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Reactions of Chlorpromazine Cation Radical with Physiologically Occurring Nucleophiles

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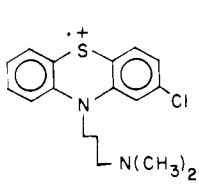
The reactions between chlorpromazine cation radical and a variety of physiologically occurring nucleophiles, which involve formation of a covalent, yet reversible bond, have been examined. As reported earlier, this reaction does not involve disproportionation of the radical but, rather, direct reaction between radical and nucleophile. The resulting adduct further reacts to form chlorpromazine sulfoxide or hydroxylated derivatives, and the original nucleophile is regenerated. The products and kinetics of the reaction depend strongly on the identity of the nucleophile, with the sulfhydryl group being the fastest and water being the slowest of the nucleophiles studied. The likely involvement of these reactions in the metabolism of chlorpromazine is discussed. In addition, it is proposed that the radical/nucleophile interaction is a reasonable model reaction for the effects of chlorpromazine radical on neuronal enzymes and receptor sites.

Since the emergence of the phenothiazine major tranquilizers such as chlorpromazine as tools of major importance in the treatment of schizophrenia, there has been substantial interest in the involvement of their cation radicals in their activity. While the importance of the radical to the antipsychotic effects of chlorpromazine remains a point of controversy, several arguments exist for radical involvement in the metabolism and activity of the drug. First, chlorpromazine cation radical (**1**) is easily



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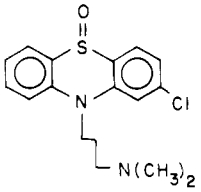

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formed in aqueous solutions by chemical,[1,2] electrochemical,[3,4] enzymatic,[5] and photochemical[6] oxidations and has been reported to have a half-life of a few seconds at physiological pH.[5] Thus the radical would be expected to be present in vivo and would be more reactive than its reduced precursor. Second, the radical is a likely intermediate in the metabolism of chlorpromazine to its sulfoxide (**2**) and hydroxylated metabolites, although the latter reaction has not been demonstrated in vitro.[5,7,8] Third, **1** affects the functions of several neuronal enzymes much more strongly than chlorpromazine itself, and an interaction between the radical and protein sulfhydryl groups was suggested as the source of the effects.[6,9,10] Fourth, **1** is known to bind strongly to macromolecules, particularly DNA, although the nature of the binding is not understood.[11] Finally, several other effects of the radical on biological membranes have been examined.[13] These observations have prompted several workers[5,7,11,12] to suggest that the radical is the active form of chlorpromazine in vivo, a hypothesis which has been neither proven nor refuted.

Because of its potential importance to drug activity, the chemistry of the radical of chlorpromazine has been studied extensively in vitro. The stability of **1** has been compared to other phenothiazine radicals in strong acid, and no correlation between radical lifetime and therapeutic potency was found.[1] The decay of radical was second order, and the authors proposed a disproportionation of radical to starting material and sulfoxide to explain the kinetics. Other workers have also proposed a disproportionation route and pointed out that the decay was very pH dependent, being faster in less acidic media.[5,14] In a study carried out in a near-neutral pH range, it was reported[5] that CPZ^+ interacted directly with the enzyme peroxidase. Unfortunately, the large majority of reports on radical chemistry has been based on experiments in strong acid, where the radical is more stable, but the results are of unknown physiological importance.

Our laboratory has carried out a detailed examination of the chemistry of chlorpromazine cation radical in aqueous solutions in the pH region from 2 to 7.[8] In an initial report, it was demonstrated that the radical did not disproportionate but rather reacted directly with solution nucleophiles, the buffer in our case. The radical/buffer

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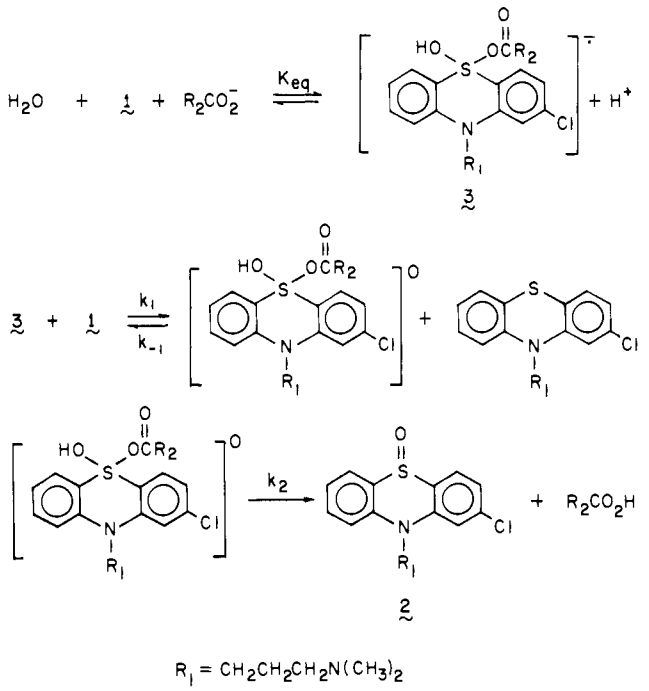
Scheme I



