THE REACTION OF 2-CHLORO-10-N-METHYLPHENOTHIAZINE WITH AROMATIC NITRILES AND LITHIUM DIALKYLAMIDES IN THF: SYNTHESIS AND STRUCTURE OF 1-CYANO-2-(3',4',5'-TRIMETHOXYBENZYL)-10-N-METHYLPHENOTHIAZINE

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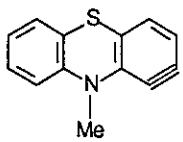
Abstract - 10-N-Methyl-1,2-didehydrophenothiazine (2), generated in situ from 10-N-methyl-2-chlorophenothiazine (1), reacts via the tandem addition-rearrangement aryne (TARA) mechanism with lithio-arylacetonitriles yielding rearranged products (3a-c), after proton quench. The X-ray structure of title compound 3a demonstrates conclusively that the initial nitrile anion addition step in the TARA reaction occurs at the 2-position of 2. In previous studies of nucleophilic additions to 2, this regioselectivity had only been assumed on the basis of the well-documented strong *meta*-directing effect of the 10-nitrogen atom.

INTRODUCTION

One of the major aspects of our recent research effort involves the investigation of the synthetic application of the aryne reaction[1a-f]. One of these studies[1e] showed that the reaction of 2-chloro-10-N-methylphenothiazine (1) with lithium amides derived from primary or secondary amines carried out in the free amine solvent yielded the corresponding 2-N-alkylamino- or 2-N,N-dialkylamino-10-N-methylphenothiazine in good yields via 10-N-methyl-1,2-didehydrophenothiazine (2). Previous to that investigation, Jones[2] demonstrated that 1 could be aminated via



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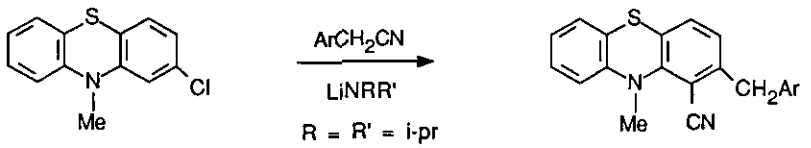
2 using sodium amide and various amines; however, the yields were considerably reduced due to extensive dehalogenation of 1 to 10-N-methylphenothiazine. We attempted to react 2 with nitrile anions in liquid ammonia; however, 2 was exclusively aminated by the solvent ammonia yielding 2-amino-10-N-methylphenothiazine[1e]. Apparently, the phenothiazine ring nitrogen atom inductively increases the reactivity of 2 to such an extent that the more reactive but less abundant nitrile anion cannot successfully compete with the less reactive but more abundant ammonia solvent[3]. In other studies[4,5], we observed that nitrile anions also did not compete successfully with ammonia solvent for certain unsymmetric arynes. Thus, 3,4-dimethoxybenzyne[4] and 3,4,5-trimethoxybenzyne[5] gave predominantly 3,4-dimethoxyaniline and 3,4,5-trimethoxyaniline, respectively, and the corresponding nitrile products in yields less than 6%.

Recently, we[6] demonstrated that nitrile anions add to methoxy-substituted aryne intermediates generated by bulky bases such as lithium diisopropylamide (LDA) and lithium isopropylcyclohexylamide in non-nucleophilic solvent such as tetrahydrofuran (THF). For example, 4-bromo-1,2-dimethoxybenzene (4-bromoveratrole) reacts with acetonitrile and LDA in THF *via* 3,4-dimethoxybenzyne to give 3,4-dimethoxyphenylacetonitrile in 60% yield, after proton quench. Interestingly, bromoarenes possessing electron-releasing groups treated similarly formed arynes to which lithio-arylacetonitriles add to yield rearranged nitrile products[7], after proton quench. As an example, 2-bromo-4-methylanisole reacts with aryl nitriles in the presence of LDA in THF to give the corresponding 3-arylmethyl-2-cyano-4-methylanisoles. A tandem-addition rearrangement aryne mechanism[7,8] was proposed to account for these results. Since 10-N-methylphenothiazine is a π-excessive heteroaromatic compound[9] we reasoned that the aryne generated from 1 might also undergo the tandem-addition rearrangement aryne reaction with lithio-arylacetonitriles.The initial results of the reaction of 1 with various aromatic and aliphatic nitrile anions with LDA in THF are reported herein.

