The Benzodiazepines

From Molecular Biology to Clinical Practice

EDITED BY E. Costa

The Benzodiazepines: From Molecular Biology to Clinical Practice

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Preface

Although Auden's expression the "age of anxiety" is rather too glibly applied to the present day, it is true that anxiety, and emotional stress in general, is more frequently seen by specialists than other mental illnesses, such as psychotic and depressive reactions. The latter however have been the object of much more profound and prolonged research (although there is still much to learn concerning the etiopathogenesis of depression, and even more of schizophrenia). Nevertheless, considering that the benzodiazepine anti-anxiety agents have been in use for a quarter of a century, it is only recently that we have begun to understand the possible mechanisms of their action. The discovery of specific binding sites for these substances some six years ago, and their now established interaction with the brain's most important inhibitory neurotransmitter, GABA, raised hopes that this knowledge could be utilized to help unravel the mystery of affective function.

This volume is a comprehensive report of the state-of-the-art in this field, dealing with both preclinical and clinical pharmacology as well as significant topics on clinical usage. The work presented here reflects the stock-taking and goal-setting processes undertaken during the World Congress of Biological Psychiatry symposium, which was held in Stockholm in July, 1981.

This volume will be of interest to all clinicians who are concerned with patients whose symptoms include anxiety and emotional distress, and to researchers working in the area of neuro- and psychopharmacology.

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Contents

PRECLINICAL ASPECTS

CLINICAL PHARMACOLOGY

SELECTED TOPICS IN CLINICAL USE

The Benzodiazepines: From Molecular Biology to Clinical Practice, edited by E. Costa.
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The Discovery of CNS Active 1,4-Benzodiazepines

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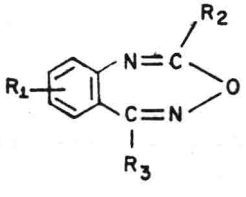
In this chapter, the chain of events that resulted in the discovery of the first centrally acting 1,4-benzodiazepine derivatives will be traced.

In the mid-1950s, when it became apparent that a new class of drugs, then known as tranquilizers, were of remarkable clinical value, Roche decided to embark on a program concerned with the search for products of this type. The tests for screening sedatives and tranquilizers in Dr. Lowell Randall's Pharmacology Department were well in hand and we chemists were asked to produce novel compounds that would be superior to the then-existing drugs. Since practically nothing was known about the mode of action of psychotropic agents and since we were chemists at heart, we selected an approach that would be most attractive and challenging to the bench chemist.

We thought that the exploration of a completely new class of compounds unrelated to any biologically active products would be quite interesting and rather attractive.

The search for such a group of compounds led us to the benzheptoxdiazines (**1**), compounds I had worked on during my dyestuff chemistry years (1,2) at



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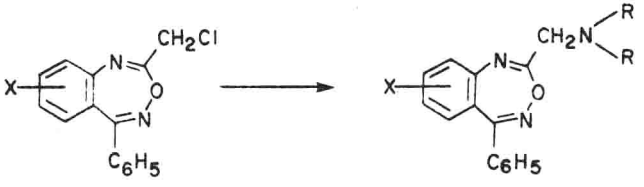
the University of Cracow. Compounds of this type looked particularly interesting. They were readily accessible, relatively unexplored, and would lend themselves to many variations and transformations.

We thought it would be desirable to prepare new types of benzheptoxdiazines into which a basic substituent could be introduced, since it is known to the medicinal chemist that basic side chains often impart biological properties. Thus, a number of the products of type **2** were synthesized and trans-

formed by treatment with secondary amines into products of type 3. The products were formed in good yield, crystallized well, gave nice water-soluble salts but, unfortunately, possessed no interesting biological properties.

However, during these studies, we found that these so-called heptoxdiazines were not heptoxdiazines at all, but were, in fact, the quinazoline 3-oxides (9) 4 and 5, a completely new class of compounds.



