esters, phosphate esters, and phosphoramides, for instance—in separate chapters.

The discussion of phosphate biochemistry occupies part of a single chapter and attempts to cover a vast area, including the photosynthesis and metabolism of carbohydrates, coupled reactions, oxidative phosphorylation, reactions of NADPH, and acetyl group transfers. This discussion should be of little value to those already reasonably well versed in biochemical concepts, and is likely to be almost incomprehensible to newcomers to the field.

The most glaring deficiency of this book is that no references are included. As a partial substitute, each chapter includes a list of books and review articles covering the field. These lists are perhaps the most valuable material in this book, but cannot compensate for the lack of references. Almost as distressing as the absence of references is the cursory nature of the index, which lists phosphorus-containing molecules by structural types but does not list many reaction types or reagents which react with the phosphorus compounds. Locating a particular reaction in the book is thus often a major operation.

Finally, it should be mentioned that there are many typographical errors in the text.

University of Massachusetts, Amherst **Bernard Miller**