RESULTS AND DISCUSSION

Initially, the reaction of 1 with 3,4,5-trimethoxyphenylacetonitrile and LDA in THF was found to give 1-cyano-2-(3',4',5'-trimethoxybenzyl)-10-N-methylphenothiazine (**3a**) in 40% isolated yield. Similarly, 1-cyano-2-(3',4'-dimethoxybenzyl)-10-N-methylphenothiazine (**3b**) , and 1-cyano-2-(4'-fluorobenzyl)-10-N-methylphenothiazine (**3c**) were obtained in yields of 20% and 30%, respectively from 1 and the corresponding nitriles. Additionally, the dechlorinated product, 10-N-methylphenothiazine (10-15%), and the aminated product, 2-N,N-diisopropylamino-10-N-methylphenothiazine (15-25%) were obtained in all cases. The yield of **3a** was increased to 60-65% by using lithium cyclohexylisopropylamide as base with only a small amount of the dechlorination product of 1 obtained.



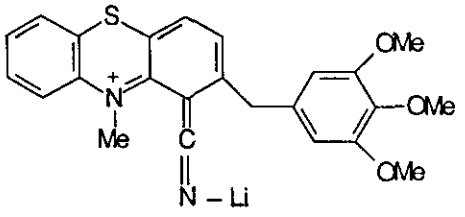
1 3

a. Ar = 3,4,5-tri-MeO-C_6H_2-

b. Ar = 3',4',-di-MeO-C_6H_3-

c. Ar = 4'-F-C_6H_4-

Light yellow single crystals of **3a** suitable for examination by X-ray diffraction procedures were obtained upon recrystallization of **3a** from ethyl acetate, which allowed us to confirm its solid state structure by X-ray crystallographic analysis. The identification and location of the atoms in **3a** are shown in the ORTEP[10] drawing in figure 1 and the bond lengths and bond angles are shown in Tables 1 and 2, respectively. The phenothiazine ring is folded with the central ring in a boat conformation, as shown by the view in Figure 1 and from those torsion angles listed in Table 3 and the 10-N-methyl group is in the axial position with respect to the central ring of **4a**. Interestingly, the dihedral angle of **3a** (defined as the folding angle of the two benzo rings of the tricyclic system) is 149.9(4)°, which is greater than that (143.7°)[11] of 10-N-methylphenothiazine itself. The reason for the increased planarity of **3a** as compared to the parent 10-N-methylphenothiazine most likely is due to resonance interactions between the 2-cyano group and the 10-nitrogen lone-pair electrons as shown in **4**.



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The shorter N(10)-C(10a) bond length (1.390[5]Å) and longer C(10a)-C(1) bond length (1.403[5]Å) in **3a** as compared to those[11] for 10-methylphenothiazine, 1.402Å and 1.386Å, respectively are consistent with such resonance interactions. (For bond lengths and bond angles see Tables 1-3 in Experimental Section.)

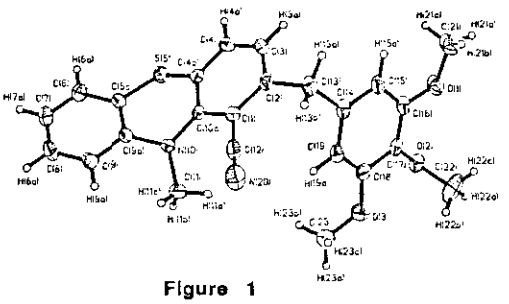
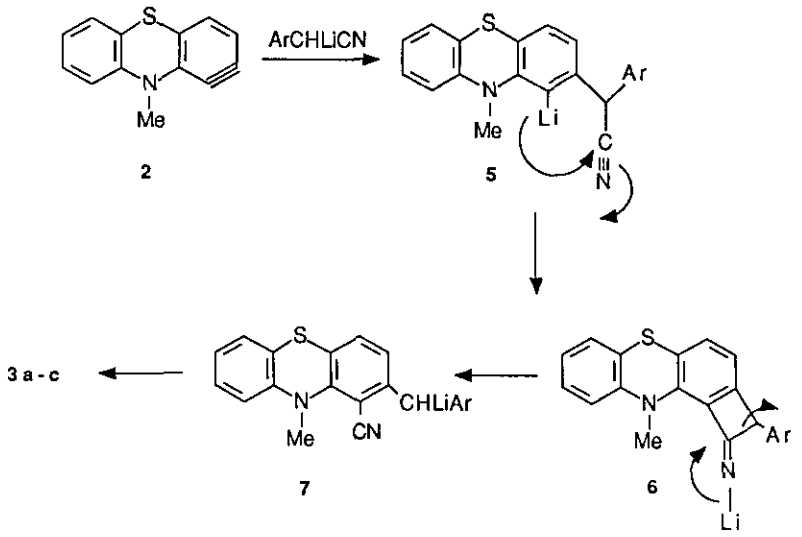


