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Synthesis and Room Temperature NMR Analysis of Dimethylpiperazines

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SYNTHESIS AND ROOM TEMPERATURE NMR ANALYSIS OF DIMETHYLPIPERAZINES

BY

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SYNTHESIS AND ROOM TEMPERATURE NMR ANALYSIS

OF DIMETHYLPIPERAZINES

This thesis is approved as a creditable and independent investigation by a candidate for the degree, Master of Science, and is acceptable as meeting the thesis requirements for this degree. Acceptance of this thesis does not imply that the conclusions reached by the candidate are necessarily the conclusions of the major department.

Thesis Adviser / Date

Head, Chemistry Department Date

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ABSTRACT

A survey of the literature has been made on the syntheses of 2,5- and 2,6-dimethylpiperazines. Several new N-substituted dimethylpiperazines were subsequently prepared. These are: cis-2,6-dimethyl-4-mesyl-piperazine (31), cis-2,5-dimethyl-1,4-dimesylpiperazine (32), and trans-2,5-dimethyl-1,4-dimesylpiperazine (33). Attempted syntheses of trans-2,6-dimethylpiperazine (4) are also discussed.

Room temperature nmr analysis of these and other previously known piperazine isomers supports the hypothesis that the more energetically equivalent equilibrating conformers are the more compact the AB portion of the ABX pattern of the piperazine ring protons. This technique provides a convenient method for suggesting the configuration and conformation at room temperature of the seventeen isomers and derivatives that were studied. Piperazine ring proton assignments are based on coupling constants and chemical shifts. Steric factors influencing room temperature nmr analysis are also discussed.

INTRODUCTION

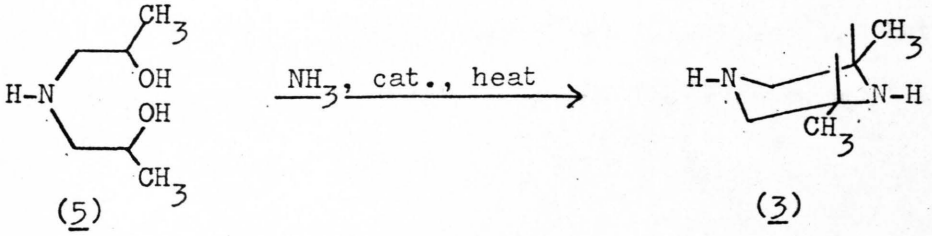
Review of Syntheses.

The dimethylpiperazines studied (Figure 1) have been prepared by a variety of reduction and cyclization processes. Cis-2,5-dimethylpiperazine (1) and trans-2,5-dimethylpiperazine (2) were first prepared in 1893 by reducing 2,5-dimethylpyrazine in anhydrous alcohol[1]. Cis-2,6-dimethylpiperazine (3) was isolated in 1914 from a tartarate salt mixture obtained from natural products[2-3]. These three geometrical isomers were initially characterized by separating optical isomers of d-hydroxymethylenecamphor derivatives[2-5]. The remaining isomer, trans-2,6-dimethylpiperazine (4), has yet to be synthesized.

Two syntheses less commonly used for the preparation of 1 and 2 have been the reduction of 2,5-dimethyl-3,6-dioxopiperazine with sodium and alcohol[6] and the catalytic (Pt-C or RaNi) hydrogenation of dimethylpyrazine[7,8] or 2,6-dimethyldihydropyrazine[9].

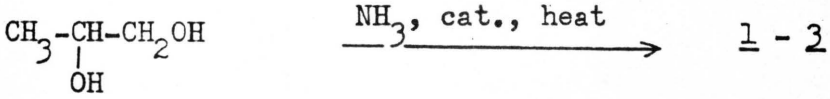
The majority of the synthetic work reported in the literature has involved either catalytic dehydration or ammonolysis of amino alcohols and glycols.

Ammonolysis of diisopropanolamine (5) in the presence of hydrogen[10,11] or without[12], utilizing a catalyst[10,12] or none[11] has been used to prepare 3.



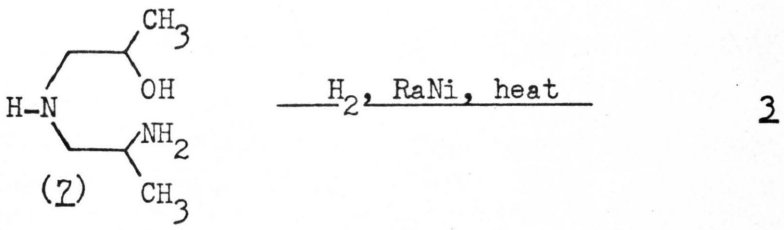
(5) (3)

Compounds 1 - 3 have been prepared by the ammonolysis of propylene glycol (6) using either Raney Nickle[13] or Cu-oxide-Cr_2O_3-Ni oxide[14] catalyst.



(6)

Catalytic dehydrogenation of N^1-(2-hydroxypropyl)-1,2-diamino-propane (7)[15,16] using Raney Nickel has also been used in preparing 3.

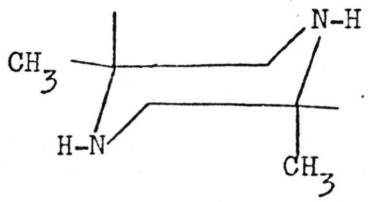


(7)

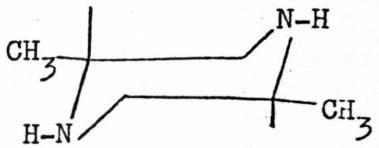
Ishiguro[16] claims to have isolated both cis- and trans-2,6-dimethyl-piperazine (3, 4) from this reaction, basing his claim on the melting points of the 1,4-ditosyl derivatives.

Industrially the catalytic bimolecular cycloamination of 2-amino-1-propanol in a hydrogen atmosphere gives 1 and 2 in economical yields. Cycling the reaction mixture through a catalyst bed improved the yield by further reducing the dimethylpyrazine byproduct[17-26].

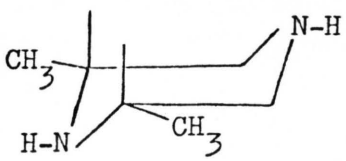
It has been found that 1 is converted in high yield to 2 by catalytic hydrogenation[8,18,20,27,28]. Trans-2,5-dimethylpiperazine (2) is found to be favored by high temperature, high pressure, increased catalyst ratio, and increased reaction times[21]. Catalytic hydrogenation of isonitrosoacetone in acetic acid using a platinum catalyst [7,29-31] has also been used to prepare 2.



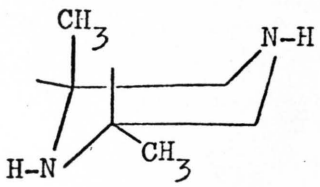
cis-2,5-dimethylpiperazine (1)



trans-2,5-dimethylpiperazine (2)



cis-2,6-dimethylpiperazine (3)

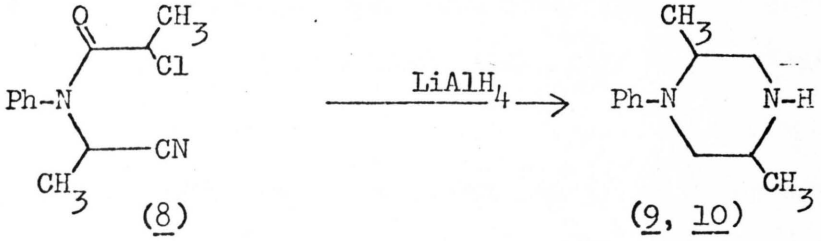


trans-2,6-dimethylpiperazine (4)

Figure 1. Predominant conformations of 2,5- and 2,6-dimethylpiperazines.

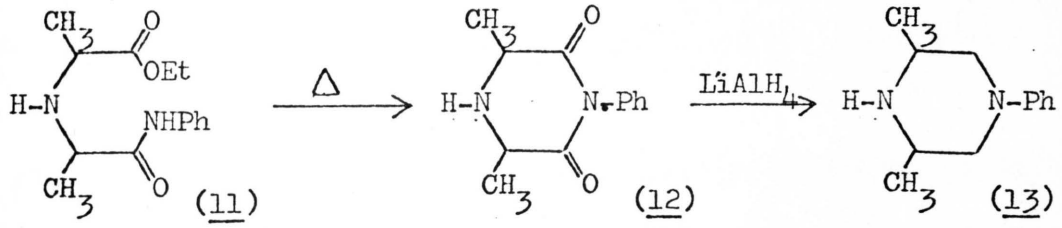
Phenyl groups have been substituted for protons on the nitrogen atoms of 1 - 3 in some manner prior to ring formation or by a combination of elimination and addition reactions after ring formation.

Halocyanomines such as 8 have been reduced with lithium aluminum hydride to prepare cis- and trans-2,5-dimethyl-1-phenylpiperazine (9, 10)[32].



(8) (9, 10)

Various N-aryl substituted cis-2,6-dimethylpiperazines have been prepared by the following reaction sequence[33,34].



(11) (12) (13)

Ethyl N-(1-anilino-2-propyl)-2-aminopropanoate (14) has been substituted for ethyl 2-amino-N-(2-propananilide) propanoate (11) to yield a mixture of cis- and trans-2,6-dimethyl-4-phenylpiperazine (13, 16)[35]. This is the first substantiated claim to the preparation of the trans-2,6-dimethylpiperazine ring.

1,4-diphenyl derivatives of 1 and 3 have been isolated by reduction of the ring contraction products of 3,7-dihydroxy-1,5-diphenyloctahydro-1,5-diazocine[36].

Bimolecular condensation of N-phenylamino alcohols using aluminum oxide or p-toluenesulfonic acid as catalysts has also produced the 1,4-diphenyl derivatives of 1 - 3[37].

1,4-diphenyl derivatives have also been prepared by reacting the appropriate dimethylpiperazine with phenyl lithium and bromobenzene[36,38] or with $NaNH_2$ and bromobenzene in anhydrous THF-HMPT[37].

The dibasic character of the dimethylpiperazines has been utilized in preparing diamides from acid chlorides. The 1,4-p-ditosyl and 1,4-dibenzoyl derivatives have been prepared by the Schoten-Bauman technique using p-tosyl chloride and benzoyl chloride, respectively[1-5]. The 1,4-ditosyl derivative of 2 has also been prepared by refluxing 2 with p-tosyl chloride in pyridine[39]. The cis-2,6-dimethyl-4-benzoylpiperazine (26) has been prepared by refluxing 3 in acetone with benzoyl chloride[2,3]. The free base is liberated from the hydrochloride salt by neutralizing with NaOH.

Although the references in the literature are abundant on the synthesis of the piperazine ring it is by no means complete. This is well evidenced by the paucity of references to the trans-2,6-dimethylpiperazine (4) as well as the other 2,5- and 2,6-dimethylpiperazines. More work is needed to ascertain the reasons for the synthetic stereo-specificity in the formation of isomeric ring structures such as 4.

Conformational and Configurational Analysis.

Little work has been done in the area of investigating the conformations and configurations of the dimethylpiperazines. The first such effort was by Pope and Read[3] who resolved the enantiomers of dl-cis-2,5-dimethylpiperazine using d-hydroxymethylenecamphor. They were unable to resolve cis-2,6-dimethylpiperazine (3)[2]. These results are consistent with the symmetry of the geometrical isomers. It was not until the nineteen-sixties that nmr specroscopy was used on the conformation and configurations of the dimethylpiperazines.

In conformational analysis a molecule is characterized in terms of a model. For six membered alicylcic molecules cyclohexane is usually chosen. Piperazines are hypothetically formed by replacing the 1- and 4-methylene groups of cyclohexane with the -NH- group. Introducing nitrogen atoms into the ring has many significant effects, some of which can be investigated by nmr spectroscopy.

Various studies[40,41] have shown that piperazine and various N-substituted piperazines exist predominately in chair conformations similar to cyclohexane. Since 1,3- and 1,4-dimethylcyclohexane have been shown to have the same conformation as cyclohexane[42], it is reasonable to suggest that 2,5- and 2,6-dimethylpiperazines will have similar conformations. On the basis of steric interactions in the chair conformation, such as gauch-butane, we would expect the conformation with the methyl groups in the equatorial positions to predominate for the trans-2,5- and cis-2,6-dimethylpiperazines (2, 3). Cis-2,5- and trans-2,6-dimethylpiperazine (1, 4)

"ring flip" to yield conformations of equivalent energy and both conformers should be present in equal amounts.

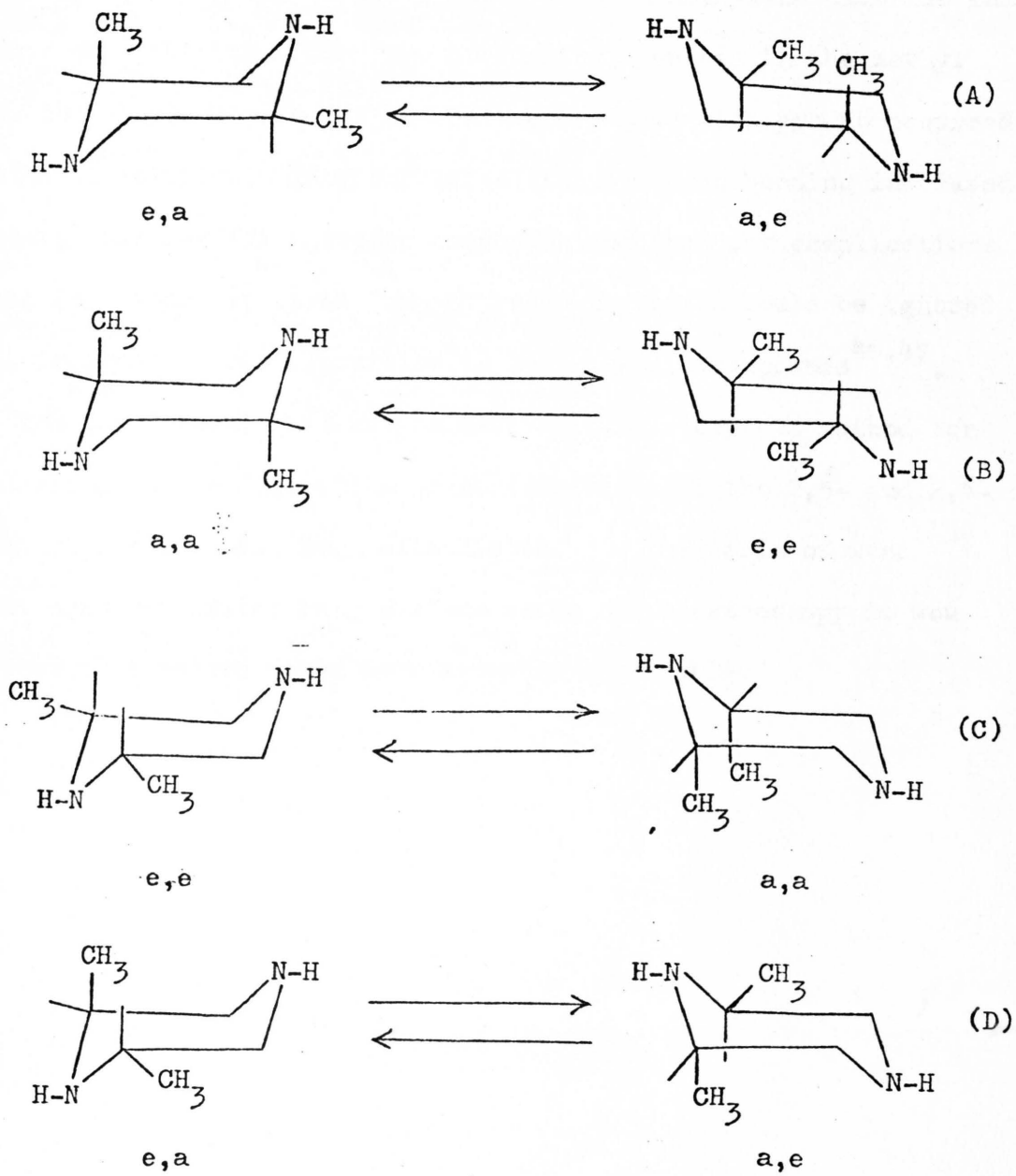
Rapid conformational change can be shown through the use of low temperature nmr spectroscopy. If the rate of conformational change is fast, protons will experience an average magnetic field. For example, consider ring methylene protons. If the rate of conformational interconversion is greater than the reciprocal of the chemical shift difference between the axial and equatorial protons then only one signal is seen[42]. As the rate slows, then the observed signal will slowly broaden and at a certain temperature two signals will appear[53].

