

**TWENTY-SIXTH NATIONAL
ORGANIC CHEMISTRY
SYMPOSIUM
of the
AMERICAN CHEMICAL SOCIETY**

AUSPICES OF THE DIVISION OF
ORGANIC CHEMISTRY

and

THE UNIVERSITY OF ARIZONA
June 24-28, 1979

Tucson, Arizona

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THE ROGER ADAMS AWARD IN ORGANIC CHEMISTRY

The Roger Adams Award in Organic Chemistry has been established with joint sponsorship by the American Chemical Society, Organic Reactions, Inc., and Organic Syntheses, Inc. The award is made biennially to an individual, without regard to nationality, for outstanding contributions to research in organic chemistry. The award consists of a medal and an honorarium of ten thousand dollars. The presentation of the award is made at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society, and the recipient delivers a lecture as part of the program of the Symposium.

The award recognizes the distinguished career of Roger Adams who played such a vital role in each of the three organizations sponsoring the award, having been Chairman of the Board of Directors as well as President of the American Chemical Society and co-founder of Organic Syntheses and Organic Reactions.

The recipient of this year's award is Professor Melvin S. Newman of the Department of Chemistry at Ohio State University. His award address is entitled "Patterns of Research: Carcinogenic Activity of Benz[a]anthracenes".



Melvin S. Newman

SPEAKERS AT THE TWENTY-SIXTH NATIONAL-
ORGANIC CHEMISTRY SYMPOSIUM



F. G. Bordwell



R. Breslow



H. F. DeLuca



P. A. Grieco



D. M. Jerina



R. E. Ireland



J. Meinwald



H. Rapoport



M. R. Uskokovic



K. P. C. Vollhardt

ORGANIZING COMMITTEES

The plans and program for the 26th National Organic Chemistry Symposium have been developed by the members of the Executive Committee of the Division of Organic Chemistry who have served during the past two years.

	1977-78	1978-79
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Chairman-elect	A. S. Kende	R. E. Ireland
Secretary-Treasurer	P. A. Beak	P. A. Beak
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The local arrangements at the University of Arizona have been made by Professor Robert B. Bates with assistance by other faculty members and students of the Arizona Chemistry Department and Ms. Judith Brown, Conference Coordinator.

PROGRAM

Registration and Meetings: Main Auditorium

SUNDAY, June 24

2:00-5:00 pm Registration

MONDAY, June 25

1:00-2:00 pm Registration

Afternoon Session

R. B. Bates, presiding

2:00 pm Welcome. JOHN P. SCHAEFER, President,
The University of Arizona

Response. A. S. KENDE, Chairman,
Division of Organic Chemistry.

Announcements. C. R. JOHNSON, Symposium
Executive Officer. R. B. BATES, Local
Arrangements Chairman.

2:30 pm R. BRESLOW, "Studies on Enzyme Models"

4:00 pm J. MEINWALD, "Organic Chemical Defense
and Communication Mechanisms in Nature"

Evening Session

C. H. Heathcock, presiding

8:00 pm H. F. DELUCA, "The Vitamin D Endocrine
System"

TUESDAY, June 26

Afternoon Session

N. A. LeBel, presiding

2:00 pm H. RAPOPORT, "Chirally-Specific Natural
Products"

3:15 pm M. R. USKOKOVIC, "Regio- and Stereoselectivity of Nitrene to Olefin Cycloadditions"

4:45 pm R. E. IRELAND, "The Total Synthesis of
Macrolide Antibiotics"

PROGRAM
continued

WEDNESDAY, June 27

Afternoon Session

H. Hart, presiding

2:00 pm F. G. BORDWELL, "Reactions in Dipolar
Nonhydroxylic Solvents"

3:30 pm D. M. JERINA, "Chemical Predictions of
Carcinogenicity for Polycyclic Hydro-
carbons - The Bay Region Theory"

Evening Session

A. S. Kende, presiding

8:00 pm Presentation of the Roger Adams Award

M. S. NEWMAN, Roger Adams Award Address,
"Patterns of Research: Carcinogenic
Activity of Benz[a]anthracenes"

THURSDAY, June 28

Morning Session

L. Mandell, presiding

9:00 am P. A. GRIECO, "Bicyclo[2.2.1]heptanes
as Building Blocks in Natural Products
Total Synthesis"

10:15 am K. P. C. VOLLHARDT, "The Cobalt Way to
Estrone"

11:30 am Closing Remarks

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STUDIES ON ENZYME MODELS

Ronald Breslow

Columbia University
New York, New York

There are two general reasons to study biochemical systems and to try to synthesize artificial enzymes. One aim is an increased understanding of natural enzymes: even after the structure of an enzyme is known, chemical studies of related structures are needed to clarify how catalysis might occur, and why fast rates would be produced by such a structure. The other aim is the generalization of enzyme catalytic principles and methods to new reactions, for which Nature has not supplied a catalyst, or to more convenient chemical substitutes for natural enzymes.

