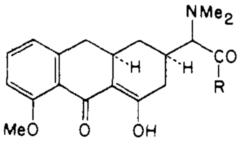
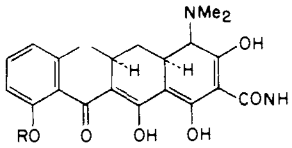


IX : R = OH
X : R = $OCOOCHMe_2$
XI : R = $CH(COOEt)CONHBu^{t}$



XII : R = Me, R' = Bu^{t}
XIII : R = R' = H

The acid IX was converted to the corresponding isopropylcarbonic mixed anhydride X[6] [m.p. 132° (dec.). Found: C, 64.32; H, 6.77; N, 3.41] in the usual manner, and condensed with the magnesium derivative of ethyl N-*tert*-butylmalonamate[7] in acetonitrile to yield the crude acylmalonamate XI.[6] The latter, by direct treatment with excess sodium hydride in dimethylformamide at 120°, gave 2-N-*tert*-butylcarbamoyl-4-dimethylamino-4,-4a,5,5a,6,11 - hexahydro - 1,3,12 - trihydroxy - 10-methoxy - 11 - oxonaphthacene (XII)[6] [m.p. 215–216° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), (initial) 254 (12,900), 325 (9,300), ~420 (21,600), 436 (26,700), ~456 (22,400) in MeOH/0.01 *N* HCl. Found: C, 66.95; H, 6.80; N, 6.04]. Hydrolysis and dealkylation of XII in hot 48% hydrobromic acid gave 4-dimethylamino-4,4a,5,5a,6,11-hexahydro-1,-3,10,12-tetrahydroxy-11-oxonaphthacene-2-carboxamide (XIII)[6] [m.p. 223–224° (dec.). Found: C, 63.27; H, 5.51; N, 6.73]. The highly characteristic and time-variable ultraviolet spectrum [$\lambda\lambda_{max}$ mμ (ϵ), (initial) 260 (12,900), 326 (10,300), ~408 (16,600), 429 (23,600), 451 (20,100) in MeOH/0.01 *N* HCl; 247 (13,600), ~262 (13,000), 378 (9,500), ~447 (17,900), 470 (24,500), 495 (22,900) in MeOH/0.01 *N* NaOH] and the paper-chromatographic behavior [ethyl acetate/nitromethane/chloroform, ethyl acetate/chloroform/pyridine, nitromethane/chloroform/pyridine/pH 3.5 paper, pyridine/toluene/water/pH 4.2 paper] of the synthetic substance were identical in all respects with the corresponding properties of an optically active sample of the same structure (XIII), prepared by degradation of 6-demethyl-6-deoxytetracycline.[8] When the synthetic (XIII), in the presence of cerous chloride (1 mole/mole) was subjected to the action of molecular oxygen in dimethylformamide/methanol solution, brought to apparent pH ~5 with glycine/sodium hydroxide, it was transformed into racemic 6-demethyl-6-deoxytetracycline (Ic), [B.HCl.0.5H_2O, m.p. 225–226° (dec.). Found: C, 54.94; H, 5.46; N, 5.66]. The characteristic ultraviolet spectrum [$\lambda\lambda_{max}$ mμ (ϵ), 267 (19,300), 347 (15,500) in MeOH/0.01 *N* HCl; 248 (16,600), ~261 (15,600), ~284 (10,100), 383 (18,300) in MeOH/0.01 *N* NaOH] and the paper chromatographic behavior [toluene/pyridine/water, nitromethane/1-butanol/toluene/pyridine, ethyl acetate/nitromethane/chloroform, ethyl acetate/chloroform/pyridine, ethyl acetate/water] of this racemic substance were identical in all respects with the corresponding properties of an authentic sample of 6-demethyl-6-deoxytetracycline.[5] It is of much interest that the synthetic racemic material was found to be exactly half as active as the levorotatory antibiotic of natural provenance when assayed turbimetrically against *K. pneumoniae*.

Acknowledgment.—The authors are indebted to Mr. E. J. Bianco for the preparation of intermediates.

MEDICAL RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC.
GROTON, CONNECTICUT
L. H. CONOVER
K. BUTLER
J. D. JOHNSTON
J. J. KORST
CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE 38, MASSACHUSETTS
R. B. WOODWARD

RECEIVED JULY 30, 1962

---

[7] Ethyl N-*tert*-butylmalonamate was prepared from ethyl cyanoacetate and isobutylene by Dr. J. W. McFarland of these laboratories.