Trans-1,4- and cis-1,3-dimethylcyclohexane (analogous to 2 and 3) exist predominately as the diequatorial conformers since temperature lowering produces no significant change in the chemical shifts for the various ring protons[42,44]. For both of these isomers the signal of the axial proton is well upfield from the equatorial proton. In fact, for the trans isomer the axial signal has approximately the same chemical shift as the methyl signal[44]. For trans-1,3-dimethylcyclohexane (analogous to 4) the axial signal is upfield from the methyl signal. At -60° the methyl signals are doublets but by -78° they have merged into a broad singlet. At -132° the two methyls are nonequivalent and give rise to two different signals. The methyl signals for cis-1,4-dimethylcyclohexane (analogous to 1) show similar behavior except that when they become nonequivalent a doublet and a singlet which coincides with the high field doublet component is produced[44].

The above observations are consistent with the predicted chair conformation. Dimethylpiperazines which would be expected to be in the chair conformations also have been shown to behave in a manner similar to the dimethylcyclohexanes although the studies have not been as thorough. The chemical shifts of the ring protons are analogous to the dimethylcyclohexanes, i.e., axial protons resonate at a higher field than equatorial protons and the methine signal varies according to conformation and configuration[45,46].

Cis-2,5-dimethylpiperazine (1), existing in an a,e === e,a (Figure 2) equilibrium, has been shown to have an nmr temperature phenomenon similar to that of cis-1,4- and trans-1,3-dimethylcyclohexane, i.e., the spectra increase in complexity with temperature lowering[46]. The nmr spectra of cis- and trans-2,6-dimethyl-4-phenylpiperazine (13, 19) have been examined at low temperature and it was found that only the trans conformer exhibits changes on temperature lowering[47]. It was concluded that the trans isomer (19) was an equilibrating mixture of equal energetic conformers whereas the cis isomer (13) was present at room temperature in predominately the diequatorial conformation.

Besides conformational interconversion there is also the possibility of nitrogen inversion. In investigating the nmr spectra of N,N'-dimethylpiperazine[48] in methylene chloride it was found that the methyl signal remained sharp even at -40°, indicating that nitrogen inversion was rapid at all temperatures and similar to ammonia which resonates in the microwave region. In another study[46]



where e,e = ring methyls are equatorial, equatorial;
e,a = ring methyls are equatorial, axial;
a,a = ring methyls are axial, axial.

Figure 2. Chair conformations of (A) cis-2,5-dimethylpiperazine (1), (B) trans-2,5-dimethylpiperazine (2), (C) cis-2,6-dimethylpiperazine (3), (D) trans-2,6-dimethylpiperazine (4).

the nmr spectra of this tertiary amine in both methylene chloride and methanol were obtained. No line broadening occurred in the methyl signal in methylene chloride at low temperatures although it occurred in methanol solution. They concluded that hydrogen bonding increased the energy barrier for nitrogen inversion and that any complications arising in the nmr spectrum from nitrogen inversion could be ignored for their study of ring inversion in heterocyclic compounds[46,47].

From the foregoing it can be seen that no clear cut method for establishing the configuration or conformations of the 2,5- and 2,6-dimethylpiperazines has been established. On the basis of work already done on similar ring systems using nmr spectroscopy it would seem that this method would be reasonably applicable.

PURPOSE

The objective of this research was to prepare trans-2,6-dimethylpiperazine (4) and its 1,4-diphenyl derivative (21) which were then and are still unknown. A second objective was to prepare 1,4-disubstituted derivatives of 2,5- and 2,6-dimethylpiperazines and to study their nmr spectra.

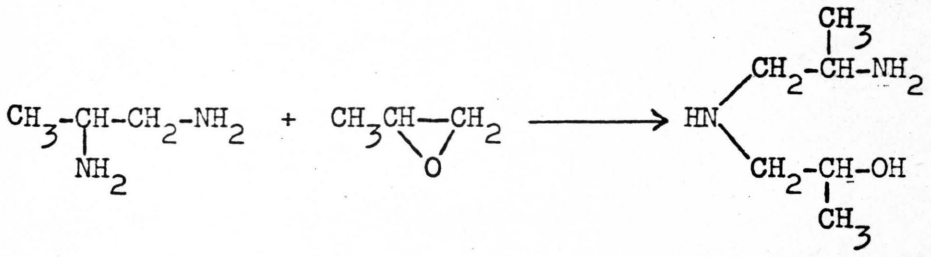
RESULTS AND DISCUSSION

Syntheses.

In the literature there are only two references for the preparation of trans-2,6-dimethylpiperazine ring system. The first[16] involves the catalytic dehydration of N^1-(2-hydroxypropyl)-1,2-diaminopropane (7) (Ishiguro procedure) and the second[35] is the thermal cyclization of ethyl 2-amino-N-(2-anilinopropyl) propanoate (14) (Cignarella procedure) with subsequent reduction of the resulting 3-ketopiperazines (17, 18). Both reaction sequences are outlined in Figures 3 and 4, respectively.

It was decided to duplicate both reaction sequences with particular concentration on the latter. The first synthesis is straight forward and all the reagents are available commercially. One of the starting materials for the Cignarella procedure, 1-anilino-2-aminopropane (16), is unavailable commercially and needed to be prepared. The reaction sequence leading to the preparation of 16 is outlined in Figure 5. Once the trans-2,6-dimethyl-4-phenylpiperazine (19) had been prepared the 1-position would be phenylated using sodium amide and bromobenzene in THF-HMPT[36]. The unphenylated isomer would then be prepared by nitrosoating[49] and subsequent hydrolysis with aqueous KOH[46] (Figure 4).

Ishiguro Procedure - In the catalytic dehydration of 7 only one dimethylpiperazine was isolated and characterized by us and by Ishiguro. The spectral properties and melting points of the isomer and its ditosyl derivative match that of commercially available



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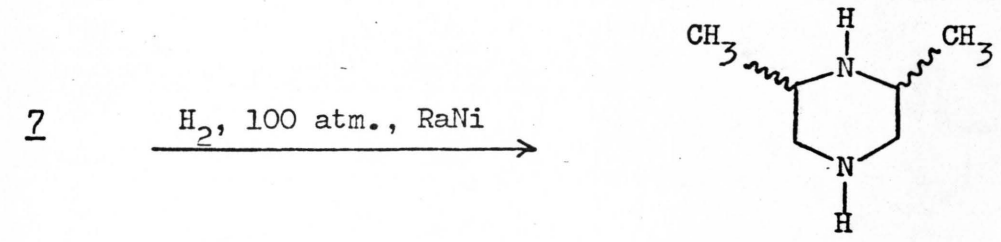
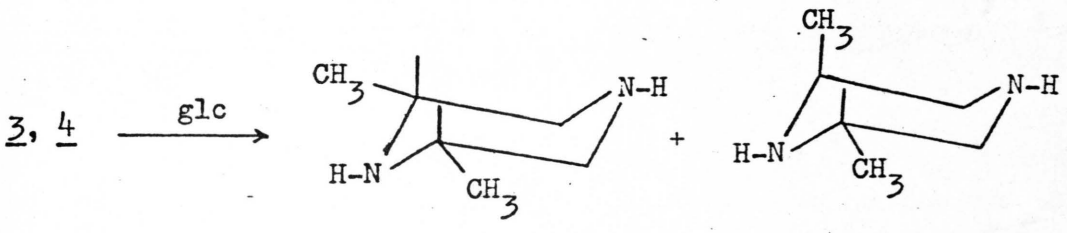
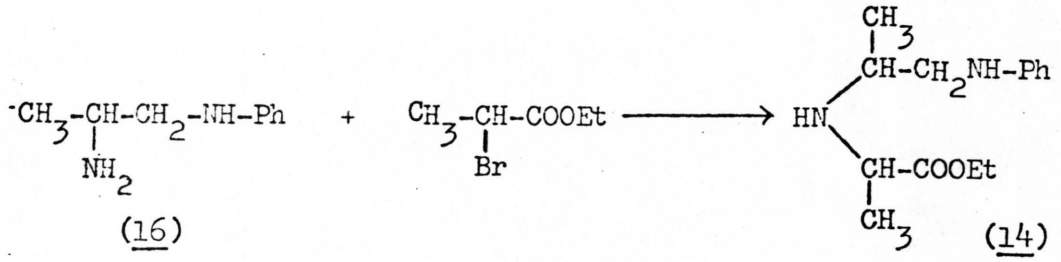


(3, 4)

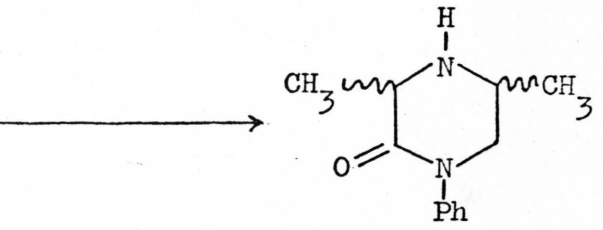


(3) (4)

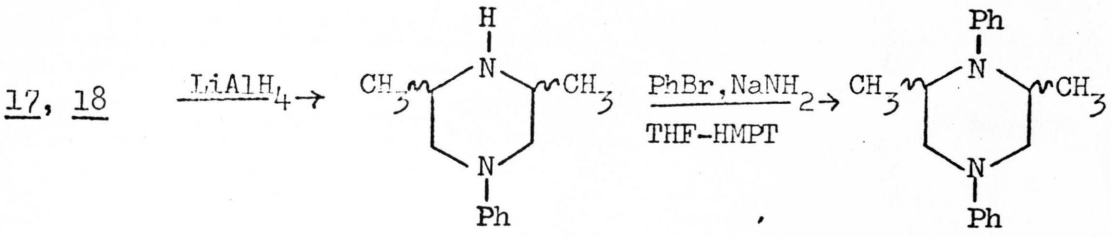
Figure 3. Ishiguro Procedure.



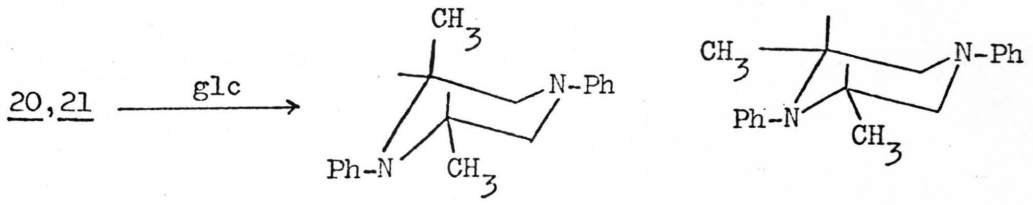
(16) (14)



(17, 18)



(13, 19) (20, 21)



(20) (21)

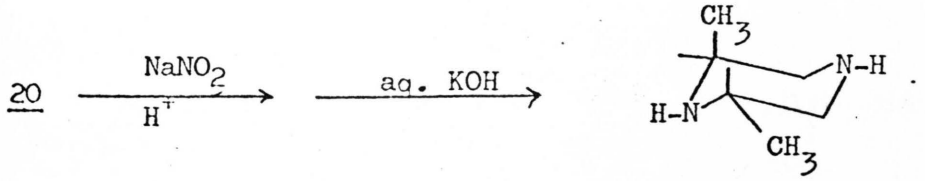


Figure 4. Cignarela Procedure.

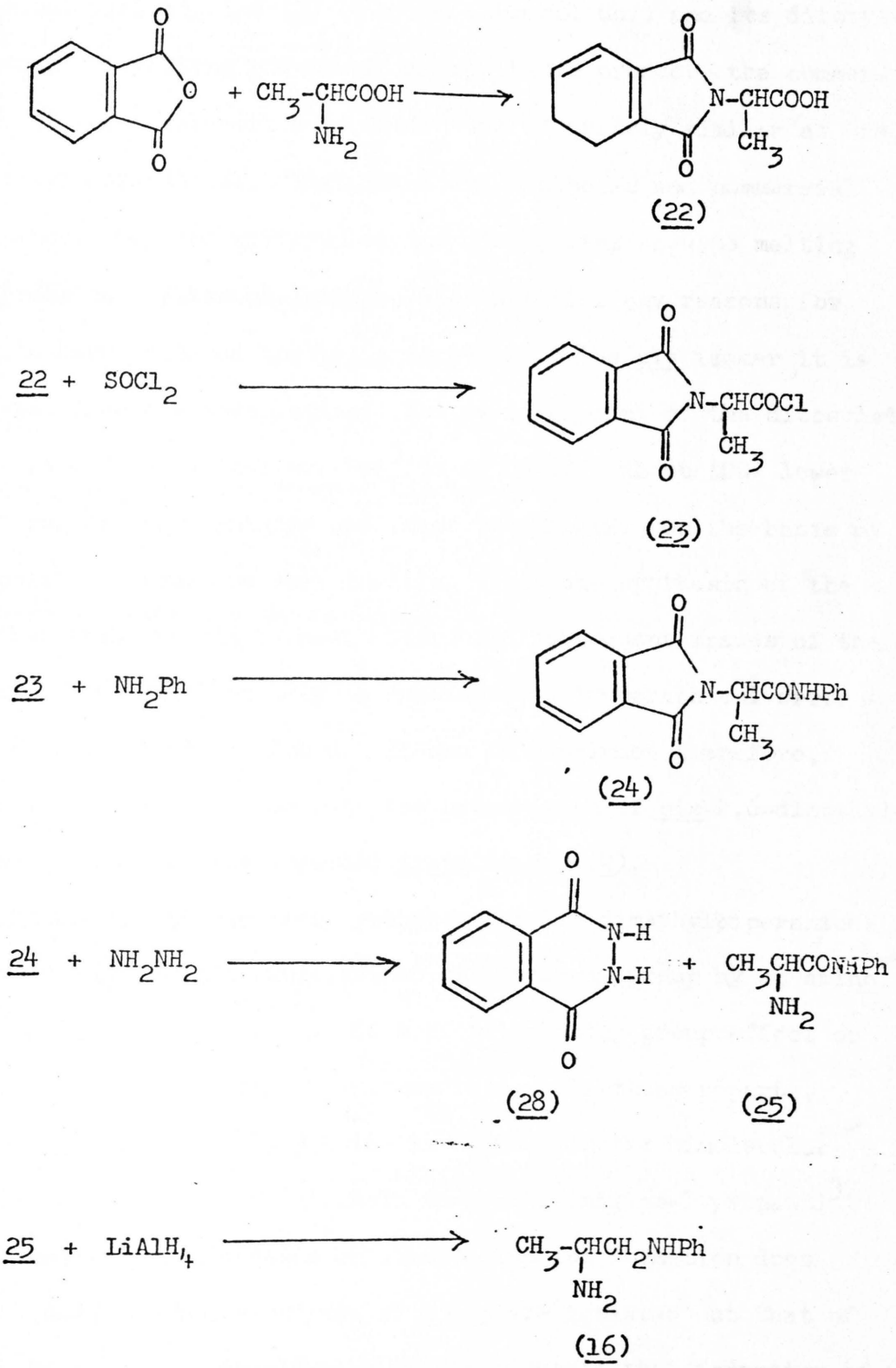
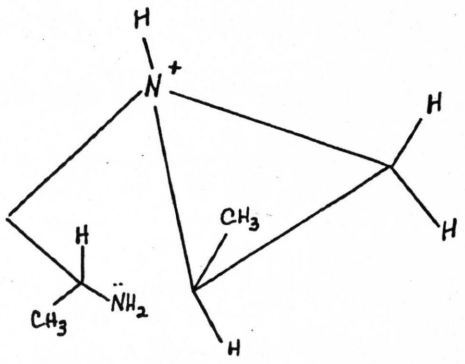


Figure 5. Preparation of 1-anilino-2-aminopropane (16).

cis-2,6-dimethylpiperazine (3) (Aldrich Chemical Co.) and its ditosyl derivative. The melting points of the synthetic product, the commercial product and the reported product[16] are adequately similar as are their ditosyl derivatives. Mixture of the synthetic and commercial dimethylpiperazines and mixtures of the ditosylates show no melting point depression. Although Ishiguro does not list any reasons for assuming to have prepared the trans rather than the cis isomer it is possible to offer one speculation. The melting point of the ditosylate of 3 is reported by earlier workers[5] to be 89-90°, about 100° lower than that reported by Ishiguro and found in my work. On the basis of melting points it would be very inviting to assume synthesis of the trans rather than the cis isomer. Searching subsequent issues of the Journal of the Chemical Society no mention of a typographical error on these melting points is found. It can be concluded therefore, that Ishiguro's synthesis leads to the preparation of cis-2,6-dimethylpiperazine (3) and not the reported trans isomer (4).