The strategy involved in our approach to artificial enzymes is also two-pronged. In one effort, we construct and modify potential catalysts, which are designed to bind a substrate and then perform an intracomplex reaction. In the other approach, we modify the substrates for a given catalyst to optimize the overall process. That is, we want to use the typical functional groups of an enzyme to perform their normal catalytic reactions on substrate functional groups, but we allow the frameworks carrying both the catalytic and the substrate groups to be variables. In this way we can explore the influence of geometric factors on the catalytic reaction rates. Thus with this version of lock and key chemistry we are willing to adjust the shape of both the lock (the catalyst) and the key (the substrate).

As one example, we have studied further the acylation of cyclodextrins by bound esters which was pioneered by Bender.¹ The reaction of

ORGANIC CHEMICAL DEFENSE AND COMMUNICATION
MECHANISMS IN NATURE

Jerrold Meinwald

Cornell University
Ithaca, New York

Chemical ecology, which is concerned with the study of chemical interactions between organisms in nature, provides a fertile field for organic chemical research. Organic chemistry plays particularly important roles in both natural communication and defense mechanisms. Pheromones, the substances responsible for carrying information between individuals of the same species, are important not only among fungi, algae, and many groups of invertebrates, but also among vertebrates, including the primates. Since the characterization of the first pheromone less than twenty years ago, the problems associated with elucidating both the chemistry and the biology of chemical communication systems have come to be more fully appreciated. Recent studies of insect pheromones at Cornell, which have revealed a hitherto undetected phenomenon in chemical communication, will be discussed.

Current work in our laboratories has also been concerned with the chemical defenses of terrestrial arthropods and of marine invertebrates. Detailed studies of the chemistry of the defensive systems of fireflies and of sea hares will be presented, and the importance of acquired distastefulness will be demonstrated.

THE VITAMIN D ENDOCRINE SYSTEM

H. F. DeLuca

University of Wisconsin
Madison, Wisconsin

The presence of a nutritional factor in cod liver oil which prevents the disease rickets, a condition in which bone fails to mineralize, was clearly demonstrated first in 1919 by Mellanby (1) and subsequently shown to be a new vitamin (D) in 1922 by McCollum (2). Steenbock and his collaborators (3) were able to demonstrate that ultraviolet light incident upon food or animals could bring about the production of this antirachitic vitamin. This provided the basic biological information required for the isolation and identification of vitamin D that was accomplished in 1931 by Askew *et al.* (4) and in 1932 by Windaus and his colleagues (5). Windaus was also able to isolate and identify vitamin D₃ from the irradiation mixtures of synthetic 7-dehydrocholesterol (6). This completed the chemical identification of nutritional forms of vitamin D. Since that time and until 1963 it had been assumed that vitamin D functioned directly in the body without metabolic alteration (7). With the chemical synthesis of radioactive vitamin D of high specific activity first accomplished in the author's laboratory and the development of sophisticated chromatographic procedures capable of separating vitamin D from its metabolites came the demonstration that vitamin D is first modified before exerting its physiologic functions (8). Using modern methods of mass spectrometry, ultraviolet absorption spectrometry, high resolution nuclear magnetic resonance spectroscopy, the isolation and identification of the first active metabolite of vitamin D was accomplished in 1968 (9). This metabolite known as 25-hydroxyvitamin D₃ (25-OH-D₃) was not only more biologically active than vitamin D₃ itself but also acted much more rapidly to stimulate intestinal calcium absorption and the mobilization of calcium from bone as well as the mineralization of rachitic cartilage and rachitic bone. A study of its further metabolism revealed it to be rapidly metabolized and converted to several polar metabolites. Because of the presence of a large number of polar metabolites it became important to distinguish between nonfunctional and functional metabolites. Therefore, in the author's laboratory the metabolite of vitamin D present in the target tissue, small intestine, was isolated in pure form and its structure identified using ultraviolet spectrophotometry and mass spectrometry to be 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) (10). The conversion of vitamin D₃ to 25-OH-D₃ was found to occur primarily in the liver although not exclusively so (11). The chemistry of this

CHIRALLY-SPECIFIC NATURAL PRODUCTS SYNTHESIS

Henry Rapoport

University of California
Berkeley, California

Our objective in the work to be described has been the exploitation of α -amino acids as inexpensive, readily available chiral starting materials for the synthesis of complex, optically active natural products. Based on the principle that chirality should be introduced at the earliest possible moment if a molecule with more than one asymmetric center is being synthesized, we considered optically active α -amino acids as ideal for this purpose.

