HINTERMEISTER, NALUKUI MWISIYA

SYNTHESIS AND NMR STUDIES OF PERI-SUBSTITUTED PROMAZINE AND IMIPRAMINE ANALOGUES

THE UNIVERSITY OF ARIZONA M.S. 1984

SYNTHESIS AND NMR STUDIES OF PERI-SUBSTITUTED PROMAZINE AND IMIPRAMINE ANALOGUES

by

Nalukui Mwisiya Hintermeister

A Thesis Submitted to the Faculty of the

DEPARTMENT OF PHARMACEUTICAL SCIENCES

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF PHARMACY
WITH A MAJOR IN PHARMACEUTICAL CHEMISTRY

In the Graduate College

THE UNIVERSITY OF ARIZONA

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STATEMENT BY AUTHOR

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SIGNED: Nalukui M. Hintermeister

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

Arnold Martin

ARNOLD R. MARTIN
Professor of Pharmaceutical Chemistry

1/24/84
Date

ACKNOWLEDGMENTS

The author would like to thank Dr. Arnold Martin for his encouragement and guidance, Dr. Richard Ortega, and Dr. Robert Bates for the X-ray analysis. I thank Mr. Brian Weck for the 90 MHz ^{1}H-NMR spectra and all the ^{13}C-NMR spectra and Ms. Sue Harvey for the 250 Hz spectra. I thank Mr. Tom Kramer for the 1-chlorpromazine and Dr. Anders Hallberg for the 1-chlorophenothiazine. A very special thanks goes to my husband Von for his support and encouragement and for proofreading this thesis.

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ABSTRACT

Peri-substituted imipramine and promazine analogs were synthesized by conventional alkylations of the corresponding peri-substituted phenothiazine or iminodibenzyl analogues. The substituents were varied in size so as to study the effect of the substituent on the conformation of the N,N-dimethylaminopropyl side chain. For alkyl or phenyl substituents, the synthetic route to these compounds involved dilithiation of 2-chlorophenothiazine at the 1,10-positions or of 3-chloro-10,11-dihydro-5H-dibenz[b,f] azepine at the 4,5-positions at -70°, followed by warming to -30° to generate the corresponding benzynes. Subsequent nucleophilic attack by excess alkyllithium at room temperature, followed by quenching with water selectively gave the peri-substituted phenothiazine or iminodibenzyl. Halo-substituted phenothiazines and iminodibenzyls were synthesized by generation of the dilithio derivatives followed by reaction with hexachloroethane or 1,2-dibromoethane as electrophiles. Conformational properties of the compounds were studied in solution using ^{1}H- and ^{13}C-nuclear magnetic resonance spectroscopy. 4-Chloroimipramine hydrochloride and 1-chlorpromazine hydrochloride were submitted for X-ray analysis.

INTRODUCTION

Depression

Depression is a feature of several clinical syndromes classified as mood disorders or affective disorders. Mood disorders can be divided into unipolar manic disorder, bipolar affective disorder and unipolar depressive illness. Unipolar depressive illness is subdivided into endogenous depression, where the cause of depression is unknown, and exogenous or reactive depression. Endogenous depression is characterized by intense feelings of sadness and despondency accompanied by loss of interest, inability to feel pleasure, feelings of inadequacy, worthlessness and guilt. The patients' preoccupation with thoughts of despondency and death results in an estimated 15% suicide rate. Depression may be accompanied by either psychomotor retardation or agitation. It is endogenous unipolar depression that can be treated by antidepressant agents known as thymoleptics.

Several neurotransmitters and neuronal systems have been implicated in the cause of depression. The anticholinergic effects of the tricyclic antidepressants are responsible for such adverse reactions as dry mouth, blurred vision and constipation [1]. Reserpine, which is known to

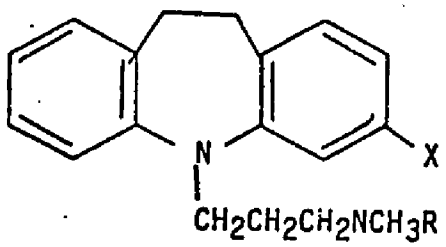
cause depression, has been found to have catecholamine depleting activity, which results in an uncompensated activity of the parasympathetic nervous system. This activity can be blocked by imipramine. Anticholinergics induce euphoria, flight of ideas and other symptoms of mania. From this observation, Janowsky and his coworkers [2] hypothesized that cholinergic factors may play a role in the etiology of affective disorders, and that depression is a state of cholinergic dominance. This can be disputed with the fact that the anticholinergic activity of the antidepressants correlates poorly with their main effects, and other strongly antimuscarinic compounds such as atropine, scopolamine and the anticholinergic parkinsonian agents are not effective antidepressants [3].

The more credible catecholamine hypothesis proposes that some, if not all affective disorders are associated with a decrease in catecholamines available at the receptor sites, and that antidepressants work by increasing the availability of catecholamines at the receptor site. The monoamine inhibitors do this by preventing catecholamine metabolism [4]. Imipramine (Ia) and structurally related compounds have been shown to block ^{3}H-norepinephrine uptake in intact rat brain [5] in addition to increasing catecholamine levels in the plasma [6]. Monoamine oxidase type A deaminates serotonin whereas type B deaminates β-phenylethylamines. Both types are inhibited by the tricyclic

antidepressants [7]. However, the potency of the tricyclic antidepressants is far inferior to that of the true monoamine oxidase inhibitors. Dopamine uptake is not significantly inhibited by tricyclic antidepressants. After intravenous administration of ^{14}C-tyrosine, the tricyclic antidepressants did not affect the rate of accumulation or disappearance of ^{14}C-dopamine formed in the brain.

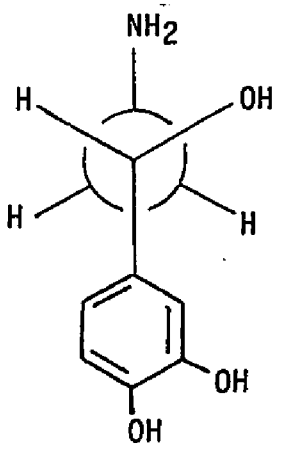
Norepinephrine NE (II) is a catecholamine believed to be involved in depression. Requirements of the norepinephrine uptake site have been investigated. Using analogues of phenylethylamines, it was discovered that the norepinephrine nerve terminals exhibited stereochemical activity. An α-methyl substituent increased affinity because it may induce a favorable change in the binding site [8]. Tricyclic compounds seem to be more potent norepinephrine uptake inhibitors when compared to mono and diphenyl analogues of desimipramine (Ib). Secondary methylamino compounds were more potent than their primary and tertiary analogues. Tricyclic compounds with coplanar or nearly coplanar phenyl rings are only weakly active, whereas compounds where the phenyl rings are non-coplanar are active. It was postulated that in the non-coplanar system, one phenyl ring binds to the receptor and the second ring is up and out of the plane of the

phenylethylamine so the terminal nitrogen has no steric hindrance [9].



I. (a) X=H, R=CH_3 imipramine; (b) X=H, R=H desimipramine; and (c) X=Cl, R=CH_3 3-chlorimipramine

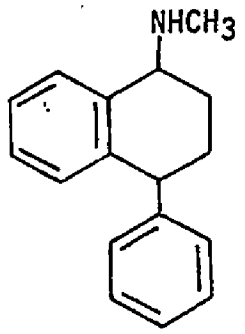
Molecular orbital (MO) calculations indicate that the norepinephrine molecule (II) may exist in the anti conformation [10]. X-ray analysis confirmed this [11] and in solution it was found that the preferred rotamer is the one where the amino group is anti to the aromatic ring and gauche to the β hydroxyl group [12]. Studies using rigid analogues of amphetamine found that the anti isomers were more potent catecholamine uptake inhibitors than the gauche isomers [13]. X-ray analysis of imipramine hydrochloride reveals two conformations. One conformation is fully extended whereas in the other the aminopropyl chain is folded back [14].



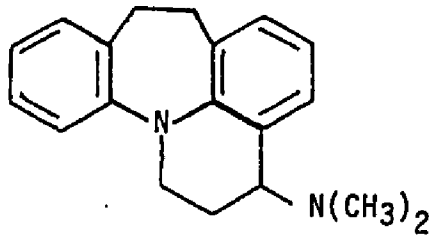
II. Anti conformation of NE

X-ray crystallography of the highly stereospecific and potent norephinephrine uptake inhibitor 1R, 4S-N-methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (III), revealed a conformation with pseudo-1,4-diaxial 1-methylamine and 4-phenyl groups. The structural similarity of this compound and of IV, the rigid analogue of desimipramine, are such that the 1-methylamino and 4-phenyl groups of III correspond to the terminal amine and A ring of IV. The spatial distance between these functions is also similar to the distance between the aromatic ring and the amine function of the extended norepinephrine molecule [15].

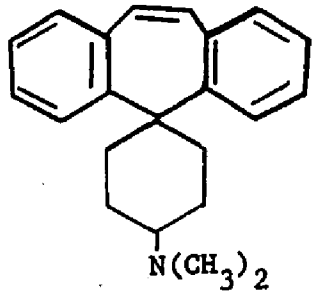
Using 31 rigid and semirigid compounds, a Swedish group correlated the potencies of these compounds and their structural similarities in terms of four intramolecular distances to N,N-dimethyl-spiro-[5H-dibenzo[a,d]-



III. 1R, 4S-N-methyl-4-phenyl-1,2,3,4-tetrahydro-1-napthylamine



IV. Rigid analogue of desimipramine



V. N,N-dimethyl-spiro[5H-dibenzo[a,d]-cycloheptane-5,1,cyclohexane]4-amine

cycloheptane-5,1,cyclohexane]-4-amine (V). They suggested that the norepinephrine uptake carrier has two active sites. One site is complementary to the structure of V, and it is that site to which the tricyclic antidepressants have affinity. The other site has a topology complementary to the structure of norepinephrine. The spiro compound, however, cannot be the optimal rigid compound since there are nonrigid compounds such as desimipramine that are more potent [16].

Abnormal indoleamine metabolism may be involved in depression and mania [19]. Serotonin (5HT) uptake can be inhibited in human platelets by tricyclic antidepressants, with the tertiary amines being more potent than the secondary amines [17, 18]. By mass fragmentation methods, the concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) was found to be low in a subgroup of depressive patients, indicating a disturbance in serotonin turnover [20]. Studies measuring 3-methyl-4-hydroxyphenyl glycol (MHPG), a norepinephrine urinary metabolite, seem contradictory. Some researchers found low levels in urine of depressive patients when compared with a control group [21], whereas others [22] found normal concentrations in the urine of depressive patients. It may be concluded that there are types of depression, some types characterized by a dysfunction in serotonin and other types characterized by low norepinephrine metabolites. The

tertiary amines seem to brighten the mood [23] and also tend to be more sedating. Their sedating effects correlate with the higher affinities for the α-noradrenergic receptor sites and their capacity to relieve psychomotor agitation [24]. Secondary amines seem to increase psychomotor activation and therefore seem to profit retarded depressive patients.

