CLINICAL USE OF PSYCHOTHERAPEUTIC DRUGS

Fifth Printing

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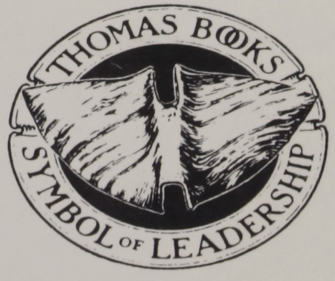

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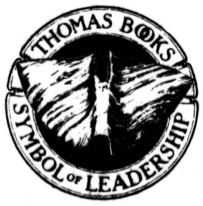

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PREFACE

ALMOST anyone who works in a field concludes, sooner or later, "I should write a book." This thought first occurred to me about a decade ago, after several years of clinical experience in the evaluation of psychotherapeutic drugs. Subsequently, a number of other books on psychotherapeutic drugs appeared, and this development, along with many other commitments of my own, allowed me to resist successfully this impulse until now.

Why write another book on the clinical use of psychotherapeutic drugs now? First, I was amazed to find while lecturing at various hospitals and teaching centers around the country how much clinicians and students desire both practical information about the use of these drugs as well as some concept of the scientific basis for their use. Second, the response to relatively brief review articles in medical journals was an overwhelming request for reprints, often in multiples, which also seemed to confirm a need. Finally, we have reached a plateau or consolidation phase in the history of psychotherapeutic drugs where radically new treatments (such as these drugs were only a little more than a decade ago) are not appearing. Much of our recent effort has been spent in trying to learn how better to use those drugs we have.

My purpose in this book has been to provide a general approach to drug therapy for mental and emotional disorders rather than a detailed description of individual drugs, doses, dosage schedules, formulations and all those bits and pieces of information which are so readily available in package inserts, the *Physicians Desk Reference,* or other sources. Rather than addressing myself to others who work in the field, so as to impress colleagues with my erudition, this book is directed to those clinical practitioners of psychiatry or other medical specialties who use these drugs in their

clinical practice, and to students, who may find that the treatment of this large group of drugs leaves something to be desired in most textbooks of pharmacology. Some attempt has been made to justify the recommendations for use based on chemical and pharmacological principles, but no pretense is made that this work is a scholarly endeavor in those recondite areas.

As in any field, differences of opinion about the proper uses of these drugs abound. Any statement, if it is not banal, will also be contentious. The reader should be warned that these are personal opinions, which although based on long clinical and investigative experience, are not to go unchallenged. My major hope is that he may be spurred to compare them with his own experience and that of others, so that he may use these agents to their fullest potential for helping his patients.

LEO E. HOLLISTER

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Clinical Use of Psychotherapeutic Drugs

CHAPTER 1

INTRODUCTION

MENTAL illness may be both more frequent and more incapacitating than any other disease or disorder. Probably one-half of all visits to physicians are based on some emotional or mental disorder. Almost two million persons in the United States are at any given moment under some formal treatment for mental illness. An epidemological survey in midtown Manhattan led to the conclusion that only 20 percent of persons could be qualified as normal. While it must be devoutly hoped that Manhattan is not a model for the rest of the world, such a statistic is staggering (17).

Psychiatrists recognize many varieties of mental or emotional disorders (it is difficult to talk of "mental diseases" in the absence of a pathogenetic basis). Such a vast number of "therapies" abound that the situation was easily made the subject of parody a number of years ago (218). Each year some new therapy is announced, usually a rediscovery or renaming of a technique known before. To some extent the same situation applies to drug therapy, as in recent years, novelty in new drugs has been more likely to be the change of one atom for another in the structural formula. Drug therapy nonetheless has an important place in modern psychiatric treatment, but, like all other treatments can be harmful if done poorly.

HISTORICAL BACKGROUND

Kraepelin published an essay, "On the influence of several medicaments on simple psychic processes" in 1892, ten years after he had begun these investigations, and before his epochal achievement in dividing functional psychoses into two major divisions, dementia praecox and manic-depressive psychosis. Freud, too, was an early psychopharmacologist, having studied cocaine, among other drugs. He apparently thought that the

solution to major mental disorders was more likely through chemical intervention than by psychoanalysis. Although these and other examples suggest that psychopharmacology is not an especially new discipline, the modern era began in the early 1950's. The first use of the word, "psychopharmacon" (from which "psychopharmacology" was derived), was in 1548 as the title of a prayer book for dying individuals (197).

