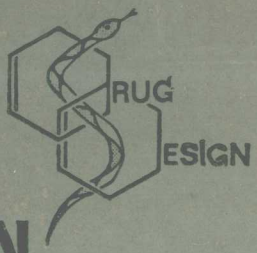

DRUG DESIGN

Edited by E. J. Ariëns

VOLUME VI

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DEPARTMENT OF PHARMACOLOGY
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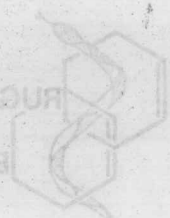

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Preface

Collation and interpretation of data obtained in drug development are of primary importance in drug design. Due to the restricted distribution of much of the information obtained by industrial investigators, this is not a simple matter.

This volume offers the reader a number of chapters dealing mainly with practical approaches to the development of bioactive compounds. An extensive survey is given of the fruitful and thorough investigation of the diphenhydramine derivatives which has resulted in many new valuable drugs and is still an area from which potentially useful compounds can be obtained. Chapters on the design of antiradiation agents, of organ-imaging radiopharmaceuticals, and of X-ray contrast media will supply the reader with new views in these instructive fields of investigation. Another group of compounds holding promise for the future is proteinase inhibitors discussed in Chapter 3. In the last chapter the researcher is given information on pesticide formulation which could prove helpful in the design of new drug application forms.

In general, "excursions" of investigators working on the design of therapeutics into the "gardens" of investigators involved in the development of other types of bioactive compounds such as pesticides may lead to a fruitful cross fertilization.

E. J. ARIËNS

Contents of Other Volumes

VOLUME I

VOLUME II

VOLUME III

VOLUME IV

VOLUME V

Contents

Chapter 3. **Rational Approach to Proteinase Inhibitors**

Shosuke Okamoto and Akiko Hijikata

Chapter 4. **The Design of Organ-Imaging Radiopharmaceuticals**

Raymond E. Counsell and Rodney D. Ice

Chapter 5. **Design of X-Ray Contrast Media**

Hans-Joachim Herms and Volker Taenzer

Chapter 1 Diphenhydramine Derivatives: Through Manipulation toward Design

A. F. Harms, W. Hespe, W. Th. Nauta, R. F. Rekker, H. Timmerman, and J. de Vries

I. Introduction. The Benzhydryl Moiety in Drugs

It is a striking fact that among the great diversity of bioactive compounds there are many that have the diarylmethylene group as a common feature. Negwer (*104*) cites among 3326 structures with 13 or more carbon atoms, 302 drugs which can be construed as diphenylmethane derivatives. If one adds those structures in which one aryl nucleus is (partly) hydrogenated or one or both are replaced by other aromatic systems such as pyridyl and thienyl, the number is far higher.

Chemically there is a great variety in structures, ranging from simple diphenylmethane derivatives to compounds in which the diarylmethylene group is part of a (poly)cyclic ring system. The biological activities, too, cover a broad range. Tables I and II* may give an impression of the importance of the diarylmethylene group as a biofunctional moiety. In this chapter we will limit ourselves to the title compounds and some closely related structures.

In 1944 Rieveschl synthesized the 2-(dimethylamino)ethyl ether of diphenylmethanol (*119*), which compound was introduced as an antihistaminic under the name of diphenhydramine in 1945 (Benadryl, Fig. 1). Rieveschl probably based his work on an earlier structure (929F) found by Fourneau in 1933 to have antihistamine activity (*40*). The product was immediately successful and now, after almost 30 years, diphenhydramine is still one of the most widely used antihistaminics.

There were several reasons why this compound aroused our interest. Investigations which had been going on since the 1930s, had demonstrated that alkyl substitution considerably affects the physicochemical properties of, for instance, tetraphenylethanes which contain the diphenylmethyl group, just like diphenhydramine (*19*). After pharmacological investigations

* Of each type of compounds only a few examples are given.

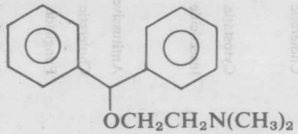


Fig. 1. Diphenhydramine (from Rieveschl, 1944).

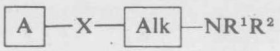
had shown that diphenhydramine possessed anticholinergic and local-anesthetic activity as well as antihistamine activity, we decided that it would be worthwhile to try to achieve compounds with greater specificity of action by adequate substitution such that the rigidity of the molecule and/or its charge distribution was modified. Already from the first series of compounds synthesized it became clear that within certain limits it was indeed possible to produce such an effect by introducing one or more alkyl substituents in one or both phenyl rings (*103*). Subsequently, systematic changes in the alkylene chain and the basic part of the molecule were studied (*102*).

In the following sections we shall first deal with the chemical routes available for the synthesis of diphenhydramine derivatives and then with their biological activities and the gradually unfolding relationships between structure and activity. In this way we hope to illustrate how a phase of molecular manipulation developed into one in which more rational attempts to design have become possible.

II. Review of the Synthetic Routes to Structures of the Diphenhydramine Type

A. Introduction

In this section we review the synthesis of amino ethers of the diphen-



hydramine type in which

A is either a (substituted) diphenylmethyl group, a (substituted) 5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl group or an aza- analog of either of these groups;

X is O or S;

Alk is a lower alkylene group, which may be branched and/or carry hydroxyl groups, or be interrupted by an oxygen atom;

R^1 and R^2 are either hydrogen or lower alkyl or aralkyl groups, or form together with the nitrogen atom, or with the nitrogen and Alk, a heterocyclic ring.