Structure Activity Relationship studies for the serotonin mechanism have not been successful in explaining its role in depression. The preferred conformation of 5HT could not be clearly established by experimental observation or theoretical calculations [25]. By MO calculations, Kier [10] predicted that 5HT exists in both anti and gauche conformations with the anti conformation being similar to the part of lysergic acid diethylamide, a 5HT antagonist (see Figure 1). The existence of more than one conformation was confirmed in solution. The difference in energy of the different rotamers is minimal [26]. The conformation in the solid state of 3-chloroimipramine, a potent serotonin uptake inhibitor, is similar to the extended form of imipramine, indicating that the 3-chloro substituent does little more than improve binding at the uptake site [18].

The presence of effective antidepressants such as mianserin (VI) and iprindole (VII) which do not block neuronal uptake [27, 28] casts doubt on the catecholamine

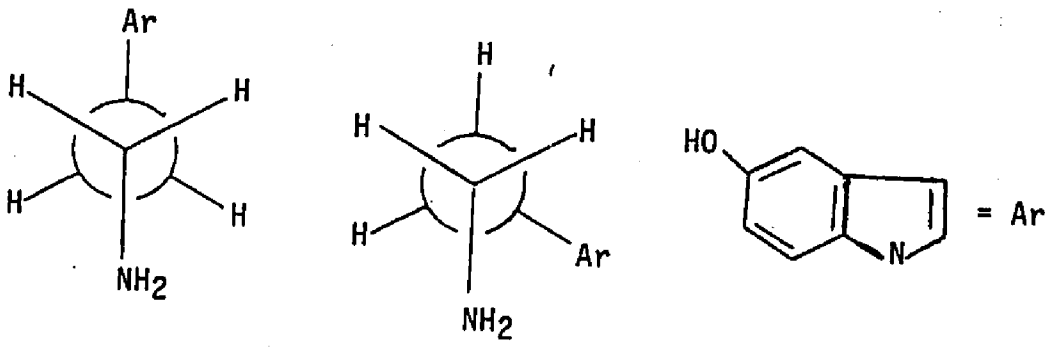
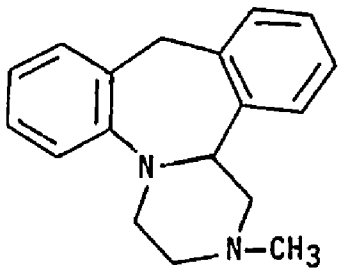
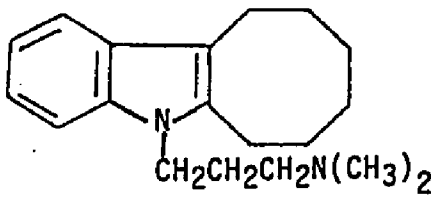


Figure 1. Anti and gauche conformers of 5HT.



VI. Mianserin



VII. Iprindole

and indoleamine hypothesis. Also, whereas neuronal uptake inhibition is immediate, the tricyclic antidepressants have a delayed onset of antidepressant action, taking several weeks before relief comes [29].

Various antidepressant treatments such as monoamine oxidase inhibitors, electroconvulsive therapy, tricyclic antidepressants and iprindole, after chronic administration, reduced the reactivity of the cAMP generating system to norepinehrine [30]. This decrease in adenylate cyclase to norepinephrine may be caused by a decrease in the number of α-adrenergic receptor sites or due to alteration of these receptors for norepinephrine. Binding studies using a potent α-adrenergic antagonist showed a decrease in the density of α-adrenergic receptors and therefore caused subsensitivity. Norepinephrine regulates its own release by stimulating a presynaptic inhibitory α receptor. After 3 weeks of therapy with desimipramine, the α_2 receptors become subsensitive to norepinephrine and therefore no longer inhibit norepinephrine transmitter release [31].

Ligand binding studies have shown that there is a reversible decrease in the density of 5HT-2 binding sites after chronic administration of a variety of antidepressant drugs, including imipramine, pargyline, iprindole and mianserin. Mianserin shows a decrease in receptor density even after acute administration. Structurally related

compounds which lack antidepressant activity, such as chlorpromazine lack such an effect on 5HT-2 receptors. However, electroconvulsive shock therapy increases the density of 5HT-2 binding sites in the cerebral cortex [32]. Chronic administration of antidepressants also was reported to cause a sensitization of serotonergic receptors. Enhanced responses to serotonergic agonists have been reported following repeated electroconvulsive shock [33]. Studies show that untreated depressed patients develop post-synaptic adrenergic receptor supersensitivity [34].

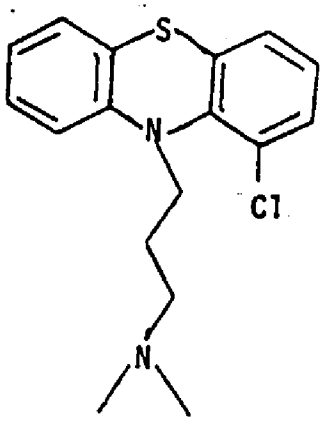
Rationale

The phenothiazines are used in psychiatric medicine as antipsychotics and major tranquilizers. However, 1-chlorpromazine (VIII) and its analogue trans-2-[1-chloro-10-phenothiazinyl]-N,N-dimethyl cyclopropanylmethylamine (IX) have been reported to have antidepressant activity and not the expected antipsychotic activity [35, 36].

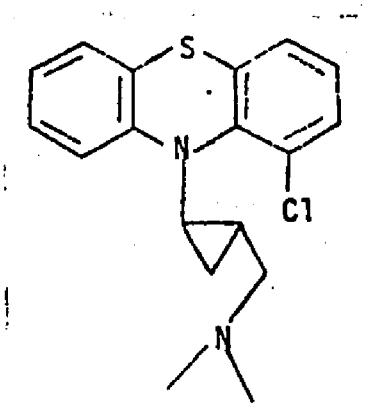
It is assumed that the 1-substituent may interact sterically with the alkylamino chain to transform the phenothiazine's nearly planar tricyclic nucleus into the non-coplanar structure, which is presumed to be required for antidepressant activity. The 1-chloro atom may also alter the propylamino group orientation relative to the ring and restrict its movements and number of possible rotations [37]. To study the effect of peri-substitution

on the propylamino group, we synthesized a series of peri-substituted promazine and imipramine analogues, the substituents varying in size. Their NMR spectra also were investigated.

A drawback in the use of the tricyclic antidepressants is their undesirable effects. These are due to the compounds' anticholinergic effects due to the flexibility of the propylamino chain and its ability to interact with various receptors. Also, the mechanism of action of the tricyclic antidepressant has not been elucidated. The synthesis and study of effective antidepressants with restricted flexibility, and therefore limited conformations could lead to the production of effective drugs with fewer side effects and may lead to an understanding of how the tricyclics work.



VIII. 1-Chloropromazine



IX. Trans 2-[1-chloro-10-phenothiazinyl]-N,N-dimethyl cyclopropanylmethylamine

CHEMISTRY

Metalation of phenothiazine with n-butyllithium, with subsequent reaction with carbon dioxide to give 1-carboxyphenothiazine, has been known for some time [38]. Other 1-substituted phenothiazines have been synthesized by the dilithiation of phenothiazine followed by reaction with electrophile [40]. 1-Methylphenothiazine has been synthesized in a multi-step synthesis via 1-carboxyphenothiazine [41] and from reacting the appropriately substituted diphenylamine with sulfur [42]. However, we have been successful in synthesizing 1-alkyl and 1-phenylphenothiazines in a one pot reaction by reacting 2-chlorophenothiazine with an excess of the required alkyllithium.

The synthesis of 1-carboxy-2-trifluoromethylphenothiazine from the dilithiation of 2-trifluoromethylphenothiazine and subsequent reaction with carbon dioxide has been reported in the literature [43]. However, researchers in our laboratory were unable to synthesize 1-carboxy-2-chlorophenothiazine by the same method. This led to the assumption that dilithiation of 2-chlorophenothiazine leads to benzyne formation.

The formation of benzyne from halobenzenes has been known for some time [44, 45, 46]. Reaction of 2-chloro-10-methylphenothiazine with metal amides selectively gave 2-substituted phenothiazines via a benzyne [47]. Benzyne formation is believed to be a two-step process. First the ortho-halo aryl proton is abstracted by a base to form the ortho-halo aryl carbanion which eliminates the halide to form the benzyne [48]. The entering group is no more than one carbon away from the leaving group.

It is not surprising that the proton in the 1-position of 2-chlorophenothiazine is the one abstracted, since metalation is a protophilic substitution and this proton is both ortho to a halogen and adjacent to a hetero atom. The abstraction is believed to be achieved through a four center transition state mechanism as shown in Figure 2. When a charged particle approaches a benzyne, it is believed that a partial ionic structure is induced in the benzyne. A variety of anions can add to this ionic benzyne. Alkyllithiums can act as carbanion sources and can add to the benzyne as depicted in Equation (3) of Figure 2.

Ideally, nucleophilic attack on an asymmetric benzyne such as the one depicted from phenothiazine should lead to the formation of two isomers. The isomer ratio would depend on the electronic and steric demands of the substituents. By thermodynamic control, the incoming