Somatic therapies in psychiatry really began with the sequence leading to the treatment of dementia paralytica with drugs and physical methods. The introduction of arsphenamine as a treatment for syphilis, the proof of the syphilitic origin of general paresis, the amelioration of organic arsenical treatment by artificially induced fever (based on the fact that patients with paresis who survived typhus fever were improved), and finally the eradication of neurosyphilis by penicillin occurred over a 35-year period preceding modern psychotherapeutic drugs. Insulin shock, drug-induced seizures and finally electrically-induced convulsions date from the 1930's. Insulin shock, because of its great dangers and expense, was on the wane before the introduction of modern drugs. Electroconvulsive therapy has been largely supplanted by drug treatment, perhaps excessively so. Prefrontal leucotomy, another product of the 1930's, was eliminated by drugs, but much less destructive and more precise types of psychosurgery are once again being experimented with.

The first modern psychotherapeutic drug, lithium carbonate, dates from 1949, but through a variety of circumstances only became popular in recent years. Lithium was found to protect guinea pigs against toxic effects of urea, producing a state of lethargy which led to its experimental use in mania. Rauwolfia root was the subject of a number of reports since 1931 in the Indian medical literature, both as a treatment for hypertension and mania. Reserpine was isolated in 1952 by two chemists in the Ciba Laboratories in Basel and soon after was put to clinical use both in cardiology and psychiatry. Chlorpromazine was synthesized in 1950 at Rhone-Poulenc Laboratories in France, as part of a program to develop antihistaminic phenothiazine derivatives (110). It was first used in 1951, along with promethazine (another antihistaminic phenothiazine) and meperidine, as part of a "lytic

cocktail" for a new type of anesthesia. It was noted that it had unusual sedative properties and in 1952 was first tested in France for the treatment of schizophrenic patients. The monoamine oxidase inhibitors had a checkered history, for sporadic trials in psychiatric patients followed the observation that iproniazid produced euphoria in patients with tuberculosis. Unfortunately, most of the trials were made with isoniazid, a better antituberculous drug but a relatively weak enzyme inhibitor. By 1952, the potent enzyme-inhibiting property of iproniazid had been described. As the importance of monoamines in the central nervous system and in the action mechanisms of other psychoactive drugs developed during the 1950s, it became inevitable that monoamine oxidase inhibitors would be tried clinically, as they were in 1957. The tricyclic antidepressants, because of their close resemblance chemically to the phenothiazines, were originally thought to be potential antipsychotic drugs. Only by the excellent clinical observation that imipramine was beneficial for depressed patients rather than schizophrenics was its antidepressant effect appreciated in 1957. A curious thread that weaves through the modern history of psychotherapeutic drugs is that most were initially planned for other uses and the psychiatric uses discovered more or less fortuitously in the clinic.

IMPACT OF MODERN PSYCHOTHERAPEUTIC DRUGS

Psychiatric thinking and practice were drastically altered by the introduction of these new psychotherapeutic drugs. One of the ways in which psychiatric thinking has changed is that one considers more and more likely the possibility that a great many "functional" psychiatric disorders have a genetic, and therefore biochemical, cause. Schizophrenia, that mysterious and crippling affliction, became both amenable to chemical treatment and possible to mimic, at least in some respects, by chemicals. The antipsychotic drugs have not cured schizophrenia, nor has the model psychosis from lysergic acid diethylamide (LSD-25) unraveled its biochemical basis. Still, we think more of genes and amines in seeking to explain schizophrenia than we do of dreams and schemes of the unconscious (94). The case for a biochemical

substrate of serious mental depressions is even more advanced. These disorders also seem to have a pattern of genetic transmission, and the ability to produce a model of them in man, by reserpine, as well as the elucidation of the mode of action of some of the antidepressant drugs, has evolved into the "amine hypothesis" of depression (43, 75). That the pendulum should swing back towards a new emphasis on biological psychiatry is not surprising. After all, the only major psychiatric disorder to be eliminated in the present century, general paresis due to syphilis, yielded to techniques of the biological sciences.