$R_1 = CH_2CH_2CH_2N(CH_3)_2$

adduct was oxidized by another molecule of radical and then eventually reacted to form the sulfoxide product, as shown in Scheme I. RCO_2^- is a representative carboxylate nucleophile. From the study, which was limited to carboxylate and phosphate nucleophiles, several conclusions of pharmacological importance emerge. First, the reactive species is the cation radical itself rather than a disproportionation product. Second, the reaction results in the formation of the sulfoxide, a primary metabolic product. Third, the radical reacts much more rapidly with weak nucleophiles than with water and is likely to interact with such nucleophiles in vivo. Fourth, the reactivity of various nucleophiles varies over three orders of magnitude, implying that the radical will interact with a mixture of nucleophiles on a selective basis. Fifth, and perhaps most important, the radical rapidly forms a covalent bond with weak physiological nucleophiles which is stable until the adduct is oxidized by another radical.

Given this mechanism it is apparent that the variations in determinations of radical stability made by other workers were caused by the use of different buffers and solution conditions. In addition, the mechanism has value as a model for the interaction of the radical with nucleophilic groups present in proteins and, therefore, at receptor sites. If the radical were generated in the presence of a receptor site, the radical would rapidly form a covalent bond with any nucleophiles present on amino acid side chains. The bond is only temporary and would only affect the receptor until the reaction was complete. Thus no permanent effects would be expected, although the receptor would be profoundly altered while the drug was present. Given that receptor binding strength is strongly correlated with the clinical efficacy of the phenothiazines,[15,16] this reaction may serve as a model for the chlorpromazine/receptor interaction.

The present work was undertaken to provide chemical evidence which bears on the pharmacological theories of chlorpromazine radical effects on physiological entities. The reactions of 1 with various nucleophiles are compared in terms of products and relative rates. In addition, the radical is shown to hydroxylate under certain conditions, leading to the formation of the second major class of chlorpromazine metabolites. The relationship of these reactions to chlorpromazine pharmacology is discussed.

Experimental Section

Controlled potential electrolysis was performed using a commercial potentiostat and standard digital integration of electrolysis current. Cyclic voltammetry was carried out with an operational amplifier of conventional design.[4] All electrochemical experiments were carried out in a small volume (3 mL) divided cell using a graphite paste or carbon cloth working electrode, platinum auxiliary electrode, and saturated calomel reference electrode (SCE). With the exception of 1, all chlorpromazine derivatives were obtained from Dr. A. A. Manian of the Psychopharmacology Research Branch, NIMH. The radical salt was synthesized as described elsewhere.[8]

A high-pressure liquid chromatograph with ultraviolet detection at 254 nm was used for product analysis. Conditions for separating chlorpromazine from its sulfoxide and hydroxylated metabolites were as follows: eluent, 40% methanol, 60% H_2O; 0.025 M borate; 0.05 M $NaNO_3$, pH 9.3; flow rate, 1.1 mL/min; column, Du Pont Zipax strong cation-exchange resin, 2 × 500 mm. Chlorpromazine and chlorpromazine sulfoxide were qualitatively identified by comparing retention times with synthesized compounds and were quantitatively determined by running calibration curves using mixed standards. A blank test was usually performed for each type of buffer.

Several unidentified peaks appeared in the chromatograms of reaction products in amine-containing buffers. Each of those peaks was eluted repeatedly and collected in a microfractionator. The fraction which corresponded to a certain unknown peak was then transferred into a rotary evaporator and the methanol was removed. The pH was adjusted to the desired value after all the methanol had been evaporated. Subsequent analyses, usually cyclic voltammetry and spectrophotometry, were conducted on the resulting solution. The analytical scale LC did not allow enough material to be separated and collected in a reasonable amount of time for further isolation or identification procedures.

