Table I—Corrected Fluorescence Excitation and Emission Maxima of Dantrolene in Solutions of Varying Acidity, Polarity, and Hydrogen Bonding Capability

	Excitation, nm		Emission, nm	
	Monomer	Aggregate	Monomer	Aggregate
Dilute sulfuric acid, pH 3	360	380	520	520
Dilute sodium hydroxide, pH 12	387	387	530	530
Chloroform	390	430	540	540
Nitromethane	400	430	580	580

Anal.—Calc. for $C_{14}H_{10}N_4O_5$: C, 53.45; H, 3.21; N, 17.83. Found: C, 53.53; H, 3.23; N, 17.78.

The corrected fluorescence excitation and emission spectra of dantrolene were recorded on a spectrofluorometer[2] in aqueous solution at pH 3 and 12 and in chloroform and nitromethane.

In aqueous solutions, the dantrolene concentration was varied from 8.0×10^{-9} to 8.0×10^{-5} *M;* in chloroform and nitromethane, the concentrations ranged from 3.0×10^{-9} to 3.0×10^{-4} *M*. The long wavelength excitation and emission spectral maxima of the highest and lowest concentrations of dantrolene employed in these solvents are reported in Table I.

As the dantrolene concentration in chloroform solutions was decreased, the long wavelength excitation maximum shifted from 390 to 430 nm (Fig. 1). Accompanying the shift was a gradual loss in vibrational structure, terminating in the diffuse spectral band with a maximum at 430 nm. Over the same concentration range, the emission spectrum demonstrated no change in band shape or position whether the wavelength of exciting light was 390 or 430 nm.

The shift to longer wavelengths of the corrected excitation spectrum with the subsequent loss of vibrational structure is consistent with the association of molecules in the ground state to form polymeric complexes (usually dimers) containing two or more monomer molecules (2, 3). Such complexes are frequently nonfluorescent (2). This situation is evidently the case with dantrolene since the emission spectrum is not altered in any way by an increase in drug concentration or a change in wavelength of exciting light. Therefore, the emission spectrum with the maximum at 540 nm must be that of the dantrolene monomer.

[2] Perkin-Elmer MPF-4, Perkin-Elmer Corp., Norwalk, Conn.

Results similar to these were obtained for solutions of dantrolene in nitromethane and in aqueous solutions at pH 3. However, in aqueous solutions at pH 12, neither the fluorescence excitation nor emission spectra exhibited any change in band shape or position as the dantrolene concentration in solution was increased. Since dantrolene has a pKa at 7.5[3], this result seems to indicate that the free acid forms polymeric aggregates while the anion does not.

The interaction of dantrolene with human serum albumin is believed to occur through complexation of the anion at a binding site containing both an electropositive and a hydrophobic region (1). If it is assumed that electrostatic attraction between the anion and the electropositive region partially neutralizes the anion, then conditions are suitable for association between unbound molecules of free acid and neutralized, bound anion. An association of this nature would explain why solutions of human serum albumin could not be saturated regardless of their dantrolene concentration.

Such associations of molecules in solution may be due to hydrogen bonding and/or van der Waals interactions. The dependence of aggregate formation upon solution acidity suggests that hydrogen bonding may occur between molecules of the free acid in aqueous solution. Apparently, the dissociable hydrogen with pKa 7.5 may be important not only to the self-association of dantrolene free acid molecules in aqueous solution but to the association of the free acid to previously bound molecules.

(1) J. J. Vallner, L. A. Sternson, and D. L. Parsons, *J. Pharm. Sci.*, **65**, 873 (1976).

(2) C. A. Parker, "Photoluminescence of Solutions," Elsevier, Amsterdam, The Netherlands, 1968, p. 344.

(3) J. Yguerabide, *J. Chem. Phys.*, **49**, 1018 (1968).

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[3] Literature on dantrolene sodium (Dantrium), Eaton Laboratories, Norwich, N.Y.

BOOKS

REVIEWS

Survey of Organic Syntheses, Vol. 2. By CALVIN A. BUEHLER and DONALD E. PEARSON. Wiley-Interscience, 605 Third Ave., New York, NY 10016, 1977. 1105 pp. 16 × 24 cm. Price $25.00.

Every synthetic chemist should appreciate this book, particularly those who are not working in the field but need to plan the synthesis of an organic compound. There is much that recommends this book, notably its convenience in leading one into the vast and seemingly inhibiting realm of the organic chemical literature and the organized way in which functional group preparations are presented.

Volume 2 spans the literature from 1969 to 1975. Over 3000 references from journal articles, reviews, and books are cited. Addenda are included at the end of each chapter, listing references to synthetic methods not available when the chapter was first written.

The organization of this volume is similar to the first volume in that there are 20 chapters, each dealing with different functional groups. Much

of the material from Vol. 1 was omitted to avoid needless repetition; however, frequent reference to Vol. 1 material is made and appears as 1 (for volume) followed by the page number. These references to Vol. 1 are found in both chapter contents and text material. New material in Vol. 2 includes the preparation of allenes, cumulenes, orthoesters, orthocarbonates, and ketenimines.