Figure 1

The assignment of structure of the phenothiazine compounds prepared by the aryne reaction prior to this study was based solely on well-established theoretical grounds[12]. Thus it was assumed that **1** yielded only the 1,2-didehydro-aryne intermediate **2**, although in principal 2,3-didehydrophenothiazine could have been formed, because of the greater acidity of the 1-hydrogen atom as compared to the 3-hydrogen atom of **1**. Further, the subsequent orientation of the nitrile anions to **2** occurred exclusively at the 2-position because of the strong meta directing effect of the 10-nitrogen atom. Thus, the X-ray structure of **3a** reported herein is not only the first reported one for a phenothiazine derivative prepared by the aryne reaction, but also confirms the previously assumed regioselectivity.

Scheme 1 shows the proposed mechanism to account for the rearranged products. Thus, aryne **2** undergoes addition with the lithio nitrile anion in the usual manner yielding the aryne adduct **5** which subsequently cyclizes to **6**. Ring

Scheme 1

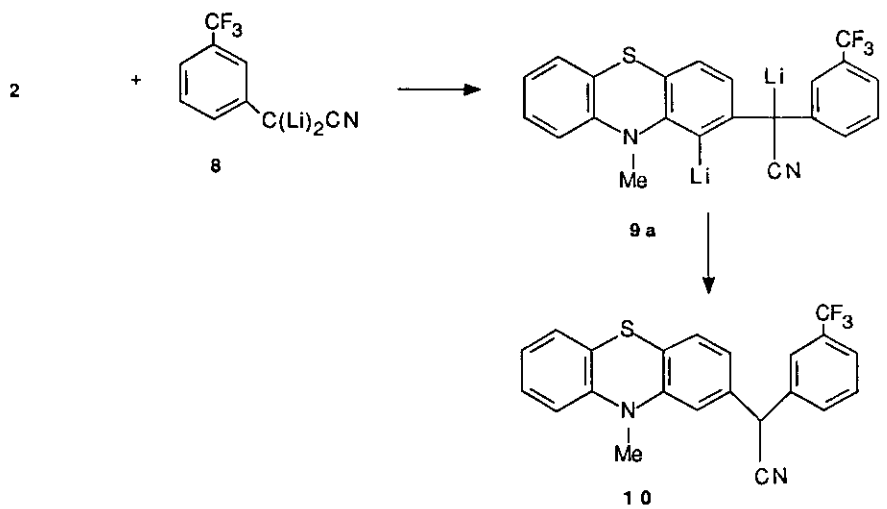


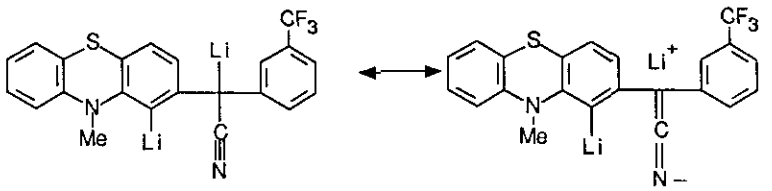
opening of **6** yields **3a-c** after neutralization of the rearranged nitrile anion **7**.

The key synthetic advantage of this tandem-addition rearrangement aryne (TARA) reaction is that it simultaneously introduces two groups *ortho* to each other. These two groups so introduced, after suitable modification, are suitably configured for ring expansion. For example, we have shown that *cis*-3,4-diarylisochroman-1-ones can be obtained[13] by trapping α-lithio-2-cyanodiarylmethane intermediates in the TARA reaction with benzaldehydes. We currently are investigating this and other electrophilic trapping reactions with the rearranged lithio adducts **7** the results of which will be reported in due course.