Nearly all of the reported syntheses for 2,6-dimethylpiperazines appear to be nucleophilic substitution of a hydroxy group by an amino group and appear to involve some form of neighboring group effect or formation of an aziridinium ion intermediate. All these reports, except Ishiguro's, list only 3 being isolated. In the bimolecular condensation of phenyl amino alcohols such as 2-anilino-1-propanol[37] where neighboring group effects or aziridinium ion formation does occur the 1,4-diphenyl derivatives of 1 - 3 are isolated but that of 4 is not. Examination of molecular models suggests that formation of

4 is inhibited by steric interactions of the methyl groups. The attack at the ring carbon bearing the methyl is less favored than attack at the methylene. This is evidenced by the percentage of 44.4% to 25.6% for formation of 2,5- to cis-2,6-dimethylpiperazine[37].



It would appear that 4 is restricted from forming when aziridinium ion forms as an intermediate primarily due to steric considerations.

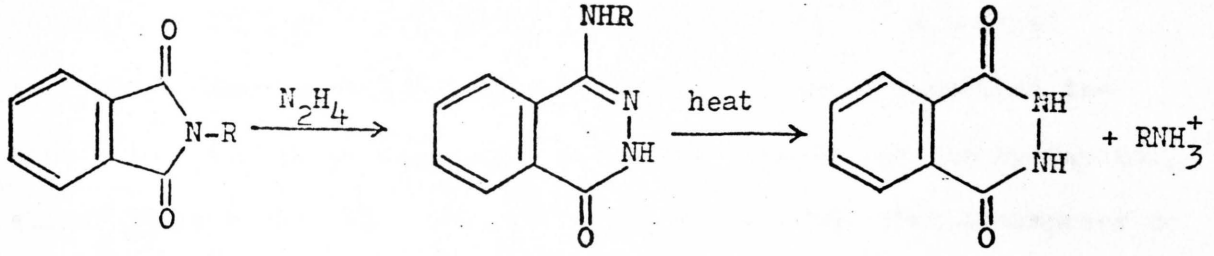
A second possible reason for the failure to isolate 4 in the Ishiguro reaction is that it may be the kinetic product, whereas 3 is the thermodynamic product. The ability to change cis-2,5-dimethylpiperazine (1) to trans-2,5-dimethylpiperazine (2) by increasing the pressure, temperature, reaction times, etc. suggests that 2 is the thermodynamic product. On the basis of symmetry cis-2,6-dimethylpiperazine (3) is analogous to 2 and trans-2,6-dimethylpiperazine (4) to 1, further suggesting 4 as a possible kinetic product. Attempts at duplicating Ishiguro's work were limited to repeated experiments at approximately 200° and 1600mm Hg. These conditions of high temperature and high pressure would favor the thermodynamic product over the kinetic.

Cignarella Procedure - Because of various difficulties encountered the reaction sequence outlined in Figure 4 was completed only as far as a single attempt at the thermal cyclization of 14 to cis- and trans-2,6-dimethyl-3-ketopiperazine (17,18). Because of the lack of quantity, pure 17 and 18 were not isolated, however, their presence could be detected by infrared spectroscopy. A spectrum obtained following attempted distillation showed a carbonyl stretching frequency at 1650 cm^{-1} which is characteristic of a six member lactam carbonyl stretch. Also, because of the lack of quantity, no attempts were made at separating 17 and 18 by the suggested elution chromatography procedure[35].

Problems arose in this synthesis in attempting to scale the preparation of 16 from 0.1 mole to molar quantities. Some of the problems arose due to the lack of a stirrer that could adequately handle thick slurries in two liter volumes with the end result being reduced yields. Another problem lay in the availability of solvents. For example, in preparing 2-phthalimidopropananilide (24) from the corresponding acid chloride, the problem was choosing a solvent that would dissolve acid chloride, anilide and aniline hydrochloride without reacting with either the anilide or acid chloride. As of yet no solvent has been found that satisfies these requirements. The result of these scale-up attempts was that the reaction sequence will need to be repeated many times at lower concentrations to obtain sufficient material for subsequent steps.

Problems also arose in that the hydrazinolysis of 24 which was found not to proceed according to reports of earlier investigators[51-54],

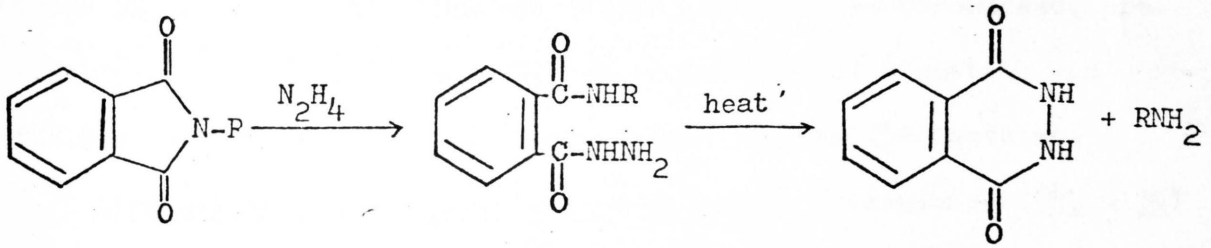
a recent review on amino acid chemistry[55] or a recent handbook on chemical reagents[56]. The reaction was reported to be:



(24) (27) (28) (29)

where R = $CH_3CHCONHPh$

According to Barber and Wragg[57], the reaction intermediate 27 is not formed but rather a thermally unstable intermediate, 30 is formed.



(24) (30) (28) (25)

The commonly accepted workup is, in brief, refluxing 24 with hydrazine in ethanol during which a white solid forms, followed by evaporation in vacuo and hydrolysis of the residue with dilute aqueous acid. After filtering, the aqueous layer is neutralized and the free amine extracted. From this sequence the removal of the initial solid and recrystallizing from water yielded a compound that did not melt below 310° (Fischer-Johns). The literature melting point for 28 is

342-43°. The infrared spectrum of this solid has bands characteristic of 1,4-phthalhydrazindiones: a very broad band near 3000 cm^{-1} (NH), carbonyl at 1650 cm^{-1} and CNH at 1540 and 1285 cm^{-1}. Elemental analysis is also compatible with $C_8H_6N_2O_2$. It would seem that the conclusions of Barber and Wragg are correct insofar as the hydrazinolysis of 24 is concerned, i.e., an intermediate forms that decomposes to 28 and 25 during the reaction.

According to these results, it would appear that 25 and 29 should be isolated regardless of whether 27 or 30 is formed. However, following the procedure outlined above, only a minute amount of 25 was isolated. By removing the solids formed during the initial reflux, evaporating the filtrate *in vacuo*, and distilling, 25 could be isolated in 84.5% yield. In the original workup 25 had to be decomposed, presumably by acid hydrolysis. The exact mechanism is uncertain and further work needs to be done to elucidate the reaction species.

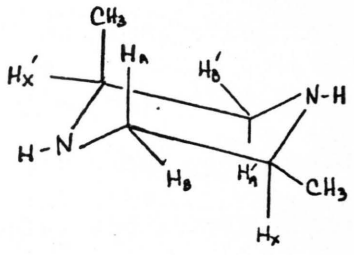
Dimethylpiperazinesulfonamide synetheses - Sulfonamides (31 - 39) of the dimethylpiperazines were prepared in either aqueous sodium hydroxide solution[1-5] or in pyridine solution[39]. Both methods resulted in satisfactory yields of the di-pptoluenesulfonamides (tosyl), dibenzenesulfonamides (besyl), and dimethanesulfonamides (mesyl) with only one exception. Neither method yielded the dimesyl derivative of cis-2,6-dimethylpiperazine (3) and only the monoderivative was obtained. Based on steric considerations and the very slight downfield shift of 0.05ppm for the methyl group signal in the nmr spectrum for 31 (Appendix, Spectrum 4; also compare the 4-phenyl and

1,4-diphenyl derivatives to the unsubstituted parent, Appendix, Spectrum 21) it is assumed the substitution is on the 4-position.

At first this appears to be incongruous in that the dibesyl and ditosyl derivatives can be prepared by both methods and these latter groups are larger than a methyl group. These results can be rationalized in terms of the stereochemistry of 3. The aryl groups can orientate themselves perpendicular to the piperazine ring and reduce steric interactions with the ring methyls whereas the mesyl methyl group cannot. The consequences of these steric interactions are discussed in the next section.

Room Temperature NMR Sectra Analysis.

The dimethylpiperazine ring protons constitute an ABX pattern. The methine proton is designated X, and the axial and equatorial methylene protons, A and B, respectively. The methine proton, X, is coupled to the geminal methyl group and to vicinal A and B resulting in a complex multiplet. A and B are represented by two four line signals being coupled with each other and with X. The methyl group



is coupled to the X proton and appears as a doublet with a coupling constant of 6.0-7.0Hz. The ABX signals are downfield from the methyl signals with the exact chemical shift and pattern highly dependent on configuration, conformational mobility, anisotropic effect and inductive effects.

Coupling constants can be approximated for the ring hydrogens of 1 - 4 by measuring the dihedral angles between the respective hydrogens and substituting into the Karplus equations[58,59]. Using Drieding models of cis-2,6-dimethylpiperazine (3), it is possible to predict different quartet patterns for both A and B resulting from two chair and two boat conformations. Comparing the four possible configurations in Figure 6 and their suggested nmr patterns with the observed spectra of various nitrogen substituted derivatives of 3 where the signals are sufficiently spread to allow easy identification, show the chair conformation with equatorial methyls to be the most predominant conformer. This is consistent with earlier work[36] and offers further justification for assuming the chair conformation to be the more predominant for dimethylpiperazines.

An earlier investigator[36] discovered that the methyl group signal underwent an upfield shift on phenylating the 1- and 4-positions of 3, whereas, the cis- and trans-2,5-dimethyl isomers displayed a downfield shift. This apparent anomolous behavior could be explained on the basis of p-pi orbital overlap and steric hinderence between piperazine ring methyls and the phenyl substituents.

Table 1. Chemical shifts for the ring protons of dimethylpiperazines.

COMPOUND	SOLVENT	δ CH_3	δ H_X	δ H_A	δ H_B
Cis-2,6-dimethylpiperazine (3)*	$CDCl_3$	1.03	2.80	2.87	2.25
---, 4-phenyl- (13)**	$CDCl_3$	1.03	2.90	3.45	2.15
---, 1,4-diphenyl- (20)*	$CDCl_3$	0.86	3.30	3.50	2.75
---, 1,4-dibesyl- (34)	CH_2Cl_2	0.93	2.84	3.50	1.72
	14.3% TFAA/CCl_4	0.95	2.83	3.43	1.63
---, 1,4-ditosyl- (37)	CH_2Cl_2	1.32	4.10	3.40	2.13
---, 4-mesyl- (31)	$CDCl_3$	1.08	2.91	3.67	2.25
Cis-2,5-dimethylpiperazine (1)*	$CDCl_3$	1.13	2.70	2.80	2.60
---, 1,4-diphenyl- (26)*	$CDCl_3$	1.16	3.60	3.31	3.06
---, 1,4-dibesyl- (35)	CH_2Cl_2	1.15	3.47	3.11	3.11
	16.6% TFAA/CCl_4	1.15	3.55	3.24	3.24
---, 1,4-ditsoyl- (38)	15% TFAA/CCl_4	1.13	3.54	3.26	3.26
	14.3% DMSO-d_6/CCl_4	1.13	3.40	3.08	3.08
	CH_2Cl_2	1.20	3.50	3.18	3.18
---, 1,4-dimesyl (32)	$CDCl_3$	1.47	4.07	3.24	3.65
Trans-2,5-dimethylpiperazine (2)*	$CDCl_3$	1.01	2.66	2.90	2.41
---, 1,4-diphenyl- (40)*	$CDCl_3$	1.12	4.05	3.45	3.25
---, 1,4-dibesyl- (36)	$CDCl_3$	1.12	4.22	3.42	3.42
	50% TFAA/$CDCl_3$	0.97	4.15	3.38	3.38
	TFAA	0.97	4.17	3.40	3.40
---, 1,4-ditosyl (39)	$CDCl_3$	0.97	4.19	3.36	3.36
	TFAA	0.98	4.17	3.41	3.41
--, 1,4-dimesyl- (33)	33% TFAA/$CDCl_3$	1.35	4.15	3.43	3.43
Trans-2,6-dimethylpiperazine, 4-phenyl- (10)**	$CDCl_3$	1.13	2.50 - 3.50 complex mult.		

* J.J. Worman, Ph.D. Thesis, University of Wyoming, Laramie, Wyoming, June, 1968.

**G.G. Gallo and A. Vigevani, J. Heterocyclic Chem. 2, 418(1965).

If the phenyl groups bonded to the nitrogen atoms in cis-2,6-dimethyl-1,4-diphenylpiperazine (20) are unrestricted, overlap between the nitrogen nonbonded electron pair and the aromatic pi orbital can occur. This overlap would change the electron density of the aromatic ring causing the nmr signal of the aromatic protons to be asymmetrical and integrate 3:2, the high field multiplet representing the ortho and para hydrogens, respectively. Examination of space filling models of 20 shows that if the methyl groups are in the axial position both phenyl substituents could be involved in p-pi overlap. With both methyl groups in the equatorial position, however, the phenyl group in the 1-position would be sterically prevented from becoming coplanar inhibiting p-pi overlap. The appearance of a more symmetrical aromatic signal for 20 (Appendix, Spectrum 21) than for the 2,5-dimethylpiperazines suggests that the chair conformation with the methyl groups equatorial is the most predominant. Also, if the phenyl group in the 1-position of 20 is not coplanar, then the methyl groups will be within the shielding cone of the phenyl group resulting in the observed upfield shift (See Table 1, Compound 20, CH_3 = 0.86).

Further substantiation for assuming that the chair conformation for 20 with both methyls in the equatorial position can be obtained from the nmr spectrum of cis-2,6-dimethyl-4-phenylpiperazine (13) (Appendix, Spectrum 17) where the signals for the methyl groups are unchanged from the unsubstituted isomer and where the aromatic signal is asymmetrical indicating the presence of p-pi overlap.

That the methyl groups of cis-2,6-dimethylpiperazine (3) sterically hinder groups bonded to the 1-position can also be confirmed by the aromatic signals of the ditosyl (34) derivative of 3 (Appendix, Spectrum 3). For the tosyl derivatives the aromatic ring protons and the aryl methyl protons exhibit one set of signals in the 2,5-dimethylpiperazine isomers with no distinction being made between the tosyl groups on either the 1- or 4-position, (Appendix, Spectra 7-9, 15, 16). Examination of models of 34 illustrates that for the tosyl in the 4-position there exists little restriction to rotation about the sulfur bond. The nitrogen atom, sulfonyl group, and benzene ring can orientate themselves so that maximum orbital overlap can occur. For the tosyl on the 1-position, however, there are steric restrictions which would reduce orbital overlap to a significant degree. The result of this would be increased electron density in the benzene ring causing an upfield shift of the nmr signals. This is observed in that two A_2B_2 patterns and two aryl methyl singlet signals appear for 34.

Steric hindrance of the two equatorial methyl groups in 3 can also be used to explain the failure to prepare the 1,4-dimesyl derivative of 3, whereas, the ditosyl and dibesyl derivatives are easily prepared. For example, if the attacking species is considered to be $R\text{-}SO_2^+$, it is readily apparent that rotation about the carbon bond of the methyl sulfonoium ion does not change its orientation relative to the piperazine ring methyls. Rotation about the same bond in the aryl sulfonium ions, however, places the aromatic ring

either perpendicular or parallel to the piperazine ring. Thus the aromatic ring can orientate itself to reduce interactions with the methyls in 3 where the mesyl methyl group cannot.