The hospital practice of psychiatry has changed remarkably in the past two decades. Before the advent of modern drugs, one of every two hospital beds in the United States was occupied by a psychiatric patient, fully 50 percent of these by victims of schizophrenia. Since 1955, when these drugs first had widespread clinical impact, the number of hospital beds occupied by psychiatric patients has steadily declined. Some hospitals have only one-quarter to one-tenth the bed occupancy of fifteen years ago. Proposals have been made to eliminate many mental hospitals and to transfer almost entirely the care of mentally ill patients to the community. Such trends would have been unthinkable without the availability of drugs which curb the deteriorating course of serious mental disorders. Unfortunately, good as drugs have been they are not good enough. We have many patients who are better and too few who are well.

Aside from changes in numbers of patients in mental hospitals, the hospitals themselves underwent remarkable changes. From being prisons, they became true hospitals, with locked wards either completely disappearing or being only reserved for the most seriously disturbed patients for brief periods of time. The rights of patients to personal belongings, to a voice in the conduct of their treatment, and to escape from involuntary confinement were accelerated, if not made possible, by the advent of effective drug therapy. Hospital personnel who used to devote most of their energies to custodial duties have now all become "therapists." While much of what passes for "psychotherapy" may be intuitively based, the assertion that persons with no medical training and relatively little experience can manage drugs

effectively is dangerous nonsense; amateur drug therapists can be disastrous.

NOMENCLATURE OF PSYCHOTHERAPEUTIC DRUGS

The initial epithet "tranquilizer" was devised because "sedative" had become a dirty word among psychiatrists after the belated discovery that barbiturates might lead to physical dependence. The implications of the two words are the same, so that widespread adoption of the term "tranquilizer" implied that drugs so labeled were really newer types of sedatives. To some extent this was true, especially in regard to the antianxiety drugs, but in the case of phenothiazine derivatives and other antipsychotics, the confusion caused by the inappropriate term is still widespread. One still hears them referred to as "chemical straitjackets" despite the abundant evidence that they are liberating rather than constricting agents. Attempts have been made to differentiate "tranquilizers" from conventional sedatives by introducing the divisions, "major" and "minor," or by coining Greek-root neologisms such as "ataractic," "neuroleptic," "psycholeptic" or "psychoinhibitor." These terms, too, suffered from some implicit assumptions about the modes of action of drugs so labeled. By the same token, one had for so long associated an "antidepressant" drug with a stimulant that even today tricyclic antidepressants are often referred to as stimulants, something they clearly are not.

A more realistic nomenclature might be based on the putative clinical uses of the various drugs. Drugs used for treating anxiety, in all its many clinical guises, would be referred to as antianxiety drugs; those for mental depressions, as antidepressants; and those used for treating schizophrenia and other psychoses would be termed antipsychotic drugs. With the advent of drugs for treating mania, one can speak of antimanic drugs. Even such a nomenclature has defects; each of the drug types may, under certain circumstances, be used for the other purposes. Nonetheless, the "anti-" system of nomenclature has greater simplicity and more clinical relevance than any of the others.

SPECIAL PROBLEMS IN EVALUATING PSYCHOTHERAPEUTIC AGENTS

Uncertain Diagnoses and Pathogenesis

Psychiatric diagnosis is almost completely based on inference. With the exception of those acute and chronic brain syndromes associated with neuropathological abnormalities, most psychiatric disorders leave none of the visible marks which provide confirmatory feed-back from the necropsy room. The data upon which we make our inferences are soft, being based on what patients tell us, what we infer from what they tell or how they act, or what other people tell us about them. Even the most precise psychological testing makes only the grossest sort of distinctions, such as a "functional" rather than an "organic" disorder.

Despite these difficulties, clinical data of the type mentioned can at least be handled in a standardized fashion. Psychometric codification of these data and criteria for their evaluation can be developed to permit a semiquantitative appraisal of the degree of departure from normal as well as a qualitative profile of the type of psychopathology present. Numerous psychiatric rating scales have been developed to assess most psychiatric disorders in some such "objective" way, especially since the advent of psychotherapeutic drugs. Experience with these methods indicates that psychometric assessments approach the validity and the level of consensual agreement between raters that one might expect from interpretations of abnormal electrocardiograms or chest x-rays.