Interestingly, the reaction of **1** with 3-trifluoromethylphenylacetonitrile and lithium isopropylcyclohexylamide gave typical aryne-addition product, **10** in 55% yield, no rearranged product was detected. One possible explanation for this apparent abnormal behavior, shown in Scheme 2, is that 3-trifluromethylphenylacetonitrile is converted to α, α–dilithio-m-trifluoromethylpohenylacetonitrile **(8)**[14] because of the strong electron-withdrawing effect of the trifluoromethyl group. Addition of **8** to **2** would give adduct **9a**, which upon quenching is converted to the simple aryne addition product α-(3-trifluoromethylphenyl)-10-N-methylphenothiazinyl-2-acetonitrile **(10)**. Here, the α-lithio group presumably decreases the electrophilicity of the cyano group by resonance, as shown in **9a** and **9b**, thus decreasing the rate of the cyclization step in the TARA pathway.

Scheme 2

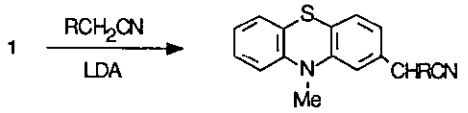




9a 9b

Alternatively, **9a** could be formed by deprotonation of the initially formed adduct between **2** and the mono lithiated 3-trifluorophenylacetonitrile[15]. We presently do not have sufficient data to distinguish between these two possibilities.

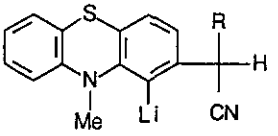
Finally, the reaction of **1** with alkyl nitriles and LDA in THF was found to yield the simple aryne addition products. For example, 10-N-methylphenothiazinyl-2-acetonitrile (**11a**) and α-(10-N-methylphenothiazinyl)-2-propiononitrile (**11b**) were obtained in 40% and 55% yields, respectively. The introduction of a cyanoalkyl side chain is



11a, R = H (40%)

11b, R = Me (55%)

particularly significant since this moiety serves as a valuable precursor to the pysiologically active β-phenethylamino group or α-substituted propionic acids[16]. The inability of aliphatic acetonitriles to undergo the TARA reaction with **2** is in accord with its behavior toward methoxybenzynes[7], and most likely reflects the decreased electrophilicity of the cyano group toward the 2-lithiated aromatic carbon atom by the electron-releasing alkyl groups in the initially-formed aryne adduct **12**.



R = alkyl

12

We are not prepared at this time to explain the failure of lithiated acetonitrile to undergo the TARA reaction with 2. Further studies in this area are currently being extensively investigated.

EXPERIMENTAL

General Comments. Melting points were determined on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 grating spectrometer. High field (200-MHz) proton and carbon-13 spectra were taken on an IBM-Bruker WP200-SY spectrophotometer. Nmr spectra were run in $CDCl_3$ solution and chemical shifts were related to Me_4Si. Gas chromatographic analysis and mass spectra (70 eV) were obtained on a Hewlett-Packard Model 5988A spectrometer using 0.2 mm x 12 m capillary column containing cross-linked methyl silicone of 0.33 micro meter film thickness. Data reported are the *m/z* values for the most abundant peaks. Microanalyses were performed on a Carbo ERBA instrument. E. Merck silica gel 9385 (230-400 mesh) was used for flash chromatography. Tetrahydrofuran (THF), diisopropylamine, 2-chlorophenothiazine, arylacetonitriles, and isopropylcyclohexylamine were obtained from Aldrich Chemical Co. and were dried and distilled or recrystallized prior to use. Butyllithium (BuLi) was obtained from Aldrich Chemical Co. and used as received.

General Procedure. All reactions were carried out in flame-dried flasks under nitrogen atmosphere and aliquots were taken. Since the reactions are all similar in many respects, typical reactions are described as specific examples. In a flame-dried flask flushed with nitrogen, LDA (60 mmol) was prepared by adding diisopropylamine (66 mmol) into a -78° C solution of n-BuLi (60 mmol, 2.5M in hexane) in THF (50 ml) under nitrogen atmosphere (using septum cap technique). After stirring the solution for 10 min at -78° C, the appropriate arylnitrile (30 mmol) in THF (50 ml) was added dropwise over 20 min. The reaction mixture was stirred at -78°C for 10 min and then allowed to warm to -40°C. A solution of 2-chloro-10-N-methylphenothiazine(15 mmol) in THF (50 ml) was added dropwise over 20 min at -40°C. The reaction mixture was stirred further and allowed to warm to room temperature slowly over a period of 2h. The dark reddish brown solution was then quenched with saturated aqueous ammonium chloride solution, THF was evaporated under reduced pressure, and the residue was extracted with methylene chloride (3 x 50 ml). The combined extracts were washed successively with 6N HCl (3 x 50 ml), water and brine. The organic layer was then dried (Na_2SO_4) and concentrated (rotary evaporator) to provide a crude product which was purified by flash column chromatography using a mixture of hexane/EtOAc [19:1] as an eluant.

