Thiothixene and the Thioxanthenes

From the Proceedings of the Third International Symposium on Phenothiazines and Structurally Related Drugs held at the National Institute of Mental Health, June 25-28, 1973, Rockville, Maryland, U.S.A.

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Thiothixene and the Thioxanthenes

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Foreword

Of the three classes of neuroleptics, phenothiazines, butyrophenones, and thioxanthenes, the thioxanthenes are the least understood. Recently, however, thiothixene (Navane®) has become more widely used in the United States.

The increased interest in thiothixene was the basis for including a special thioxanthene session in the Third International Symposium on Phenothiazines and Structurally Related Drugs.

This publication includes the proceedings of this thioxanthene session.

Co-Chairman's Preface

Victor Borge tells the story of his uncle who spent 20 years in the laboratory finally to emerge with the cure for a disease which didn't exist. A similar fate almost overtook thiothixene. Although a drug usually finds its disease eventually, there are times when it can stagger around trying to determine where it belongs.

Thiothixene successfully found its way home. Not only schizo-affective disorders but also any of the schizophrenic conditions in which the patient needs "activating" are prime indications for thiothixene. Too often we are able to clear up the secondary symptoms of schizophrenia, such as hallucinations or delusions, only to be left with a flat, unmotivated, affect-less shell of a person. Without the dangers of overstimulation which might result from the addition of antidepressants, a switch to thiothixene results in continued freedom from psychotic ideation plus enough "get-up and go" to begin working toward social, economic, and personal rehabilitation.

To banish psychopathology is not enough: we must return the patient to productive participation. We in the United States have a great deal to learn from our colleagues in the Scandinavian countries and in Europe (East and West). They have been at it much longer and are much farther advanced in many ways. Responsibility does not end with treatment. The ultimate goal, of which medical treatment is only a part, involves the total habilitation (or re-habilitation) — making fit or able (again) — of the patient. For long-term use when activation is a necessary ingredient for successful treatment, the appropriate drug can be of crucial importance. Thiothixene is more often than not the drug of choice.

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Co-Chairman's Preface

Much has been written about the effect that minor structural changes have on the activity and side effects of psychotropic drugs. The papers in this volume indicate that a slight change in the phenothiazine ring has converted the phenothiazine thioproperazine to the thioxanthene thiothixene, eliminating many of the potentially serious side effects. This particular thioxanthene derivative shows an unusual spectrum of activity, and its clinical effectiveness has not yet been fully appreciated by all clinicians.

Studies in this volume offer interesting new approaches to treatment of the psychotic child and adult as well as the depressed patient. It should be remembered that the greater the number of psychotropic compounds available, the more probable the chances of success in treatment. Only with further laboratory and clinical psychotherapeutic research will progress continue to be made toward eliminating the cancer of the mind known as schizophrenia.

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Chemical, Pharmacological, and Metabolic Considerations on Thiothixene

Albert Weissman

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INTRODUCTION: CHEMICAL AND PHARMACOLOGICAL RELATIONSHIP OF THIOXANTHENES AND PHENOTHIAZINES

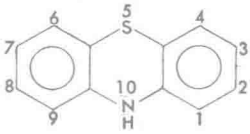
The thioxanthene nucleus is a 6,6,6-tricyclic system closely related to the phenothiazine nucleus (Table 1). Like phenothiazine derivatives, all thioxanthenes in therapeutic use as antipsychotics have a 3-carbon side chain terminating in an amine grouping, and are substituted in the 2-position of the nucleus. Certain structural features of thioxanthenes differ significantly from those of phenothiazines because free rotation of the side chain is prohibited by the double bond at the Δ-9 position. This provides for a separation of thioxanthene derivatives into *cis* and *trans* spatial isomers (Fig. 1). Of considerable theoretical interest regarding the configurational requirements for antipsychotic drugs (3) is the fact that *cis* and not *trans* isomers are the active compounds (2, 7, 9).

The psychopharmacological activities of thioxanthenes generally parallel those of the analogous phenothiazines. One likely difference lies in the magnitude of extrapyramidal effects seen in the two series. For example, thiothixene (Navane®) is the thioxanthene analog of the phenothiazine, thioproperazine (marketed in England as Majeptil®). This phenothiazine is an active antipsychotic, but one that produces marked extrapyramidal side effects. Probably on that account, thioproperazine has never been developed for use in the United States. In animal studies (9) as well as in clinical experience, thiothixene appears to be less potent than thioproperazine in producing this class of side effects.