Not only do we lack the ability to verify diagnosis by the ultimate demonstration of some pathological change, but we have little concept of the pathogenesis of the illnesses we are treating. Theories of pathogenesis for the functional psychiatric disorders abound, but evidence for any of these is relatively scanty. Nosologic nomenclature has become the refuge of our ignorance. At times, frustration with psychiatric nomenclature has led to the suggestion that all psychiatric diagnosis be abandoned and that patients be described in terms of disturbances in psychodynamics. To many, this suggestion is analogous to substituting the intangible for the nebulous. Recently, the tendency has been to

classify empirical groupings of psychiatric disorders based on the presenting clinical symptoms and signs and demographic variables in patients (143, 169). Such groupings have verified the major traditional diagnostic categories of psychiatric patients but have decreased the subdivisions. They appear to have some value in differentiating between responses to drugs. Still, it is highly doubtful that such empirical classifications will add to our basic understanding of the various functional psychiatric disorders.

Confounding Variables

Due to uncertainty regarding pathogenesis, multifaceted treatment programs are used with most emotional disorders. The old adage that the lack of a single effective treatment encourages multiple treatments is nowhere more evident. The number of "therapies" offered psychiatric patients continues to multiply. While no one could argue against any measures which may help patients, it is obvious that the many treatments offered confound the problem of drug effects to varying degrees.

Controlled Clinical Trials

Besides the influence of concurrent treatments, the course of many emotional disorders is variable, with some spontaneous improvement or remission. Not every anxious patient is always so; environmental influences play a considerable role in determining the degree of anxiety. The same is true of depression, a fact which has been documented repeatedly during controlled studies of antidepressant drugs. Schizophrenic reactions also may remit spontaneously, although apparently not as often as thought. They may also become worse in the absence of effective treatment.

To control for these extrinsic variables, controlled clinical trials have been used extensively for evaluating psychotherapeutic drugs. Such trials are based on large, homogeneous samples of patients, random assignments of treatments, blind controls, objective recording, and statistical analysis of data. Although none of these techniques was initiated by clinical psychopharmacologists, it is fair to say that they reached full flower in the study of

psychotherapeutic drugs.

One should not be dogmatic about controlled trials. Valid observations can be made by good clinicians in the absence of formal controls; premature controlled studies may even be misleading. They are to be done only after the proper indications, dose, and most common side effects of a drug are known. Finally, it should be realized that controlled studies scarcely ever reveal a new treatment, but simply confirm or deny expectations about a drug. In making clinical judgments about the effectiveness of drugs as therapy, however, evidence from controlled studies should be given greatest weight.

OVER- OR UNDER-USE

Psychotherapeutic drugs accounted for 17 percent of all prescriptions in a survey of drug use in an American community. "Tranquilizers" accounted for 7.7 percent of all prescriptions, hypnotics and sedatives for 3.6 percent and amphetamines for 3.4 percent, the latter being the eighth in rank of frequently prescribed drugs (221). Such surveys only tap the use of psychotherapeutic drugs in the private sector of medicine. As most hospital care of mental disorders is done by the public sector, the percentage for the latter would very likely be much higher. No one can argue that these drugs are not widely used.

The argument seems to center about whether or not they are wisely used. On the one hand are those who directly accuse the pharmaceutical companies of "mystifying" the indications for their drugs, by means of promotional material suggesting use of drugs to relieve trivial symptoms (140). For instance, an antianxiety drug was promoted for treating the anxiety children suffer when they first leave their families to go away to school. Such anxiety is obviously better worked through rather than relieved by the artifice of drugs. Implicit in such accusations are that physicians are easily gulled by such advertisements. Such an assertion is by no means established (in fact it may be questioned how many of these advertisements are actually read) but is easily made. Others, whose bias is clear from the pejorative term "over-medicated society" in the title of their paper, suggest that

physicians are not just stupid, but rather lazy (161). They prescribe psychotherapeutic drugs because they don't want to take the time to deal with patients. Kafka put it much better: "Writing prescriptions is easy; understanding patients is difficult." Of course, one assumes that given a proper amount of time, a physician (or more likely some "therapist" of varied credentials) would be able to deal with the patient in such a way that drugs would not be needed, again an assertion which lacks genuine proof.