Crystal Data and Data Collection and Processing. Yellow cubic shaped crystal (0.5 x 0.4 x 0.3 mm) was mounted on Nicolet R3m/V diffractometer unit cell parameters by least-squares fit of 25 reflections in the range $15<2\theta<23°$. **a** = 17.673(3), **b** = 16.971(5), **c** = 7.607(2)Å, β = 111.83(2). Space group Cc (hkl, h+k odd; h0l, l odd) was confirmed by satisfactory refinement. Graphite monochromated MoKα radiation (λ = 0.71073Å), $2\theta/\theta$ scan mode, scan speed 3.0-15.0 deg min^{-1}, 2179 measured reflection 2075 independent reflections in the range $3<2\theta<50°$, hkl range h -21-->19, k 0-->20, l 0-->9, 1693 observed reflections with $F>6\sigma(F)$. Three standard reflections measured after every 100 reflections showed crystal and electronic stability. Lorentz-polarization, absorption correction based on psi-scans, and no extinction correction were applied.

Structure Analysis and Refinement. Direct methods. Full-matrix least-squares refinements with all non hydrogen atoms anisotropic. Hydrogen atom in calculated positions and riding model with fixed isotropic parameters. Find R = 0.034 and wR = 0.048, $w = [\sigma^2(F)] + 0.0022\ F^2]^{-1}$, $\Sigma w(|Fo|-1|Fc|)2$ minimized. SHELXTL-Plus 88[17] on microvax II was used. Final positional parameters and thermal parameters and their estimated standard deviations are available on request as supplementary material.

Preparation of 2-Chloro-10-N-methylphenothiazine (1): 2-Chloro-10-N-methylphenothiazine (1) was prepared by successively treating a THF solution of 2-chlorophenothiazine with 1.1 equivalents of sodium hydride and 1.3 equivalents of methyl iodide then stirring the mixture for 24 h at room temperature. After quenching the mixture with 1.4 equivalents of methanol, the solvent was removed (rotatory evaporator) and pure 1 was obtained by chromatographing the crude product on silica gel using hexane as an eluant. White solid (from hexane) mp 81-82°C; ^1H nmr ($CDCl_3$) δ 3.37 (s, 3H, N-Me), 6.78-7.2 (m, 7H, Ar-H); ms, m/z 249 ($M^{+\cdot}$) 251 (M + 2). Anal. calcd for $C_{13}H_{12}ClNS$: C, 62.51; H, 4.84; N, 5.6. Found: C, 62.35; H, 4.87; N, 5.55.

1-Cyano-2-(3',4',5'-trimethoxybenzyl)-10-N-methylphenothiazine (3a): Light yellow crystals (from EtOAc); mp 133-135°C; ^1H nmr ($CDCl_3$) δ 3.79 (s, 3H, 4'-MeO), 3.84 (s, 9H, 3',5'-MeO and 10-N-Me), 4.06 (s, 2H, benzylic-CH_2), 6.49 (s, 2H, $C_{2'}$ and $C_{6'}$ Ar-H), 6.47 (d, J = 8 Hz, 1H, C_3Ar-H), 6.79-7.18 (m, 5H, Ar-H); ir ν_{max} ($CHCl_3$) cm^{-1} 2220 (nitrile); ^{13}C nmr ($CDCl_3$) δ 40.28, 40.76, 55.98 (2 x MeO), 60.62, 101.40, 106.12, 117.06, 117.35, 123.33, 124.69, 126.45, 127.06, 127.54, 130.33, 134.18, 136.31, 145.04, 145.79, 148.58, 153.16; ms, m/z 396 ($M^{+\cdot}$). Anal. calcd for $C_{24}H_{22}N_2O_3S$: C, 66.64; H, 6.1; N, 7.06. Found: C, 66.37; H, 6.18; N, 7.12. The ^1H nmr and ^{13}C nmr spectra of **3-a** were consistent with the proposed structures. The ^1H nmr spectrum of **3a** is worthy of note. The chemical shift of the N-methyl protons coincides with those of 3',5'-methoxy protons. The

Table 1. Bond lengths (A)