The first reaction we investigated was that of aminoacylation. Based on our own experience with β -amino acids, in which highly successful aminoacylation had been achieved, we sought to apply this procedure to α -amino acids. In the past, this method has received little use and has usually been accompanied by low yields and much racemization.

This lack of utility is easily understood if one considers the ease of racemization of the intermediate acid chloride and its rapid decarboxylation to the corresponding iminium ion, as shown in Figure 1.

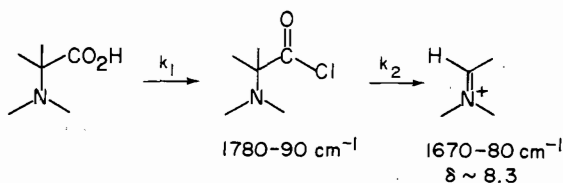


Fig. 1. Conversion of α -amino acid to acid chloride and subsequent decarboxylation to iminium ion.

REGIO- AND STEREOSELECTIVITY OF NITRONE
TO OLEFIN CYCLOADDITIONS

M. R. Uskokovic

Hoffmann-La Roche
Nutley, New Jersey

Intermolecular cycloadditions of nitrones to double bonds of allylic alcohols, allylic esters, enol ethers, enol esters, and thioenol ethers produce regiospecifically isoxazolidines in which the nitrone oxygen is added at the end of the double bond proximal to the oxygen or sulfur function¹. We have studied the intramolecular version of these processes and observed the opposite regiospecificity when allylic or enol oxygen (X or Y = O in 1), or enol sulfur (Y = S in 1), were part of three-atom chains connecting the nitrone and the double bond functions. In all cases studied, we have observed the formation of the cis-fused [3.3.0]-bicyclic products (2) as would be expected from the previous work of Norman LeBel in the corresponding carbocyclic series². None of the alternative [3.2.1]bridged bicyclic products (3) were formed (Scheme 1).

In the course of these cycloadditions three chiral centers are introduced. When R_N or the α -carbon to nitrone were chiral, significant enantioselectivity with respect to newly formed chiral centers was observed. This provided us with an efficient general method for the chiral synthesis of various optically active heterocyclic natural products, especially those with three contiguous chiral centers, each bearing a heteroatom.

1) D.St.Clair Black, R.F. Crozier and V.C.Davis, *Synthesis*, 205-221 (1975) and references therein.

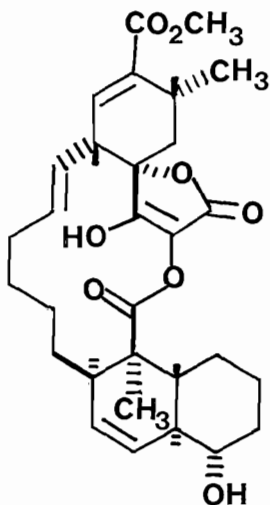
2) N.A. LeBel, *Trans.N.Y. Acad.Sciences*, 858-867 (1973).

THE TOTAL SYNTHESIS OF MACROLIDE ANTIBIOTICS

Robert E. Ireland

California Institute of
Technology
Pasadena, California

Chlorothricolide (1) is the aglycone of the macrolide antibiotic chlorothricin [W. Keller-Schierlein, R. Muntwyler, W. Pache and H. Zänner, Helv. Chim. Acta., 52, 127 (1969)].



1

A convergent approach to the total synthesis of this system has been developed which is based on the use of the enolate Claisen rearrangement to join a top to a bottom half of the aglycone.

REACTIONS IN DIPOLAR NONHYDROXYLIC SOLVENTS

Frederick G. Bordwell

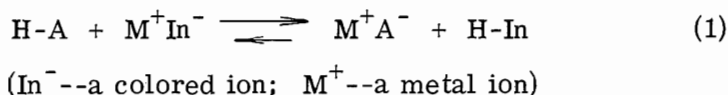
Northwestern University
Evanston, Illinois

Our work during the past seven years has been concentrated mainly on the development of new acidity scales in dipolar nonhydroxylic ("aprotic") solvents. Using about 30 indicators and 30 standard acids scales in dimethyl sulfoxide (Me₂SO) and N-methylpyrrolidin-2-one (NMP) have been developed that cover the pK_a range 0 to 32.¹ These scales are the first, other than that in water, to rest on an absolute base. It is estimated that well over 50% of all organic compounds are acidic enough to be measured in these solvents, whereas less than 1% are acidic enough or soluble enough to be measured in water.

