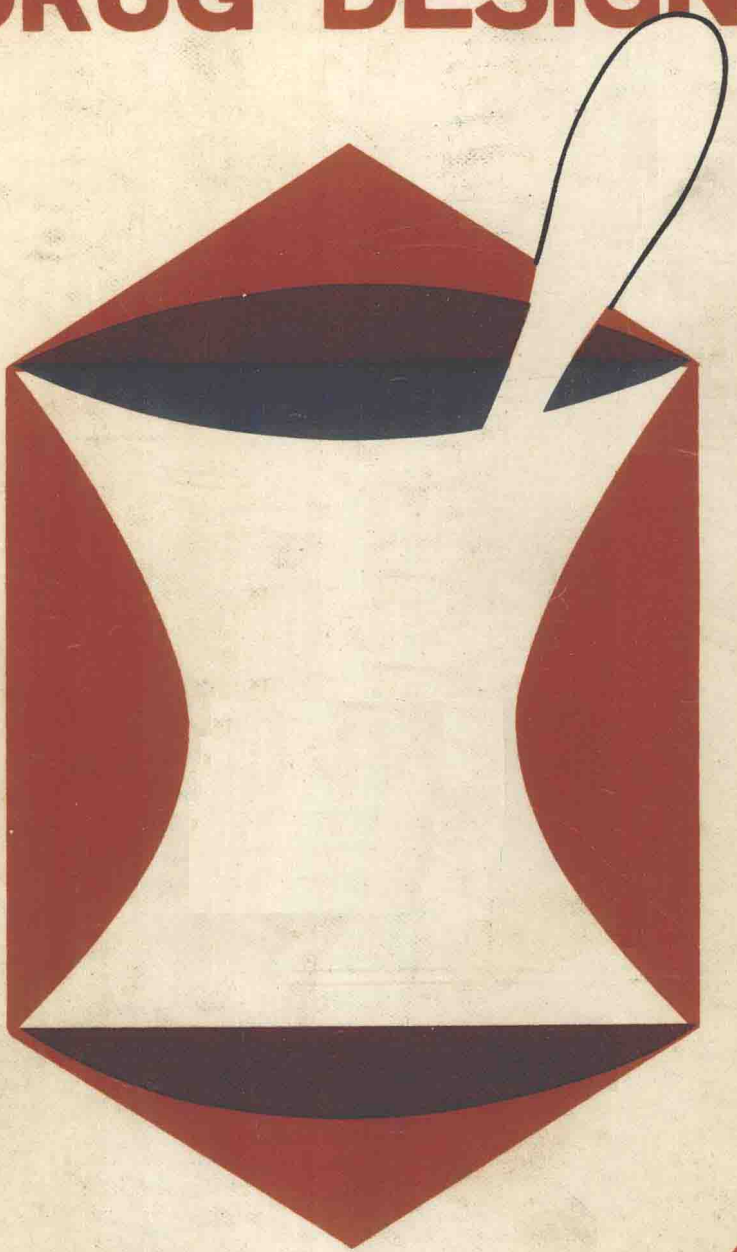
# molecular modification in
# DRUG DESIGN



*advances in chemistry series* 45

# Molecular Modification in Drug Design

A symposium sponsored by
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Chemistry at the
145th Meeting of the
American Chemical Society
New York, N.Y., Sept. 9–10, 1963

**Fred W. Schueler,** *Symposium Chairman*

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# FOREWORD

ADVANCES IN CHEMISTRY SERIES was founded in 1949 by the American Chemical Society as an outlet for symposia and collections of data in special areas of topical interest that could not be accommodated in the Society's journals. It provides a medium for symposia that would otherwise be fragmented, their papers distributed among several journals or not published at all. Papers are reviewed critically according to ACS editorial standards and receive the careful attention and processing characteristic of ACS publications.

# PREFACE

The specific aim of this symposium is a review of the salient features of molecular modification, which has become the hallmark of modern drug research. Molecular modification guided by deduction, induction, and serendipity via the prepared mind has produced in the last 25 years more potent and more useful drug agents in various areas of therapeutics than have been reported in all previous history.

But a brief cursory view of this two-day program reveals the unique, professionally synergistic character of modern drug research through presentations by some of the most outstanding medicinal chemists and clinicians that have contributed to the modern science of chemical therapeutics. Operating from the broad and deep bases of modern chemistry and pharmacology which are rooted in the enormous informational and technical resources of a score of other sciences, has evolved a new methodology, molecular modification, that is of the profoundest importance to all mankind.