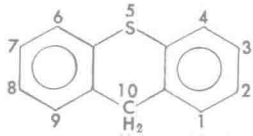
No proof exists that animals can become psychotic and hence the efficacy of antispsychotic drugs can be documented only by clinical studies. Nevertheless, some prototypical psychopharmacological features of known antipsychotic drugs in animal studies have been identified. These include (a) selective suppression of conditioned avoidance behavior, (b) blockade of the behavioral effects of amphetamine, and (c) antiemetic effects against apomorphine-induced emesis in dogs. In each of these respects thiothixene exerts outstanding activity as compared with other antipsychotic drugs.

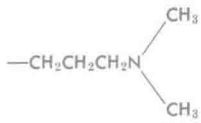
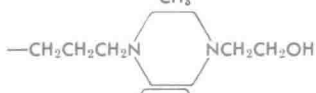
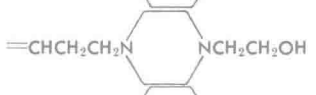
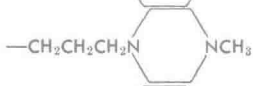
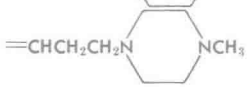
TABLE 1. *Relationship between phenothiazine and thioxanthene nuclei and derivatives active in psychotic patients*

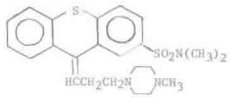
Phenothiazine



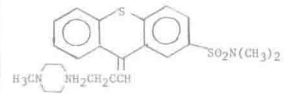
Thioxanthene



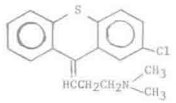
2-Substituent	10-Position side chain	Nucleus	Compound
Cl		P	Chlorpromazine (Thorazine®)
Cl		T	Chlorprothixene (Taractan®)
Cl		P	Perphenazine (Trilafon®)
Cl		T	Clopenthixol [not available in U.S.]
$SO_2N(CH_3)_2$		P	Thioproperazine [not available in U.S.]
$SO_2N(CH_3)_2$		T	Thiothixene (Navane®)



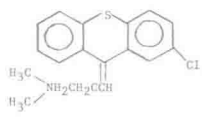
thiothixene
(Navane(R))



trans-isomer of thiothixene
(inactive)



chlorprothixene
(Taractan(R))



trans-isomer of chlorprothixine
(inactive)

Fig. 1. Structures of thiothixene, chlorprothixene, and their inactive *trans* isomers.

SELECTIVE SUPPRESSION OF CONDITIONED AVOIDANCE BEHAVIOR

Perhaps the simplest test of this type performed with thiothixene is one in which rats were first trained to avoid foot shock by leaping onto a platform mounted above the floor of a shock box and extending outwards from the box. During each trial the conditioned stimulus consisted of cues from the box itself for 10 sec and a tone plus these cues for the next 10 sec. If a rat failed to avoid during these 20 sec, foot shock was delivered for 10 sec, or until the animal escaped by leaping onto the platform. Following training, rats were divided into groups and exposed to drug treatment.

In a direct comparison of thiothixene with two other thioxanthenes, chloroprothixene and clopenthixol, thiothixene disrupted conditioned avoidance behavior in most animals at doses of 3.2, 10, and 32 mg/kg (Fig. 2; Ref. 10). The peak effects of thiothixene occurred between 2 and 6 hr after administration. Avoidance disruption after thiothixene was selective; with very few exceptions, rats continued to escape shock when it was presented following the 20-sec avoidance period. After chlorprothixene or clopenthixol, on the other hand, there was a loss of both escape and avoidance behavior. While the onset of action of chloroprothixene and clopenthixol was more rapid, the duration of action of thiothixene was considerably longer.