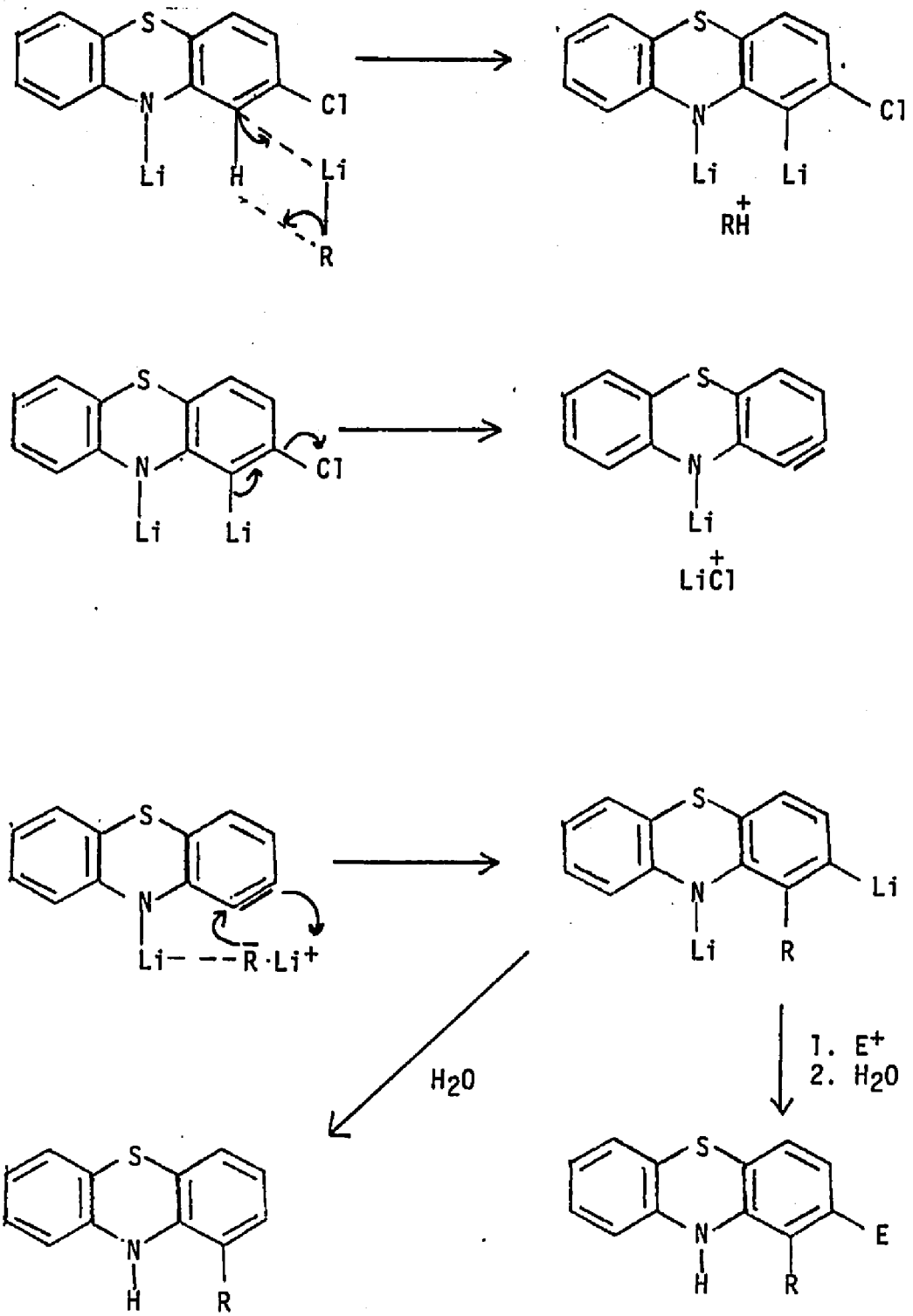


Figure 2. Mechanism for the synthesis of 1-substituted phenothiazines.

nucleophile will go where the resulting negative charge is best stabilized by the substituents. Kinetic control reflects the electron density at the two carbon atoms of the dehydrobenzene bond. When 2-chloro-10-methylphenothiazine is reacted with excess metal amides only, the 2-amine isomer was obtained because of steric hindrance from the 10-methyl substituent. In the reaction of 2-chlorophenothiazine with excess alkyllithium, only the 1-alkylphenothiazine was formed. It is suggested that the alkyl part of the organolithium associates with the lithium on the nitrogen. The nucleophilic alkyllithium then attacks the closest carbon of the dehydrobenzene bond, which is the 1-carbon. Furthermore, the intermediate 2,10-dilithio-1-alkylated intermediate can be trapped by reaction with an electrophile such as CO_2.

The yields of 1-substituted phenothiazines are reported in the Experimental Section. Adding the electron donating complexing agent tetramethylethylenediamine (TMEDA) had no effect on the yields, except to increase metal halogen exchange, resulting in the formation of the unsubstituted product. Metal-halogen exchange was seen in all the alkylation and arylation reactions but was less in the reactions using phenyllithium and methyllithium. This was probably because methyllithium and phenyllithium are not as basic as the other alkyllithium reagents.

Although not all the reaction products were separated and analyzed, the major products were identified by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) as the 1-substituted phenothiazine, the metal halogen product, the unsubstituted phenothiazine and the starting material.

The yields could not be increased by increasing the amount of organolithium used. Six equivalents of organolithium gave the same yield as four equivalents. Because of the high reactivity of t-butyllithium, only three equivalents of the organolithium were used. For the same reason, tetramethylethylenediamine (TMEDA) was not used. The reaction mixtures were separated by column chromatography using 10% ethyl acetate in hexane.

Metalation of 10,11-dihydro-5H-dibenz[b,f]azepine (iminodibenzyl) has been used in N-alkylation reactions [49]. 10,11-Dihydro-5H-dibenz[b,f]azepine-4-carboxylic acid has been synthesized by the dilithiation of iminodibenzyl with n-butyllithium followed by addition of carbon dioxide [50]. Later, 4-substituted derivatives were synthesized by reacting the 4,5-dilithio compound with electrophiles [51].

Organolithium compounds have been reported to react with halides to give the corresponding halide [52]. Hexachloroethane and 1,2-dibromoethane have been used in 'reverse metal-halogen exchange' with organolithium to give the corresponding chloride or bromide [53, 54, 55].

Earlier Hallberg and coworkers [56] reported the one-step synthesis of 1-chlorophenothiazine from reacting 1,10-dilithiophenothiazine with hexachloroethane in high yields. 1-Bromophenothiazine was synthesized by the same method using 1,2-dibromoethane [56]. Prior to this, multi-step syntheses were required for the preparation of 1-bromophenothiazine and 1-chlorophenothiazine [57, 58].

Using these methods 4-chloro-10,11-dihydro-5H-dibenz[b,f]azepine was synthesized in 60% yield. The reaction was extremely exothermic and was complete in fifteen minutes. 4-Bromo-10,11-dihydro-5H-dibenz[b,f]azepine was also synthesized from dibromoethane. This reaction was not as exothermic and gave a 52% yield. In both reactions, the dilithiated iminodibenzyl acts as a carbanion source and the halide as an electrophile (Figure 3).

Attempts to synthesize 4-methyl-10,11-dihydro-5H-dibenz[b,f]azepine from 4-chloro-10,11-dihydro-5H-dibenz [b,f]azepine and 4-bromo-10,11-dihydro-5H-dibenz-[b,f] azepine failed. When the chloro compound was reacted with 4 equivalents of methyllithium in dry ether for 24 hours at room temperature, the starting material was recovered. The reaction was repeated in the presence of TMEDA and again there was no reaction. Other workers in our laboratory had attempted to synthesize 4-methyl-10,11-dihydro-5H-dibenz [b,f]azepine from the reaction of methyllithium and 4-chloro-10,11-dihydro-5H-dibenz[b,f]azepine in THF in the

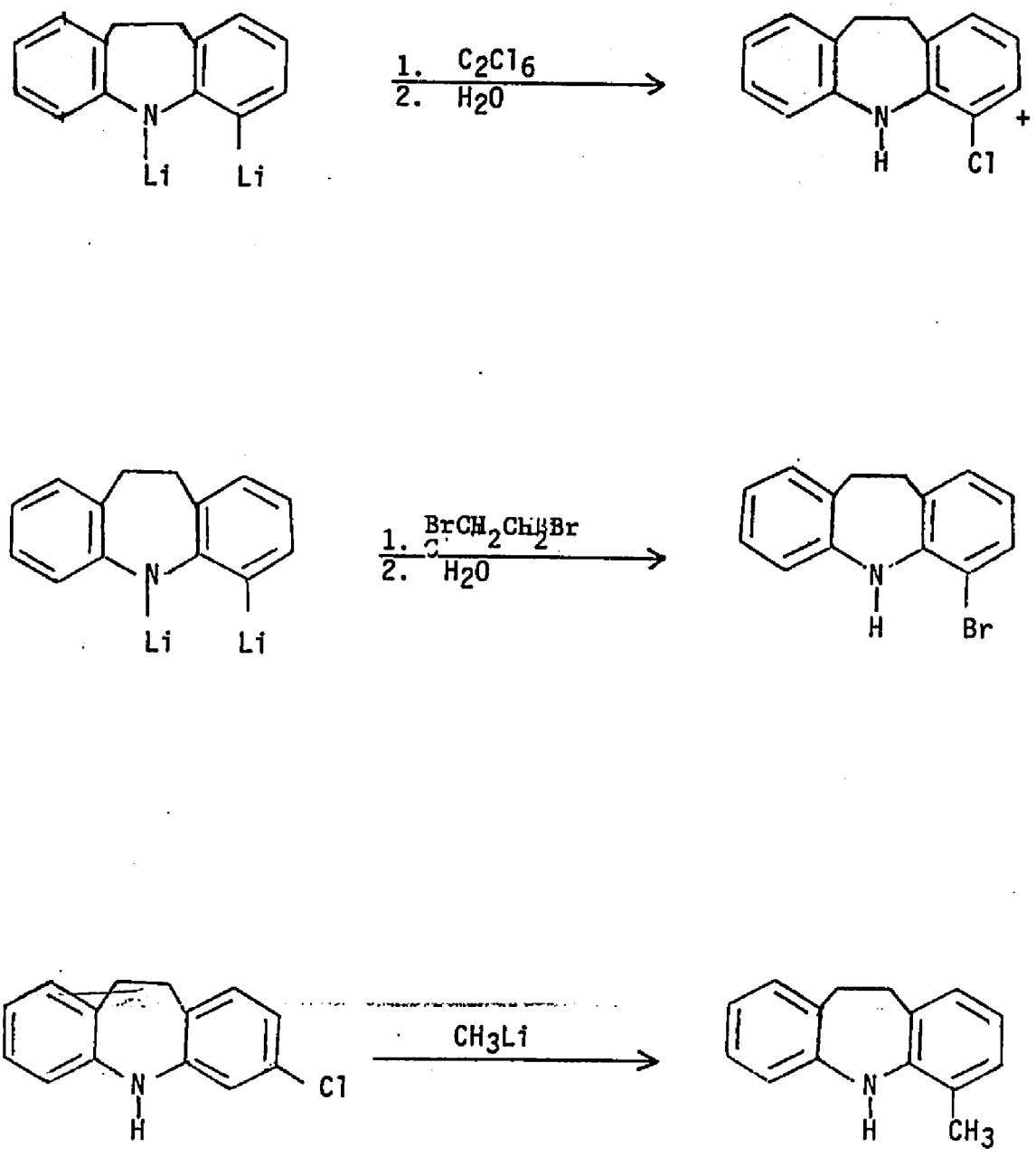


Figure 3. Synthesis of 4-substituted iminodibenzyls.

presence of TMEDA. These attempts also failed [59]. These results were rather disappointing since the same researchers successfully synthesized 1-s-butylphenothiazine (14% yield) from 1-chlorophenothiazine and s-butyllithium in THF with TMEDA. The reaction of 4-bromo-10,11,dihydro-5H-dibenz[b,f]azepine with methyl lithium and TMEDA in dry ether gave the halogen metal exchange debrominated product, 10,11-dihydro-5H-dibenz[b,f]azepine.

However, 4-methyl-10,11-dihydro-5H-dibenz[b,f]azepine was successfully synthesized via a benzyne by reacting 3-chloro-10,11-dihydro-5H-dibenz[b,f]azepine with four equivalents of methyllithium at room temperature in ether at 30% yield. Other products of the reaction were the unsubstituted 10,11-dihydro-5H-dibenz[b,f]azepine and the starting material.