Since most of this audience is interested in structural effects on reactivity, rather than in structural effects on equilibrium, I will review only briefly the extensive work carried out on equilibrium acidities. Instead, I will concentrate on new insights that these data provide with respect to a number of base-catalyzed reactions, including alkene isomerizations, the Wolff-Kishner reduction, the Claisen condensation, deuterium exchange with weak acids, and the benzoin condensation. We will also consider the structures and some reactions of α-sulfonyl carbanions, and the reactivity-selectivity principle as applied to the alkylation of carbanions.

Acidity Scales in Dipolar Nonhydroxylic Solvents

Acidity scales for weak acids depend on the determination of the position of equilibrium 1.

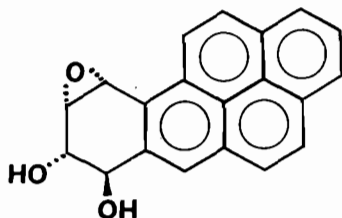


CHEMICAL PREDICTIONS OF CARCINOGENICITY FOR
POLYCYCLIC HYDROCARBONS - THE BAY REGION THEORY

Donald M. Jerina

National Institutes of Health
Bethesda, Maryland

The alternant polycyclic aromatic hydrocarbons represent a class of chemical carcinogens which are well suited for attempts to identify structure-activity relationships both because of their wide range of carcinogenic activity and because of the facility with which calculational methods can be applied to such continuous π -electron systems. Nonetheless, an understanding of the mechanisms of action of these carcinogens has only been forthcoming in the past few years with the identification of (+)-7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene as the principal reactive metabolite responsible for the carcinogenic activity of benzo[a]pyrene.



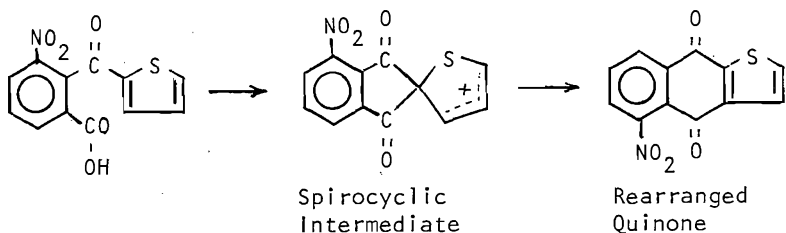
When in the fall of 1975 it became almost certain that a 7,8-diol-9,10-epoxide was indeed an ultimate carcinogen of benzo[a]pyrene, we sought to develop a generalized theory which would predict which of the several possible isomeric diol epoxides of a given hydrocarbon would be the most active and which would predict relative activity of such isomers from different hydrocarbons. In attempting to formulate this theory, we assumed that high chemical reactivity of an epoxide toward nucleophiles should be associated with high biological activity. With the knowledge that the 3,4-epoxide of 1,2,3,4-tetrahydrophenanthrene was much more reactive than the 1,2-epoxide and that the

ROGER ADAMS AWARD ADDRESS: PATTERNS OF RESEARCH:
CARCINOGENIC ACTIVITY OF BENZ[a]ANTHRACENES

Melvin S. Newman

Ohio State University
Columbus, Ohio

In this talk the history of my involvement with the synthesis of carcinogenic hydrocarbons will be traced from my first work with Louis F. Fieser to recent times. The earliest developments arose from the synthesis of 4,5-dimethylchrysene, which led to much work in the field of intramolecular overcrowding leading to the synthesis of hexahelicene, and the discovery that 2-benzoyl-1-naphthoic acid on refluxing with methanolic-HCl gave the pseudo methyl ester. Since *o*-benzoylbenzoic acid under these conditions gives the normal methyl ester much study of the chemistry of substituted *o*-benzoylbenzoic acids was undertaken to understand the mechanisms of esterification. From this work steric acceleration as well as hindrance was observed. In addition reactions involving spirocyclic and bicyclic intermediates were discovered. Comments regarding the generality of each of these reaction paths will be made.