Rapid conformational interchange between chair conformations can be shown through the use of nmr spectroscopy. If the rate of conformation change is faster than the nmr radio frequency, a single signal is observed[42] for two equilibrating protons: i.e., the signals are time averaged. An example of this is the axial and equatorial protons of a methylene group in cyclohexane. If the rate of interconversion of these protons in conformation change is reduced, as occurs on temperature lowering, then the single sharp signal observed at room temperature will slowly broaden and at a certain temperature a doublet will appear[43,60]. At room temperature a single signal is observed for the methylene protons which on cooling slowly broadens to a doublet showing the effects of geminal and long range coupling, the latter serving primarily to broaden the signals. At -70° the spectrum stopped changing significantly as the rate of conformational interconversion essentially had sufficiently slowed so that the nmr was observing both energetically equivalent conformations and was superimposing the signals.

It has been shown that for cis-2,5-dimethylpiperazine (1)[46] and trans-2,6-dimethyl-4-phenylpiperazine (19)[47] (Appendix, Spectrum 20) the nmr signals for the ring protons become more complex on temperature lowering, whereas, the ring proton signals of trans-2,5-dimethylpiperazine (2)[46] and cis-2,6-dimethyl-4-phenylpiperazine (19)[47] (Appendix, Spectrum 18) show little change. Examination of models

and Figure 2 for 1 and 19 shows C_i symmetry and that two different ABX patterns are possible for either chair conformation. Also, both chair conformations are seen to be energetically equivalent. The increasing complexity of the nmr signals on temperature lowering implies a decrease in the rate of conformational interconversion. The rate becomes less than that of the nmr radiofrequency and an ABX pattern becomes superimposed over a nonequivalent A'B'X' pattern resulting in the observed increased complexity.

Examination of models and Figure 2 also shows that two energetically nonequivalent conformations exist for 2 and 19. And that the piperazine ring protons should show an $A_2B_2X_2$ pattern. From the evidence previously presented the chair conformation with the ring methyls equatorial should predominate with the equilibrium being shifted in that direction at room temperature. On cooling the lower energy conformation of two energetically nonequivalent conformations should predominate. That 2 and 19 show little change on temperature lowering offers further evidence that the chair conformation with the methyls equatorial predominates even at room temperature.

In isomeric piperazines, as one conformation of two in equilibrium begins to predominate, $\delta A - \delta B$ for 1 to 3 is seen to be 20, 49, and 62Hz, respectively. This trend can be observed in the chemical shifts listed in Table 1 insofar as the ABX pattern is adequately resolved. It appears that at room temperature $\delta A - \delta B$ can be used to qualitatively determine the conformational preference in isomeric piperazines.

Except for the data obtained from the literature, the chemical shifts reported in Table 1 have been determined solely by inspection. Except for the isomers of cis-2,6-dimethylpiperazine (3), where the chemical shifts are sufficiently large to permit proton signal assignment by inspection of the overlapping of patterns, similarity of chemical shifts due to conformational equilibria, resulting in time averaging of the signals, made the determination of individual chemical shifts impossible. Because chemical shifts could not be assigned to the ring methylene protons the various inductive, resonance, and anisotropic effects of the nitrogen atom and its substituents can not be determined at this time.

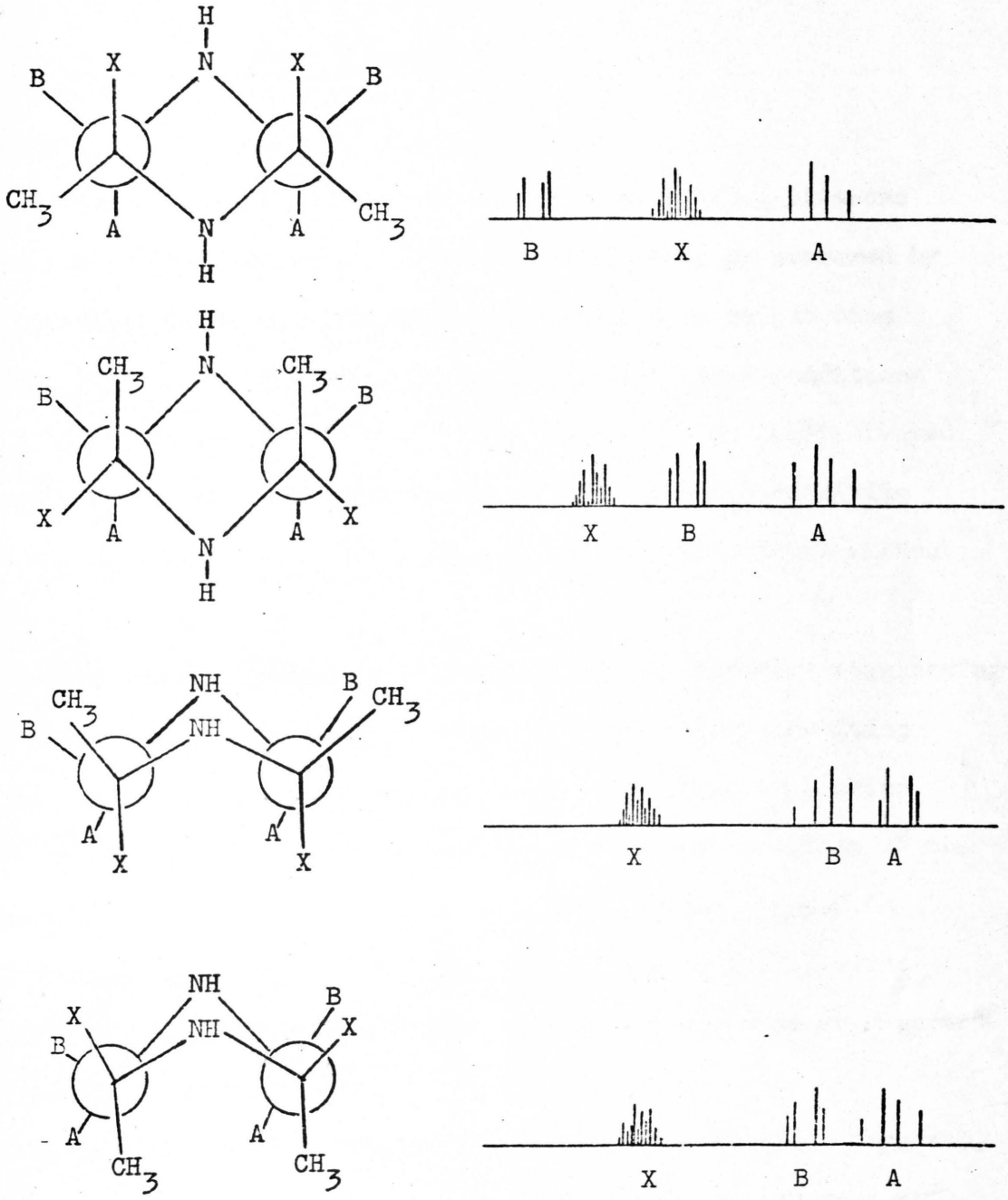


Figure 6. Newman projections of boat and chair conformations of cis-2,6-dimethylpiperazine (3) with estimated nmr ABX signal patterns (not drawn to scale).

CONCLUSIONS

Syntheses.

Because of steric inhibitions in the intermediate, it seems unlikely that trans-2,6-dimethylpiperazine (4) will be prepared by reactions that involve aziridinium ion formation or neighboring group effects that approximate the azirinium ion under conditions used by Ishiguro and in our work. This conclusion is substantiated by this work and the work of many others who have used catalytic dehydration of amino alcohols and amino alcohol derivatives without having isolated 4.

By not proceeding via an aziridinium ion or involving neighboring group effects as in the Ishiguro procedure, but rather involving nucleophilic displacement of an ester ethoxy group by an anilino group, the Cignarella procedure avoids the steric restriction of the Ishiguro procedure and should provide a route to the trans-2,6-dimethylpiperazine ring system. The compound, 1-anilino-2-amino-propane (16), has been prepared and the reaction sequence in Figure 4 is currently being followed.

The hydrazinolysis of 2-phthalimidopropananilide (24), Figure 5, has been found not to proceed as described in the literature. It appears that either the suggested intermediate, 4-(2-propananilide)-1-phthalazone (27) does not form; or it is not as thermally stable as described or a second possible intermediate, N-(2-propananilide)-N'-aminophthalamide (30), which is claimed by the literature to be

thermally unstable, is formed. No investigation of these intermediates was done.

Several new dimethylpiperazine derivatives were prepared. Cis-2,6-dimethyl-4-mesylpiperazine (31), cis-2,5-dimethyl-1,4-dimesylpiperazine (32), trans-2,5-dimethyl-1,4-dimesylpiperazine (33).

Room Temperature NMR Analysis.

On the basis of chemical shift and coupling constant data conclusions concerning the stereochemistry of the dimethylpiperazines, 1 - 3 and their nitrogen substituted derivatives can be drawn.

The three isomeric piperazines studied at room temperature exist predominately in the chair conformation and can be considered to be in equilibrium between two possible chair conformations. The cis-2,6-dimethylpiperazine (3) isomer exists predominately in the chair conformation with the methyl groups located equatorially. In this conformation the methyl groups interact sterically with groups bonded to the 1-position and substantially determine the reaction chemistry at that position. The cis-2,5-dimethylpiperazine (1) isomer exists in equilibrium with both equally energetic conformers present in equal amounts.

In the isomeric piperazines studied, 1 -3, and their nitrogen substituted derivatives, insofar as chemical shifts could be determined, $\delta A - \delta B$ can be used to determine the conformational preference of two equilibrating conformers. As $\delta A - \delta B$ increases, one of the

two conformers predominates, presumably the lower energy conformer. By examining the ABX pattern it is possible to suggest the stereochemistry of the predominant conformations.

SUGGESTIONS FOR FURTHER WORK

In the course of the preceding study several questions arose that merit further investigation in addition to the completion of the work already begun.

It has been found that cis-2,5-dimethylpiperazine (1) can be converted into trans-2,5-dimethylpiperazine (2) by catalytic hydrogenation and that 2 can be the favored product by increasing the temperature, pressure or the length of the reaction time in the catalytic hydrogenation of amino alcohols. This suggests that perhaps 2 is the thermodynamic product and 1 the kinetically favored product. It is then tempting to draw an analogy between the 2,5- and 2,6-dimethylpiperazines and suggest that trans-2,6-dimethylpiperazine (4) may be the kinetic product and cis-2,6-dimethylpiperazine (3) is the thermodynamic product. Since only high temperature and pressures were used in this work a suggested study would be one where the solvents, catalysts, temperature, pressure, atmospheres and reaction time are varied and the products isolated and characterized. The analysis of this study would have to consider the stereochemistry of the possible intermediates, as steric factors may be the determining factors and not necessarily the thermodynamic or kinetics of the system.

A second study would be the characterization of the hydrazinolysis of 2-phthalimidopropananilide. Such a study would include the determination of the reaction mechanism, as this appears to be in doubt and the characterization of any intermediates formed in the reaction.

Except for the data obtained from the literature, the chemical shifts recorded in Table 1 are only approximate inasmuch as overlapping of patterns, similarity of chemical shifts due to averaging and the complexities of spin-spin coupling increase the complexity of the spectra to the point where exact chemical shifts could not be ascertained by inspection. In order to determine the chemical shifts and assignments of the signals it will be necessary to obtain spectra on a spectrometer equipped with a spin decoupler. By the spin decoupling of protons and evaluation of the resulting splitting patterns, chemical shifts and proton assignments can be made with reasonable certainty. Through the use of the spin decoupler changes in signal intensity (Nuclear Overhauser Effects) can be also used to verify the assignments.

In order to evaluate the resonance and inductive effects of the nitrogen derivatives on the dimethylpiperazine ring protons, as shown by nmr spectroscopy, it will be necessary to prepare and obtain the nmr spectra of the following compounds: 1-phenyl-,1-tosyl-, 4-tosyl-, 1-besyl-, 4-besyl-, 1-mesyl-, 1,4-dimesyl derivatives of cis-2,6-dimethylpiperazine (3), the unsubstituted trans-2,6-dimethylpiperazine (4) and a series of derivatives analogous to that of 3. Finally, the monophenyl, monotosyl, monobesyl, and monomesyl derivatives of cis- and trans-2,5-dimethylpiperazines (1, 2) should be prepared.

To supplement the results obtained from the nmr study on the dimethylpiperazines it will also be necessary to obtain accurate infrared spectra and ultraviolet spectra on each piperazine

derivative. Changes in the stretching frequency of the sulfur-oxygen and sulfur-nitrogen bonds may allow further evaluation of the electron delocalization between the piperazine nitrogen, the sulfonyl group, and the group bonded to the sulfonyl group. The size of the sulfur atom and the tetrahedral arrangement of its substituents may render the changes in stretching frequencies too small to be determined by infrared spectroscopy and the ultraviolet would then be needed to detect these changes.

EXPERIMENTAL

The following experimental work was done at South Dakota State University located in Brookings, South Dakota, which has an elevation of 1620 feet above sea level and an approximate atmospheric pressure of 720mm Hg.

All infrared spectra were obtained on a Perkin-Elmer Model 700 spectrometer and the significant peaks noted. Spectra were obtained neat or as nujol mulls on NaCl plates.

Nuclear magnetic resonance data were obtained on a Varian Model A60-A spectrometer at the normal operating temperature of 39°. Chemical shifts are reported as delta (δ) values relative to tetramethylsilane (TMS) which was used as an internal standard.

Elemental analyses were performed in duplicate by a departmental technician and the average value is listed.

Melting points were obtained using pyrex capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected.

Preparation of 2-Phthalimidopropanoic Acid (22).

A solution of 148g (1 mole) phthalic anhydride and 89g (1 mole) dl-alanine in 500cc toluene was refluxed until water ceased to form, about 2-3 hours. The mixture was cooled, the solvent removed in vacuo, and the residue recrystallized from ethanol and water. Initial cooling had to be done at room temperature as the product tended to oil on rapid cooling. Recrystallizing yielded 225g (95%) white crystals, mp 161-62°, lit. 160-61°(H_2O)[61]. The infrared spectrum showed bands at 3450, 1780, 1760, 1725, 1390, 1260, 1000, 960, 920, and 720 cm^{-1}. The nmr spectrum obtained in $CDCL_3$ gave δ10.80 (s, 1H, -COOH), δ 7.75 (m, 4H, arom), δ 3.00(q, J = 7.5Hz, 1H, -CH-), δ1.67(d, J = 7.5Hz, 3H, $-CH_3$). V.P.O. gave molecular weights of 218.9 and 221.3 in acetone.

Anal. Calcd for $C_{11}H_9NO_4$: C, 60.30; H, 4.11.
Found: C, 59.64; H, 4.39.

Preparation of 2-Phthalimidopropanoyl Chloride (23).

To a solution of 109.5g (0.5 mole) of 22 in 500cc toluene, 74.5g (0.63 mole) thionyl chloride was added slowly with stirring. The temperature was brought to 60-70° and the mixture stirred overnight. Thionyl chloride was removed by distillation until the boiling point of toluene was reached. The mixture was cooled and the remaining solvents removed in vacuo. The resulting brown solid was then recrystallized from boiling hexane. A steam jacketed funnel had to be used as the acid chloride is insoluble below the boiling point of the solvent. The resulting white crystals were dried overnight

in vacuo (0.75mm Hg) at room temperature. The reaction yielded 120g (95%) white crystals, mp 69.5-70.5°, lit. 71° (ligroin)[62]. The infrared spectrum showed bands at 1810, 1790, 1770, 1705, 1330, 1180, 1140, 1000, 990, 930, and 720 cm^{-1}. The nmr spectrum obtained in CCl_4 gave δ7.82(m, 4H, arom), δ5.14(q, J = 7.5Hz, 1H, -CH-), δ1.74(d, J = 7.5Hz, 3H, $-CH_3$).

Anal. Calcd for $C_{11}H_8NO_3Cl$: C, 55.89; H, 3.39.

Found: C, 55.99; H, 3.36.

Preparation of 2-Phthalimidopropananilide (24).