As final attestors to the "magic ring" of informational feedback—that is, the spirit of molecular modification in the light of pharmacologic evaluation—are the clinicians who gather the ultimate evidence of its success. Thus, the present symposium may be viewed as a monument to the coming of age of a new science which has grown naturally—that is to say, organically—through integration and differentiation since its conception from those ancient parents—chemistry and medicine.

FRED W. SCHUELER

Department of Pharmacology
Tulane University School of Medicine
New Orleans, La.

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# Molecular Modification in Modern Drug Research

**MAX TISHLER**

*Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N. J.*

**Examples of molecular modification in nature include morphine, codeine, and thebaine among the opium alkaloids; atropine, scopolamine, and cocaine among the tropine alkaloids; and testosterone, progesterone, and estradiol among the sex hormones. Through structure modification the medicinal chemist has developed local anesthetics from cocaine, useful agents from atropine and scopolamine, MAP from progesterone, and Enovid from estradiol. Prontosil, the first sulfonamide of therapeutic significance, gave rise to a series of valuable sulfa drugs and drugs for tuberculosis, diabetes, gout, leprosy, hypertension, and cardiovascular disorders. Critics of the drug industry have found fault with the many congener drugs that offer choice to the clinician. The new drug regulations have created a new environment which will require medicinal chemists to choose compounds more selectively for development and studies in man.**

A little over three years ago, at the 50th Anniversary Symposium of the Division of Medicinal Chemistry, I spoke of the sources of discoveries in chemistry which during the previous quarter century brought forth the greatest array of useful, chemical therapeutics ever known to the practice of medicine. The last two sentences of my talk (*6*) bespeak the boundless pride and peerless confidence that pervaded the halls of the symposium.

The accomplishments of the past gave us the strength and inspiration to meet the challenges of our time and the years ahead. Let us strengthen our dedication to the service of mankind so that those who inherit our responsibilities may derive even greater pride from their own achievements when they meet at the centennial anniversary 50 years from now.

Much has happened and crowded the past three years!

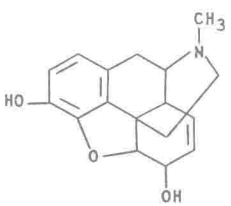
For those of us who have devoted our lives to medicinal chemistry, and particularly to the search for chemotherapeutic agents in the laboratories of the pharmaceutical industry, events of the past three years have brought bewilderment and chagrin. For the first time our objectives were questioned and our contributions were belittled. These criticisms of us as research workers in medicinal chemistry have left their mark on us—for how else can we explain a Symposium on the Influence of Molecular Modification on Drug Design?

If the soundness of molecular modification as a tool of research in medicinal chemistry has been questioned, let us remind ourselves and our critics that chemists have arrived at molecular modification by emulating nature itself. Molecular modification by nature has been going on since the beginning of life on this planet. In the relatively short time since chemistry has developed into a science, chemists had learned well from nature the significance of small changes in chemical structures of drugs to the biological activity in living organisms.

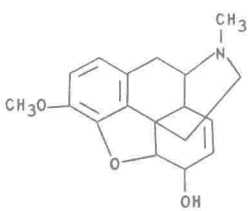
Let us recall a few examples of molecular modifications of drugs as they occur in the plant and animal kingdoms.

### *Opium Alkaloids*

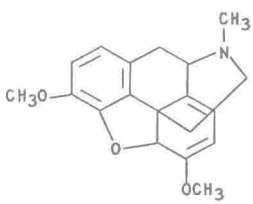
Opium, the sun-dried latex of the unripe fruit of *Papaver somniferum*, cultivated from early times for this drug, contains at least 23 alkaloids. Of the major alkaloids three—morphine, codeine, and thebaine—contain the morphinan ring system.




MORPHINE




CODEINE




THEBAINE

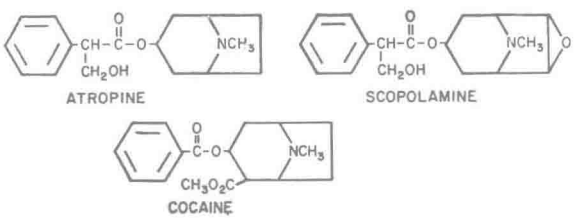
Morphine for over a century has been the most important agent for the relief of pain. Codeine, with its phenolic hydroxyl group protected by methyl, has about one tenth the analgesic activity of morphine, but as such has found its place in the relief of mild pain and as an antitussive agent.

