be a slightly better reversing agent than PIN on a molar basis (Table II). Presumably, the adamantoyl group is removed by hydrolysis before the compound penetrates the cell membrane.# The other two derivatives, which have the less readily hydrolyzable ester and isopropylidene groups, were either less effective (isopropylidene-5′-adamantoyl-PIN[9]) or completely ineffective (3-*p*-nitrobenzoyl-4′,5′-isopropylidene-PIN[10] and dipalmitoyl-PAL[11]).

Thus, by a minor modification of the 4 position, we have obtained an analog of pyridoxal which is a more potent vitamin B_6 antagonist than 4-DOP and also has a different type of action. The biochemical basis for the potency of 4-VPAL is currently under investigation.**

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Tlc (Silica gel) was used routinely as described earlier.[13] Ir spectra were determined with a Perkin-Elmer 457 spectrophotometer, and nmr spectra with a Varian A-60A instrument. Peaks were assigned on the basis of previous work.[14]

3,α^5-*O*-Dibenzyl-4-deformyl-4-vinylpyridoxal (2). Triphenylmethylphosphonium bromide (1.62 mg as a 21.5 wt % hexane solution) and potassium *tert*-butoxide (900 mg)–*tert*-butyl alcohol (1:1) in dry ether (8 ml). After stirring for 2 hr, 3,α^5-*O*-dibenzylpyridoxal (1, 1.05 g, 3 mmol) in THF (4 ml) was slowly added to the ylide solution, and the reaction mixture was stirred for about 15 hr, when the reaction was complete, as indicated by tlc (EtOAc was used for development). After filtration the solution was washed with concentrated $NaHSO_3$ solution, 20% NH_4Cl solution, and H_2O. After drying ($MgSO_4$), the filtrate was evaporated and the oil was taken up in a small amount of EtOAc and chromatographed on a silica gel column (BIO-SIL "A," 100–200 mesh). Elution with EtOAc was followed by tlc; the combined fractions were evaporated yielding 740 mg (71%) of a pale yellow oil (740 mg, 71%) which was converted to the hydrochloride in ethereal HCl: mp 114° (from acetone); nmr [$(CF_3)_2CO \cdot D_2O$, from Tier's salt] δ 2.45 (2-CH_3), 4.70 (2CH_2), 5.00 (CH_2), 6.55–7.03 (m,†† 4-C*H*=CH_2), 5.90–6.22 (m,†† 4-CH=C*H*$_2$), 7.40 (phenyl), 8.27 (C_6-H); ir λ_{max} (KBr) 1630 cm^{-1} (CH=CH_2). *Anal.* ($C_{23}H_{24}ClNO_2$) C, H, Cl, N.

4-Deformyl-4-vinylpyridoxal (3). Hydrolysis of benzyl groups in **2** (200 mg, 0.5 mmol) was accomplished by refluxing with 4 *N* HCl (5 ml) for 22 hr. The solution was evaporated to dryness and coevaporated with H_2O to remove the benzyl alcohol. The solid residue was recrystallized from acetone, yielding 75 mg (72%) of a yellowish powder: mp 204° dec (from MeOH–acetone); nmr (D_2O, from Tier's salt) δ 2.70 (2-CH_3), 4.83 (5-CH_2), 6.80–7.13 (m,†† 4C*H*=CH_2), 5.85–6.18 (m,†† 4-CH=C*H*$_2$), 8.28 (C_6-H); ir λ_{max} (KBr) 1625 cm^{-1}.

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#5′-Adamantoyl-PIN was found to be inactive as an inhibitor of mouse mammary adenocarcinoma cells but was found to be a weak inhibitor of *S. carlsbergensis*; see ref 9.

**The 5 isomer of 4-VPAL, 3-hydroxy-4-(hydroxymethyl)-2-methyl-5-vinylpyridine, has recently been prepared and was found to be inactive as an inhibitor of the growth of mammary adenocarcinoma cells in tissue culture.[12]

††These complex multiplets are typical of an ABC spectrum as found in styrene; see, *e.g.*, ref 15.