Our earlier work indicated that the rate of decay of 1 in aqueous buffers depends on pH, buffer concentration, ionic strength, and the concentration of neutral chlorpromazine.[8] Accordingly, all rate comparisons for different nucleophiles were carried out in solutions in which these parameters were carefully controlled. The pH of the solution was checked before and after each kinetic run to verify sufficient buffering capacity. For experiments in poorly buffered media the pH was continuously monitored and maintained within ±0.05 unit by manually adding dilute NaOH. The reaction was initiated by direct dissolution of chlorpromazine radical perchlorate salt in the appropriate buffer solution. When it was necessary to monitor the pH and add base, a flow cell and peristaltic pump connected the experiment to an external beaker. The decay of radical was monitored at 525 nm, using a spectrophotometer interfaced to a laboratory computer.[8]

Results

Product Distribution. The products of the reactions between 1 and nucleophiles depended heavily on the identity of the nucleophile. For anions of oxygen acids, such as citrate, maleate, succinate, phosphate, AMP, ATP, acetate, and cacodylate, the product distributions were identical within experimental error. In these cases, 1 mol of 1 reacted to form 0.5 mol of original chlorpromazine and 0.5 mol of the sulfoxide **2**. The yields of the two products deviated no more than 2% from 50/50 values for this class of nucleophiles.

The reactions of 1 with amine and sulfhydryl nucleophiles yielded much different product distributions from the 50/50 yields discussed above. Figure 1, curve b, shows a liquid chromatogram of the products of the reaction of 1 with a tertiary amine, Mes [2-(*N*-morpholino)ethanesulfonic acid], at pH 6.5, compared with the products of the reaction with phosphate (curve a). Peaks II and III are sulfoxide and chlorpromazine, respectively, while peaks I and IV result from reactions with amines, such as Mes, Hepes (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic

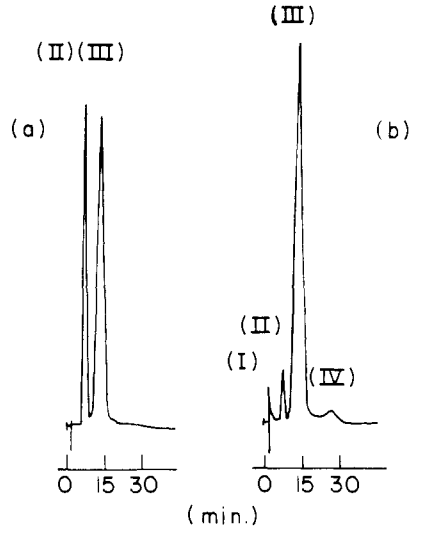


Figure 1. Liquid chromatograms of the products of the reaction of chlorpromazine radical with two classes of nucleophiles: curve a, nucleophiles derived from oxygen acids, phosphate in this case (pH 7); curve b, amine nucleophiles, Mes in this case (pH 6.5). II is sulfoxide; III is chlorpromazine.

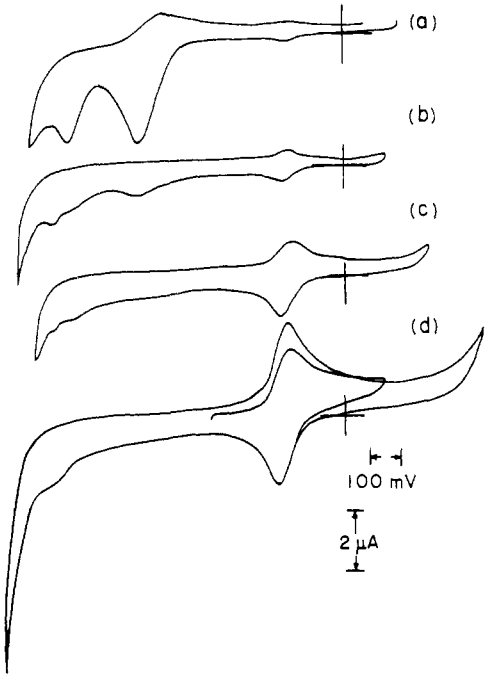


Figure 2. Cyclic voltammograms taken during the course of electrolytic oxidation of chlorpromazine in the presence of Mes. Scan rate = 0.1 V/s, graphite paste electrode. Curves a–c: voltammograms taken 6, 36, and 66 min after initiation of electrolysis. Curve d: voltammogram of LC fraction corresponding to peak I.

acid), and isopropylamine. The yields of sulfoxide and chlorpromazine from the amine reaction are 12 and 65%, respectively, based on original radical concentration.