Thebaine, which differs from codeine by the addition of methylene groups and the removal of two hydrogen atoms, is neither an analgesic nor an antitussive. Instead, it resembles strychnine and brucine in its spinal convulsant properties. It is not used in medicine; it has utility, however, in the synthesis of codeinone derivatives, some of which are useful as analgesics.

The chemist has unraveled the morphine-analgesic pattern and has gone far beyond nature in his quest for an analgesic with the power of morphine but without its liabilities.

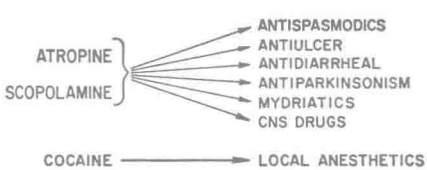
*Tropine Alkaloids*

The tropine alkaloids are another illustration. Atropine, scopolamine, and cocaine are structurally related, each having the tropine nucleus. While atropine and scopolamine overlap in pharmacodynamic activities, cocaine has uniqueness in this series, being a topical anesthetic and a potent addicting agent.




In this case, nature's molecular modification cannot be attributed to a special metabolism within a species. Cocaine and atropine are not related botanically. They originate from different plants.

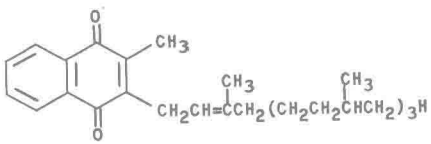
**Extension of Tropine Alkaloids.** Here again, medicinal chemists have gone beyond nature by molecular modification. While cocaine possesses topical anesthetic activity but no local infiltration value as an anesthetic, a number of very useful, local anesthetic agents such as procaine and lidocaine have been derived from our knowledge of the structure of cocaine. Chemists have broadened the scope of usefulness of the cocaine structure.



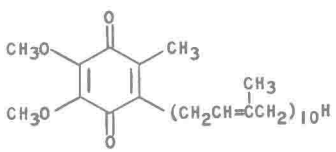

Atropine and its related oxide, scopolamine, have given rise to a number of important agents useful in the treatment of a number of disease conditions. The drugs applicable to each class of pharmacodynamic activity are all anticholinergics and block the parasympathetic nervous system with varying degrees of specificity. By molecular modification, it has been possible to produce a series of compounds having qualitative effects resembling cutting of the parasympathetic nerve to a particular organ.

*Vitamin K and Coenzyme Q*

Vitamins $K_1$ and $K_2$ exist in nature and are essential to the animal for their effect on the blood-clotting mechanism. While 2-methylnaphthoquinone itself and its related derivatives having isoprenoid side chains in position 3 also promote blood coagulation in varying degrees, coenzyme $Q_{10}$ shows no activity in the blood-coagulating mechanism. Coenzyme $Q_{10}$, also called ubiquinone because of its ubiquitous occurrence in animal tissues, is important in its own right, since it plays an essential role in oxidative phosphorylation. As in the case of the vitamin K series, the size of the isoprenoid side chain does not appear to be critical with respect to the oxidative phosphorylation activity of the coenzyme Q series.