To a cold solution of 118.8g (0.5 mole) of 23 in 500cc methylene chloride, 50g freshly distilled aniline was slowly added with vigorous stirring. The reaction was carried out at ice bath temperatures to keep N-phenylphthalimide from forming. The reaction mixture was allowed to warm to room temperature maintaining stirring after the aniline was added. The solvent was removed in vacuo and the residue recrystallized from methyl alcohol and water yielding 110.2g (75%) white crystals, mp 165-66°, lit. mp 173° (alcohol)[63]. The infrared spectrum showed bands at 3225, 3200, 1770, 1775, 1710, and 1670, 1540, and 1260 cm^{-1}. The nmr obtained in CCl_4 acetone d_6 gave δ8.46 (s, 1H, -HN-), δ7.80(s, 5H, arom), δ7.29(m, 4H, arom), δ4.95(q, J = 7.5Hz, 1H, -CH-), δ1.72(d, J = 7.5Hz, 3H, $-CH_3$).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.03; H, 4.79.

Found: C, 68.85; H, 4.74.

Preparation of 2-Aminopropananilide (25).

A solution of 20.8g (0.65 mole) hydrazine hydrate in 50cc ethanol was slowly added to a solution of 92g (0.318 mole) 24 in 1500cc ethanol with constant stirring. The mixture was refluxed for eight and one-half hours, cooled, filtered and the volatile materials removed in vacuo. The oily residue was filtered and vacuum distilled yielding 44.0g (84.5%) of a light yellow oil, bp 150-80° (10mm Hg) lit. bp 190-96° (15-16mm Hg)[64]. The infrared spectrum showed bands at 3300, 3050, 1675, 1605, 1530, 1250, 1180, 1130, 760, and 695 cm^{-1}. The nmr spectrum obtained in CCl_4 gave δ7.14(m, 5H, -NH-, arom), δ3.19(s, $-NH_2$), δ1.23(d, J = 7Hz, 3H, $-CH_3$).

Anal. Calcd for $C_9H_{12}N_2$): C, 65.82; H, 7.37.

Found: C, 66.58; H, 7.95.

Preparation of 1-Anilino-2-aminopropane (16).

To 200cc THF (dried over $LiAlH_4$), 12g $LiAlH_4$ were added with stirring until a homogeneous slurry resulted. A solution of 24g (0.16 mole) 25 in 100cc dry THF was added at a rate sufficient to maintain gentle reflux. After the initial reaction slowed, the mixture was heated to maintain reflux for three hours and then cooled. Water was added very slowly dropwise with vigorous stirring. Extreme caution was necessary as the reaction was extremely exothermic and evolved H_2 gas. The reaction was allowed to subside before an additional drop of water was added. Enough water was added to destroy the excess $LiAlH_4$ which was noted by the slurry turning from

grey to a yellowish-white color. Excess water was avoided as the slurry became difficult to filter. The slurry was stirred for 15 minutes and filtered twice. The volatiles were removed in vacuo and the liquid extracted twice with chloroform. The extracts were combined, dried over anhydrous potassium carbonate, evaporated in vacuo and the residue vacuum distilled yielding 15g (66.6%) light yellow oil, bp 110-45°(5-10 mm Hg), lit. bp 106°(0.4mmHg)[64]. The infrared spectrum showed bands at 3350, 3050, 3000-2850, 1600, 1500, 1470, 1380, 1320, 1270, 1080, 1030, 870, 755, and 695 cm^{-1}. The nmr spectrum obtained in CCl_4 gave 6.7(m, 6H, $-NHC_6H_5$), 2.80(m, 5H, $-CH_2(NH_2)-$), 0.85(d, J = 6Hz, 3H, $-CH_3$).

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39.
Found: C, 71.49; H, 9.32.

Preparation of Ethyl N-(2-(1-anilino)propyl)-2-aminopropanoate (14).

A mixture of 7.5g (0.05 mole) 16, 12.0g (0.0665 mole) ethyl 2-bromopropanoate and 6.7g (0.0665 mole) triethylamine in 75cc toluene was refluxed for 7 hours. The slurry was filtered, evaporated in vacuo, and dissolved in 100cc ethyl ether. The etherate was extracted with 60cc 10% aq. HCl and the extract cooled in ice and saturated aqueous sodium carbonate added with stirring until the solution became basic. This solution was extracted with 80cc diethyl ether, the extract dried over anhydrous potassium carbonate and evaporated in vacuo. The residue was vacuum distilled yielding 5.36g (42.8%) light yellow oil, bp 125-75° (5-10mm Hg), lit. bp 145-56° (0.8mm

Hg)[35]. The infrared spectrum showed bands at 3375, 3050-2850, 1715, 1450, 1375, 1260, 1320, 1180, 870, 750, and 690 cm^{-1}. The nmr spectrum obtained in CCl_4 gave δ6.95 (m, 5H, arom), δ4.20(vb s, 1H, -NH-), 4.10(m, 2H, $-OCH_2-$), δ3.45(m, 1H, -CH-), δ2.95(m, 3H, $-CH-CH_2-$), δ2.2(vb s, 1H, -NH-), δ1.2(m, 9H, $-CH_3$).

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.16; H, 8.86.

Found: C, 66.83; H, 8.84.

Preparation of N^1-(2-hydroxypropyl)-1,2-diaminopropane (7)

To a solution of 59.2g (0.8 moles) 1,2-diaminopropane in 100cc methyl alcohol immersed in an ice bath, 44.8g (0.8 moles) 1,2-epoxypropane was added dropwise with stirring at a rate such that the temperature of the mixture did not rise above the ice bath temperature. The reaction was allowed to warm to room temperature overnight with stirring. The solvents were removed in vacuo and the residue vacuum distilled to yield 39.61g (37.9%) colorless oil, bp 115-35° (5mm Hg), lit. bp 125-27° (15mm Hg)[16]. The infrared spectrum showed bands at 3350, 3250, 3050-2850, 1480, 1400, 1150, 970, and 870 cm^{-1}. The nmr spectrum obtained in CCl_4 gave δ6.7(m, 2H), δ2.5-4.2(m, 7H), δ1.00(m, 2H, $-CH_3$).

Anal. Calcd for $C_6H_{16}N_2O$: C, 54.50; H, 12.20.

Found: C, 54.04; H, 11.79.

Catalytic Dehydrolysis of N^1-(2-hydrozypropyl)-1,2-diaminopropane (7).

The pressure chamber of a Parr series 4000 autoclave was charged with 10.5g (0.078 mole) of 7, 100cc freshly distilled dioxane and 2g

Raney Nickle-dioxane slurry. The chamber was charged to 1000psi with hydrogen and heated to 185° for 5 hours during which the pressure reached 1650psi. Cooling to room temperature the catalyst was gravity filtered and the majority of the dioxane removed in vacuo. All of the dioxane could not be removed by this procedure because of the tendency of the dimethylpiperzine product to sublime. The resulting slurry was filtered and the solid sublimed (14-20mm Hg, 50-60°) yielding 5.6g white crystals, mp 109-11°. The infrared spectra showed bands at 3225, 2900-2600, 1500, 1400, 1370, 1340, 1320, 1280, 1200, 1150, 1130, 1070, 100, 980, 960, 880, 800 cm^{-1}. The spectra is superimpossible with that obtained on commercial cis-2,6-dimethylpiperazine (Aldrich Chemical Co.). The nmr spectrum obtained in CCl_4 gave δ 2.39(m 6H, ring hydrogens), δ 1.30(s, 2H, -NH-), δ1.13(d, J = 6.5Hz, 6H, $-CH_3$). An nmr spectrum taken of the residue resulting from the evaporation of the filtrate gave signals identical to these.

Reacting the white crystals with p-tosyl chloride under Schotten-Bauman conditions yielded a white compound which when recrystallized from ethanol melted at 198-99°. Mixed with the tosyl derivative prepared from commercial cis-2,6-dimethylpiperazine under identical conditions a melting point of 197.5-98° was obtained. The nmr and infrared spectra of both ditosyl derivatives were identical.

Anal. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.82; H, 5.58.

Found: C, 54.76; H, 5.72.

Preparation of the Sulfonamides of 2,5- and 2,6-dimethylpiperazines (31 - 39).

Schoten-Bauman Technique (Method A) - To 1.14g (0.01 mole) of the dimethylpiperazine in an ice bath 2.29g (0.025 mole) methanesulfonyl chloride (mesyl chloride), 4.41g (0.025 mole) benzenesulfonyl chloride (besyl chloride), or 4.75g (0.025 mole) p-toluenesulfonyl chloride (tosyl chloride) was slowly added with stirring followed by 20cc 10% aq. NaOH. The mixture was heated for one-half hour, cooled, and filtered. After air drying overnight the crude sulfonamide was recrystallized.

Pyridine Method (Method B) - To 1.14g (0.01 mole) of the dimethylpiperazine in 25cc freshly distilled pyridine, 2.29g mesyl chloride, 4.41g besyl chloride, or 4.75g tosyl chloride were added with stirring. The mixture was refluxed for one-half hour, cooled and poured into 20cc cold water and air dried overnight. The crude material was then recrystallized.

Cis-2,5-dimethyl-1,4-dimesylpiperazine (32) prepared by Method A was recrystallized from chloroform and hexane yielding 0.85g (31.8%) white crystals, mp 162-63°. The infrared spectrum included bands at 1340, 1280, 1070, 920, and 960 cm^{-1}. The nmr spectrum obtained in $CDCl_3$ gave δ 4.07(m, 2H), δ 3.65(m, 2H), δ3.24(m, 2H), δ2.97(m, 6H), δ1.47(d, J = 6Hz, 6H, $-CH_3$).

Anal. Calcd for $C_8H_{18}S_2N_2O_4$: C, 35.53; H, 6.71.

Found: C, 35.43; H, 6.67.

Cis-2,6-dimethyl-4-mesylpiperazine (31) - prepared by Method A was recrystallized from chloroform and hexane yielding 0.96g(35.6%) white crystals, mp 184-86°. The infrared spectrum included bands at 3300, 1280, 1070, 920, and 760 cm^{-1}. The nmr spectrum obtained in $CDCl_3$ gave δ3.67(m, 2H), δ2.91(m, 2H), δ2.78(s, 3H), δ2.25(m, 2H), δ1.0 (d, J = 6Hz, 6H).

Anal. calcd for $C_7H_{16}N_2SO_2$: C, 43.72; H, 8.39.

Found: C, 41.83; H, 8.09.

Trans-2,5-dimethyl-1,4-dimesylpiperazine (33) prepared by Method A was recrystallized from acetonitrile yielding 0.75g(27.8%) white crystals, mp 228-29°. The infrared spectrum included bands at 1350, 1280, 1050, 910 and 760 cm^{-1}. The nmr spectrum obtained in 33% Trifluoroacetic Acid (TFAA) in $CDCl_3$ gave δ4.15(m, 2H), δ3.43(m, 4H), δ2.96(s, 6H), δ1.35(d, J = 6.5Hz, 6H); in 40% DMSO-d_6 in CCl_4 the nmr spectrum gave δ3.87(m, 2H), δ3.38(m, 4H), δ2.78(s, 6H), δ1.18(d, J = 6.0Hz, 6H).

Anal. Calcd for $C_8H_{18}N_2S_2O_4$: C, 35.53; H, 6.71.

Found:

Cis-2,6-dimethyl-1,4-ditosylpiperazine (37) prepared by Method B was recrystallized from ethanol yielding 1.25g(29.6%) white crystals, mp 196-7°, lit. 89-90° (alcohol and petroleum ether)[5]. The infrared spectrum included bands at 1590, 1490, 1350, 1270, 1090, 900, and 920 cm^{-1}. The nmr spectrum obtained in CH_2Cl_2 gave δ7.54(m, 4H, arom), δ7.48(m, 4H, arom), δ4.10(m, 2H), δ3.40(m, 2H), δ2.35(s, 3H), δ2.30 (s, 3H), δ2.13(m, 2H), δ1.32(d, J = 7Hz, 6H).

Anal. Calcd for $C_{20}H_{26}N_2S_2O_4$: C, 56.84; H, 6.20

Found: C, 56.45; H, 5.96.

Recrystallizing 37 prepared by Method A from ethanol yielded 1.10g (26.1%) white crystals, mp 197-98°. Infrared and nmr spectra are identical with the compound prepared by Method B.

Trans-2,5-dimethyl-1,4-ditosylpiperazine (39) obtained by Method B yielded 0.98g(23.2%) yellow crystals, mp 226.5-27°, lit. 225° (washed with water)[5]. The infrared spectrum included bands at 1600, 1340, 1270, 1040, 920, 820 and 710 cm^{-1}. The nmr obtained in $CDCl_3$ gave δ7.54(m, 8H), δ4.19(m, 2H), δ3.36(m, 4H), δ2.43(s, 6H), δ0.97(d, J = 6.5Hz, 6H); in TFAA, δ7.48(m, 8H), δ4.17(m, 2H), δ3.41(m, 4H), δ2.37(s, 6H), δ0.98(d, J = 6.5Hz, 6H).

Anal. Calcd for $C_{20}H_{26}N_2S_2O_4$: C, 56.84; H, 6.20.

Found: C, 56.14; H, 6.12.

Cis-2,5-dimethyl-1,4-ditosylpiperazine (38) prepared by Method B was recrystallized from chloroform and ethanol yielding 1.05g(24.9%) white crystals, mp 145-46°, lit mp 146-47° (alcohol)[3]. The infrared spectrum included bands at 1590, 1490, 1350, 1170, 920 and 810 cm^{-1}. The nmr spectrum obtained in CH_2Cl_2 gave δ7.52(m, 8H, arom), δ3.50 (m, 2H), δ3.18(m, 4H), δ2.40(s, 6H), δ1.20(d, J = 6.5Hz, 6H); in 15% TFAA in CCl_4, δ7.23(m, 8H), δ3.54(m, 2H), δ3.26(m, 4H), δ2.38(s, 6H), δ 1.13(d, J = 6.)Hz, 6H); in 14.3% DMSO-d_6 in CCl_4, δ7.22(m, 8H), δ3.40(m, 2H), δ 3.08(m, 4H), δ2.35(s, 6H), δ1.13(d, J = 6.)Hz, 6H).

Anal. Calcd for $C_{20}H_{26}N_2S_2O_4$: C, 56.84; H, 6.20

Found: C, 56.63; H, 6.23.

Cis-2,6-dimethyl-1, 4-dibesylpiperazine (34) prepared by Method A was recrystallized from methylene chloride and hexane to yield 1.15g(34.2%) white crystals, mp 118-19.5°. The infrared spectrum included bands at 1590, 1350, 1290, 1060, 930, 760 and 690 cm^{-1}. The nmr spectrum obtained in CH_2Cl_2 gave α7.43(m, 10H), δ3.84(m, 2H), δ2.84(m, 2H), δ1.72(m, 2H), δ0.93(d, J = 6.0Hz, 6H); in 14.3% TFAA in CCl_4, δ7.37(m, 10H), δ3.43(m, 2H), δ2.83(m, 2H), δ1.63(m, 2H), δ0.95 (d, J = 6.0Hz, 6H).

Cis-2,5-dimethyl-1,4-dibesylpiperazine (35) prepared by Method A was recrystallized from CH_2Cl_2 and hexane to yield 0.91g(23.3%) white crystals, mp 122-23°. The infrared spectrum included bands at 1590, 1350, 1290, 1060, 910, 740 and 690 cm^{-1}. The nmr spectrum obtained in CH_2Cl_2 gave δ7.40(m, 10H), δ3.47(m, 2H), δ3.11(m, 4H), δ1.15(d, J = 6.5Hz, 6H); in 16.6% TFAA in CCl_4, δ7.37(m, 10H), δ3.55(m, 2H), δ3.24(m, 4H), δ1.13(d, J = 6.5Hz, 6H).

Trans-2,5-dimethyl-1,4-dibesylpiperazine (36) prepared by Method A was recrystallized from CH_2Cl_2 and hexane to yield 1.11g(35.8%) white crystals, mp 220-21°. The infrared spectrum included bands at 1590, 1340, 1280, 1050, 920, 760, and 690 cm^{-1}. The nmr spectrum obtained in $CDCl_3$ gave δ7.66(m, 10H), δ4.22(m, 2H), δ3.43(m, 4H), δ0.92(d, J = 6.5Hz, 6H); in 50% TFAA in $CDCl_3$, δ7.45(m, 10H), δ4.17 (m, 2H), δ3.40(m, 4H), δ0.97(d, J = 6.5Hz, 6H); in TFAA, δ7.50(m, 10H), δ4.17(m, 2H), δ3.40(m, 4H), δ0.97(d, J = 6.5Hz, 6H).