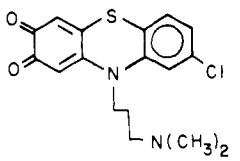
When a solution of chlorpromazine and Mes buffer at pH 6.5 was electrolyzed at +0.7 V vs. SCE, the voltammograms of the solution changed with time, as shown in Figure 2, curves a–c. The two large waves apparent in curve a correspond to the generation of chlorpromazine radical and chlorpromazine dication. The +0.7-V electrolysis potential generated only radical, and as the electrolysis proceeded, a new couple at +0.1 V appeared. The redox couple at +0.1 V corresponds to neither chlorpromazine nor its sulfoxide and does not occur in the

Table I. Rates of Decay of 1 in Oxygen Acid Buffers[a]

buffer	obsd rate constant, k_2,[b] M^{-1} s^{-1}	rel rate
citrate	484	1052
succinate	340	738
oxidized glutathione	70.4	153
maleate	40.1	87
phosphate	32.2	70
ATP	27.6	60
AMP	21.6	47
acetate	9.2	20
glycine	1.4	3
monochloroacetate	0.46	1

[a] pH 3.8, [CPZ] = 1.9×10^{-3} M, [buff] = 0.02 M. [b] Adjusted for buffer concentration as described in the text.

oxygen acid buffers. Peak I was collected from the LC of the electrolysis mixture; its voltammogram is shown in Figure 2, d. The fraction was pink, with a visible maximum at 508 nm, identical with that of 7,8-dioxochlorpromazine (4). While the presence of 4 in the product mixture of



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the amine reaction is established by these observations, it is not the only component of peak I. The voltammetric peak current in Figure 2, d, is too large for the concentration of 4 determined spectrophotometrically, so other species with similar voltammetry must be present in the product mixture. Finally, it was determined that the electrolysis of chlorpromazine in Mes buffer required over four electrons per molecule of starting material, indicating that the products have higher oxidation states than the sulfoxide (+2 relative to chlorpromazine).

The reaction of 1 with glutathione, a sulfhydryl-containing tripeptide, yielded a product distribution similar to that for the amine case, except for the lack of peak IV in the liquid chromatogram. The possibility that glutathione was directly reducing the radical was ruled out by the observation that the reaction was catalytic in glutathione, and the decay proceeded by clean second-order kinetics when the molar ratio of radical to glutathione was 10:1.

Kinetics. The detailed kinetics for the reaction of 1 in carboxylate and phosphate buffers has been reported,[8] and the radical decay was found to be second order in 1, first order in nucleophile, inverse first order in H^+, and strongly dependent on reduced chlorpromazine concentration. A series of similar physiological nucleophiles was examined in the present work to arrive at a ranking of relative decay rates. The decay was monitored in a series of solutions in which the pH, chlorpromazine concentration, and ionic strength were constant. In all cases involving buffers of oxygen acids, the radical decay was second order, and the mechanism of Scheme I applied. A wide range of decay rates was encountered and the entire series could not be compared at a single buffer concentration without fast experiments. Since the reaction is first order in buffer anion for this class of nucleophiles, plots of observed rate constant vs. buffer concentration could be extrapolated to a single buffer concentration. At this single concentration, the relative rates of the reaction for different buffers could be determined. The relative rates of various oxygen acid buffers at pH 3.8 are shown in Table I. Comparisons at

Table II. Product Distributions for Reactions of 1 with Various Buffers[a]

buffer	pattern	buffer	pattern
Mes	N	Mes + acetate	N
citrate	O	citrate + glycine	O
acetate	O	citrate + isopropylamine	O
isopropylamine	N	acetate + isopropylamine	O
glycine	N	water	N
Mes + citrate	N		

[a] pH 7.0; N indicates amine type products (Figure 1b) and O indicates oxygen type (Figure 1a).

pH 7 were not performed because of the speed of the reactions at this pH value. The range of buffer concentrations used in this study depended on the identity of the buffer but was from 0.01 to 0.2 M. The data of Table I were acquired at pH 3.8, but the same mechanism applies for oxygen acid buffers in the pH range from 2 to at least 6.

The decay of 1 in amine buffers, including glycine (pH >5), isopropylamine, Mes, and Hepes was first order and increased rapidly with increasing pH. Since the complete products and stoichiometry were not known, little can be said about the mechanism of the reaction when amines are the nucleophiles.