VITAMIN $K_1(20)$



COENZYME $Q_{10}$

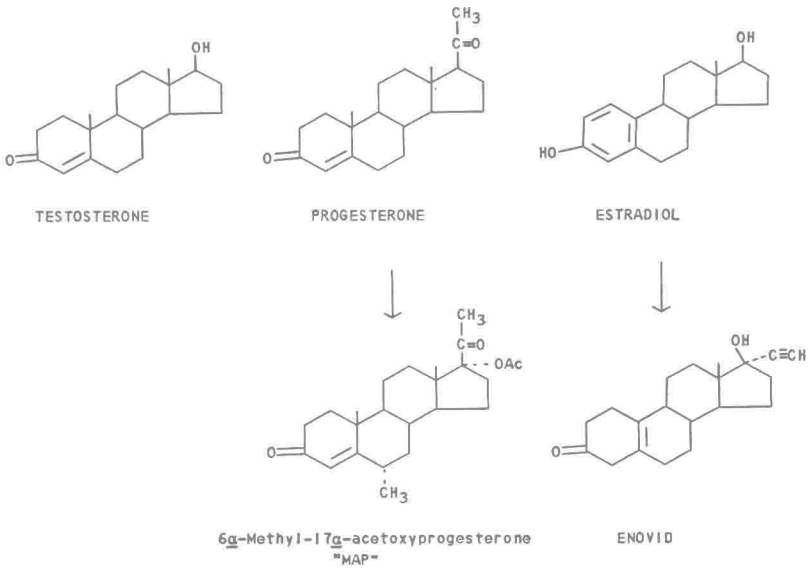
*Sex Hormones*

Nature is at its best in the sex hormone field. Here are three hormones containing steroid nuclei, each of which has a very specific pharmacological activity and a very specific role in sex physiology.

Testosterone, the testicular hormone, is identified as a male hormone. Estradiol (17$\beta$), which differs from testosterone only by loss of a methyl group and aromatization of ring A, is the ovarian hormone. Progesterone is the progestational hormone and is essential for fertilization and maintenance of pregnancy. Once again medicinal chemists, by further alteration of structures, have made more potent oral and more useful progestins.

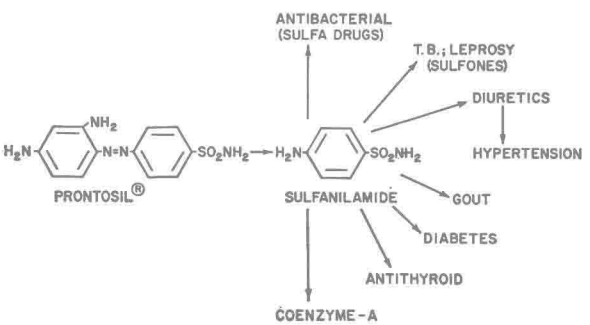
6$\alpha$-Methyl-17$\alpha$-acetoxyprogesterone is at least 100 times as potent as progesterone by the oral route. Norethynodrel (Enovid), also derived through molecular modification of the estradiol type structure, is the first significant orally active anovulatory agent and oral contraceptive.

Up to now, I have placed emphasis on molecular architecture in nature and how medicinal chemists elaborated on nature. Let us now turn to some structures discovered in chemical laboratories, structures conceived and synthesized by man.



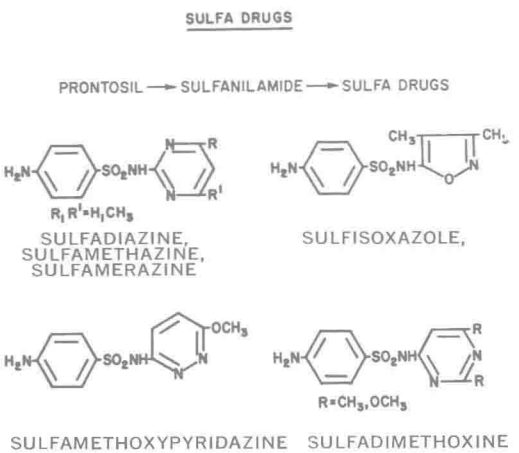

*Sulfanilamide Developments*

No review of medicinal chemistry and particularly of the utility of molecular modification in drug development is complete without at least a brief discussion of the sulfonamides. Domagk's discovery in 1934 of the therapeutic activity of the dye Prontosil rubrum, followed by the brilliant investigations of the French chemists Fourneau and the Tréfouëls, implicating the metabolite sulfanilamide as the active agent, gave new life to chemotherapy. Since then, medicinal chemists have synthesized literally thousands of compounds containing sulfonamide groupings in a search for better drugs and for a more complete understanding of molecular structure and biological activity. As this process went on, it became apparent to medicinal chemists and pharmacologists that the sulfonamide grouping had a rather exalted position, since new and unexpected biological effects were being uncovered, occasionally by accident. Let us briefly review where the initial observations of Domagk have taken us.



The foregoing diagram shows in a classical manner one of the greatest virtues of molecular modification. The medicinal chemists following Domagk's discovery have broadened the usefulness of the sulfanilamides and have created new drugs for conditions entirely unrelated to bacterial infections. Who in the early forties could have predicted that the sulfonamide grouping would have had so great an impact on the practice of medicine? Some of our best advances in the medical sciences are represented here.