Attempted Preparation of 2,6-Dimethyl-4-phenyl-3-ketopiperazine (17, 18).

Using a sand bath 5.37g (0.023 mole) 14 was heated at 260-70° for 4 hours with stirring. During this period 0.75cc of a colorless liquid was evolved. The infrared spectrum of this liquid included bands at 3350, 2975-2875, 1090, 1050, and 850 cm^{-1}. The spectrum was superimposible upon a spectrum obtained from absolute ethanol. After heating the residue was vacuum distilled yielding 1.05g yellow oil. Cut I was obtained at 140-60°(0.25mm - 0.09mm Hg). The infrared spectrum included bands at 3350, 3050-2850, 1720, 1640, 1590, 1490, 1450, 1280, 1180, 870, 750 and 690 cm^{-1}. The nmr spectrum obtained neat gave δ6.6(m, arom), δ4.4(vb s, -NH), δ3.75(q, J = 8Hz), δ3.3-2.5(m), 0.9(m, $-CH_3$). Cut II was obtained at 170-75°(0.09mm Hg). The infrared spectrum of cut II included bands at 3300, 3050-2850, 1730, 1650, 1600, 1500, 1320, 1280, 1260, 870, 760, 740 and 700 cm^{-1}. The nmr obtained in CCl_4 gave δ7.15(s, arom), δ6.7(m, arom), δ4.0-2.0 (multiplet), δ1.0(m, $-CH_3$).

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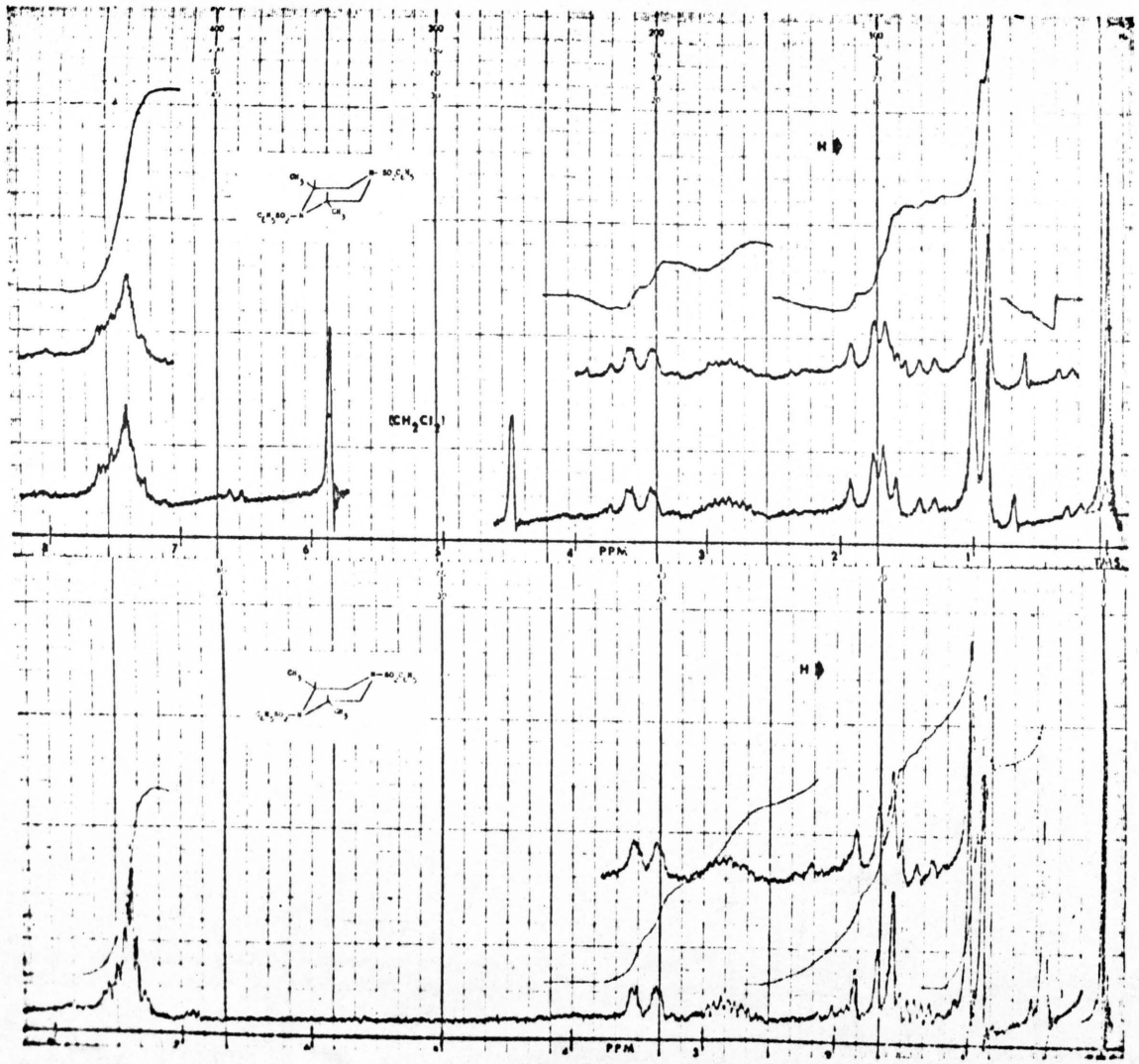
APPENDIX

This section contains the nmr spectra of the seventeen 2,5- and 2,6-dimethylpiperazines studied. The nmr spectral data recorded in the Experimental Section were taken from these spectra. In the Results and Discussion Section these spectra are referred to in order to verify conclusions on structural analysis.

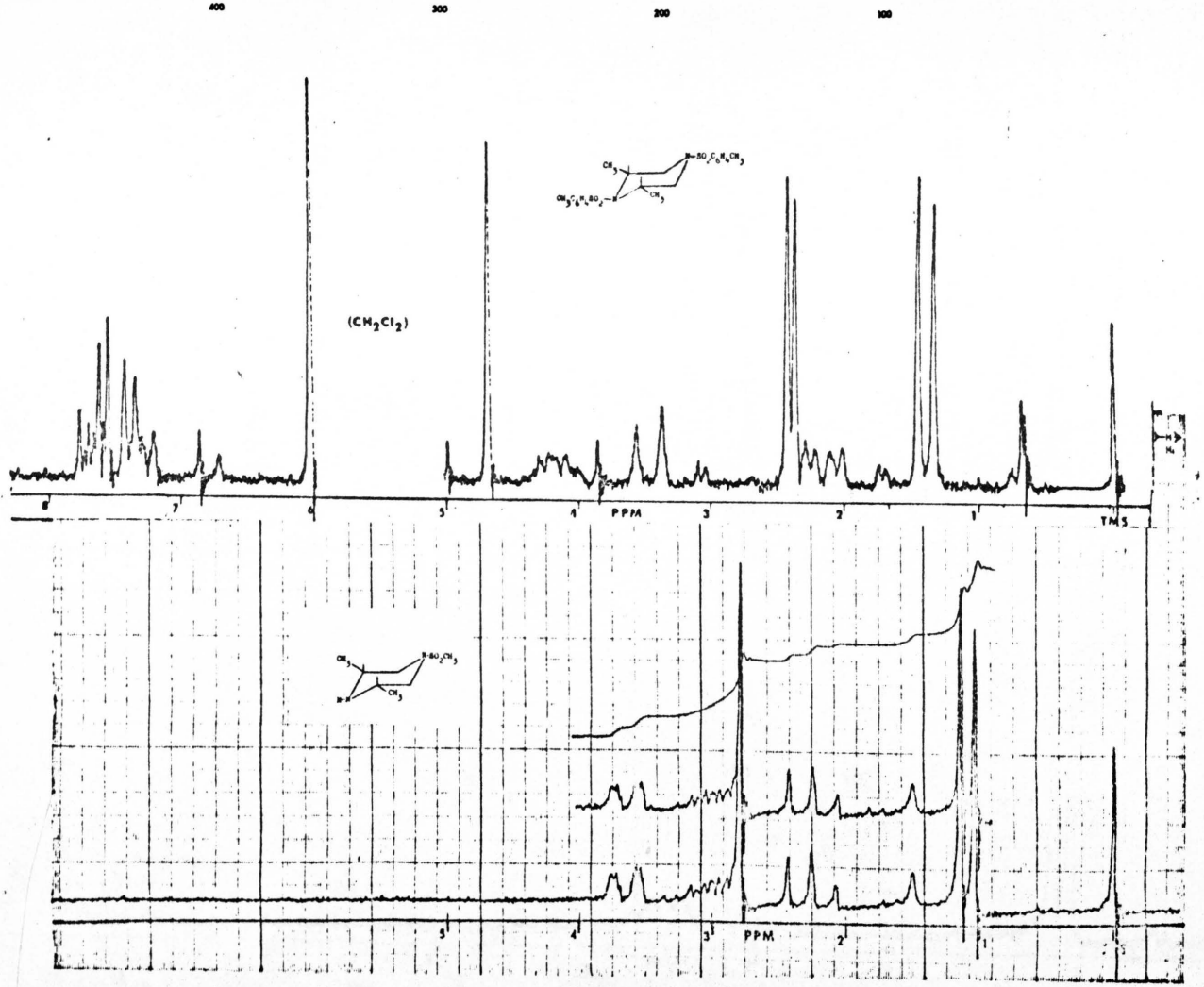


1.

2.

Spectrum 1. Cis-2,6-dimethyl-1,4-dibesylpiperazine (34) in CH_2Cl_2.

Spectrum 2. Cis-2,6-dimethyl-1,4-dibesylpiperazine (34) in DMSO-d_6/CCl_4.

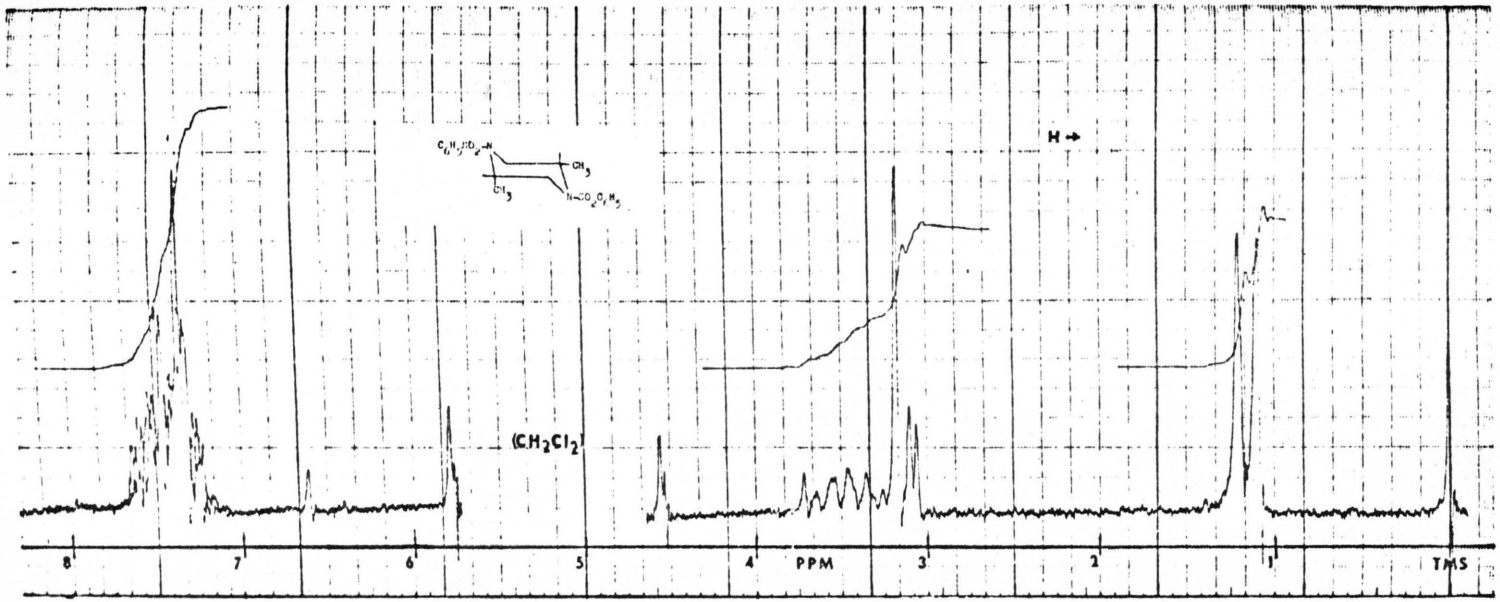


3.

4.

Spectrum 3. Cis-2,6-dimethyl-1,4-ditosylpiperazine (37) in CH_2Cl_2.

Spectrum 4. Cis-2,6-dimethyl-4-mesylpiperazine (31) in $CDCl_3$.



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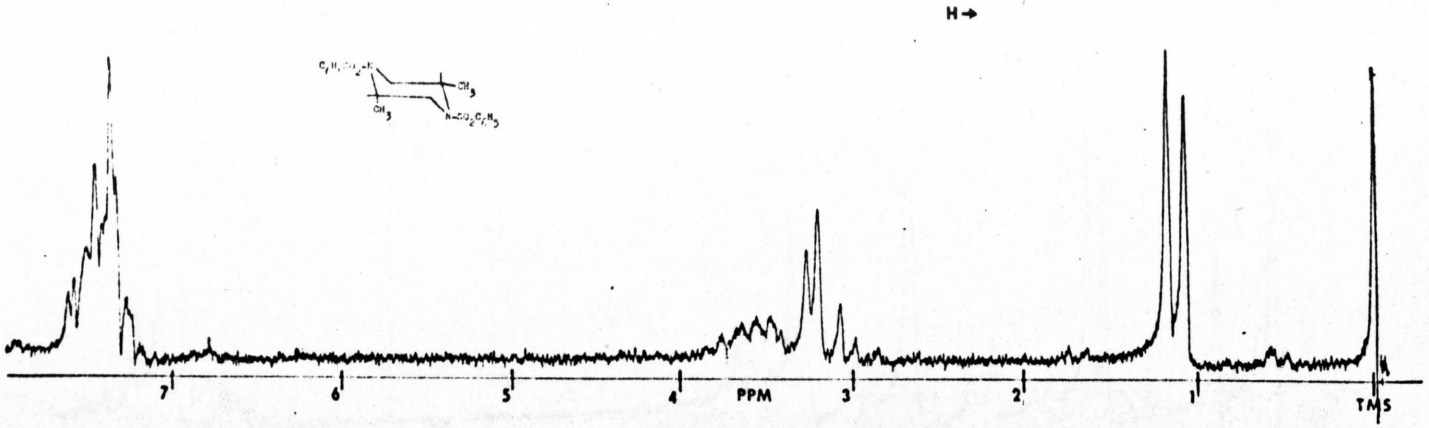
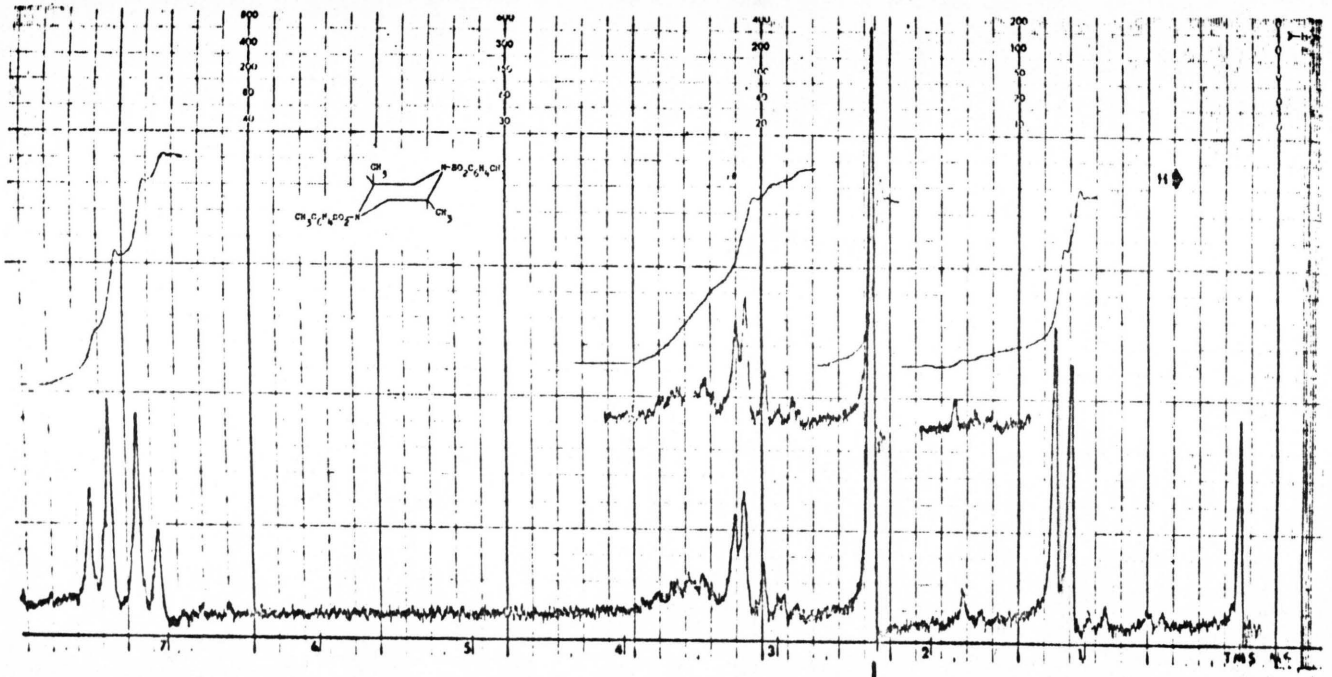


6.