S(5)-C(4A)	1.763 (4)	S(5)-C(5A)	1.764 (4)
O(1)-C(16)	1.366 (4)	O(1)-C(21)	1.413 (8)
O(2)-C(17)	1.378 (5)	O(2)-C(22)	1.397 (7)
O(3)-C(18)	1.368 (6)	O(3)-C(23)	1.416 (5)
C(1)-C(2)	1.420 (6)	C(1)-C(10A)	1.403 (5)
C(1)-C(12)	1.445 (6)	C(2)-C(3)	1.375 (6)
C(2)-C(13)	1.522 (6)	C(3)-C(4)	1.368 (6)
C(4)-C(4A)	1.381 (6)	C(4A)-C(10A)	1.401 (5)
C(5A)-C(6)	1.382 (5)	C(5A)-C(9A)	1.397 (5)
C(6)-C(7)	1.385 (6)	C(7)-C(8)	1.371 (8)
C(8)-C(9)	1.381 (6)	C(9)-C(9A)	1.393 (5)
C(9A)-N(10)	1.416 (4)	N(10)-C(10A)	1.390 (5)
N(10)-C(11)	1.452 (5)	C(12)-N(20)	1.139 (6)
C(13)-C(14)	1.509 (5)	C(14)-C(15)	1.387 (5)
C(14)-C(19)	1.396 (6)	C(15)-C(16)	1.393 (6)
C(16)-C(17)	1.380 (6)	C(17)-C(18)	1.396 (5)
C(18)-C(19)	1.384 (6)		

Table 2. Bond angles (°)

C(4A)-S(5)-C(5A)	99.3(2)	C(16)-O(1)-C(21)	118.7(4)
C(17)-O(2)-C(22)	116.3(4)	C(18)-O(3)-C(23)	117.5(4)
C(2)-C(1)-C(10A)	122.0(3)	C(2)-C(1)-C(12)	117.7(4)
C(10A)-C(1)-C(12)	120.3(3)	C(1)-C(2)-C(3)	117.7(4)
C(1)-C(2)-C(13)	121.4(4)	C(3)-C(2)-C(13)	120.9(4)
C(2)-C(3)-C(4)	121.1(4)	C(3)-C(4)-C(4A)	121.1(4)
S(5)-C(4A)-C(4)	119.1(3)	S(5)-C(4A)-C(10A)	119.8(3)
C(4)-C(4A)-C(10A)	120.8(4)	S(5)-C(5A)-C(6)	119.5(3)
S(5)-C(5A)-C(9A)	119.3(3)	C(6)-C(5A)-C(9A)	121.0(3)
C(5A)-C(6)-C(7)	120.0(4)	C(6)-C(7)-C(8)	119.2(4)
C(7)-C(8)-C(9)	121.5(4)	C(8)-C(9)-C(9A)	119.7(4)
C(5A)-C(9A)-C(9)	118.6(3)	C(5A)-C(9A)-N(10)	120.3(3)
C(9)-C(9A)-N(10)	121.0(3)	C(9A)-N(10)-C(10A)	120.9(3)
C(9A)-N(10)-C(11)	117.6(3)	C(10A)-N(10)-C(11)	121.4(3)
C(1)-C(10A)-C(4A)	116.9(3)	C(1)-C(10A)-N(10)	123.5(3)
C(4A)-C(10A)-N(10)	119.7(3)	C(1)-C(12)-N(20)	175.8(6)
C(2)-C(13)-C(14)	109.4(4)	C(13)-C(14)-C(15)	120.9(4)
C(13)-C(14)-C(19)	119.5(3)	C(15)-C(14)-C(19)	119.4(4)
C(14)-C(15)-C(16)	119.7(4)	O(1)-C(16)-C(15)	123.9(4)
O(1)-C(16)-C(17)	115.1(3)	C(15)-C(16)-C(17)	121.0(3)
O(2)-C(17)-C(16)	120.0(3)	O(2)-C(17)-C(18)	120.6(4)
C(16)-C(17)-C(18)	119.3(4)	O(3)-C(18)-C(17)	116.3(3)
O(3)-C(18)-C(19)	123.8(3)	C(17)-C(18)-C(19)	119.9(4)
C(14)-C(19)-C(18)	120.6(3)		

Table 3. Torsion angles(°)