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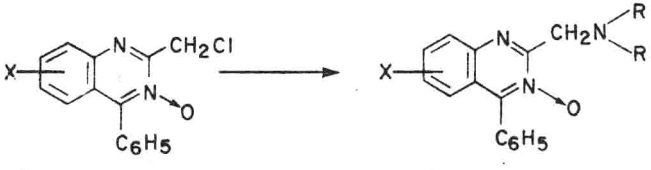

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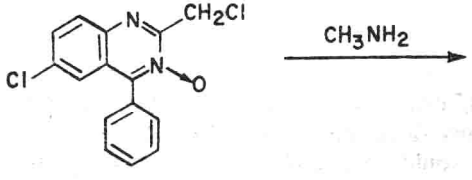
Shortly after this discovery, our work with these compounds had to stop since other problems seemed to be more important and required our full attention. This intensive work in new areas of research resulted finally in a critical situation in April 1957. The laboratory benches were covered with dishes, flasks, and beakers containing various more or less crystalline samples and mother liquors. The work area had shrunk to almost zero and a major house cleaning was in order.

During this clean-up operation, my co-worker, Mr. Earl Reeder, drew my attention to a few hundred milligrams of two compounds, a nicely crystalline base and its hydrochloride. The base had been prepared in 1955 by treatment of the quinazoline N-oxide 6 with methylamine, a primary rather than a



6

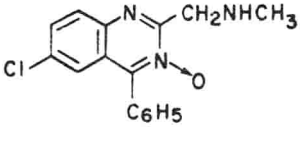
secondary amine. Its hydrochloride was made shortly afterward. The products were not submitted for pharmacological testing at that time because of our involvement with other problems.

In May 1957, we finally submitted the water-soluble salt for pharmacological evaluation. We were quite prepared for another negative result, but thought that the completion of these studies would give us at least a chemically interesting publication. Little did we know that this experiment would start a program that would keep us busy for many years.

Within a few days Dr. Randall informed us that the compound possessed very interesting pharmacological properties. He had compared it with meprobamate, chlorpromazine, reserpine, and even phenobarbital in tests indicating sedative, muscle-relaxant, and anticonvulsant properties (3,4). It was superior in every test to meprobamate; in some of the tests approached the activity of chlorpromazine; and compared very favorably with phenobarbital.

In addition, it showed a pronounced taming effect in monkeys. It is also worth noting that, unlike chlorpromazine and reserpine, it had no effect whatsoever on the autonomic nervous system. Particularly encouraging was the low toxicity, which, as was found later, is typical of all members of this group.

The compound underwent a whole gamut of pharmacological tests by Dr. Randall and his staff; we in our laboratory were concerned with the chemistry of this unusual product, since its UV and IR spectra indicated that the compound was not the expected reaction product. Our studies showed that the compound did not have structure 7, but was the result of an unusual ring enlargement to the benzodiazepine derivative 8 (10). Instead of the six-



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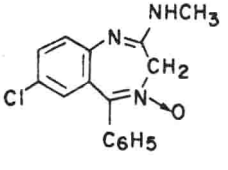


8

membered pyrimidine ring, the compound contained a seven-membered diazepine ring.

We elucidated the reaction mechanism (6) and synthesized a number of related compounds (12), which enabled us to file a patent application in May 1958. Because of the novelty of this class of products, the patent (5) was granted without any difficulty, and appeared in July 1959.

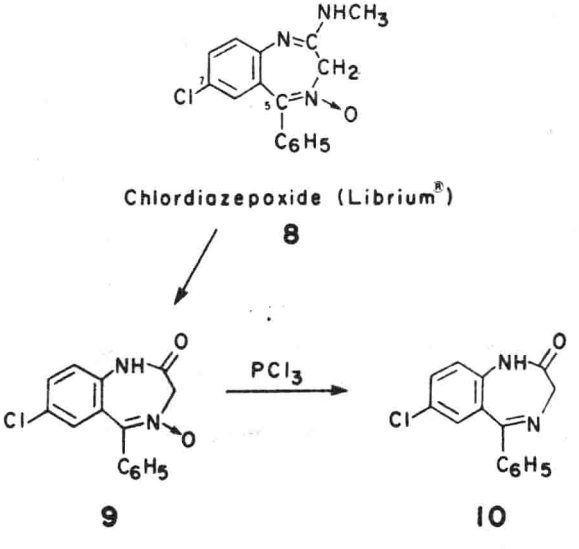
Dr. Randall's pharmacological evaluation of all 2-aminobenzodiazepines then on hand showed that none were superior to our first product. It was,