Spectrum 5. Cis-2,5-dimethyl-1,4-dibesylpiperazine (35) in CH_2Cl_2.

Spectrum 6. Cis-2,5-dimethyl-1,4-dibesylpiperazine (35) in TFAA/CCl_4.



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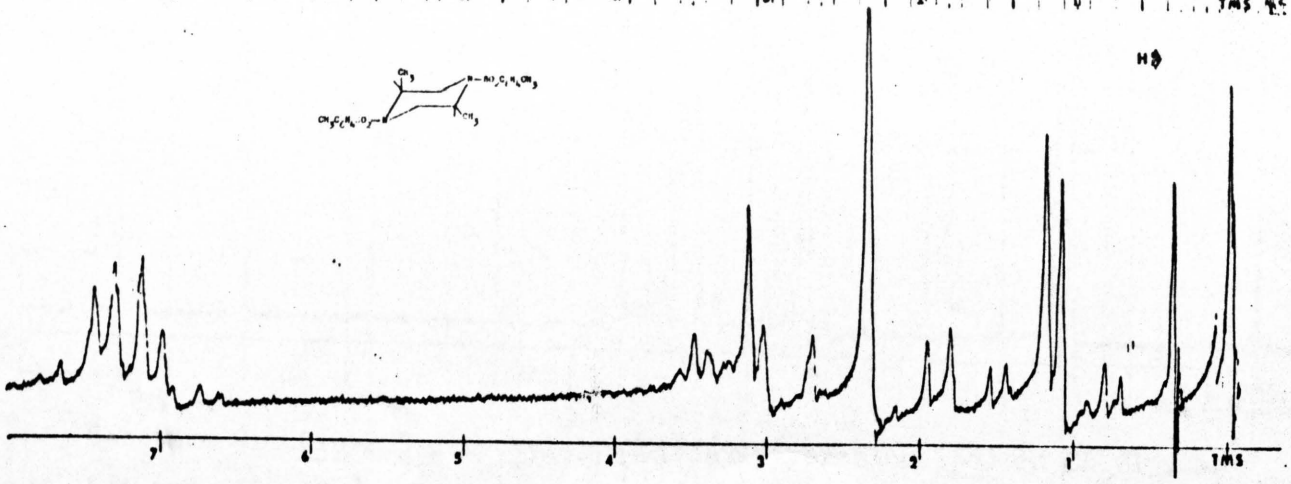
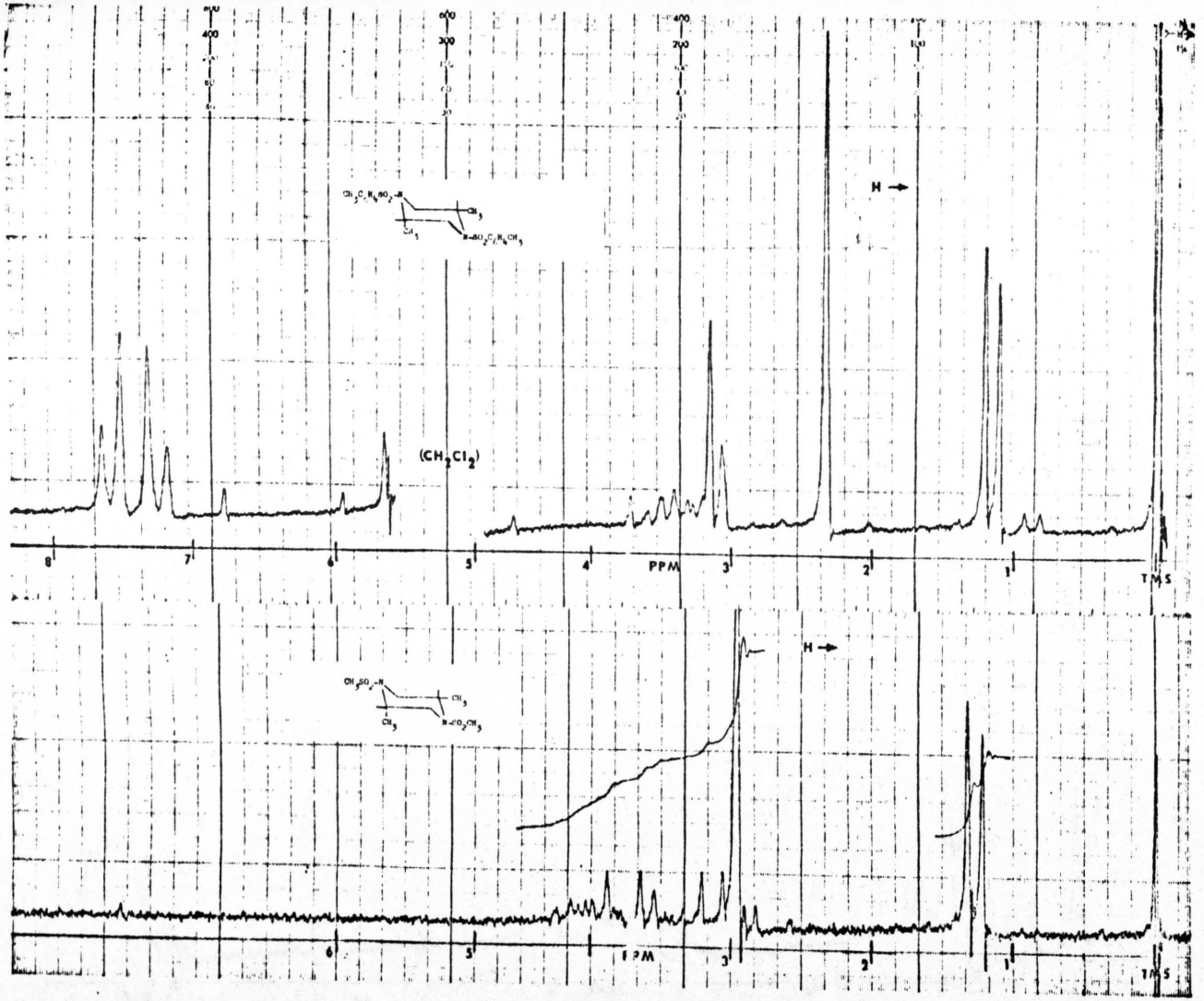


8.

Spectrum 7. Cis-2,5-dimethyl-1,4-ditosylpiperazine (38) in TFAA/CCl_4.

Spectrum 8. Cis-2,5-dimethyl-1,4-ditosylpiperazine (38) in DMSO-d_6/CCl_4.

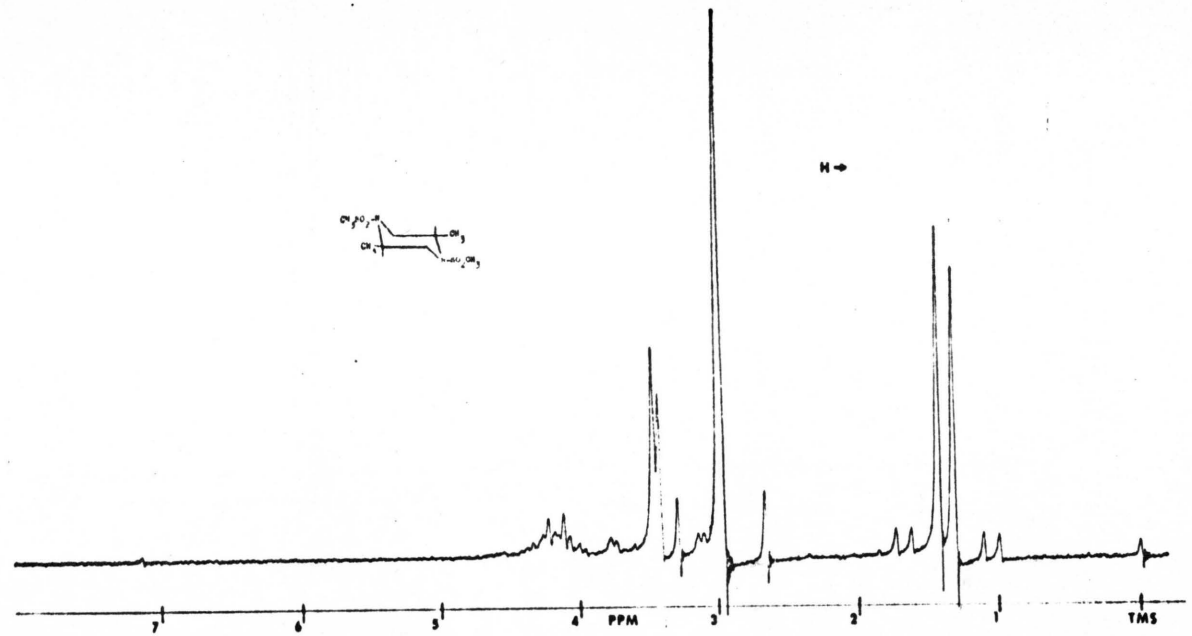


9.

10.

Spectrum 9. Cis-2,5-dimethyl-1,4-ditosylpiperazine (38) in CH_2Cl_2.

Spectrum 10. Cis-2,5-dimethyl-1,4-dimesylpiperazine (32) in $CDCl_3$.



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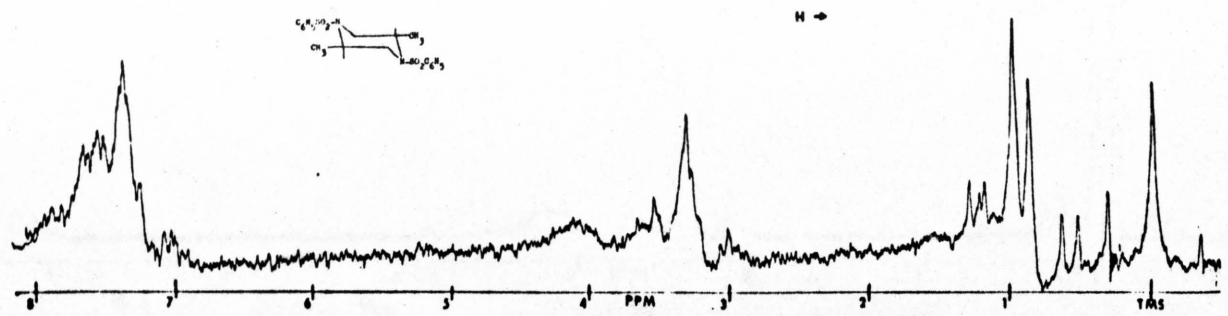
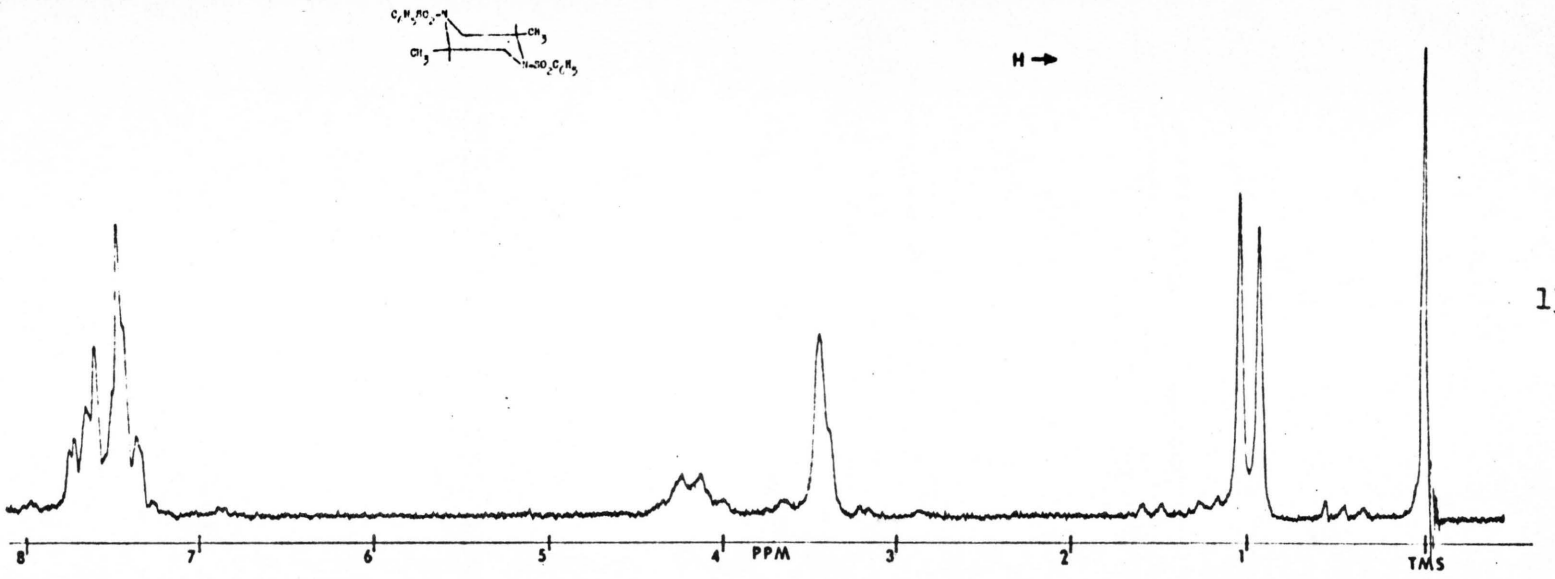


12.

Spectrum 11. Trans-2,5-dimethyl-1,4-dimesylpiperazine (33) in $CDCl_3$.

Spectrum 12. Trans-2,5-dimethyl-1,4-dibesylpiperazine (36) in $CDCl_3$.