N-alkylation

N-alkylation was performed by a classical method described in 1961 by Craig and coworkers [60]. The proton on the nitrogen was abstracted with sodium hydride instead of sodamide, with subsequent reaction with 3-dimethylaminopropyl chloride in dry toluene. The abstraction of the N-proton in 4-bromo-10,11-dihydro-5H-dibenz[b,f]azepine required more vigorous conditions and was achieved in the higher boiling solvent xylene (Figure 4). Various salts of the 1-substituted promazine analogues

appeared to be hydroscopic, so they were stored as the free base. The alkylation reaction gave fairly high yields which are reported in the Experimental Section.

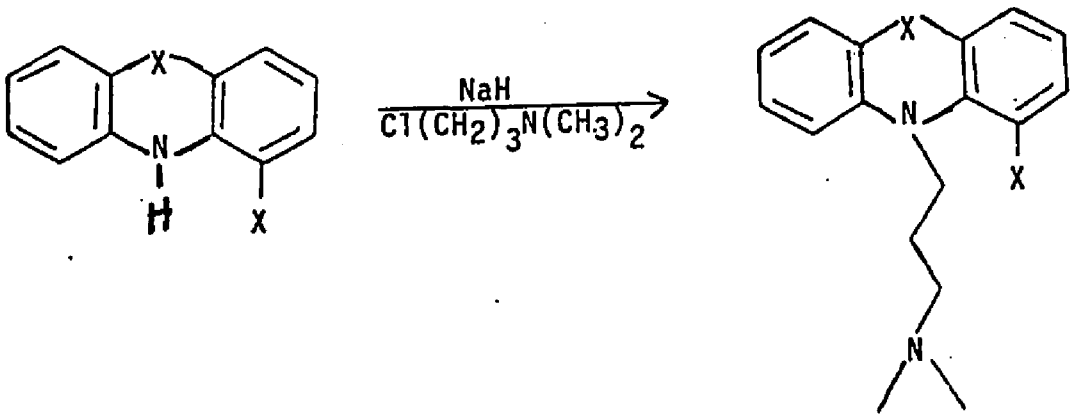


Figure 4. N-alkylation.

RESULTS

10,11-Dihydro-5H-dibenz[b,f]azepines

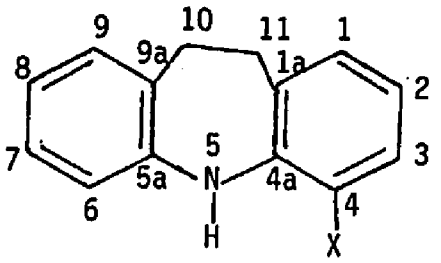
Ethanobridge Protons

As the data in Table 1 show, the ethanobridge protons are magnetically equivalent in the 4-substituted-10,11-dihydro-5H-dibenz[b,f]azepines. Addition of the propylamino substituent introduces non equivalence in the ethanobridge and transforms the A_4 spin system into an ABCD spin system (Table 3). This type of pattern has been reported for 5-acyl-10,11-dihydro-5H-dibenz[b,f]azepine [61]. The ethanobridge chemical shifts and spectral patterns for all three 4-substituted imipramine analogues are very similar so only 4-chloroimipramine was studied in much detail. We assume the information obtained for 4-chloroimipramine is applicable to 4-bromoimipramine and 4-methylimipramine. Table 4 shows the J values obtained by decoupling studies. From that data we were able to identify each proton in the ethanobridge.

Temperature-Dependent Studies

In the spectrum of 4-chlorimipramine, protons of the ethanobridge show variation with temperature. The variable temperature spectra were run in d_6-DMSO on a 250

Table 1. ^{1}H-NMR chemical shifts (δ) for 4-substituted 10,11-dihydro-5H-dibenz[b,f]azepine.



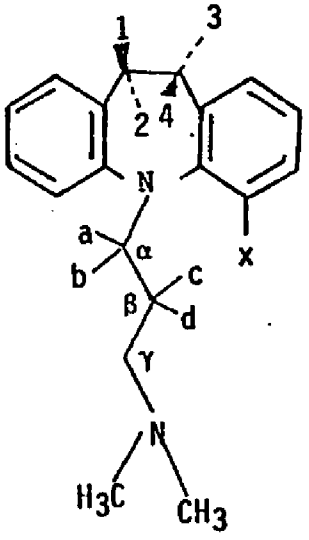
X	Aromatic	NH	Ethanobridge
Cl	6.5-7.19 ppm*	in aromatic region	3.04 ppm
Br	6.4-7.38 ppm	in aromatic region	2.95 ppm
CH_3	6.55-7.05 ppm	5.25 ppm	3.02 ppm

* For specific assignments see Table 2.

Table 2. ^{1}H-NMR chemical shift assignments for 4-chloro-10,11-dihydro-5H-dibenz[b,f]azepine (aromatic proteins).

X	Aromatic Proton	(ppm)
Cl	1	6.9
	2	6.65
	3	7.17
	6	6.81
	7	7.08
	8	6.78
	9	7.03

Table 3. ^{1}H-NMR chemical shift data (in ppm) of imipramine and analogs.

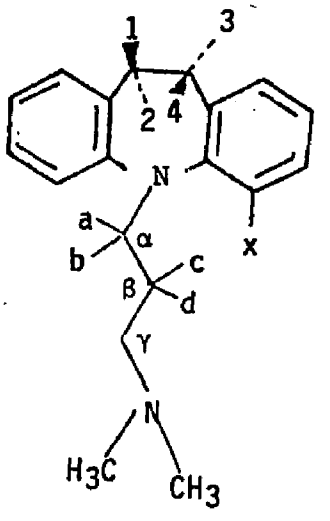


X		Ethanobridge	α	β	γ	NCH_3
CH_3	Imipramine	3.6 10H(e), 2.6 10H(a), 3.2 11H(e), 2.8 11H(a)	3.4, 3.9	2.24	1.64	2.13
Cl	Imipramine	3.6 10H(e), 2.6 10H(a), 3.2 11H(e), 2.8 11H(a)	4.0, 3.7	2.24	1.64	2.03
Br	Imipramine	3.6 10H(e), 2.6 1-O-H(a), 3.2 11H(e), 2.8 11H(a)	4.0, 3.6	2.25	1.62	2.13
Imipramine		3.08	3.7	2.26	1.67	2.07

Table 4. ^{1}H-NMR chemical shifts and coupling constants for ethanobridge of 4-chloroimipramine protons (see Table 3 for numbering).

Proton	(ppm)	J (HZ)	
H_1	3.67	$J_{1,2}$	12.9
		$J_{1,3}$	2.7
		$J_{1,4}$	3.8
H_2	2.70	$J_{2,3}$	5.7
		$J_{2,4}$	3.5
H_3	2.87	$J_{3,4}$ (geminal)	12.6
H_4	3.25		

Table 5. Coupling constants for the protons dimethylaminopropyl chain of 4-chloroimipramine.



Coupling Constant	J Value (Hz)
$J_{a,b}$ geminal	13.3
$J_{b,c}$	10.0
$J_{a,c}$	3.6
$J_{a,d}$	3.6
$J_{d,b}$	2.1
$J_{\beta,\gamma}$	7.3

MHz instrument. As mentioned earlier, at room temperature the protons form an ABCD spin system. By slowly raising the temperature, this system is gradually transformed into an apparent ABC_2 with absorption at 3.4 ppm, 3.2 ppm and the two axial protons centering at 3.1 ppm. The coalescence temperature with all four protons centering at 3.1 ppm was 388°K. At 393°K the spectrum approaches an apparent A_4 system centered at 3.04 ppm. The chemical shift of the ethanobridge of imipramine is 3.08 ppm.

The presence of a 4-substituent on imipramine restricts the inversion of the central seven-membered azepine ring. Ring flip via nitrogen inversion or ring inversion would involve steric interaction between the dimethylaminopropyl side chain and the 4-substituent, and so the 10,11-carbon atoms are fixed in a certain conformation. At high temperature the inversion barriers are overcome and the 4 ethanobridge protons collapse into an apparent A_4 system represented by a singlet on the NMR spectrum.

Dimethylaminopropyl Chain

The dimethylaminopropyl chain was studied as two ethylene groups. Vicinal and geminal coupling constants (J values) were measured for 4-chloroimipramine by decoupling studies. The presence of the 4-substituent limits the movement of the dimethylaminopropyl chain, causing the two

α protons to be non-equivalent. From the J values shown in Table 5, we conclude that the tricyclic nucleus and the methylamino groups are held in a gauche conformation. However, there is free rotation about the C_β, C_γ bond so the J value is time-averaged. The ^1H NMR spectrum was analyzed to pick up the parameter N = 2J for the $RCH_2CH_2N(CH_3)_2$ fragment, according to the techniques of Abraham and coworkers [62]. The observed N value was introduced into the equation

$$\Delta E = \Delta E_g - \Delta E_t = RT \ln 2 \frac{(N - N_g)}{N_t - N}$$

to obtain the energy difference between the anti and gauche rotamers. Values of Ng and Nt are those derived by Abraham and coworkers from the model compound t-butyl-$CH_2CH_2N(CH_3)_2$, which exists solely in the anti conformation, and piperidine which exists only as a gauche conformer. The fractional amounts of each conformer can be deduced from the equation $ng/nt = 2\exp^{-\Delta E/RT}$. When the anti conformer is >33% then it is favored. If the anti is <33% then the gauche is favored. This is based on the fact that there are two possible gauche rotamers and one possible anti rotamer in a free rotating system. We calculated the energy to be 0.445 Kcal mol^{-1} and the percentage anti to be 51% for the C_β, C_γ bond. The C_β, C_γ

fragment can, therefore, be concluded to have a preference for the anti conformation.

Variable Temperature Studies

At room temperature the two α protons are nonequivalent. At 388K the protons center at 3.95 ppm. The complex multiplet representing the β protons simplifies drastically to a quintuplet. The temperature studies were stopped at 433K. At this temperature the α protons were simplified to a triplet with $J_{\alpha,\beta}$ measured at 6.9 Hz. Using the method of Abraham et al., we calculated the energy for the C_β, C_γ rotational barrier to be 0.105 Kcal mol^{-1} and the percentage anti at 37%. The percentage anti for the C_β, C_γ fragment was also 37%.

It is interesting to note that the smaller methyl substituent was just as successful as the larger chlorine or bromine atoms in restricting the side chain conformation. At room temperature in solution, the conformation of the 4-substituted imipramine of $C_\alpha C_\beta$ gauche and $C_\beta C_\gamma$ anti is the predominant conformer of imipramine hydrochloride in solution and also the preferred conformation of norepinephrine in uptake studies [5]. The free base of imipramine, on the other hand, shows no conformational preference [62].

At high temperature the steric restrictions from the 4-substituent on the dimethylaminopropyl chain are

overcome and the side chain rotates freely and shows no conformational preference.

^{13}C-NMR was used to further characterize the compounds we synthesized. Peak assignments were made by calculations based on 10,11-dihydro-5H-dibenz[b,f]azepine as the reference. Addition of a 4-substituent to the 10,11-dihydro-5H-dibenz[b,f]azepine introduces non-equivalence to the chemical shift of the ethanobridge carbons. The peaks observed are averages of rapid ring inversion of the azepine central ring. Addition of the dimethylaminopropyl chain at N-5 freezes the ring inversion as can be seen by the increase in chemical shift difference of the ethanobridge carbons (Tables 6 and 7).