In a direct comparison against three phenothiazine derivatives (9), the data from thiothixene were virtually identical to those in Fig. 2, and closely resembled data after thioproperazine. Chlorpromazine and prochlorperazine

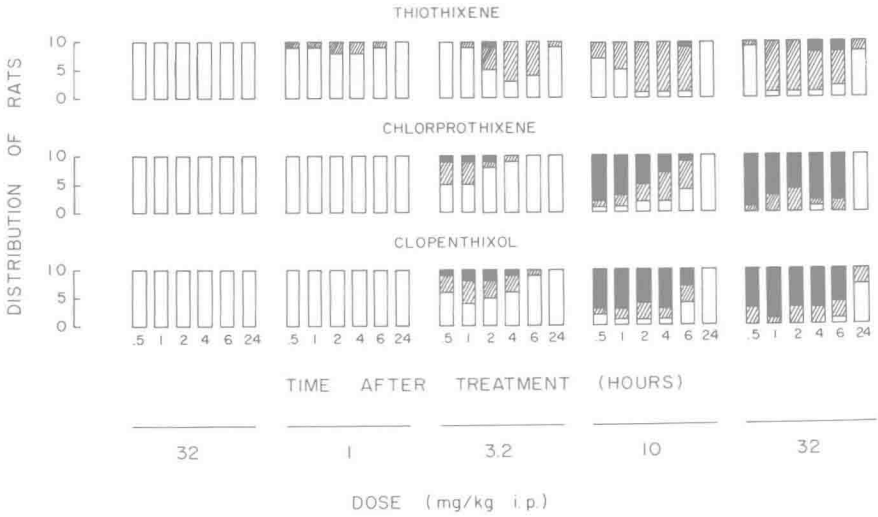


Fig. 2. Effect of thiothixene, chlorprothixene, and clopenthixol on discriminated avoidance behavior. Each bar shows the distribution of avoidance scores among the 10 rats exposed to that dose at the time after treatment shown. Open areas: number of rats unaffected; striped areas: number of rats exhibiting loss of avoidance behavior but retention of escape behavior; black areas: number of rats exhibiting loss of both avoidance and escape behavior.

were distinctly less selective. Additional confirmation of the potent, selective disruption of conditioned avoidance behavior by thiothixene has been published (1, 8, 11).

Thus, thiothixene can be shown to block avoidance behavior in rats over a wide dose range, while animals do not fail to escape the shock when it is presented. This type of selectivity is interpreted to mean that the action of thiothixene is not accompanied by pronounced sedation, muscle weakness or analgesia.

What is the meaning of this selective disruption of conditioned avoidance behavior? The neurological basis for avoidance behavior and its blockade has been studied for many years, but conclusions at the neurological level are still so tenuous and complex that it is probably better to stress psychological explanations which have been proposed. In avoiding the shock when the signal is presented, the animal may be exhibiting a specialized anxiety or fear response; antipsychotic drugs may act to dissipate this fear reaction. A second explanation focuses on the possibility that psychotic behavior in humans itself represents avoidance of life's realities, and a drug which blocks avoidance responses in animals may serve to block such irrational "avoidance responses" as psychotic behavior in man. Still another explanation is that drugs may block the attention paid by animals to emotion-provoking signals such as the tone, and serve to correct attentional deficits in schizophrenics. It should be stressed, however, that the major known antipsychotic drugs have repeatedly been demonstrated to exert a suppressing effect on this type of behavior in animals, and that the test thereby enjoys good empirical validity.

BLOCKADE OF THE BEHAVIORAL EFFECTS OF AMPHETAMINE

Thiothixene is particularly potent in blocking the motor stimulant and stereotyped behavioral effects of amphetamine (9, 10). It also blocks the lethal effects of high doses of amphetamine given to grouped mice. In each case, effective doses of thiothixene are less than 1 mg/kg. It is of interest that the effect of thiothixene in blocking stereotyped symptoms is relatively greater than that in blocking aggregation toxicity, as compared with chlorpromazine (Table 2). This may be attributed to the relatively slight peripheral

TABLE 2. *Antiamphetamine effects of thiothixene and related compounds* (9)

Compound	Antiamphetamine ED_{50} (mg/kg i.p.)		
	Aggregation-mortality in mice	Hyperactivity in mice	Stereotyped symptoms in rats
Thiothixene	0.3	0.8	0.1
Thioproperazine	0.3	0.5	0.1
Chlorpromazine	1.6	8.6	6.0
Prochlorperazine	0.9	5.6	1.2
P-4657A	10–32	>32	>32

adrenergic blocking properties of thiothixene (6). Here again, these effects of thiothixene are important primarily because known antipsychotic drugs also exert the effect. It is worth recalling, however, that in humans amphetamine in high doses is known to produce psychotic side effects and mania, and perhaps this is why blockade of amphetamine in animals remains a useful way to select antipsychotic drugs. Indeed, the stimulant effect of amphetamine in animals looks very much like uncontrolled mania.