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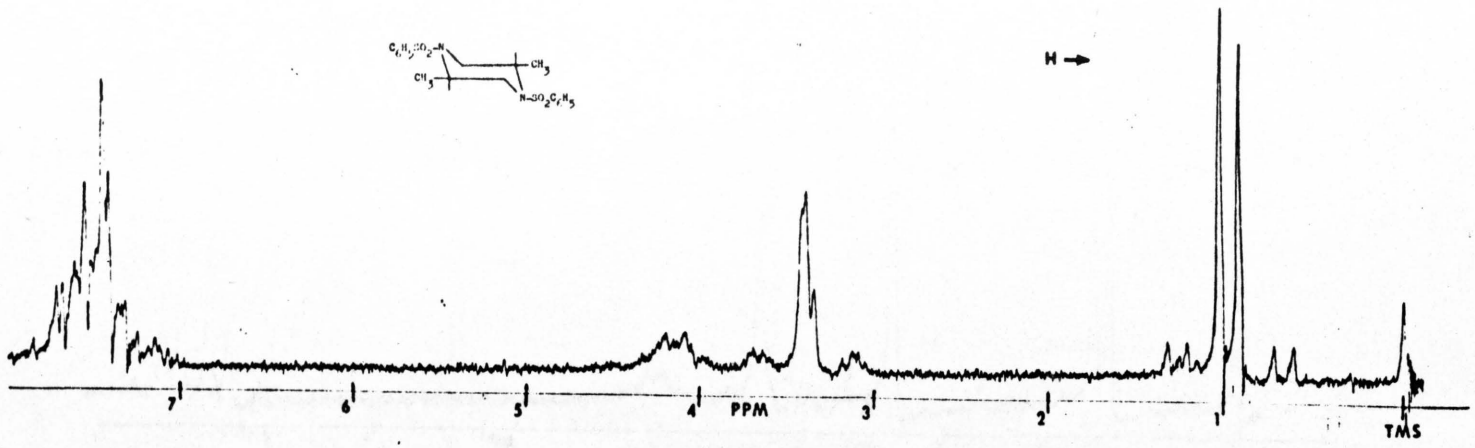
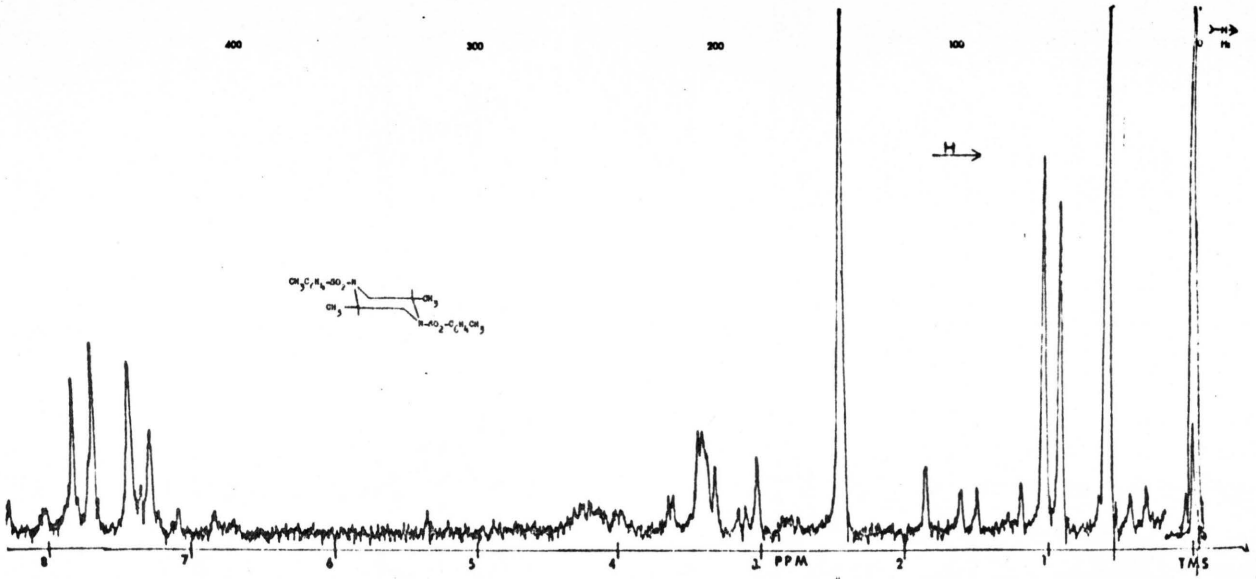


14.

Spectrum 13. Trans-2,5-dimethyl-1,4-dibesylpiperazine (36) in TFAA.

Spectrum 14. Trans-2,5-dimethyl-1,4-dibesylpiperazine (36) in TFAA/$CDCl_3$.



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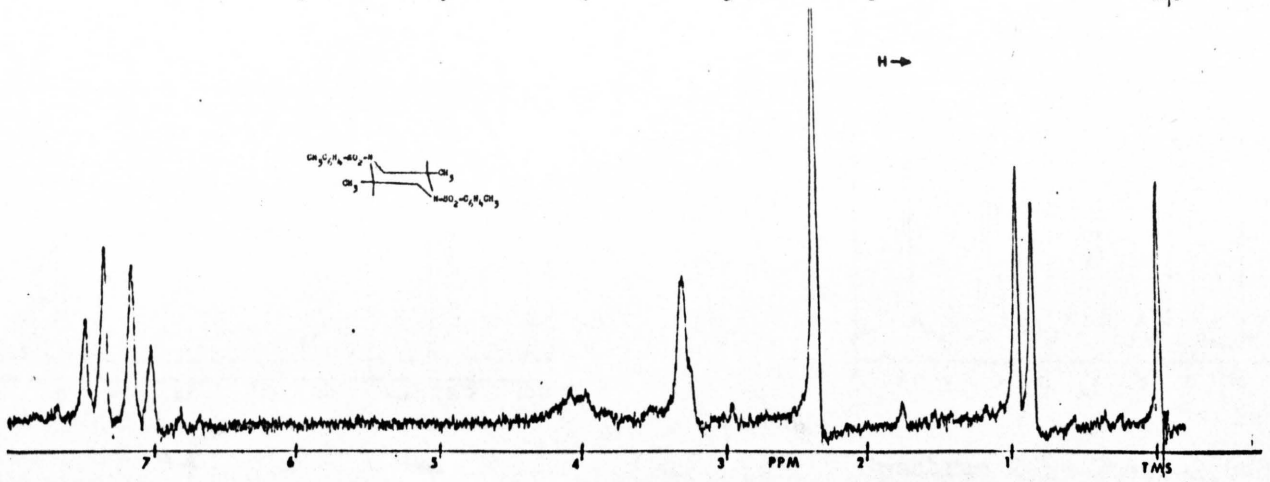
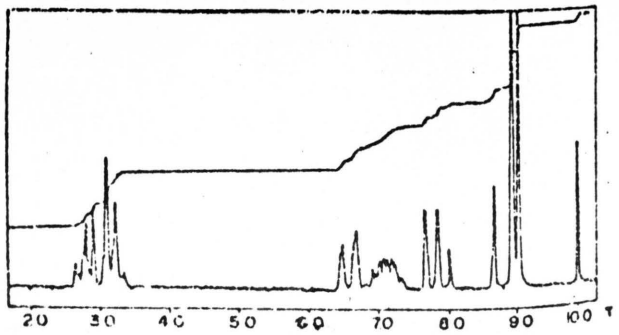


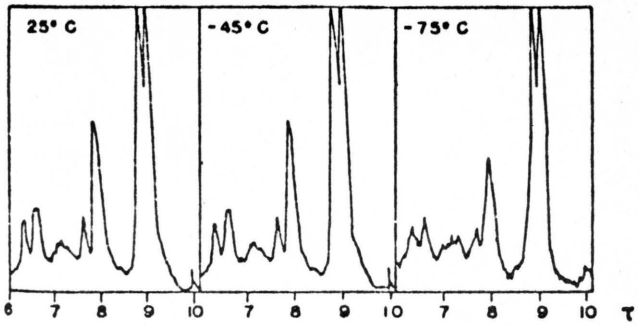
16.

Spectrum 15. Trans-2,5-dimethyl-1,4-ditosylpiperazine (39) in $CDCl_3$.

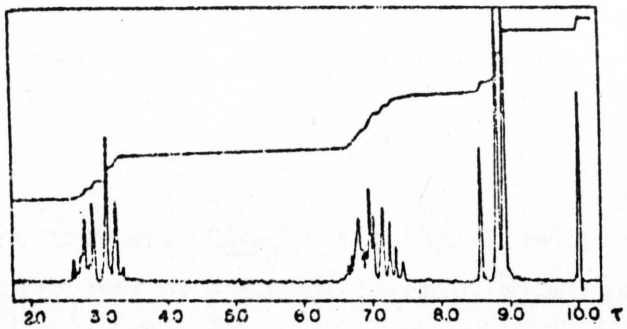
Spectrum 16. Trans-2,5-dimethyl-1,4-ditosylpiperazine (39) in TFAA/CCl_4.



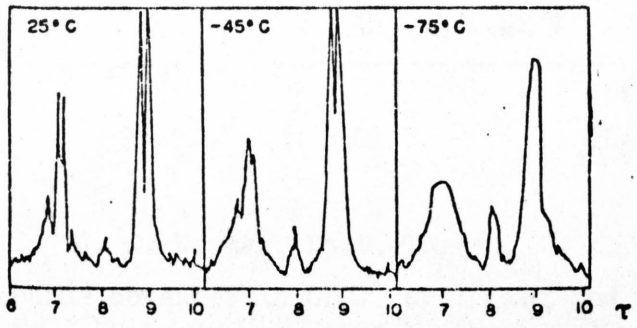
Spectrum 17. Cis-2,6-dimethyl-4-phenylpiperazine (13) in $CDCl_6$ at 60mHz (room temperature).



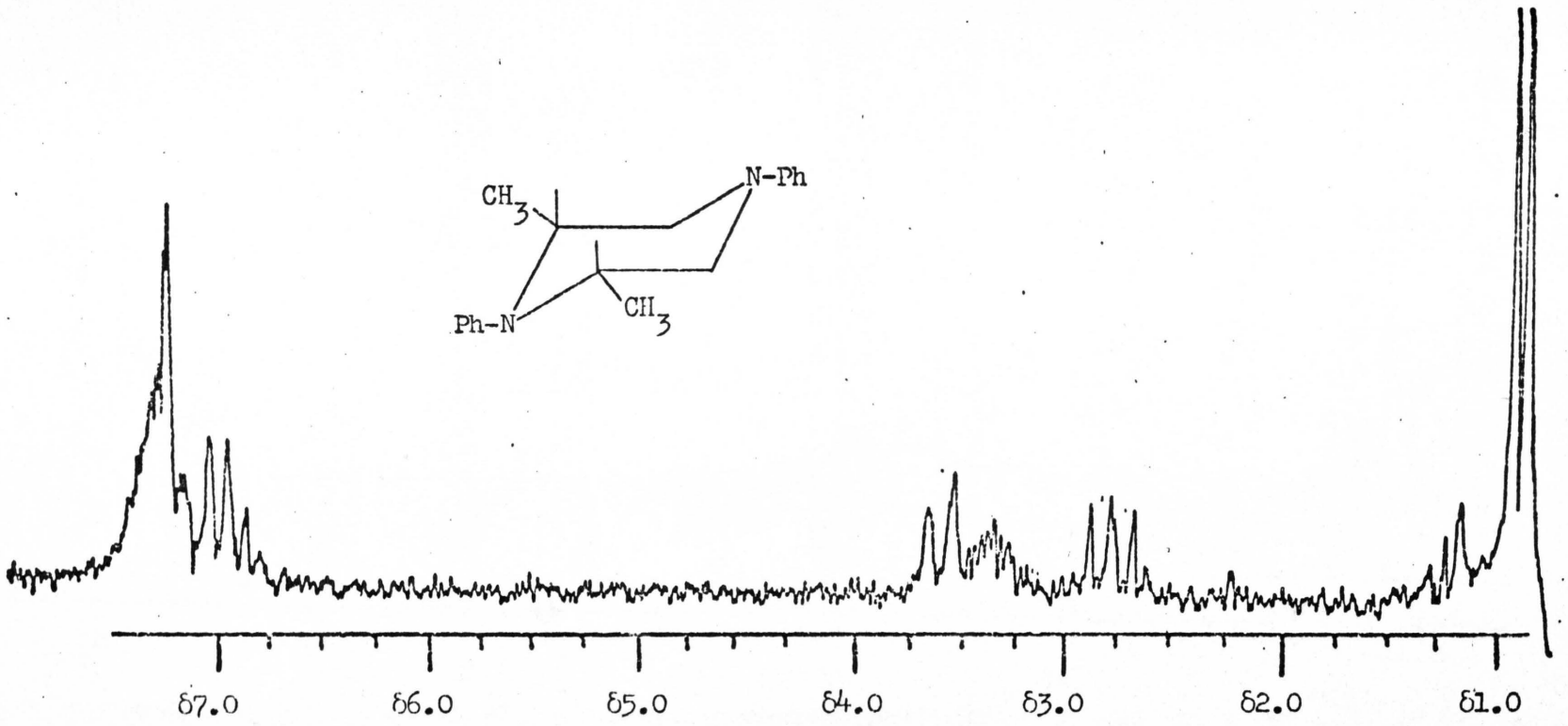
Spectrum 18. Cis-2,6-dimethyl-4-phenylpiperazine (13) in acetone-d_6 as a function of temperature (40mHz).



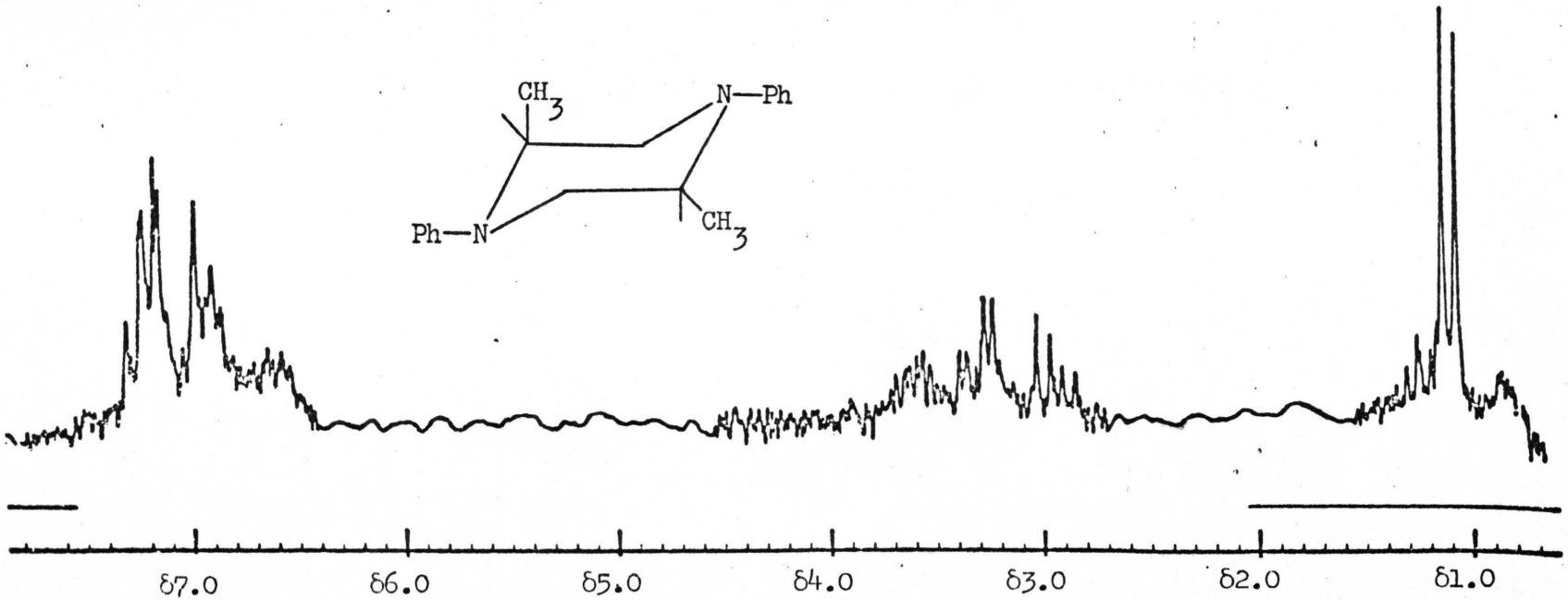
Spectrum 19. Trans-2,6-dimethyl-4-phenylpiperazine (15) in $CDCl_6$ at 60mHz (room temperature).



Spectrum 20. Trans-2,6-dimethyl-4-phenylpiperazine (15) in acetone-d_6 as a function of temperature (40mHz).



Spectrum 21. Cis-2,6-dimethyl-1,4-diphenylpiperazine (20). J. J. Worman, Ph.D. Thesis, University of Wyoming, Laramie, Wyoming, June, 1968. Spectrum obtained in $CDCl_3$ at 100mHz and at room temperature.



Spectrum 22. Cis-2,5-dimethyl-1,4-diphenylpiperazine (26). J. J. Worman, Ph.D. Thesis, University of Wyoming, Laramie, Wyoming, June, 1968. Spectrum obtained in $CBCl_3$ at 100mHz and at room temperature.