**Sulfa Drugs.** The sulfa drugs are still important agents for the control of bacterial-infectious diseases.



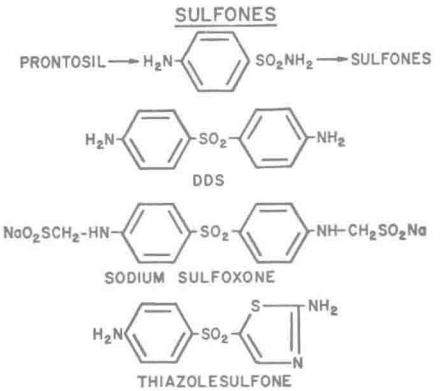

Over the years, however, the sulfa drugs used in medicine have not remained static, as one might have predicted in the early forties. Three of the most widely used sulfa drugs today have been developed rather recently: sulfisoxazole, sulfadimethoxine, and sulfamethoxypyridazine. Sulfanilamide, itself, sulfathiazole, and sulfapyridine have been displaced largely by these drugs in human therapy. This illustrates drug obsolescence.

**Sulfones.** In 1937, there were two distinct leads arising from the Prontosil discovery for agents active against bacterial infections, the sulfa drugs represented by sulfanilamide, and the sulfones, represented by 4,4′-diaminodiphenyl sulfone. Each had its own advantages and disadvantages. Medicinal chemists were divided into two groups and while the protagonists of the sulfa drug had written more exciting chapters, the sulfones did reach distinction.

4,4′-Diaminodiphenyl sulfone may be considered the first major advance in the chemotherapy of tuberculosis. However, it was overshadowed a few years later by streptomycin. DDS did find an important place in the treatment of leprosy following its first clinical use in 1943.

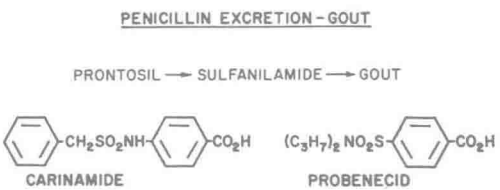
The initial clinical studies served as the first indication that Hansen's disease could be treated by means of a specific antibacterial agent. Up to then, leprosy had for centuries been regarded as incurable.

DDS is still used widely for leprosy, even though other related and possibly better tolerated compounds have been uncovered. Its low cost makes it ideal




for mass treatment in areas of the world where cost of medication is a serious problem.

**Probenecid and Gout.** The story of the discovery of probenecid and its usefulness in the treatment of gout is well known to medicinal chemists. Certain sulfanilamide compounds were observed to decrease the renal clearance of penicillin in a study aimed primarily at increasing the usefulness of penicillin during those days when this antibiotic was difficult and expensive to make.

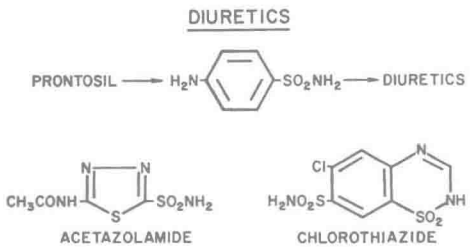



The first compound to arouse interest in the laboratory is the sulfamyl derivative of *p*-aminobenzoic acid. This was followed by carinamide, which was found to produce high plasma levels of penicillin for long periods of time even when relatively low doses of the antibiotic were administered orally. Probenecid, a structural modification of carinamide, was much more potent on a weight basis and on a dosage basis practical for oral administration. In fact, the combination of penicillin and probenecid was a practical oral formulation and was widely used for the treatment of infections until the costs and availability of penicillin were no longer factors and the better orally active penicillins became available.

Notwithstanding its obsolescence in the treatment of infectious diseases, probenecid found a very important place in the physician's armamentarium because of its uricosuric activity. Its interference with the reabsorption of uric acid through the renal tubular membrane was an unexpected observation. Probenecid is the first useful synthetic compound for the control of uric acid excretion and the age-old disease, gout.

**Diuretics and Hypotensives.** One of the side effects of sulfanilamide therapy recognized during the early development of the sulfa drugs as anti-infection agents was the loss of sodium in patients. This observation led to the discovery

that sulfanilamide inhibited the enzyme carbonic anhydrase in carrying out its function—namely, the catalysis of the exchange between carbon dioxide and bicarbonate. Medicinal chemists and pharmacologists quickly recognized the implication of these observations and directed efforts towards molecular modification of the sulfanilamide molecule in the hope of finding a superior and much needed diuretic.