In sulfhydryl-containing media, the radical decay is second order at pH 1, where the reaction was slow enough to monitor. The rate of decay was proportional to glutathione concentration, even when the glutathione was only one-tenth as concentrated as the radical. At pH 7, the decay of radical in glutathione-containing medium was instantaneous, while the decay at the same pH with the same concentration of Mes required about 2 min.

Since the kinetics and mechanisms for the reaction of 1 with amine and carboxylate or phosphate nucleophiles differ, no direct comparison of rate constants can be made. To determine which class of nucleophiles reacts faster at pH 7, competition experiments were performed using the product distribution as an indication of which nucleophile reacted. Mixtures of buffers of equal concentration were prepared at pH 7 and allowed to react with the radical. An LC analysis of the products revealed a product distribution characteristic of an oxygen type nucleophile (Figure 1, a) or an amine nucleophile (Figure 1, b). The results are summarized in Table II.

Finally, the decay of 1 in unbuffered water, with the pH being maintained manually at pH 7, was first order with a half-life of about 4 min at room temperature.

Discussion

Several important conclusions are available from the present data about the possible involvement of the chlorpromazine cation radical in the parent drug's pharmacology. First, the lifetime of the radical in neutral aqueous solution can vary from a few milliseconds to several minutes, depending on the presence of nucleophiles. If the radical is generated in vivo, by a number of routes, it will survive long enough to interact with the physiological environment. Second, the radical forms a covalent bond with a variety of physiologically occurring nucleophiles, which eventually degrades to restore the nucleophile to its original form. Thus if this reaction accurately models a drug/receptor interaction, the interaction would be strong but not irreversible. This covalent bond is stable until oxidized by another radical or another solution component. Third, certain nucleophiles, particularly amines and sulfhydryl groups, promote hydroxylation of the radical to eventually form 7,8-dioxochlorpromazine. An intermediate in this process is presumably 7-hydroxychlorpromazine, which is rapidly oxidized by the radical to form 7,8-dioxochlorpromazine and other products. The formation of 7,8-dioxochlorpromazine upon chemical and electrochemical oxidation of 7-hydroxychlorpromazine has been demonstrated previously.[4,17,18] Since these hydroxylated products have been identified as chlorpromazine metabolites, the hydroxylation of the radical in the presence of amines provides a possible mechanism for their formation in vivo. Fourth, the radical reacts much more rapidly with any of the nucleophiles tested than it does with water. If the radical is formed in vivo, interaction with surrounding nucleophiles is much more likely than a reaction with water or another molecule of chlorpromazine. The lifetime of chlorpromazine radical may indeed be short in vivo, but its degradation directly involves an interaction of potential pharmacological importance.

The rates of reaction between 1 and the series of nucleophiles studied cannot be compared rigorously because of differences in mechanisms and probably rate-determining steps. However, the results provide a reliable indication of which nucleophiles are most likely to react with the radical. It is apparent that polyfunctional carboxylic acids are more reactive than phosphate, but that phosphate is more reactive than monofunctional carboxylic acids. At pH 7, a tertiary amine (Mes) is more reactive than the fastest carboxylic acid (citrate). The primary amine, isopropylamine, reacts slower than acetate; yet, the amine group on glycine reacts faster than its carboxylate, judging from the competition experiments at pH 7. It is also apparent that the rate of reaction of reduced glutathione with radical far exceeds the other nucleophiles examined. Thus an ordering of reaction rates at pH 7 is glutathione >> Mes > citrate > phosphate > glycine-($-NH_2$) > acetate > isopropylamine >> H_2O. The relatively rapid reaction of Mes may be caused by its low pK_a (6.2), causing a greater fraction of the buffer to be present in the deprotonated, nucleophilic form. The high reactivity of glutathione, or specifically its free sulfhydryl group, was not unexpected, given the strong nucleophilicity of sulfhydryl reagents in other reactions.

It is not the intent of this work to establish the radical of chlorpromazine as the active pharmacological entity. However, in the likely circumstance that the radical is generated in vivo, the present work establishes the probable routes of its degradation. The most likely is a reaction with sulfhydryl groups, as suggested by others to explain the effects of the radical on microsomal enzymes.[10] If sulfhydryl groups are not present, the radical is likely to interact with other protein nucleophiles much more rapidly than it will react with water. The products formed from these reactions lend strong support for the hypothesis that the radical is an intermediate in the metabolic formation of the sulfoxide and the hydroxylated derivatives.[7]

The involvement of the radical in vivo and, therefore, the pharmacological relevance of this work remain subjects of controversy. The recent finding that the butyrophenones, the other major class of antipsychotic drugs, also form cation radicals is of interest in this regard.[19] The importance of these radicals to in vivo effects remains unknown, but the model reactions studied here provide some insights into possible modes of action of the phenothiazine tranquilizers. In addition, these results provide insight into the mechanisms of formation of the sulfoxide and hydroxy-substituted chlorpromazine metabolites.