An effect of the 4-substituent on the dimethylaminopropyl group was also observed. When compared to imipramine, the α-carbons of the dimethylaminopropyl chain are 3 ppm downfield. This may be due to steric effects (δ effect) from the 4-substituent.

In the aromatic rings the presence of the N-dimethylaminopropyl chain has the general effect of a downfield shift of all carbon atoms, especially the bridgehead carbons which shifted 3-6 ppm. The dimethylaminopropyl chain has a deshielding effect on the aromatic nucleus (Table 8).

From the data of the torsional angles measured by X-ray chrystallographic analysis, we concluded that the

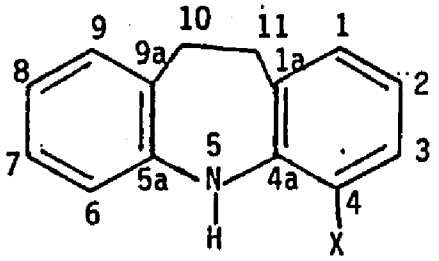
dimethylaminopropyl side chain of 4-chloroimipramine HCl in the solid state (Figure 5) is oriented in a C_α, C_β anti, C_β, C_γ anti conformation. The $N-C_\alpha$ bond holds the A ring and the methylamino group in an almost trans conformation and the B ring and methylamino group are in a gauche conformation. The bond angles, 4a-5-1' = 117.2°, 5a-5-1' = 120.2°, 4a-5-5a = 122.6°show that the nitrogen is trigonal (Table 9). The 1' carbon (α) is closer to C-6 (2.92 Å) than C-4 (3.08 Å), showing that the side chain is twisted away from the chlorine atom. A-N and B-N are distances from the geometric centers of the A ring (benzene ring containing the chlorine substituent), and B ring (benzene ring without a substituent) to the side chain nitrogen. A-N was found to be 6.47 Å and B-N was 6.7 Å. Imipramine HCl in the solid state has two conformations differing in side chain conformations [14]. One conformation has an A-N distance of 7.22 Å and B-N of 6.24 Å, whereas the other conformation has an A-N distance of 6.07 Å and B-N of 6.55 Å. 3-Chloroimipramine HCl is similar to the latter conformation of imipramine HCl and has an A-N distance of 6.10 Å and B-N of 6.55 Å [63].

The proton NMRs of all the 1-substituted promazines except for t-butylpromazine are fairly simple with the α and γ protons represented by triplets and the β protons as quintets, indicating free rotation of the dimethylaminopropyl side chain. The t-butyl group is bulky

Table 6. Comparative ^{13}C-NMR chemical shift data (δ in ppm) of imipramine and 4-substituted analogues. For numbering see Table 5.

	Aromatic	NMe	Ethanobridge	α	β	γ
4-chloroimipramine	121.7-145.8	45.2	31.7, 33.9	51.5	27.1	57.7
4-bromoimipramine	121.7-145.9	45.2	31.8, 33.9	51.6	27.4	57.8
4-methylimipramine	120.8-147.26	45.4	31.5, 34.5	51.9	27.3	57.8
imipramine	119.2-147.8	45.2	32.2	48.7	26.1	57.5

Table 7. Chemical shift assigments (in ppm) of 10,11-dihydrodibenz[b,f]azepine and 4-substituted analogues, aromatic carbons (tentative).*



Carbon Atom	X = CH_3	X = Cl	X =H
1	130.44 (127.75)	128.92 (128.75)	130.65
2	119.86 (119.34)	120.39 (120.74)	119.44
3	128.34 (127.48)	127.27 (127.18)	126.78
4	124.15 (126.82)	121.47 (124.12)	117.92
4a	142.77 (142.55)	141.80 (142.85)	142.45
5a	141.40	139.07	142.45
6	118.49	118.98	117.92
7	126.78	126.97	126.78
8	119.51	119.52	119.44
9	130.97	130.78	130.65
9a	128.63	129.07	128.68
1a	128.48 (128.58)	130.58 (129.98)	128.68
10,11	34.82, 35.21	34.67, 35.16	34.94

* ( ) Calculated value.

Table 8. ^{13}C-NMR chemical shifts assignments (δ in ppm) of aromatic region 4-substituted imipramine analogues aromatic region (tentative). For numbering see Table 7.

Carbon	X = Cl	X = CH_3
1.	130.62	131.51
2.	121.99	121.42
3.	128.47	129.27
4.	126.28	125.46
4a.	145.83	147.26
5a.	143.73	141.75
6.	121.70	120.88
7.	126.52	126.24
8.	121.99	121.42
9.	132.62	131.51
9a.	131.62	135.70
1a.	131.25	135.70

Table 9. Selected torsion and bond angles for 4-chlorimipramine.

Torsion System	Angle
Torsion Angles	
4a-5-1'-2'	110.3
5a-5-1'-2'	71
5-1-2'-3	177
1'-2'-3'-4	170
9a-10-11-1a	69.9
4-4a-5-1'	61
6-5a-5-1'	-39
$H11_a$-11-1a-1	-127.9
$H11_b$-11-1a-1	9.8
$H10_a$-10-9a-9	-75.4
$H10_b$-10-9a-9	40.1
Bond	**Angle**
Bond Angles	
4a-5-1'	117.2
5a-6-1'	120.2
4a-5-5a	122.6

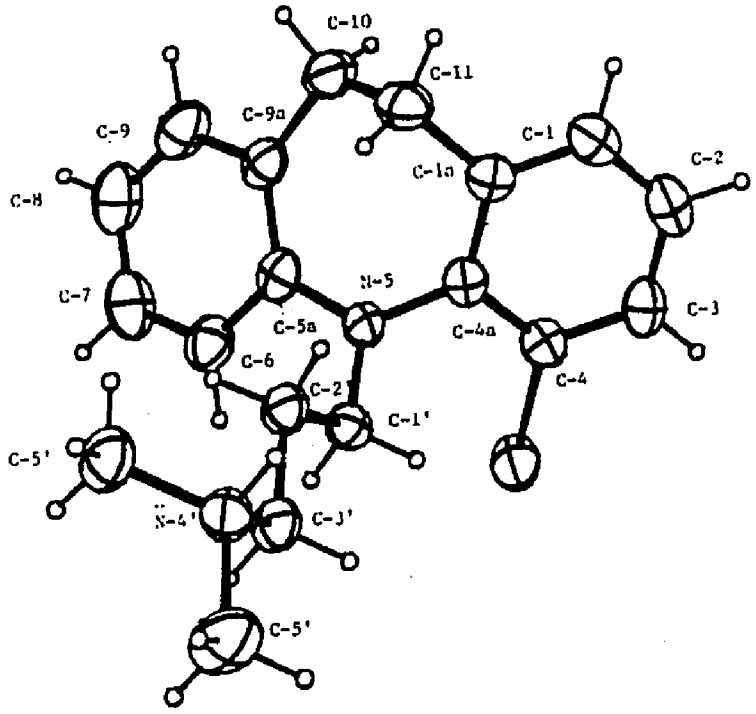


Figure 5. Ortep of 4-chloroimipramine.

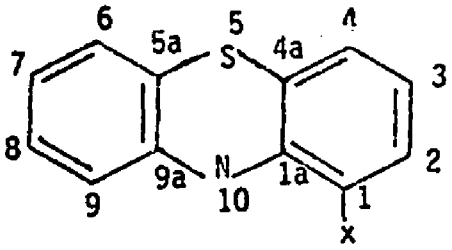
enough to complicate the spectrum and will be discussed in detail later.

The dimethylaminopropyl side chain will be treated as two ethylene fragments. Both the C_{α}, C_{β}, and C_{β}, C_{γ} fragments are free-rotating so the J values are time-averaged. Table 11 expresses the data necessary to calculate the fractional distribution of anti and gauche conformers in each fragment, as well as the percentage of the anti conformation.

The proton NMR spectrum of t-butylpromazine was extremely complex, leading us to believe that the 1-t-butyl group limits the movement of the dimethylaminopropyl side chain, causing the two α protons to be nonequivalent and the two β protons to be nonequivalent. The spectrum is further complicated by the fact that the N-methyl absorbs in the region where the γ protons appear and there is also overlap between the absorption region of the β protons and the t-butyl group at 250 mHz.

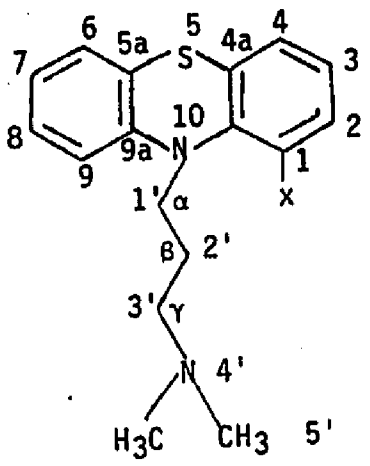
Specific decoupling studies were performed on a 250 Hz instrument, but we were not successful in identifying all the protons of the dimethylaminopropyl chain and in determining its conformation. We were able to extract the geminal coupling constant between the protons that absorb at 3.6 ppm and 2.7 ppm and we were able to identify them as α_a and α_b. Decoupling at 1.4 ppm removes some coupling with J value 4.2 Hz at 1.9 ppm and 2.2 ppm. This led us to

Table 10. ^{1}H-NMR chemical shift data (δ in ppm) of 1-substituted phenothiazines.



X	Aromatic	NH	1'	2'	3'	4'
CH_3	6.7-7.2	6.5	2.17			
$CH_2CH_2CH_2CH_3$	6.7-7.2	6.5	2.64	1.45	1.45	0.94
$CHCH_2CH_3$ CH_3	6.5-7.2	6.5	1.25	2.65	1.6	0.89
$C(CH_3)_3$	6.7-7.2	6.5	1.47			
Phenyl	7.1-7.6	6.5	In aromatic region			
Cl	6.6-7.1	6.4				

Table 11. Conformational analysis of the N,N-dimethylamino propyl side chain.

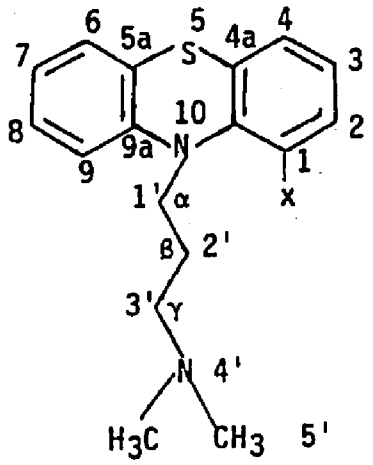


	$N(C_\alpha, C_\beta)$	Δε	% Anti	$N(C_\beta, C_\gamma)$	Δε	% Anti
1-methylpromazine	14.0	0.20	41	14.0	0.20	41%
1-n-butylpromazine	14.2	0.27	44	13.4	0.08	30%
1-s-butylpromazine	14.0	0.20	41	14.0	0.20	41%
1-phenylpromazine	13.0	-0.19	27	14.8	0.52	55%
1-chlorpromazine	13.6	0.01	34	14.9	0.58	57%
promazine	13.9	0.15	39	14.3	0.33	46%
2-chlorpromazine	13.9	0.15	39	13.9	0.15	39%

Table 12. ^{1}H-NMR chemical shift data (δ, in ppm) of promazine and 1-substituted analogues. For numbering, see Table 11.