At the start of each chapter is a brief, concise overview of some of the synthetic methods presented in the following text. This overview is pleasantly written and focuses on emergence of new reagents, improvements in methodology, and advantages and disadvantages of alternative methods. In the text that follows, structural formulas are used liberally and references are supplied faithfully. Yields and experimental conditions for many reactions are given. The inclusion of theoretical aspects such as mechanisms, stereochemistry, and substituent effects give the text an added dimension.

The functional group transformations listed involve no more than one or two steps, with emphasis on fundamental aliphatic–aromatic chemistry. Excluded are synthetic preparations of nucleotides, peptides, lipids, and heterocycles, which would have been useful and of more interest to the biochemist.

A rather elaborate reaction index is cross-referenced to Vol. 1. Instructions on the use of the index are provided, but it is somewhat complex to use. The subject index is quite complete; unfortunately, an author index is omitted. The lack of proofreading oversights is notable, and the print and format are good.

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Pharmacology of Steroid Contraceptive Drugs (Monographs of the Mario Negri Institute for Pharmacological Research, Milan, Italy). Edited by S. GARATTINI and H. W. BERENDES. Raven, 1140 Avenue of the Americas, New York, NY 10036. 1977. 391 pp. 16 × 24 cm. Price $28.00.

This book comprises 30 chapters by 91 authors from eight countries. Its purpose was to present current information and opinion concerning steroid contraceptive side effects; that aim has largely been achieved. A third of the references cited were published between 1973 and 1976; some were in press in 1977. Several chapters contain new data not published previously nor in press.

The book consists of articles presenting basic *in vivo* and/or *in vitro* research data, clinical research data, and/or literature reviews concerning specific side effects. Chapter contents vary considerably, because of different types of study presented and types of side effect studied.

Some chapters concern investigations into biochemical mechanisms of action and cellular and subcellular sites of action, aiming to contribute to the data base on which occurrence of various side effects might eventually be explained. Others discuss metabolism and excretion, mainly human, of contraceptive steroids. Also presented are basic and clinical research data concerning steroid contraceptives and lipids. Drug interactions are briefly reviewed, and experiments explaining a mechanism by which rifampin (rifampicin) may decrease contraceptive efficacy are described.

In the chapter Oral Contraceptive Use and Breast Diseases, available data are summarized and the way pointed for future research; other chapters concern basic research on this topic. Concisely reviewed are quite recent data associating liver tumors with oral contraceptive use. Lack of studies concerning endometrial carcinoma and combination-type oral contraceptives and lack of standardized criteria for histological diagnosis of early cervical neoplasia are noted.

Additional chapters concern oral contraceptives and the cardiovascular system. One discusses serial plasma fibrinogen chromatography, a technique that might prove useful in screening women for predisposition to thromboembolism and/or for evaluating thrombogenicity of steroid contraceptive preparations. Others are concerned with hypertension and myocardial infarction; Mann's "Discussion" of a preceding chapter, however, is in poor taste and should not have been included.

A disappointing chapter is Oral Contraceptives—The Clinical Perspective. It merely summarizes, in a less enlightening manner, data already published in 1974 by the Royal College of General Practitioners; that reference, which "contains an extensive bibliography," is the chapter's only citation. Included are comparisons between incidence of several side effects and three dosage ranges of progestogen or of estrogen; since only the lowest dosage range in each case approximates doses found in the majority of oral contraceptive preparations currently available in both England and the United States, the information is of little practical value.

It is somewhat disconcerting to find that although all chapters have numbered references, about half have them numbered based on alphabetical listing of first authors, while in the others they are numbered based on their chronological appearance within the given chapter. This distinction also applies to the references to chapters coauthored or authored, respectively, by the two editors! The titles of journal articles are missing from the references to three of the chapters, and two coauthors cited twice in each of two other chapters have their names spelled differently in the text and/or references to these two chapters.

The index, listing over 800 items, contains insufficient cross-indexing. Norethindrone and norethisterone, for example, are not cross-indexed. Authors apparently used whichever term they preferred, but only those pages on which one or the other appears are listed under that term in the index. Furthermore, in one chapter, norethisterone and norethindrone are mentioned as the fourth and seventh progestogens, respectively, in a list of agents reportedly associated with liver tumors!

The shortcomings of this book really are minor, although the insufficient cross-indexing could present a problem to the student or to someone whose major field of interest is somewhat remote from steroid pharmacology. Its greatest asset is that, in general, it is a rather up-to-date review. A few chapters are somewhat technical and specialized and, therefore, may have a somewhat narrower appeal, to individuals engaged in similar research, for example. Much of the book, however, contains valuable information, usually adequately referenced, for anyone whose interests and/or specific professional duties require knowledge of the potential(?) disadvantages of steroid contraception as well as the advantages.

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NEW JOURNALS

Clinical and Experimental Hypertension. Edited by MICHAEL J. ANTONACCIO. Dekker Journals, P.O. Box 11305, Church Street Station, New York, NY 10249. January 1978. 17 × 26 cm. Price $90.00 (6 issues).

Journal of Environmental Science and Health. Part C: Environmental Health Sciences. Edited by Robert J. Rubin. Dekker Journals, P.O. Box 11305, Church Street Station, New York, NY 10249. January 1978. 15 × 22.5 cm. Price $44.00 (4 issues).