ANTIEMETIC EFFECTS

Thiothixene is among the most potent known antiemetic drugs in blocking the vomiting response to apomorphine (Tables 3 and 4; Refs. 4 and 9). This

TABLE 3. *Antiapomorphine effects of thiothixene and related drugs in dogs (9)*

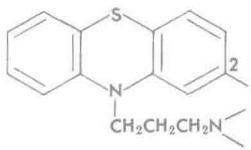
Drug	ED_{50} (mg/kg)	
	i.v.	p.o.
Thiothixene	0.0022	0.07–0.1
Thioproperazine	0.0034	0.07–0.1
Chlorpromazine	~0.7	10–32
Prochlorperazine	0.122	~1.5

effect, seen in dogs, is of importance not only because other antipsychotic drugs, with very few claimed exceptions, are also effective in preventing apomorphine-elicited emesis, but because apomorphine is widely reported to stimulate dopamine receptors in the brain.

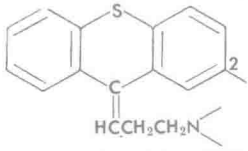
EFFECTS ON DOPAMINE METABOLISM IN BRAIN

Much evidence suggests that the above effects common to known antipsychotic drugs of the phenothiazine, thioxanthene, or 4-phenylbutylamine types, and achieved with great potency by thiothixene, are in large part caused by blockade of dopamine receptors in the brain. Biochemical evidence supports this contention. As one example, thiothixene has been shown by Dr. B. K. Koe (*unpublished data*) in our laboratories to greatly enhance the accumulation of DOPA in the dopamine-rich corpus striatum of the rat brain, when decarboxylase activity is blocked by a known drug inhibitor (Table 5). This biochemical effect is believed to be caused by an enhancement of the dopamine synthetic machinery in the dopaminergic neuron, a compensatory feedback mechanism for the blocked activity at the dopamine receptor. Another resulting effect is seen in the data of Lahti et al. (5), who showed that thiothixene profoundly increases the amount of homovanillic acid in the mouse

TABLE 4. *Antiemetic potency of analogous thioxanthenes and phenothiazines in dogs (4)*



phenothiazines



thioxanthenes

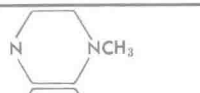
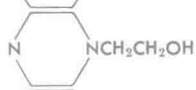
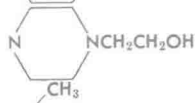
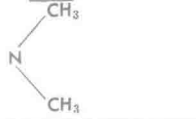
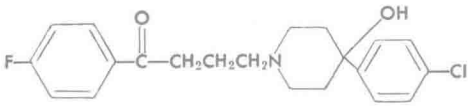
2-Position	Side Chain Amine	Compound and Class T = Thioxanthene P = Phenothiazine B = Butyrophenone	Minimal Antiemetic Dose in Dogs (mg/kg s.c.)
$SO_2N(CH_3)_2$		Thiothixene (T)	0.00125
		Thioproperazine (P)	0.00250
Cl		Perphenazine (P)	0.01
		Clopenthixol (T)	0.02
CF_3		Fluphenazine (P)	0.005
		Flupenthixol (T)	0.02
Cl		Chlorpromazine (P)	0.31
		Chlorprothixene (T)	0.63
		Haloperidol (B)	0.01

TABLE 5. *DOPA accumulation in rat corpus striatum after inhibition of decarboxylase activity*[a]

Treatment	Dose (mg/kg i.p.)	DOPA[b] (% of control)
Thiothixene	17.7	477
Reserpine	5.0	218
Apomorphine	15.7	33

[a] By 2 doses of NSD-1024.
[b] Control DOPA level was 0.728 μg/g.

brain (Table 6). This acid is the end product of dopamine degradation. Its elevation by thiothixene can be blocked by apomorphine, which is believed to stimulate dopamine receptors, and thus to counter the action of receptor blockers. The blockade of dopamine receptors by antipsychotic drugs probably accounts for the extrapyramidal symptoms they cause. In common with

TABLE 6. *Effect of various doses of apomorphine on the thiothixene-induced elevation in homovanillic acid in mouse brain (5)*

Treatment	Dose (mg/kg)	HVA (μg/gm)
Saline		0.09
Thiothixene	2.0	0.37
Thiothixene + apomorphine	2.0 + 10.0	0.20
Apomorphine	10.0	0.05

other neuroleptics, thiothixene does exert cataleptic effects in animals and humans although less than does its phenothiazine analog, thioproperazine (9).

SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS

Among the side effects other than extrapyramidal effects commonly produced by many neuroleptics in man (particularly chlorpromazine and thioridazine), and readily seen in animal studies as well, are sedative and muscle relaxant effects (sometimes reflected as analgesia), disturbances in thermoregulation, antiadrenergic effects, and anticholinergic effects. These side effects have been progressively reduced with the more modern, selective neuroleptic drugs, and thiothixene is among the very most selective of these recent agents. In other words, despite its marked potency in disrupting conditioned avoidance behavior, in blocking amphetamine-elicited stimulation, and in antagonizing apomorphine emesis, thiothixene is exceedingly weak in producing sedative, thermoregulatory antiadrenergic, anticholinergic, and related effects. We have already mentioned how the failure of thiothixene to disrupt avoidance behavior over a wide dose range may be interpreted as a lack of sedative effectiveness. Let us examine some of the other relevant animal data bearing on side effects common to chlorpromazine.

RELATIVE ABSENCE OF SEDATIVE AND MUSCLE WEAKNESS EFFECTS AFTER THIOTHIXENE

In one study (9), thiothixene was distinctly weaker than chlorpromazine and prochlorperazine in prolonging the duration of sleep after both hexobarbital and ethanol. For example, a dose of 100 mg/kg s.c. of thiothixene caused mice treated 2 hr later with hexobarbital to sleep for a median of 88 min. Only 10 mg/kg of chlorpromazine, given prior to hexobarbital, caused sleep for 114 min. Thiothixene also failed to potentiate ethanol-induced sleep. Analogous results from ether- and thiopental-induced sleep in mice have been reported by Ueki et al. (8). These authors also reported that thiothixene, even at 100 mg/kg in mice, exerted no muscle relaxant effect on an inclined plane test in mice; chlorpromazine, perphenazine, and dia-

zepam showed a marked relaxant effect. On a mouse rotorod test of muscle coordination as well, thiothixene was far less effective than comparison standards.

RELATIVE ABSENCE OF ANTIADRENERGIC AND THERMOREGULATORY EFFECTS

Unlike chlorpromazine, thiothixene exerts virtually no ptotic effect in mice (8) or rats (4). Even at a dose of 10 mg/kg orally to conscious dogs, thiothixene lowered blood pressure by an average of only 8 mm/Hg (Scriabine, *unpublished data*). Unlike chlorpromazine, prochlorperazine, chlorprothixene, or clopenthixol, thiothixene exerts only slight effects on thermoregulation. At room temperature (21°C) thiothixene produces only a mild hypothermia in mice, and when mice are placed in a cold environment, they do not rapidly die of hypothermia after thiothixene, as they do after less selective agents (9, 10).

RELATIVE ABSENCE OF ANTICHOLINERGIC ACTIVITY

The *in vitro* spasmolytic activity of thiothixene and chlorpromazine has been evaluated on guinea pig ileum suspended in Tyrode solution (Table 7).

TABLE 7. *In vitro spasmolytic effect of thiothixene and chlorpromazine on guinea pig ileum (data from J. W. Constantine, unpublished)*

	EC_{50} (μg/cc) in antagonizing contractions of guinea pig ileum induced by:			
Compound	Barium chloride (100 μg/cc)	Histamine (2.5 μg/cc)	Serotonin (1.5 μg/cc)	Acetylcholine (0.2 μg/cc)
Thiothixene	2.4	2.4	3.4	8.7
Chlorpromazine	1.4	0.05	0.7	1.8

Thiothixene was a weak, nonspecific spasmolytic agent and considerably less effective than chlorpromazine in antagonizing histamine-, serotonin-, and acetylcholine-induced muscle contractions (Constantine, *unpublished results*).

DOES THIOTHIXENE RESEMBLE TRICYCLIC ANTIDEPRESSANTS IN ANIMAL STUDIES?