	α	β	γ	NMe
1-methylpromazine	3.7	1.72	2.15	2.15
1-n-butylpromazine	3.66	1.72	2.20	2.07
1-s-butylpromazine	3.57	1.78	2.26	2.08
1-t-butylpromazine	3.57, 2.7			2.03
1-phenylpromazine	3.09	1.5	2.13	1.99
promazine	3.9	1.97	2.38	2.13
1-chlorpromazine	3.88	1.96	2.38	2.08

Table 13. ^{13}C-NMR chemical shift data (δ in ppm) of promazine and analogues.



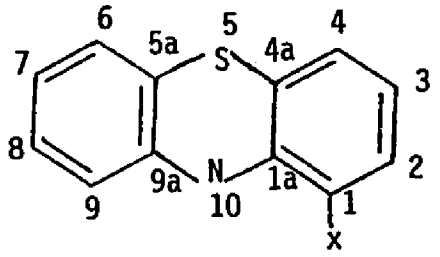
	Aromatic	NMe	α	β	γ
1-methylpromazine	122.2-147.0	45.3	53.3	27.4	57.2
1-n-butylpromazine	123.8-147.0	45.3	53.9	27.4	57.3
1-s-butylpromazine	124.1-147.0	45.3	55.3	27.6	57.3
1-t-butylpromazine	125.2-147.9	45.3	51.7	27.3	57.6
1-phenylpromazine	119.2-141.1	45.2	51.3	26.9	56.9
promazine	115.4-145.4	45.6	45.4	25.3	57.1
1-chlorpromazine	121.9-146.5	45.3	52.7	27.4	57.2 [65]
2-chlorpromazine		45.5	45.5	25.0	56.9 [65]

believe that β protons are spread between 1.7 ppm and 2.4 ppm, and we had decoupled one proton or part of the one of the protons. Decoupling at 3.6 (α_a) brought the expected change in the proton at 2.7 (identified as α_b) and removed some coupling at 1.9 ppm. Decoupling at 2.2 ppm simplified the 1.4 ppm region and removed a geminal coupling in the 1.9 region. Decoupling the α_b proton simplified the α_a proton and the 1.9 ppm region. From these exercises we were able to confirm that the proton at 3.6 ppm is geminally coupled to the proton at 2.7 ppm.

From the results of ^{1}H-NMR, it appears that it takes a very bulky substituent such as a t-butyl group to have an effect on the rotation of the dimethylaminopropyl chain in a substituted promazine. On the other hand, the results of the conformational analysis of the other 1-substituted promazines showed that the 1-substituent had very little effect on one conformation being preferred over the other.

^{13}C-NMR peak assignments were made by calculations based on chemical shifts of phenothiazine and of promazine. The effects of the 1-substituent of the dimethylaminopropyl chain was to shift the chemical shift of the α carbon downfield 6 to 8 ppm (in comparison to the α carbon of promazine). We were unable to correlate the chemical shift of the α carbon and the preferred conformation in solution.

Table 14. ^{13}C-NMR chemical shift (δ in ppm) for data of 1-substituted phenothiazine analogues.*



Carbon Atom	X=CH_3	X=$CHCH_2CH_3$ CH_3	X=Phenyl	X=Hydrogen	X=Chlorine
1a	140.00 (142.49)	139.25 (139.79)	138.07 (140.69)	141.79	140.63 (142.19)
1	122.05 (123.38)	131.07 (134.58)	128.10 (127.58)	114.48	120.30 (120.68)
2	128.97 (128.10)	124.88 (125.4)	126.24 (126.30)	127.40	127.51 (127.8)
3	121.32 (122.72)	122.34 (122.64)	122.10 (123.02)	122.62	122.25
4a	119.17 (118.23)	119.86 (118.33)	119.27 (118.73)	118.33	119.17 (119.63)
4	124.93 (123.92)	124.73 (124.32)	126.24 (125.62)	126.82	125.07 (124.92)
5a	118.15	119.03	119.13	118.33	118.25
6	126.78	126.73	126.73	126.82	126.63
7	122.73	122.68	122.60	122.62	123.22
8	127.22	127.17	127.22	127.40	127.37

Table 14 -- Continued

Carbon Atom	X=CH_3	X=$CHCH_2CH_3$ CH_3	X=Phenyl	X=Hydrogen	X=Chlorine
9a	141.75	141.75	141.89	141.79	140.63
9	114.93	114.74	114.52	114.48	115.18
1'	16.68	35.07	138.97 (141.6)		
2'		20.27	o 128.63		
3'		12.00	m 129.27		
4'		29.80	p 127.95		

* ( ) Calculated value.

Table 15. Comparative ^{13}C-NMR chemical shift (δ, in ppm) assignments for 1-substituted promazine analogues. For numbering, see Table 14.*

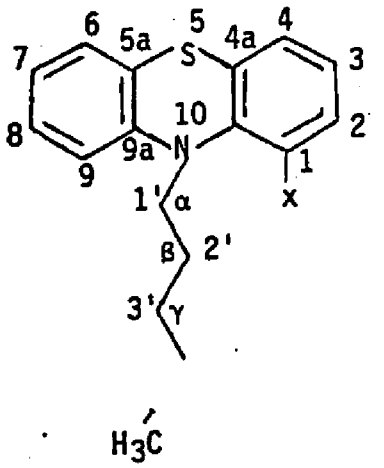
Carbon Atom	X=CH3	n-butyl	s-butyl	t-butyl	X=Phenyl	X=Hydrogen	X=Chloro
1a	143.0(145.9)	143.55	143.55(143.2)	145.0	141.11	145.2	146.52(145.6)
1	124.0(124.3)	137.56(137.6)	133.5(135.5)	136.37(137.6)	128.58(128.5)	115.4	121.95(121.6)
2	130.10(128.0)	129.02	126.35(125.3)	125.86(123.9)	126.34(126.2)	127.3	127.80(127.7)
3	122.20(122.20)	123.85	124.7(122.3)	125.59(121.9)	123.71(122.7)	122.3	123.81(123.6)
4a	125.02(124.9)	125.07(124.9)	125.75(125.0)	126.67(124.6)	123.71(124.6)	125.0	125.49(126.3)
4	123.56(124.2)	124.39	124.96(124.6)	125.51(124.0)	126.34(125.9)	127.1	125.85(125.2)
5a	125.02	125.07	125.70	125.21	126.34	125.0	124.49
6	126.88	126.97	127.0	127.23	127.12	127.1	126.93
7	122.78	123.51	124.60	124.2	123.72	122.3	123.80
8	127.32	126.97	127.0	127.23	127.37	127.3	127.41
9a	147.0	147.01	147.01	147.9	141.11	145.2	141.85
9	115.61	123.51	124.1	124.2	119.17	154.4	121.95

* ( ) Calculated value.

The addition of the dimethylaminopropyl chain to the 1-substituted phenothiazine has the overall effect of shifting the entire aromatic region downfield as much as 6 ppm for the bridgehead carbons and the C-9. The downfield shift of C-9 may be due to the orientation of the dimethylaminopropyl which may lie away from the 1-substituent. This is not confirmed, however, in the solid state structure (Figure 6) determined by X-ray crystallography. The conformation of the dimethylaminopropyl chain in the solid state was found to be $C_\alpha C_\beta$ anti, C_β, C_γ anti (see Table 16).

In an attempt to explain the difference in activity toward electrophiles between N-substituted phenothiazines and non-substituted phenothiazines, different conformations of the ring nitrogen substituent have been proposed [64]. By electron spin resonance (ESR) and polagraphic oxidation potential studies of the phenothiazine radical, it was proposed that when the nitrogen is substituted by hydrogen the hydrogen is in an intra conformation. When the nitrogen is substituted by anything larger than hydrogen, the extra conformer dominates. Attempts to observe the two conformations by NMR variable temperature studies on N-methylphenothiazine failed [66]. However, the ^{13}C-NMR downfield shift of the bridgehead aromatic carbons in N-substituted phenothiazines when compared to the unsubstituted phenothiazines was seen as an increase in the

Table 16. Selected torsion and bond angles for 1-chloropromazine hydrochloride.



Torsion Angles	
Torsion System	Angle (degrees)
1a-10-1'-2'	89.2
9a-10-1'-2'	-63.8
10-1'-2'-3'	-174.6
1'-2'-3'-4'	177.5
1-1a-10-1'	67.7
9-9a-10-1'	-62.2
Bond Angles	
Bond	Angle (degrees)
9a-10-1'	118.6
1a-10-1'	116.7
1a-10-9a	119.0

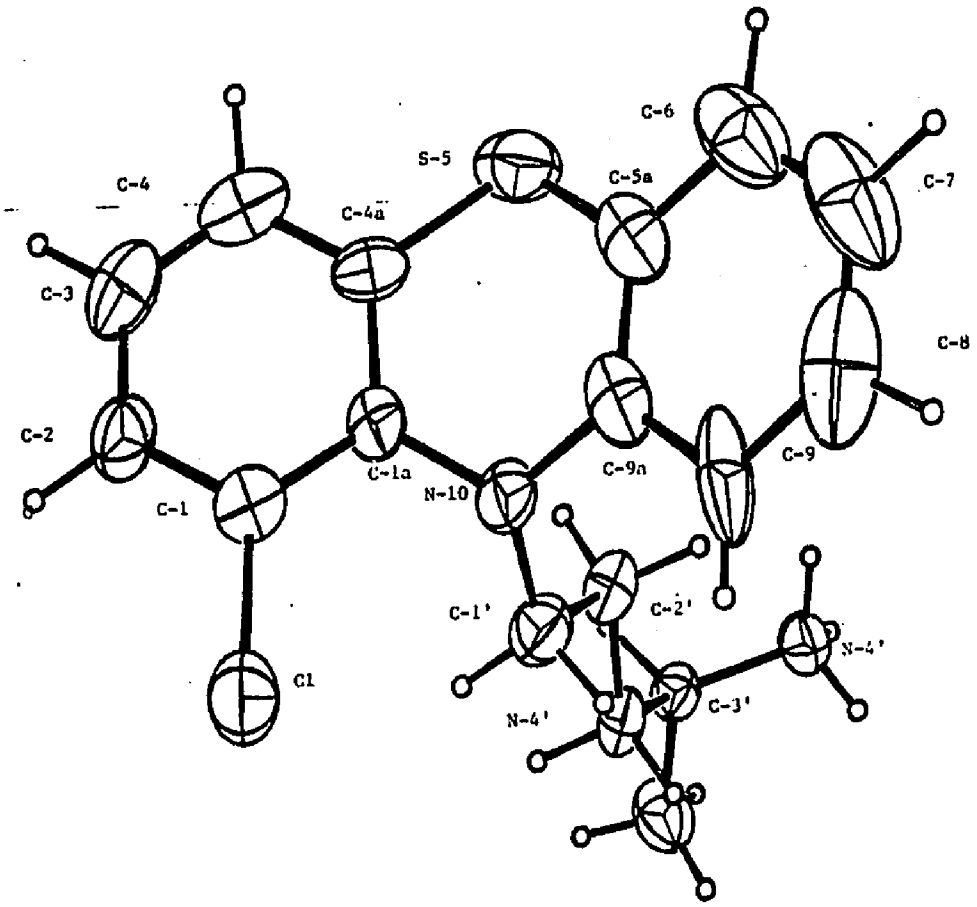


Figure 6. Ortep of 1-chlorpromazine.

substituted versus unsubstituted phenothiazines indicates a slight trend toward sp^3 character in the former. The sum of the three bonds involving the ring nitrogen for phenothiazine [68], and 2-trifluoromethylphenothiazine [69] are 360° and 359° respectively whereas for 1-chlorpromazine (Table 16), phenothiazine-N-3-proprionitrile [70] and chlorpromazine [72] the sums of angles are 354.3°. 354.6° and 353.9°, respectively.