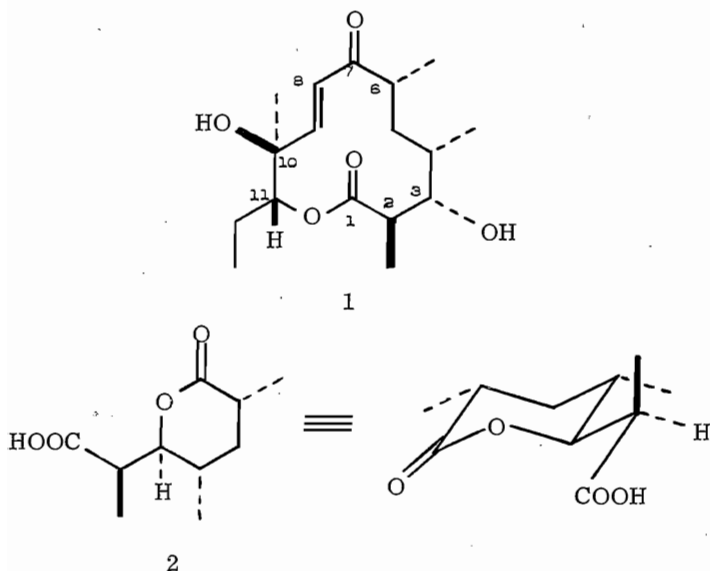
See M. S. Newman, *Accounts of Chem. Res.*, **5**, 354 (1972) for coverage of spirocyclic intermediates.

BICYCLO[2.2.1]HEPTANES AS BUILDING BLOCKS IN
NATURAL PRODUCTS TOTAL SYNTHESIS

Paul A. Grieco

University of Pittsburgh
Pittsburgh, Pennsylvania

Efforts directed toward the total synthesis of the macrolide antibiotic methymycin¹ have evolved around the Prelog-Djerassi lactone 2,² a key degradation product of methymycin retaining the original four chiral centers present in the C(1) to C(7) segment of the aglycone methynolide 1. Since the first synthesis of (±)-2³ which was employed by Masamune in the only total synthesis of methymycin recorded to date,⁴ two additional syntheses of (±)-2 have appeared.⁵ We wish to report our synthetic efforts in the area which have resulted in (a) an efficient, highly stereoselective synthesis of the Prelog-Djerassi lactone in both racemic and optically active forms employing the hydroxy lactone 11 (Scheme I) which constitutes a key intermediate for methymycin total synthesis, (b) construction of the C(8) to C(11) fragment 3 which represents the left hand



THE COBALT WAY TO ESTRONE

K. P. C. Vollhardt

University of California
Berkeley, California

The field of organometallic chemistry, concerned with the interaction between organic molecules and metallic nuclei, particularly the transition metals, has been characterized by an explosive growth in recent years. The various subdivisions of chemistry have had a field-day trying to unravel the problems posed by the often bewildering array of reactions when organic molecules are brought into the vicinity of metals. In the transition metal area the use of catalytically active and stoichiometric reagents for the construction of small and simple, or large and complicated molecules has been of major concern in the more immediate past. Dictated by world events that have led to a high price of oil and a shortage of natural gas research into the interaction of carbon monoxide with transition metals to give a variety of hydrocarbon and alcohol structures has received renewed impetus. An understanding of the mechanisms of these reactions as well as the ability to control their outcome is one of the primary concerns of modern researchers working in the field. On the other hand, the increased cost of labor and the dwindling of certain natural supplies of complex molecules used in drug manufacture have led to an increased interest in the use of transition metal catalysts and reagents for the specific syntheses of complex medicinal agents and natural products. Our level of understanding of this type of organometallic chemistry has reached a stage where it is beginning to be possible to design organometallic reagents and catalysts that will effect these specific chemical transformations. The prerequisite to this ability is a detailed knowledge of reactant structures, reaction mechanisms, and most important of all, the discovery of new reactions.

Our contribution to this area of scientific endeavor has been concerned with the cobalt catalyzed chemo-, regio-, and stereospecific construction of complex organic molecules by inter- and intramolecular cyclizations of unsaturated moieties (alkynes, alkenes, nitriles, isonitriles, carbon monoxide).

Synthesis of Indans, Tetralins, and Anthraquinones

We have found that cooligomerization of 1,6-heptadiyne and 1,7-octadiyne with substituted monoalkynes catalyzed by η^5 -cyclopentadienyl cobalt dicarbonyl provides a general synthetic entry into indans and tetralins with essential control of substitution (Scheme I). The use of bis(trimethylsilyl)acetylene (BTMSA) (employed as solvent)