One beneficial clinical effect of thiothixene that has frequently been reported is an activating component sometimes even termed stimulation, or

antidepressant activity. It should be made clear that in the usual animal tests for antidepressant activity, however, thiothixene essentially lacks the behavioral and biochemical properties of tricyclic antidepressants. Thus, thiothixene does not reverse the behavioral depression or hypothermia caused by reserpine-like drugs, and thiothixene does not block the uptake of norepinephrine into noradrenergic neurons (Table 8). Similarly, at no dose does

TABLE 8. *Inhibiting effect of various tricyclic drugs on the uptake of H^3-norepinephrine into rat heart (data from B. K. Koe, unpublished)*

Compound	Dose (mg/kg i.p.) required for 50% inhibition of uptake
Desipramine	0.4
Imipramine	1.7
Amitriptyline	7
Doxepin	7
Chlorpromazine	7
Thiothixene	>56

thiothixene exert stimulant effects in such devices as photocell cages, jiggle cages or operant conditioning chambers. If pressed to extrapolate from animal studies to explain the activating or energizing action of thiothixene, I would do so as follows: thiothixene exhibits potent psychopharmacological effects prototypical for antipsychotic drugs, but does so with great selectivity. There are virtually no sedative, antiadrenergic or anticholinergic effects. Extrapolating to man, it appears that the proven antipsychotic action of thiothixene is not achieved by means of debilitation, and that the energizing effects represent a move towards normal activity.

METABOLISM OF THIOTHIXENE

The pharmacokinetics and metabolism of thiothixene in laboratory animals has been studied by Hobbs with the use of drug labeled with Sulfur-35. Thiothixene is rapidly absorbed from the gastrointestinal tract as determined by a comparison of tissues and excreta following intraperitoneal doses with those after oral doses. Following single doses, radioactivity is primarily excreted in the feces, in most part within two days. This fecal elimination is the result of extensive biliary secretion as determined in animals bearing implanted bile cannulas.

In the rat thiothixene and its metabolite are widely distributed throughout a number of tissues from which they are then removed with varying half-lives. The pigmented rat eye contains higher concentrations than a number of other tissues examined and drug and metabolites are removed with a half-life somewhat greater than that of other tissues. *In vitro* experiments, however, show

that thiothixene is less strongly bound to melanin than are a number of other tricyclic psychotherapeutic drugs including chlorpromazine.

Numerous metabolites of thiothixene, most of them currently unidentified, are seen in extracts of bile feces and liver. In contrast, extracts of rat brain contain unchanged drug only.

In summary the disposition of thiothixene is basically similar to that of the other tricyclic psychotherapeutic drugs in that it is rapidly absorbed and distributed, extensively metabolized, and excreted via urine and feces within a relatively short interval.

CONCLUSIONS

Thiothixene exerts several potent actions in animals long recognized to be characteristic for antipsychotic drugs. It selectively blocks conditioned avoidance behavior, blocks amphetamine-induced stimulation, and blocks apomorphine emesis. Biochemical findings suggest that thiothixene blocks dopamine pathways. On the other hand, thiothixene exhibits marked selectivity, as exemplified by its lack of pronounced sedative, adrenolytic, or anticholinergic side effects. Based on animal studies, extrapyramidal effects would be expected after thiothixene, but clinical experience reveals that these are controllable at therapeutic doses. Despite frequent clinical reports of "activating" and "antidepressant" effects of thiothixene, animal studies reveal that thiothixene does not share key pharmacological properties of tricyclic antidepressants.

REFERENCES

1. Cahen, R., Pham-Ba, T., and Hue, M., *Thérapie,* **23,** 591 (1968).
2. Dunitz, J. D., *Helv. Chim. Acta,* **47,** 1897 (1964).
3. Horn, A. S., and Snyder, S., *Proc. Nat. Acad. Sci. U.S.A.,* **68,** 2325 (1971).
4. Janssen, P. A. J., in *Modern Problems of Pharmacopsychiatry, Vol. 5: The Neuroleptics,* Bobon, D. P., et al. (Ed.), Karger, Basel, 1970.
5. Lahti, R. A., McAllister, B., and Wozniak, J., *Life Sci.,* **11 (I),** 605 (1972).
6. Leslie, G. B., and Maxwell, D. R., *Brit. J. Pharmacol.,* **22,** 301 (1964).
7. Schaefer, J. P., *Chem. Comm.,* **15,** 743 (1967).
8. Ueki, S., et al., *Igaku Kenkyu (Acta Medica),* **39,** 433 (1969).
9. Weissman, A., *Psychopharmacologia,* **12,** 142 (1968).
10. Weissman, A., in *Modern Problems of Pharmacopsychiatry, Vol. 2: The Thioxanthenes,* Freyhan, F. A., et al. Ed., Karger, Basel, 1969.
11. Muren, J. F., and Weissman, A., *J. Med. Chem.,* **14,** 49 (1971).