C(5A)-S(5)-C(4A)-C(4)	-151.1(4)	C(5A)-S(5)-C(4A)-C(10A)	34.6(4)
C(4A)-S(5)-C(5A)-C(6)	150.3(4)	C(4A)-S(5)-C(5A)-C(9A)	-34.7(4)
C(21)-O(1)-C(16)-C(15)	8.7(6)	C(21)-O(1)-C(16)-C(17)	-171.6(4)
C(22)-O(2)-C(17)-C(16)	97.1(5)	C(22)-O(2)-C(17)-C(18)	-86.9(5)
C(23)-O(3)-C(18)-C(17)	-176.5(4)	C(23)-O(3)-C(18)-C(19)	3.2(6)
C(12)-C(1)-C(2)-C(3)	-170.0(4)	C(12)-C(1)-C(2)-C(13)	12.0(6)
C(2)-C(1)-C(10A)-N(10)	173.5(4)	C(12)-C(1)-C(10A)-C(4A)	170.1(4)
C(12)-C(1)-C(10A)-N(10)	-8.9(6)	C(2)-C(1)-C(12)-N(20)	35(5)
C(10A)-C(1)-C(12)-N(20)	-143(5)	C(13)-C(2)-C(3)-C(4)	175.7(4)
C(1)-C(2)-C(13)-C(14)	92.9(4)	C(3)-C(2)-C(13)-C(14)	-85.0(5)
C(2)-C(3)-C(4)-C(4A)	-2.9(7)	C(3)-C(4)-C(4A)-S(5)	-171.3(4)
C(3)-C(4)-C(4A)-C(10A)	3.0(7)	S(5)-C(4A)-C(10A)-C(1)	176.4(3)
S(5)-C(4A)-C(10A)-N(10)	-4.6(5)	C(4)-C(4A)-C(10A)-C(1)	2.2(6)
C(4)-C(4A)-C(10A)-N(10)	-178.8(4)	S(5)-C(5A)-C(6)-C(7)	178.1(5)
C(9A)-C(5A)-C(6)-C(7)	-1.9(8)	S(5)-C(5A)-C(9A)-C(9)	-174.8(4)
S(5)-C(5A)-C(9A)-N(10)	5.4(7)	C(6)-C(5A)-C(9A)-N(10)	-179.7(5)
C(8)-C(9)-C(9A)-C(5A)	2.1(6)	C(8)-C(9)-C(9A)-N(10)	-178.0(5)
C(5A)-C(9A)-N(10)-C(10A)	35.4(6)	C(5A)-C(9A)-N(10)-C(11)	-149.1(5)
C(9)-C(9A)-N(10)-C(10A)	-144.4(5)	C(9)-C(9A)-N(10)-C(11)	31.1(7)
C(9A)-N(10)-C(10A)-C(1)	143.3(4)	C(9A)-N(10)-C(10A)-C(4A)	-35.6(6)
C(11)-N(10)-C(10A)-C(1)	-32.0(6)	C(11)-N(10)-C(10A)-C(4A)	149.1(4)
C(2)-C(13)-C(14)-C(15)	106.0(5)	C(2)-C(13)-C(14)-C(19)	-70.0(5)
C(14)-C(15)-C(16)-O(1)	-179.9(4)	O(1)-C(16)-C(17)-O(2)	-5.9(6)
O(1)-C(16)-C(17)-C(18)	178.1(4)	C(15)-C(16)-C(17)-O(2)	173.8(4)
O(2)-C(17)-C(18)-O(3)	5.8(5)	O(2)-C(17)-C(18)-C(19)	-173.9(4)
C(16)-C(17)-C(18)-O(3)	-178.2(4)	O(3)-C(18)-C(19)-C(14)	-179.8(4)

decoupled ^{13}C nmr spectrum of **3a** showed two peaks at chemical shifts 40.28 and 40.76 ppm, respectively, for the N-methyl carbon and the benzylic carbon. From the decoupled spectrum it was not possible to assign the chemical shifts for each of these two carbons. However, with the aid of a coupled spectrum it was possible to assign the chemical shift 40.28 ppm for the benzylic carbon and 40.76 ppm for the N-methyl carbon. It is noteworthy that the chemical shift of N-methyl protons in the ^1H nmr spectrum of **3a** was resolved in presence of europium shift reagent $Eu(FOD)_3$. N-Methyl protons were shifted considerably to lower fields with respect to the 3' and 5' methoxy protons, indicating that the complexing site for the shift reagent is the nitrogen lone pair of electrons. Methoxy, benzylic, and $C_{2'}$ and $C_{6'}$ aromatic protons were also shifted to lower fields. A study of chemical shifts of these protons in the presence of various concentrations of shift reagents was carried out and the results are shown below.