[8] R. K. Blackwood, H. H. Rennhard and C. R. Stephens, *J. Am. Chem. Soc.*, **82**, 5194 (1960).

BOOK REVIEWS

Molecular Structure. The Physical Approach. By J. C. D. BRAND, Ph.D., D.Sc., Lecturer in Chemistry in the University of Glasgow, and J. C. SPEAKMAN, Ph.D., D.Sc., Senior Lecturer in Chemistry in the University of Glasgow. St. Martin's Press, Inc., 175 Fifth Avenue, New York 10, N. Y. 1960. viii + 300 pp. 15.5 × 23.5 cm. Price, $6.00.

When a reviewer begins with the phrase, "should be in the hands of every graduate student," the reader may be forgiven for suspecting either nepotism or a quote from a dust jacket. With the book under review, however, the comment is justified. The authors set out to provide an introduction to the study of the structures and properties of molecules in their ground electronic state, and have succeeded admirably. Although the book is designed for the general chemical reader rather than the specialist, each chapter with its bibliography could serve as excellent point of departure for the beginner in that field. The book as a whole would make a good text for a one-semester course in molecular structure determination.

After an introduction and one of the most lucid introductions to molecular and crystallographic symmetry that the reviewer has encountered, successive chapters deal with elementary wave mechanics, molecular rotation and dipole moments, nuclear magnetic resonance, molecular vibration, polarizability and Raman spectroscopy, X-ray diffraction and electron diffraction. Electronic spectra and electron spin resonance are excluded by the stated limits of the book, and neutron diffraction is treated briefly in the chapter on X-rays. The discussion of group theory begun in the symmetry chapter is continued in an appendix.

One of the prime merits of the book is its clarity of style and the skill with which new principles and concepts are set forth. In the chapter on X-ray diffraction, for example, a surprising number of relatively sophisticated topics are treated with ease and understandability. Although some subjects such as diffraction geometry and the Ewald construction are presented without proof, the authors do not oversimplify matters, and there is nothing which would have to be unlearned later by the advanced student. The bibliography in this chapter has been selected well, and it is presumed that equal care has been taken with those of other chapters.

In sum, although some fault could doubtless be found with each chapter by a specialist in that field, the non-specialist could hardly ask for a better introduction to the several fields. The reviewer has made the chapters on symmetry and X-ray diffraction required reading for new research students for nearly two years, and the comments in this review stem in part from the excellent results which have ensued. There are some books which are a pleasure to read as well as to learn from, and this is one of them.

Department of Chemistry
and Chemical Engineering Richard E. Dickerson
University of Illinois
Urbana, Illinois

Toxicity of Beryllium Compounds. By Lloyd B. Tepper, M.D., Research Fellow to the Beryllium Case Registry and Clinical Fellow in Medicine at the Massachusetts General Hospital, Boston (Mass.), Harriet L. Hardy, M.D., Medical Department, Occupational Medical Service, Massachusetts Institute of Technology, Cambridge (Mass.), and Richard I. Chamberlin, B.S., Industrial Hygiene Engineer, Occupational Medical Service, Massachusetts Institute of Technology, Cambridge (Mass.). D. Van Nostrand Company, Inc., 120 Alexander Street, Princeton, New Jersey. 1961. viii + 190 pp. 13 × 19 cm. Price, $4.00.

The authors summarize the toxicology of beryllium and its compounds in language and with a point of view appropriate for the industrial hygiene engineer and for the physician specializing in occupational disease. Because two of the authors are specialists in occupational health and the third is an industrial hygiene engineer, the successful fusing of these interests is understandable.

Chapter one defines the terminology of beryllium disease and follows its history and epidemiology in painstaking detail. The role of one of the authors (H.L.H.) in identifying the chronic illness is modestly cited: "The clinical syndrome, now designated as chronic beryllium disease did not appear in the literature until 1946, when Hardy and Tabershaw described illness in 17 fluorescent lamp workers in Salem, Masachussetts, under the diagnostic heading of 'delayed chemical pneumonitis.'" The authors' authoritative discussion is based on "the 616 known cases of beryllium disease in the United States" (including 47 "neighborhood cases") whose records are maintained in the Beryllium Case Registry at the Massachusetts General Hospital, Boston.