Book Reviews

Progress in Drug Research. Vol. 16. Edited by E. Jucker. Birkhäuser Verlag, Basel and Stuttgart. 1972. 472 pp. 23.6 × 18 cm.

While research on drug design and drug action plods ahead in a few new and many older fields, most medicinal scientists in the pharmaceutical industry anxiously contemplate whether even their best efforts will *ever* lead to a new clinically useful drug. In an article on the art and science of contemporary drug development, A. J. Gordon and S. G. Gilgore (Pfizer Pharmaceuticals) review all stages of development to final FDA approval and product marketing for therapeutic chemicals. Although one cannot generalize a typical chronology of a new program of conception, development, and preclinical and clinical testing, one can estimate average time ranges for these activities. They vary with the type of drug (life-saving antibiotics take the least time), the number of investigators and patients involved, the sociopolitical climate at the time of the study, and FDA attitudes reflecting such a climate. Overall time periods from initiation of chemical research to approval of marketing average 5.5 to 17 years, with 11.25 years appearing as a desirable goal for a functional drug. These sobering figures and the hurdles along the way should be considered carefully by any company embarking on such a program. They suggest that only a few of the strongest organizations can undertake the development of a *novel* drug. The days when a small newcomer could enter the competition are over, probably once and for all; those were the days, my friend. . . .

One of the fields in which novel drugs are generally expected is immunosuppression. Effective immunosuppressive agents are available and the present wide search is aimed at *better* drugs than those we now have. G. W. Camiener and W. J. Wechter (Upjohn Co.) present all stages of chemical immunosuppression, their complex mechanisms of action, accessory procedures such as enhancement, thymectomy, and radiation assistance, and pitfalls and applications in diseases with autoimmune components. Since the latter reach into such divergent symptomatology as arthritis and cancer, the well-

documented speculations and prognoses of immunosuppressive research are timely and thought provoking. In another chapter on lysostaphin as a model for a specific enzymatic approach to infectious disease, W. A. Zygmunt and P. A. Tavormina (Mead Johnson Research Center) pinpoint similar concepts at a biochemical level amenable to detailed study.

The chemotherapy of two parasital invasions, schistosomiasis (S. Archer and A. Yarinsky) and that of intestinal nematodes (J. W. McFarland), is reviewed definitively in the outstanding manner and style one has become accustomed to expect of these authors. Drug metabolism receives attention in an article by W. Lenk on biochemical acyl hydroxylations. Progress of the neuropharmacology of the brain is presented interestingly in two reviews by J. A. Izquierdo (Department of Pharmacology, Buenos Aires).

A useful feature of this volume is a tabular compilation of the substructure of proteins by R. Kleine (University of Halle; in German). This labor of love with 222 hard-to-get references arranges hundreds of proteins and especially enzymes from the point of view of oligomeric structures, subunits, maintenance of conformation, allosteric modifications, etc. Anyone speculating about active sites of very high-molecular oligopolymers or heteropolymers should scan these tables before drawing oversimplified conclusions concerning such molecular regions.

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Methods of Neurochemistry. Edited by Rainer Fried. Marcel Dekker, New York, N. Y. 1972. 290 pp.

The third volume of "Methods of Neurochemistry" contains five chapters covering a diverse range of subjects of interest to scientists concerned with the biochemistry of the nervous system. The first chapter by C. F. Baxter is concerned with methodology involved in the measurement of γ-aminobutyric acid in biological extracts and in the assay of various enzymes (L-glutamic acid decarboxylase, γ-aminobutyric acid–α-oxoglutaric acid transaminase, and succinic semialdehyde dehydrogenase) that are concerned with the formation and metabolism of this putative neurotransmitter. The author covers the field thoroughly with discussion of the shortcomings and relative value of various colorimetric, manometric, fluorometric, chromatographic, and radioisotopic methods. Detailed and by in large adequate protocols and discussion are presented in each case for selected procedures.