The search was rewarding and opened up new vistas. The first breakthrough in this field was acetazolamide, a potent inhibitor of carbonic anhydrase. This compound induces increased sodium ion excretion and diuresis. It found wide medicinal application in the treatment of cardiac edema, acting presumably by suppression of carbonic anhydrase activity in the renal tubules. Unfortunately, drug tolerance developed in patients, limiting its utility. This deficiency stimulated medicinal chemists to persist in the modification of the sulfanilamide molecule and led to the discovery of chlorothiazide and the thiazide family of drugs.

I need not dwell on the importance of the chlorothiazide discovery. The thiazides have not only proved to be useful diuretics but they have also found very wide application in the treatment of hypertension used either alone or in combination with other hypotensive drugs. As a class they probably represent the greatest chemotherapeutic advance in the cardiovascular diseases.

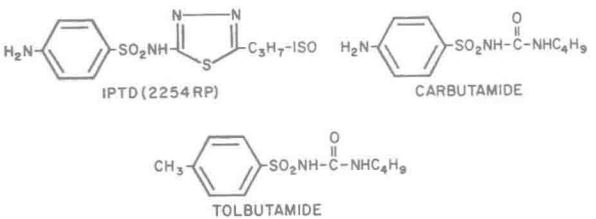
Contrary to the views expressed in many published reviews of this development, the hypotensive effect of chlorothiazide was predicted by those responsible for its discovery. On the basis of known effects of the "rice diet" in hypertensives, the chemists and pharmacologists almost from the beginning of their studies believed that an effective saluretic agent would control the disease more uniformly and effectively than diet.

**Diabetes.** It has been known since the early forties that some of the sulfa drugs produced hypoglycemia as a "side effect." One of the most potent hypoglycemic sulfa drugs, 2254RP, was described by Janbon in 1942.

Oddly enough, the isopropyl group in position 5 is essential for this effect, since the corresponding methyl or ethyl congeners are respectable sulfa drugs. 2254RP was abandoned and the significance of its hypoglycemic property lay dormant until Franke and Fuchs in 1955 reported on the oral hypoglycemic effects of carbutamide. Since the incidence of side effects, particularly blood dyscrasias, was considered excessive, it was never marketed in this country. The methyl isostere tolbutamide was found to be superior with respect to side effects and became the first orally effective agent for the control of diabetes in the "adult-onset" stable patient.

DIABETES

PRONTOSIL → SULFANILAMIDE → DIABETES




The long-sought "substitute for insulin" arose from the astute observation made in the clinic on a potential sulfa drug—a serious side effect turned into a valuable asset.

### *Accomplishments in Drug Research*

The structures shown illustrate just a few of the important advances made through molecular modifications. Starting with Prontosil, we have come a long way. New chapters of greater dimensions have been added to our textbooks of medicinal chemistry. A red-orange dye, of little consequence to Bayer in 1934, has dramatically changed the treatment of important diseases and has saved an untold number of lives. The exciting drama of the intervening years flowed from the labor of countless medicinal chemists employing their most potent weapon of drug design.

Up to now, I have attempted to define molecular modification and its usefulness to the medicinal chemist with living examples. Although our knowledge of the relationship of molecular structure to biological activity has not reached a state where medicinal chemists can circumvent the arduous task of synthesizing large numbers of compounds, we are encouraged by the progress which has been made during the past two decades. We are beginning to sense a pattern which comes into play whenever an interesting observation is made in our screening programs. We have developed over the years a perspective of the field and a capacity to be more selective in our programs to modify structures. Medicinal chemistry stands in its development today where organic chemistry did 30 years ago.

Nevertheless, we have been proud as a group of the accomplishments of the past quarter century. Not only has our science advanced in its fundamentals, but it has had a tremendous impact on the practice of medicine. We were delighted with statements such as those which appeared in a recent report from the New York Academy of Medicine (5): "It is estimated that 90% of present prescriptions are for drugs that were unknown as therapeutic agents 15 years ago." Hence, it is readily understandable why we have become indignant in recent days with what some of us feel to be unfair and even irresponsible attacks on the fruits and methods of our research. It was all the more painful to us that among our critics are eminent scientists of varied medical disciplines, some of whom have shared with us the experiences in creating useful drugs.