Acknowledgment. This work was supported by Grant MH 28412-02 from the National Institute of Mental

Health. Gifts of compounds from Dr. A. A. Manian were greatly appreciated.

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Synthesis and Biological Evaluation of Some 2-Amino-4-aryl-3*H*-1,5-benzodiazepine Analogues of Clozapine

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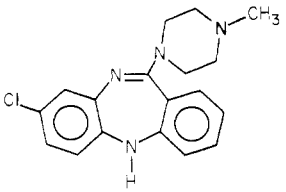
2-Amino-4-aryl-3*H*-1,5-benzodiazepines were prepared and evaluated for potential neuroleptic activity. Compound **6o** showed some activity in the four assays; however, the activity was not consistently observed among other members of the series. The data reflected that the structural modifications led to a decrease in activity relative to clozapine. It was apparent that the 1,5-benzodiazepine portion of clozapine is not responsible for its antipsychotic activity.

Clozapine (**1**), an example of a new class of neuroleptic



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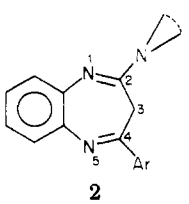

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piperazinyldibenzoazepines,[1] is particularly significant because it lacks extrapyramidal side effects in man.[2] This has given renewed momentum to the search for new psychotropic drugs with diminished side effects compared to standard drugs such as chlorpromazine and haloperidol. Because the piperazinyldibenzoazepines such as **1** do not structurally resemble other clinically active antipsychotic agents, it was our intention to investigate whether a portion of the molecule might be responsible for its activity. It is interesting that there are both a 1,4- and a 1,5-benzodiazepine moiety contained within the framework of **1**. Because the 1,4-benzodiazepines are more familiar as antianxiety agents,[3] we have undertaken a study of some 2-amino-4-aryl-3*H*-1,5-benzodiazepine analogues of **1** (such as **2**) and have evaluated them for potential neuroleptic activity.

One theory of schizophrenia, the dopamine hypothesis,[4] suggests that the putative neurotransmitter, dopamine, mediates the observed disorders associated with schizophrenia and that the antipsychotic drugs act by inhibition of dopamine at the postsynaptic receptor. Even though the effects of **1** may not be mediated by blockade of dopamine receptors,[5] the 2-amino-1,5-benzodiazepines (**2**) do have a spatial relationship between the aromatic ring and the 2-amino substituent that is similar to the extended trans conformation[6] of dopamine. It was anticipated that the title compounds could interact at the dopamine receptor via that structural feature. The compounds were, therefore, also evaluated for action on dopaminergic systems.

Screening for antipsychotic agents is complicated by the lack of suitable animal models and, therefore, has depended on assays that make comparisons with the observed effects of clinically active antipsychotic agents in animals.[7] The activity profile of clozapine does not resemble the more traditional neuroleptic agents,[5] however, and since it lacks extrapyramidal side effects in man[2] our goal was to find a compound with activities similar to **1** in the biological evaluation of **5**–**7**.

Chemistry. Synthesis of the title compounds was accomplished by displacement of a methylthioimino ether by secondary amines as outlined in Scheme I. Treatment of a 1,5-benzodiazepine-2-thione (**3**) with sodium hydride and methyl iodide in refluxing benzene afforded the methylthioimino ether, **4**, which was used without further purification. Displacement of the methylthio group was carried out in refluxing chloroform or toluene in the presence of excess amine and glacial acetic acid. The products have been classified according to the type of amine that was used for the displacement: **5** from *N*-methylpiperazine, **6** from 4-arylpiperidines, and **7** from some miscellaneous secondary amines. The most distinguishable spectral property of these amidines (**5**–**7**) was the UV spectrum. The UV absorptions and other data about these compounds are given in Tables I–III. General procedures for their preparation are given in the Experimental Section.

The thiolactam intermediates (**3**) were prepared similarly to literature methods[8,9] as outlined in Scheme II. Various substituted acetophenones were reacted with

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