On the other hand, data from a survey of drug use in California adults suggests that perhaps drugs are being used rather wisely. Although 50 percent of persons have used some psychotherapeutic drug during their lifetime, and 30 percent within the past year, frequent use occurs in only about 17 percent of adults. Women use drugs more than men (the latter no doubt using the social drug, alcohol, in lieu of prescribed drugs), and those whose supports in the form of religion (no affiliation) or family (divorced or separated) are lacking tend to use them the most. The patterns of frequent drug use change with age, stimulants being used by men in the 30's, tranquilizers in the 40's and 50's and sedatives in the 60's. Such data suggest that despite such frequent use of these drugs, they are used selectively and with some apparent rationale (149).

A small minority insist that drugs are under-used, that many patients suffer needlessly because physicians have become so fearful of creating drug dependent individuals that they use drugs less often than required. While such a situation may happen occasionally, it is doubtful that it is the rule. Nonetheless, physicians can be moved to strange positions by prevailing public opinion. Witness the absurd situation in regard to amphetamines. Physicians are now eagerly confessing that for over thirty years they employed a group of drugs with no therapeutic use. Why? Because some clucks have taken the same drug and have given it to themselves intravenously in 10 to 100 times the usual oral doses used for treatment and have had some harmful effects from this practice. Had aspirin been abused in a similar fashion, the results would have been far more devastating. But would it make sense to deny the efficacy of aspirin because of such abuse?

Extreme positions are rarely valid. The proper use of psychotherapeutic drugs is not to be measured by how many people use them, or how often, but under what circumstances and with what effects. The prudent use of psychotherapeutic drugs demands the same skills required for the use of any other type of drug: proper diagnosis, proper selection of drug, proper doses and dosage schedules, and careful clinical followup. If these conditions are met, one need not worry about whether patients are getting too much or too few of these drugs.

DESIDERATA

The ideal psychotherapeutic drug would: (a) cure or alleviate the pathogenetic mechanisms of the symptom or disorder; (b) be rapidly effective; (c) benefit most or all patients for whom it is indicated; (d) be nonhabituating and lack potential for creating dependence; (e) not have tolerance develop; (f) have minimum toxicity on the therapeutic range; (g) have a low incidence of secondary side effects; (h) would not be lethal in overdoses; (i) be adaptable both to inpatients and outpatients; and (j) not impair any cognitive, perceptual or motor functions. No such drug exists, but to a fairly surprising degree many of the available drugs meet the majority of these desiderata. It has been both our blessing and our curse that we had effective drug therapy for emotional disorders before we had a science of behavioral pathology. Our best hope for getting better psychotherapeutic drugs is to understand better the causes of emotional disorders.

CHAPTER 2

ANTIPSYCHOTIC DRUGS

FEW illnesses compare with schizophrenia in taking such a toll of the most useful years of an individual's life. Few illnesses have been so frustrating to explain or treat. Few illnesses create such sadness and guilt in those who cannot find ways to help their affected loved one. "Cures" are rare indeed; probably less than 15 percent of individuals seriously affected who require any kind of prolonged hospitalization ever again function "normally." Schizophrenia and alcoholism are the two major problems in psychiatry; they deserve far more attention than they have been given in the past.

Although the disaster that is schizophrenia has been partially mitigated by drugs, our knowledge of the pathophysiological mechanisms of this disorder is still meager. The impetus provided by the success of drugs in treating this disorder resulted in many inquiries into the biological bases for it (228). Older notions that schizophrenia is a reaction to social-psychological influences, such as that it represents a disordered learning process initiated and sustained by conflicting messages from mother, have few remaining adherents. The present tendency is to regard schizophrenia as a genetically determined disorder with biological mechanisms whose phenotypic expression may be influenced in part by life experiences. As antischizophrenic drugs were discovered fortuitously, our continuing lack of knowledge of the pathogenesis of the disorder has limited development of more effective drugs. We have new chemicals, but old drugs.

The term "antipsychotic" drug should in no way imply that these drugs are curative. Rather one might consider them analogous to bacteriostatic as contrasted with bacterial antibiotics. They may simply relieve secondary symptoms of schizophrenia and arrest or ameliorate the natural course of the disorder. Even should these drugs prove ultimately to have provided no more

than symptomatic relief, they should not be denigrated. Most treatment in medicine is symptomatic, despite our desires to think the contrary.