Furthermore, comparison of the distances from the centers of the substituted ring (A) and the unsubstituted ring (B) to the side chain nitrogen in 1-chloropromazine and 2-chlorpromazine revealed that the A-N distance was 6.59 Å for 1-chlorpromazine and 6.2 Å for 2-chlorpromazine. B-N for 1-chlorpromazine is 6.37 Å and for 2-chlorpromazine is 6.7 Å [73]. The side chain nitrogen was 4.80 Å above the plane of the A ring and 4.87 Å above the plane of the B ring for 1-chlorpromazine. For 2-chlorpromazine these values were 4.1 Å and 3.7 Å, respectively. The comparable values for other neuroleptics are much lower [73], indicating a preference for a more planar structure. The pharmacological significance of these data are not known since most of the compounds are conformationally flexible and could adopt a different conformation in solution or at the receptor. The dimethylaminopropyl chain of 1-chlorpromazine appears to project above the ring nitrogen and lie nearer the sulfur atom compared with other

extra conformer population. It was proposed that when the ring nitrogen has a large substituent, there is peri-overcrowding from a substituent at C-1 or C-9, so the intra conformation is destabilized. With the extra conformer the delocalization of the nitrogen electrons is lowered, charge density is decreased and therefore there is a low field shift in the bridgehead carbons. The intra conformer is stabilized by the nitrogen lone pair delocalization into the aromatic ring (Figure 7).

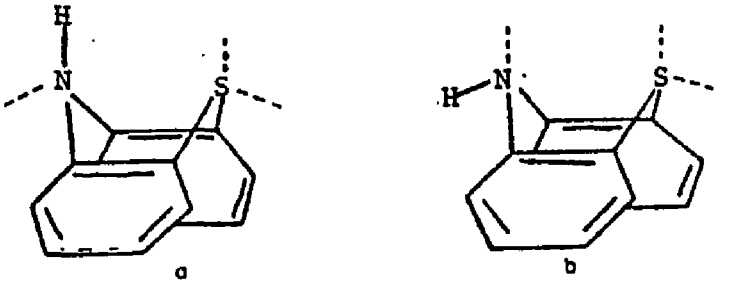


Figure 7. Configurations of phenothiazines. -- (a) H-extra; (b) H-intra.

On the other hand, Aroney and coworkers concluded from dipole moments and molar Kerr constants that phenothiazine, N-methylphenothiazine and N-phenylphenothiazine in solution each prefers the intra conformation [67].

We were unable to find in a search of the literature an example of a phenothiazine derivative with N-substituent held in the extra conformation in the solid state. Comparison of bond angles for the ring nitrogen in N-alkyl

10-substituted phenothiazines [71], showing a pseudo-axial conformation.

We made models of 1,10-disubstituted phenothiazine where the ring nitrogen was an sp^2 (trigonal) nitrogen and found that when nitrogen is trigonal, ring inversion produced two possible conformers that are equivalent. In all the 1-alkylpromazines except for 1-t-butylpromazine there was minimum peri-overcrowding between the dimethylaminopropyl side chain and the 1-alkyl substituent. The t-butylpromazine was the only one which appears unable to exist with an sp^2 nitrogen because of the peri-overcrowding between the bulky t-butyl group and the dimethylaminopropyl chain. On the other hand, if the nitrogen is sp^3 (tetrahedral) the extra conformer is much less sterically crowded than the intra conformer. For this compound we would like to propose that the dimethylaminopropyl chain is held in an extra orientation. Unfortunately, we have no X-ray data on this compound.

EXPERIMENTAL

General

All NMR spectra were run on a JEOL FX 90Q. Spectra of the 4-chloro-10,11-dihydro-5H-dibenz[b,f]azepine, 4-chloro-5-(3-dimethyl)-aminopropyl-10,11-dihydro-5H-dibenz-[b,f]azepine, 4-bromo-5-(3-dimethylaminopropyl)-10, 11-dihydro-5H-dibenz[b,f]azepine, 4-methyl-5-(3-dimethyl-aminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine, and 1-t-butyl-(3-dimethylaminopropyl)-phenothiazine were run on a Bruker WH250 instrument. All the ^{1}H-NMR spectra were also run in $CDCl_3$ with TMS used as an internal standard. For ^{13}C-NMR spectra $CDCl_3$ was used as an internal standard. Melting points were done on an Electrathermal^{R} melting point apparatus and are not corrected. Elemental analyses were performed by the University of Arizona Analytical Center and Mic Anal of Tucson. The term chromatographed twice refers to liquid chromatography in a packed column using silica gel 60, then evaporation of the solvent followed by liquid chromatography in a packed column using finer silica gel.

Before using the 50% NaH in oil, it was washed several times with pentane to remove the oil. The xylene and toluene were dried by distillation over sodium. All

reactions were done under an atmosphere of dry nitrogen. The hydrogenchlorides were made by dissolving the free base in ether and treating with ether saturated with hydrogen chloride gas, evaporating the ether off slowly and recrystallizing the solid with hot methanol.

4-Chloro-10,11-dihydro-5H-dibenz[b,f]azepine

To a solution of 10 g (51 mmoles) 10,11-dihydro-5H-dibenz[b,f]azepine dissolved in dry ethyl ether was added 78.6 mL (130 mmoles) of 1.65 n-butyllithium in hexane. After stirring the reaction at room temperature for 24 hours 30.8 g (130 mmoles) of hexachloroethane was added in portions. The dark green solution was stirred for 20 minutes and ice water added. After stirring for 20 minutes the layers were separated and the ether layer was dried over sodium sulfate and the solvent evaporated. The crude oil was purified by silica gel chromatography (developing solvents 1:1 hexane/ toluene) to give 8 g (68%) of a dark yellow oil. Anal. Calcd. for $C_{14}H_{12}ClN$: C, 73.19; H, 5.27; N, 6.10. Found: C, 73.82; H, 5.19; N, 5.99.

4-Chloro-5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine

2.5 g (33 mmoles) of KOH was dissolved in water and treated with a solution of 6.9 g (33 mmoles) dimethylaminopropyl chloride hydrochloride. The mixture was extracted with toluene and kept overnight over 4 A° molecular sieves.

A solution of 5g (22 mmoles) of 4-chloro-10,11-dihydro-5H-dibenz[b,f]azepine in hot dry toluene was added to a toluene suspension of 1.6g (33 mmoles) of 50% NaH in oil. After refluxing the stirred mixture for 2 hours, the toluene solution containing the free base, 3-dimethylaminopropyl chloride, was added and refluxing continued for 17 hours. After cooling the mixture, ice water was added and stirring continued for 20 minutes. The layers were separated and the toluene layer extracted several times with a 15% hydrochloric acid solution. The combined extracts were cooled in an ice bath and treated with 40% sodium hydroxide. The alkaline solution was extracted with dichloromethane. The solvent was dried over magnesium sulfate and evaporated to give an oil. The oil was absorbed on silica gel 60 and purified by column chromatography with 1% dimethylamine in toluene to give 5g of oil. The oil was dissolved in dry ether and treated with ether saturated with HCl. The ether was evaporated and the white solid recrystallized twice from methanol, m.p. 221°, yield 75%: Anal. Calcd. for $C_{19}H_{24}Cl_2N_2$: C, 64.94; H, 6.89; 7.97 N, Found: C, 64.53; H, 6.86; N, 7.66.

4-Bromo-10,11-dihydro-5H-dibenz[b,f]azepine

10,11-Dihydro-5H-dibenz[b,f] azepine (11.7 g, 30 mmoles), was dissolved in dry ether. To the stirring solution was added 70.4 ml (120 mmoles) of 1.7M

n-butyllithium in hexane. After stirring at room temperature for 24 hours, 10.34 ml (45 mmoles) of 1,2-dibromoethane was added to the brown mixture and stirring continued for 20 minutes. The layers were separated and the ether layer was dried over magnesium sulfate before evaporation. The remaining oil was purified by column chromatography using silica gel 60 and 5% ethyl acetate in hexane to give 8.66g (52%) of yellow oil. Anal. Calcd. for $C_{14}H_{12}BrN$: C, 61.32; H, 4.42; N, 5.11. Found: C, 61.63; H, 4.31; N, 5.25.

4-Bromo-5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine

A solution of 7.9g (50 mmoles) of 3-dimethylaminopropyl chloride hydrochloride was made alkaline with a KOH solution. The basic solution was extracted with toluene and the organic layer was stored over 4Å molecular sieves for 24 hours. 5.5g (20 mmoles) of 4-bromo-10,11-dihydro-5H-dibenz[b,f]azepine was dissolved in hot dry xylene and was added to a xylene suspension of 1.8g (75 mmoles) of 50% NaH in oil. After refluxing the stirred mixture for 2 hours, the basic toluene solution contaning 3-methylaminopropyl chloride was added. After refluxing for 17 hours, the mixture was cooled and ice water added while stirring. The layers were separated and the toluene layer was extracted several times with 15% hydrochloric acid solution. The combined acidic layers

were treated with 40% NaOH and extracted with ethyl ether. The organic layer was dried over magnesium sulfate and evaporated to give a crude black oil. The oil was washed with hexane several times and chromatographed on basic alumina. The HCl salt was made and recrystallized twice from methanol to give product; m.p. 221°. Anal. Calcd. for $C_{19}H_{24}BrClN_2$: C, 57.65; H, 6.15; N, 7.08. Found: C, 61.94; H, 6.46; N, 7.54.