^1H Nmr Shift Reagent Studies[a] of 3a

Shift Reagent $Eu(FOD)_3$ (mmol)	Chemical Shift				
	C_4-MeO	$C_{3'}$ and $C_{5'}$ MeO	N-Me	benzylic-CH_2	$C_{2'}$ and $C_{6'}$ Ar-H
no shift reagent	3.79	3.84	3.84	4.06	6.47
0.005	3.79	3.91	4.14	4.12	6.63
0.010	3.84	4.11	4.77	4.27	6.97
0.015	3.87	4.24	5.24	4.39	7.22
0.020	3.88	4.28	5.35	4.42	7.28

a, 0.2 molar solution (0.5 mL) of **3a** in $CDCl_3$ was used.

1-Cyano-2-(3',4'-Dimethoxybenzyl)-10-N-methylphenothiazine (3b): Thick oil; ^1H nmr ($CDCl_3$) δ 3.82 (s, 3H, N-Me), 3.91 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.11 (s, 2H, benzylic-CH_2), 6.79-7.16 (m, 9H, Ar-H); ir ν_{max} ($CHCl_3$) cm^{-1} 2220 (nitrile); ms, m/z 382 ($M^{+\cdot}$).

1-Cyano-2-(4'-fluorobenzyl)-10-N-methylphenothiazine (3c): Colorless thick oil; ^1H nmr ($CDCl_3$) δ 3.78 (s, 3H, N-Me), 4.1 (s, 2H, benzylic-CH_2), 6.74-7.26 (m, 10H, Ar-H); ir ν_{max} ($CHCl_3$) cm^{-1} 2220 (nitrile); ms, m/z 352 ($M^{+\cdot}$).

α-(*m*-Trifluoromethylphenyl)-10-N-Methylphenothiazinyl-2-acetonitrile (10): Yellow oil; ^1H nmr ($CDCl_3$) δ 3.79 (s, 3H, N-Me), 5.12 (s, 1H, CH-CN), 6.70-7.61 (m, 11H, Ar-H); ir ν_{max} ($CHCl_3$) cm^{-1} 2240 (nitrile); ms, m/z 393 ($M^{+\cdot}$).

N-Methylphenothiazinyl-2-acetonitrile (11a): White solid (from CH_2Cl_2/hexane); mp. 91-93°C; ^1H nmr ($CDCl_3$) δ 3.39 (s, 3H, N-Me), 3.70 (s, 2H, benzylic-CH_2), 6.74 (s, 1H, C_1Ar-H), 6.85 (m, 1H, C_3Ar-H), 6.91 (d, J =

7.2 Hz, 1H, C_4Ar-H), 6.96-7.20 (m, 4H, C_5, C_6, C_7 and C_8 Ar-H); ir ν_{max} ($CHCl_3$) cm^{-1} 2240 (nitrile); ^{13}C nmr ($CDCl_3$) δ 23.33, 35.22, 113.41, 114.25, 117.72, 121.68, 122.68, 122.79, 123.30, 127.02, 127.32, 127.53, 129.18, 145.11, 146.32; ms, m/z 252 ($M^{+\cdot}$). Anal. calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.1. Found: C, 71.23; H, 4.74; N, 11.16.

α-(10-N-Methylphenothiazinyl)-2-propiononitrile (11b): White crystals (from EtOAc/hexane) mp 105-108°C, ^1H nmr ($CDCl_3$) δ 1.64 (d, J = 7.3 Hz, 3H, CH-$\underline{CH_3}$), 3.41 (s, 3H, N-Me), 3.86 (q, J = 7.3 Hz, 1H, $\underline{CH}$-CH_3), 6.78 (d, J = 1.2 Hz, 1H, C_1Ar-H), 6.87 (m, 1H, C_3Ar-H), 6.94 (d, J = 9.5 Hz, 1H, C_4Ar-H), 6.96-7.24 (m, 4H, C_5, C_6, C_7 and C_8 Ar-H); ir ν_{max} ($CHCl_3$) cm^{-1} 2240 (nitrile); ^{13}C nmr ($CDCl_3$ δ 21.39, 31.09, 35.31, 112.29, 114.24, 120.48, 121.35, 122.72, 122.96, 123.51, 127.09, 127.48, 127.54, 136.52, 145.28, 146.49; ms, m/z 266 ($M^{+\cdot}$). Anal. calcd for $C_{16}H_{14}N_2S$: C, 71.14; H, 5.3; N, 10.51. Found: C, 71.35; H, 5.37; N, 10.55.

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