The chapter by Y. Kishimoto and M. Hoshi covers techniques for the hydrolysis of various classes of lipids, conversion of the resultant fatty acids into methyl esters, and methods for separation and analysis of various classes of fatty acids and fatty acid esters. The chapter also discusses structure determination of unsaturated, branched chain, hydroxyl-containing, or radioisotope-labeled fatty esters and contains brief sections on the determination of short chain fatty acids, fatty aldehydes, and cholesterol and its esters. A brief description of methodology involved in the measurement of biosynthesis of fatty acids in biological preparations is presented. The chapter in view of its comprehensive nature should provide a valuable source of information and methodology related to the assay of fatty acids in the nervous system. The reader will, however, find that he must seek other source material with regard to techniques for extraction and fractionation of lipid from biological sources prior to hydrolysis and subsequent assay.

The chapter by H. F. Bradford is introduced by a discussion of the value of brain slice and synaptosome preparations for the study of the biochemistry of the central nervous system. It continues with a succinct and adequate description of the preparation, incubation, and electrical stimulation of brain slices and synaptosomes. The discussion of many of the pitfalls that are present in this field of research and the clear description of the techniques make this chapter a valuable brief treatise on the use of brain slices and synaptosomes.

The chapter by S. Varon, J. Nomura, J. R. Perez-Polo, E. M. Shooter, and J. P. Kennedy, Jr., presents a brief survey of the literature on nerve growth factor proteins and detailed protocols for the isolation and assay of these proteins. Alternative procedures are presented and problems inherent in certain steps are discussed.

The chapter by A. M. Golub presents in a fairly objective manner a survey of research on the behavioral effect of injection of mammalian brain extracts from trained animals into control animals, prior to training or testing of these control animals. Some discussion of experiments with planarians and goldfish are also included. Protocols for experiments with rats and mice are presented in some detail and the author concurrently attempts to delineate many of the variables which will influence whether or not positive results will be obtained in such experiments. One point that is made is that the experimental measurements should be as free from subjective bias as possible, but little or no discussion of the utility or application of double blind studies in this field is presented. The chapter provides a valuable and different review of this field since it is written primarily from the standpoint of the experimental design involved in such research.

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Carotenoids. Edited by Otto Isler and two coeditors with 17 contributors. Birkhäuser Verlag, Basel. 1971. xii + 932 pp. 24.5 × 16 cm. $37.70.

This book contains twelve chapters entitled: Introduction (O. Isler), Occurrence (B. C. L. Weedon), Isolation, Reactions (S. Liaaen-Jensen), Spectroscopic Methods (W. Vetter, *et al.*), Stereochemistry (B. C. L. Weedon), Total Synthesis (H. Mayer and O. Isler), Biosynthesis (T. W. Goodwin), Metabolism (H. Thommen), Function (N. I. Krinsky), Vitamin A (G. A. J. Pitt), Use of Carotenoids (J. C. Bauernfeind, *et al.*), and Lists of Natural Carotenoids (O. Straub).

This is a book that presents a huge amount of information that will be useful not only to scientists and students in the field but also to those with a peripheral interest in the subject. It is particularly valuable for its contributions in those areas of carotenoid chemistry which are most fully developed, namely, the isolation, reactions, physical methods of analysis, stereochemistry, and total synthesis. Also of importance is the publication of a total list (including structures) of carotenoids reported up to mid 1970. Other chapters, particularly those on biosynthesis, metabolism, and function, present much information. However, these chapters suffer from the fact that the subjects covered are less fully developed than the area of carotenoid chemistry. In addition, some of this material is not as critically reviewed as one would expect. Certain types of investigation, particularly enzymatic studies, are far more significant to an understanding of the biosynthesis and metabolism of carotenoids than are those involving less direct methods; yet, the results of these studies are not emphasized. In numerous instances, as has been the case in many published papers in the past, references to original papers are not cited. Instead, a later paper or a review is cited. This certainly gives the reader an erroneous view of the development of the subject and the identity of those who did the original work. In addition, little mention is made except by Dr. Isler of the publication of "Criteria and Specifications" for 49 carotenoids and related compounds. These criteria are very comprehensive and certainly form a worthy addendum to some of the information presented in Dr. Isler's book.

In spite of the rather numerous criticisms that may be raised about certain aspects of this book, it does contain a wealth of information which will be highly useful to a wide diversity of individuals. It seems quite probable, therefore, that this book will be the principal reference source for information on the carotenoids for many years to come.

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