4-Methyl-10,11-dihydro-5H-dibenz[b,f]azepine

1.3M Methyllithium (62 mL, 80 mmoles) in ether was added to a stirring solution of 4.58g (20 mmoles) 3-chloro-5H-dibenz[b,f]azepine in an anhydrous ether. After 24 hours of stirring at room temperature, ice water was added and stirring continued for 10 minutes. The layers were separated, and the ether layer was dried over magnesium sulfate. The crude oil obtained on evaporating off the solvent was purified by column chromatography (10% dichloromethane in petroleum ether) to give 1.3g (30%) of a brown oil. Anal. Calcd. for $C_{15}H_{15}N$: C, 886.07; H, 7.24; N, 6.70. Found, C, 85.83; H, 7.41; N, 6.34.

4-Methyl-5-(3-dimethylaminopropyl)-10,11-dihydrodibenz[b,f]azepine

1.38 g (8.73 mmoles) of 3-dimethylaminopropyl chloride HCl was dissolved in water and basified with KOH solution to liberate the free base. The mixture was

extracted with toluene and the toluene solution was stored overnight over molecular sieves. To a separate toluene suspension of 0.2 g (8.69 mmoles) of 50% NaH in oil was added a stirring hot dry toluene solution of 0.75 g (3.6 mmoles) of 4-methyl-5H-dibenz[b,f]azepine. After refluxing with stirring for 2 hours, the toluene solution containing the free base was added and the mixture left to reflux for 17 hours. After cooling, ice water was added and the reaction mixture stirred for 10 minutes. The two layers were separated and the toluene layer extracted several times with 15% hydrochloric acid solution. The acidic extracts were combined and treated with 40% KOH solution. After an extraction with ether, the solvent was dried over magnesium sulfate and evaporated to give a dark oil. The oil was chromatographed on neutral alumina and eluted with hexane to give 0.78 g (72%) of a reddish brown oil. Anal. Calcd. for $C_{20}H_{26}N_2$: C, 81.56; H, 8.90; N, 9.2. Found C: 79.64; H, 8.71; N, 8.57.

1-Methylphenothiazine

To 4.6 g (20 mmoles) of 2-chlorophenothiazine in dry ether was added 53 ml (80 mmoles) of 1.5M methyllithium in ether. After continuous stirring at room temperature for 6 hours, ice water was added and stirring continued for 10 minutes. The layers were separated, the ether layer dried over magnesium sulfate and evaporated to give an oil.

The crude oil was chromatographed twice using petroleum ether. A cream-colored powder was obtained, m.p. 113°, which was recrystallized from toluene and petroleum ether to give colorless crystals, m.p. 138° (lit. 137-138° [42]).

1-Methyl-10-(3-dimethylaminopropyl)-phenothiazine

1-Methylphenothiazine (2.1 g, 10 mmoles) was dissolved in hot dry toluene and added to a toluene suspension of 0.75 g (30.6 mmoles) of 50% NaH in oil. The previous day 2.42 g (15 mmoles) of 3-dimethylaminopropyl chloride was dissolved in water and added to a solution of 1.12 g (15 mmoles) KOH dissolved in water. The free base was extracted with toluene and the toluene extract stored over molecular sieves. This toluene solution was added to the reaction mixture that had been refluxing for 2 hours and refluxing and stirring continued for 17 hours. After cooling, cold water was added and stirring continued for 10 minutes. The layers were separated and the toluene layer was extracted several times with 15% HCl solution. The combined acidic extracts were made alkaline with 40% sodium hydroxide. The alkaline solution was extracted with methylene chloride and dried over sodium sulfate. The solvent was evaporated to give 2.1 g (75%) of brown oil. Anal. Calcd.: $C_{18}H_{22}N_2S$, 72.43; H, 7.44, N, 9.38. Found: C, 71.8; H, 6.96; N, 7.96.

1-n-Butylphenothiazine

To a stirring solution of 4.6 g (20 mmoles) 2-chlorophenothiazine in dry ether was added 47 ml (80 mmoles) of 1.7M n-butyllithium in hexane. After stirring at room temperature for 6 hours, the reaction was quenched by adding ice water. Stirring was maintained for 10 minutes. The layers were separated. The ether layer was dried over magnesium sulfate before evaporating the solvent. The oil was purified twice by chromatography and eluted by 10% ethyl acetate in hexane to give 2.86 g (28%) of a green oil. Anal. Calcd.: $C_{16}H_{17}NS$: 75.23; H, 6.72; N, 5.48. Found: C, 73.51; H, 5.86; N, 5.38.

1-n-Butyl-10-(3-dimethylaminopropyl)-phenothiazine

2.5 g (10 mmoles) of 1-n-butylphenothiazine was dissolved in hot dry toluene and added to a toluene suspension of 50% NaH in oil. The mixture was refluxed for two hours. The previous day a solution of 2.42 g (15 mmoles) of 3-dimethylaminopropyl chloride HCl had been treated with 1.12 g KOH solution. After an extraction with toluene, the organic layer had been dried with magnesium sulfate and stored over 4Å molecular sieves. This was added to the refluxing mixture and refluxing was maintained for 17 hours. After cooling, ice water was used to terminate the reaction and vigorous stirring continued for ten minutes. The layers were separated. The toluene layer

was extracted several times with 15% HCl solution. The acidic layers were combined and treated with a KOH solution until they were basic and then extracted with ether. After drying over sodium sulfate, the solvent was evaporated by aspirator to give an oil. The greenish oil was chromatographed on alumina and eluted with 1% dimethylamine in toluene to give 2.45 g (72%) green oil. Anal. Calcd. for $C_{21}H_{28}N_2S$: C, 74.05; H, 8.30; N, 8.23. Found: 73.60; H, 8.07; N, 8.03.

1-s-Butylphenothiazine

A solution of 4.6 g (20 mmoles) of 2-chlorophenothiazine in dry THF was cooled in a dry-ice/ethanol bath maintained at -70°. 1.25M sec-butyl-lithium (61.5 ml, 80 mmoles) in cyclohexane was added and stirred at -70° for 2 hours. The temperature was raised to -30° and maintained for 4 hours, then allowed to come to room temperature. Ice water was added to the reaction. After 10 minutes of stirring, the mixture was extracted with ethyl acetate. The solvent was dried over magnesium sulfate and evaporated to give an oil which was purified twice by silca gel chromatography to give 1.5 g (28%) of a tan powder, m.p. 72°. Anal. Calcd. for $C_{16}H_{17}NS$: C, 75.29; H, 6.72; N, 5.40. Found: C: 75.39; H, 6.67; N, 5.33.

1-s-Butyl-10-(3-dimethylaminopropyl)-phenothiazine

3-Dimethylaminopropyl chloride HCl (3.17 g, 20 mmoles) was dissolved in water and treated with 1.12 g (20 mmoles) KOH solution. The basic solution was extracted with toluene and the toluene layer stored overnight on molecular sieves. To a toluene suspension of 0.72 g (30 mmoles) of 50% NaH in oil was added a hot dry solution of 2.55 g (10 mmoles) s-butylphenothiazine in dry toluene. After 2 hours of refluxing, the 3-dimethylaminopropyl chloride in toluene solution was added and refluxing continued overnight. After cooling, water was added and the layers separated. The toluene layer was extracted with 15% HCl solution. The combined extracts were treated with 40% NaOH solution and extracted with ether. The ether was dried over magnesium sulfate and evaporated to give 2.4 g (70%) of a reddish oil, which was purified over alumina: Anal. Calcd. for $C_{21}H_{28}N_2S$: C, 75.45; H, 6.58; N, 8.37. Found: C, 75.39; H, 6.67; N, 8.00.

1-t-Butylphenothiazine

2-Chlorophenothiazine (4.6 g, 20 mmoles) was dissolved in dry THF and chilled in a dry ice/ethanol bath and temperature maintained at -70°. To it was added 30 ml (60 mmoles) of 2M t-butyllithium in pentane with stirring and the reaction mixture maintained at -70° for 2 hours. The temperature was raised to -30°. After 4 hours of

stirring at -30°, the temperature was allowed to come to room temperature. Water was added very slowly with stirring. After an extraction with ethyl acetate, the solvent was dried over magnesium sulfate and evaporated to give an oil which was chromatographed twice on silica gel. A dark green solid was obtained which was recrystallized with toluene/pet ether to give 0.56 g (11%) colorless crystals. Anal. Calcd. for $C_{16}H_{17}NS$, C: 75.45; H, 6.58; N, 8.37. Found C, ___, H ___, N ___.

1-t-Butyl-10-(3-dimethylaminopropyl)-phenothiazine

A 3.17 g (20 mmoles) solution of 3-dimethylaminopropyl HCl was basified with a solution of 1.12 g of potassium hydroxide. The basic solution was extracted with toluene and stored overnight over molecular sieves. t-Butylphenothiazine (2 g, 7.8 mmoles) dissolved in hot dry toluene was added to a suspension of 0.72 g (30 mmoles) of 50% NaH in toluene. After refluxing for 2 hours, the basic toluene solution was added and refluxing continued for 17 hours. After cooling to room temperature, water was added and stirring continued for 10 minutes. The layers were separated and the toluene layer was extracted several times with a 15% HCl solution. The combined acidic extracts were treated with 40% NaOH solution. After drying over magnesium sulfate, the solvent was evaporated to give a

reddish oil. It was purified over alumina to give 1.84 g (69%) of a colorless oil.

1-Phenylphenothiazine

To 4.7 g (20 mmoles) of 2-chlorophenothiazine dissolved in anhydrous ether and stirred at room temperature, 30 ml (72 mmoles) of 2.4M phenyllithium in benzene was added. After stirring for four hours at room temperature, ice water was added and stirring continued for 10 minutes. The layers were separated and the organic layer was dried over magnesium sulfate and evaporated to give an oil. The oil was chromatographed on a silica gel 60 column (hexane:ethylacetate 9:1) to give 1.65 g (30%) of rust-colored oil. Anal. Calcd. for $C_{18}H_{13}NS$: C, 78.50; H, 4.77; N, 5.08. Found: C, 76.97; H, 4.77; N, 5.23.

1-Phenyl-10-(3-dimethylaminopropyl)-phenothiazine

3-Dimethylaminopropyl chloride (2.4 g, 20 mmoles) in water was added to 1.12 g of KOH solution. It was extracted with toluene and stored overnight over molecular sieves. A solution of 3.0 g (10.9 mmoles) of 1-phenylphenothiazine in hot toluene was added to a suspension of NaH (0.8 g, 0.33 mmoles) in dry toluene. After refluxing the stirred mixture for two hours, a solution of the 3-dimethylaminopropyl chloride was added and the mixture was refluxed and stirred for 17 hours. After cooling, water was added and stirring continued for

20 minutes. The layers were separated and the toluene layer was extracted several times with an acid solution. The combined acid extracts were treated with 40% NaOH solution and the alkaline solution extracted with methylene chloride. The solvent was evaporated, leaving an oil which was chromatographed on silica to give 2.9 g (75%) of brown oil. Anal. Calcd. for $C_{23}H_{24}N_2S$: C, 76.61; H, 6.72; N, 7.77. Found: C, 76.80; H, 6.23; N, 7.86.

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