therefore, studied in great detail; all the pharmacological, toxicological, and the first clinical studies gave excellent results. The clinical investigations under the efficient direction of Dr. Leonard Hines was expanded, and within a short time about 16,000 patients had been treated with this drug. The NDA application was submitted, and thanks to the then-existing positive attitude of the FDA, approval was obtained in record time. The drug was introduced under the trade name Librium® in 1960, 2½ years after the pharmacological studies had started. The generic name that was later generally accepted was chlordiazepoxide.

While this drug was prepared for introduction, we became interested in a form that would lend itself to the preparation of a pharmaceutically acceptable elixir or a syrup for pediatrics or geriatric use. This was done since chlordiazepoxide hydrochloride, the water-soluble clinically used salt, was extremely bitter—not surprising at all since it is well-known that any useful drug is bitter, hygroscopic, or unstable. This compound was rather interesting; it possessed all three properties.

During this search, we did not find the desired tasteless form, but observed that the hydrochloride was not stable in aqueous solution, as could have been expected. It hydrolyzed to the lactam N-oxide **9** (11), which possessed the same pharmacological properties as chlordiazepoxide.

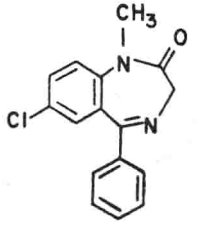
Furthermore, removal of the N-oxide oxygen to form **10** did not affect its



activity. Thus, it turned out, that some of the unique chemical features that seemed so characteristic of chlordiazepoxide were not needed at all for its pharmacological activity. The N-oxide function, and particularly the basic substituent that was the cornerstone of our initial working hypothesis, proved

to be only unnecessary adornments. The only features common to these biologically active compounds were the 1,4-benzodiazepine ring system bearing a chlorine in the 7-position and the phenyl group in the 5-position.

In the search for a product that would be superior to Librium, we started a broad program devoted to molecular modification of 1,4-benzodiazepines. We were particularly attracted to the simple compounds of type 3 and developed new methods (8) for their synthesis, and compared the thus-prepared benzodiazepinones with Librium. Near the end of 1959, we found a product that was, in most of the tests, 3 to 10 times as potent as chlordiazepoxide. We hoped that this superior potency would be associated with other advantages in its clinical spectrum of activity and selected it for a thorough evaluation. The pharmacological and toxicological data looked very promising; the clinical results were equally encouraging and led ultimately near the end of 1963 to the introduction of diazepam, under the trade name Valium®. The product was



Diazepam (Valium®)

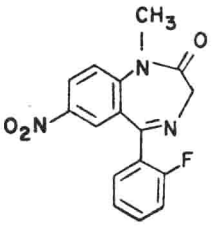
11

more potent and indeed had a broader spectrum of activity than Librium; in particular the muscle relaxant properties are more pronounced. In this case, the time elapsed between the first pharmacological testing and introduction was 4 years.

Our intensive efforts with an increased staff of chemists and pharmacologists led to thousands of products that were all pharmacologically evaluated. The thus acquired knowledge of the structure-activity relationships in this series of compounds made it possible to synthesize at will highly active products (7) as exemplified by the potent hypnotic flunitrazepam (Rohypnol®) (**12**), which was synthesized by Dr. Fryer.

The study of benzodiazepine derivatives has been continued throughout the last 20 years; many variations were carried out and many sophisticated novel derivatives were synthesized.

At present, over 25 1,4-benzodiazepine derivatives are on the market and research in the benzodiazepine field is still in progress. The discovery of



Flunitrazepam (Rohypnol®)

12

receptor sites in the brain facilitates the study of their biological action and might ultimately shed some light on the mysteries of the functioning of the brain.

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