CHEMICAL AND PHARMACOLOGICAL DIFFERENCES

At present, nine chemical classes of compounds are known which ameliorate psychoses and evoke extrapyramidal reactions, the two unique properties of antipsychotic drugs. The three classes currently in use in the United States are shown in Figure 2-1. Although some close resemblances between the chemical structures of the phenothiazines and thioxanthenes are apparent, resemblances between these types of drugs and the butyrophenones are less obvious.

The structures of most antipsychotic drugs can be viewed as tertiary or rarely, secondary, amines derived from methylethylamine (-C-C-N-C). Phenothiazine antipsychotics have the following common S-shaped configuration, regardless of which subfamily they belong to (R-N-C-C-C-N-C). The thioxanthenes show a similar

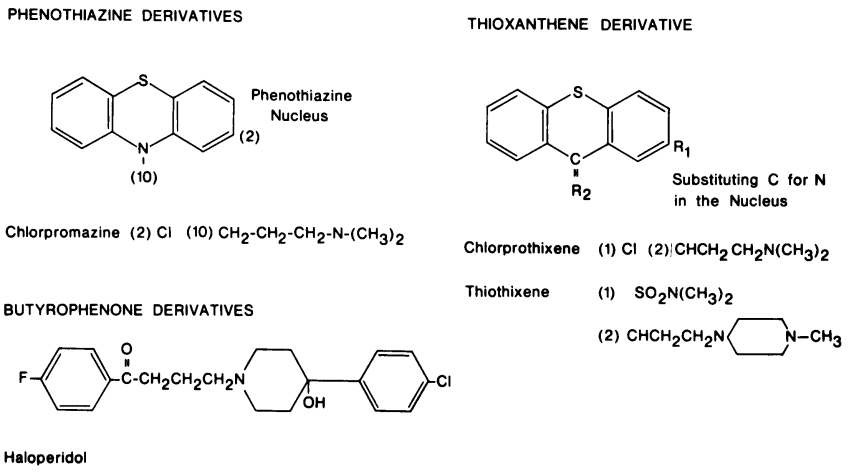

Figure 2-1. Structures of the three classes of antipsychotic drugs available in the United States.

nucleus (R-C-C-C-C-N-C), as do the butyrophenones (R-C-C-C-C-N-C). This conformation of the molecule may be critical to its effect (116, 217). On the other hand, the side chain substituents which show this conformation are not specific to antipsychotic drugs, as similar configurations can be found among some of the tricyclic antidepressants. Here the major difference may be in the planarity of the molecule, the phenothiazines being coplanar while the tricyclics are not.

The phenothiazine derivatives are the longest known and most popular antipsychotics. Partly because of chemical differences but also because of variations in pharmacological actions and potency, distinction between the three chemical subfamilies of phenothiazines should be made (Fig. 2-2). Compounds with an aliphatic dimethylaminopropyl side-chain, such as chlorpromazine, are relatively low in potency and high in sedative effects. Substitution at the 2-position of the phenothiazine nucleus creates a more potent compound than no substitution; for example, chlorpromazine is more potent than promazine. Some substituents such as the trifluoromethyl group confer more potency than a simple chlorine atom (triflupromazine is more potent than chlorpromazine). The nuclear substituents may increase potency by increasing fat solubility of the molecule. The piperidine side-chain is represented by thioridazine and its side-chain sulfoxide metabolite, mesoridazine, both most different from other phenothiazines in pharmacological actions. Piperacetazine, technically a piperidinyl phenothiazine, has pharmacological properties which are more like those of the piperazine group, to which it has a closer spatial configuration. Three variants of the piperazine side-chain, along with variations of the ring substituent, create a rather large class of piperazinyl phenothiazines. These compounds are much more potent than their ring-substituted analogs in the aliphatic series. They tend to possess less sedative effects than the other two classes, but are more likely to produce extrapyramidal reactions at equivalent therapeutic doses.

The relationship between the thioxanthenes and the phenothiazines is clearly evident (See Fig. 2-1). Substitution of the carbon-atom for the nitrogen-atom in the ring alters the geometry of the molecule somewhat. Chlorprothixene is the thioxanthene