The second chapter describes acute beryllium disease: *viz.*, dermatitis, ulcer, conjunctival inflammation, and two forms of acute pneumonitis. Chapter three discusses with illustrative case material chronic beryllium disease, its latency, its signs and symptoms—pulmonary and systemic—its course and prognosis, its differential diagnosis and treatment. The X-ray changes in beryllium disease are illustrated in chapter 4. The pathology of acute and chronic disease is tersely described in chapter 5. The usefulness of pulmonary function tests (chapter 6) and of the beryllium patch test (chapter 7) is critically assessed, *e.g.*, ". . .the use of the (patch) test in screening persons who are to be exposed to beryllium is undoubtedly best avoided." In chapter 8 experimental animal studies are reviewed, including carcinogenic effects. The authors on occasion leave the final decision up to the reader: "granulomata in the lungs of rats and guinea pigs have been produced by exposure of the animals to several beryllium compounds. It is not possible to say that these lesions represent an experimental counterpart to chronic beryllium disease in man, ..." (p. 113). Patterns of distribution and excretion of beryllium (chapter 9) depend on dose size, *i.e.*, tracer quantities or with carrier. Attempts to treat beryllium disease with chelating agents, such as ATA or sodium salicylate, are reported, although objective evidence of improvement cannot be furnished. Chapter 10 entitled "Industrial hygiene aspects of beryllium toxicology" gives (a) materials and uses (b) the principal sources of exposure, (c) recommended methods of air sampling, (d) evaluation of the maximum permissible concentrations which "may be over-conservative" but demonstrate "that the use of beryllium need not be associated with hazardous exposures." A 13-page reference list and a brief index conclude the volume.

This book is clearly stated, readable, and authoritative. The resumes are buttressed by carefully selected detail. The authors offer their own expert opinions to illuminate the subject.

Department of Pharmacology Harold C. Hodge
University of Rochester School of Medicine
Rochester, New York

Molecular Orbital Theory for Organic Chemists. By Andrew Streitwieser, Jr., Associate Professor of Chemistry, University of California, Berkeley, California. John Wiley and Sons, Inc., 440 Park Avenue South, New York 16, N. Y. xvi + 489 pp. 15.5 × 23.5 cm. Price, $14.50.

This book attempts a number of things and, on the whole, is remarkably successful, although not all the topics come off equally well. The major fraction of the book (306 out of about 450 pages) is a critical survey of literature concerned with the correlation of measurable properties by Hückel type molecular orbital calculation and its fairly straightforward extensions. No one is better qualified to do such a job than the author and he has done it superbly. The review is both exhaustive and critical and the original work is frequently extended with calculations appearing here for the first time.

The book is also intended to serve as a textbook for the student learning to make molecular orbital calculations. The workbook sections closely resemble Roberts' recent book, "Notes on Molecular Orbital Calculations," and both bear a family resemblance to a set of notes on the same subject which were in use at M.I.T. when the reviewer was a student there. Both current versions are good and will be very helpful to a beginner in this field. The reviewer is inclined to think that the Roberts' version will be easier for a neophyte to follow but this will, no doubt, vary somewhat with the individual.

Chapters introducing quantum mechanics, more advanced methods, and describing matrixes and group theory are also included. (The dust jacket calls specific attention to the latter.) The first two seem too short to be really effective. The first chapter may serve to jog the memory of one who has already had an introduction to quantum mechanics, and it wisely emphasizes those topics that are related to what follows. It will not serve well as an introduction to the subject for the student who is not already well grounded. The chapter on group theory will also be very rough going unless supplemented from other sources. The chapter on advanced methods does a good job of outlining the direction taken by more rigorous methods and this is plainly all that is intended.

Department of Chemistry
University of Minnesota Maurice Kreevoy
Minneapolis 14, Minn.

Advanced Organic Chemistry. By Louis F. Fieser, Sheldon Emery Professor of Organic Chemistry, Harvard University, and Mary Fieser, Research Fellow in Chemistry, Harvard University. Reinhold Publishing Corporation, 430 Park Avenue, New York 22, N. Y., 1961. ix + 1158 pp. 16.5 × 24 cm. Price, $14.00.

The Fiesers' "Advanced Organic Chemistry" may be viewed as a new edition of their "Organic Chemistry" which first appeared in 1944 followed by second and third editions in 1950 and 1956. As the authors indicate, the current title was selected to distinguish the present volume from its predecessors and is "advanced" only in the sense of addressing itself to students of all levels of competence.