Spectra–Structure Correlations of Phenothiazines by Infrared, Ultraviolet, and Nuclear Magnetic Resonance Spectroscopy

By R. J. WARREN, I. B. EISDORFER, W. E. THOMPSON, and J. E. ZAREMBO

The infrared, ultraviolet, and nuclear magnetic resonance spectra of 23 phenothiazines of varying structure have been recorded and analyzed. Spectra–structure correlations and assignments of the absorption bands are presented and discussed. The collection of phenothiazines includes all of the commercially available analogs currently in use in the field of medicine and provides a comprehensive source for the identification and structure elucidation of samples from biological, forensic, and medical research.

ALTHOUGH the literature is replete with publications on phenothiazines, there has been to date no attempt to organize and correlate spectral data on this class of compounds. The purpose of this paper is to report the results of such a spectral study. Infrared, ultraviolet, and nuclear magnetic resonance spectra of 23 phenothiazine derivatives have been analyzed, and the correlations from these spectral data make possible a positive identification of all of the commercially available pharmaceutically useful phenothiazines.

EXPERIMENTAL

The infrared spectra were recorded between 4000–625 cm.$^{-1}$ with a Perkin-Elmer model 21 spectrometer with a sodium chloride prism. The phenothiazines were prepared as natural films.

The ultraviolet spectra were recorded between 200 and 400 mμ with a Cary model 14 recording spectrophotometer using matched fused silica cells with a 1-cm. light path.

The NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard on a Varian Associates model A-60 spectrometer.

All spectral data were obtained on the same samples. These were analytical standards with a purity of 98% or greater. (See Table I.)

DISCUSSION OF RESULTS

Infrared Spectra.—The infrared spectra of the phenothiazines are shown in Figs. 1–6. Seventeen of the 23 phenothiazines are substituted in the

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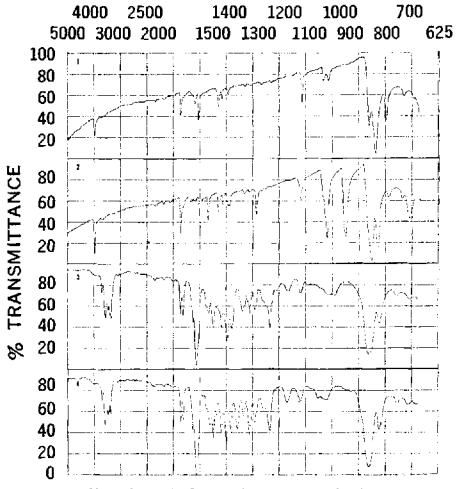


Fig. 1.—Infrared spectra 1–4.

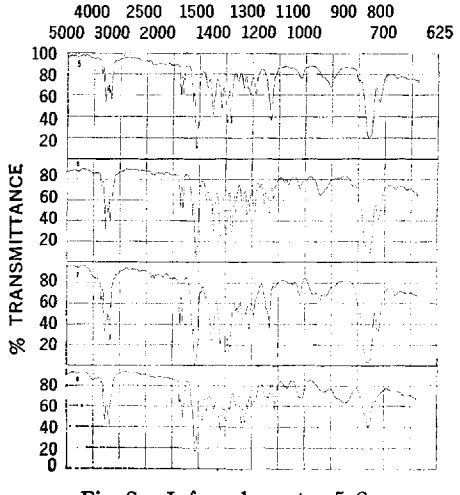
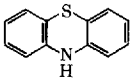
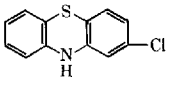
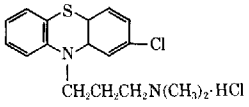
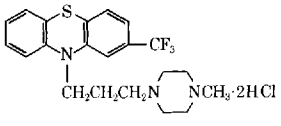
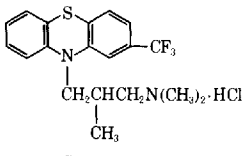
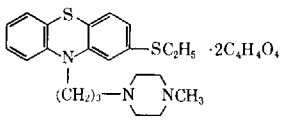
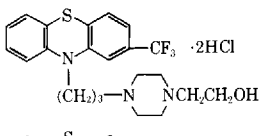
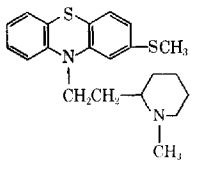
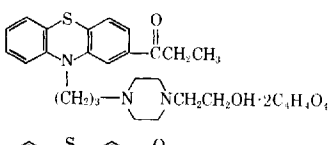
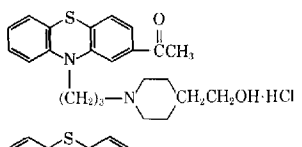
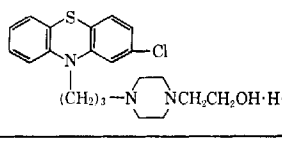


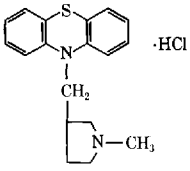
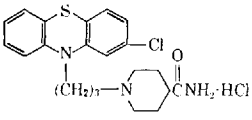
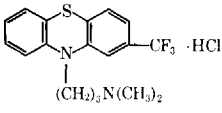
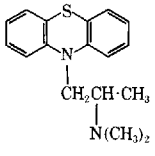
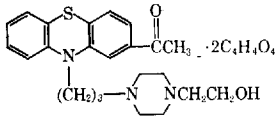
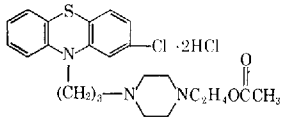
Fig. 2.—Infrared spectra 5–8.

TABLE I.—SPECTRAL DATA FOR PHENOTHIAZINES

Compd.	Structural Formula	U. V. Data[a] $\lambda_{max.}$ mμ	Log ε	$\lambda_{min.}$ mμ	Log ε	I.R. Spec. No. of Free Base	NMR Spec. No. of Free Base
Phenothiazine		253 320	4.64 3.64	280	3.00	1	1
2-Chlorophenothiazine		256 320	4.71 3.69	285	3.03	2	2
Chlorpromazine hydrochloride		256 310	4.54 3.60	280	3.16	21	3
Prochlorperazine dihydrochloride		256 309	4.54 3.62	280	3.11	20	17
Trifluoperazine dihydrochloride		258 307.5	4.50 3.50	280	3.08	16	13
Trifluoromeprazine hydrochloride		308 258 238sh	3.60 4.55 4.18	279 240 223	3.21 4.18 4.02	15	5
Thiethylperazine maleate		316 264	3.69 4.59	300 239	3.51 4.28	8	20
Vespazine hydrochloride		309 259	3.58 4.53	279 224	3.23 4.00	9	19
Thioridazine hydrochloride		314 263	3.66 4.58	288	3.72	10	9
Carphenazine maleate		278 243	4.39 4.46	256 230	4.25 4.36	14	15
Piperacetazine hydrochloride		280 244	4.35 4.40	256 220	4.15 4.23	12	12
Perphenazine hydrochloride		310 257	3.66 4.57	278 225	3.23 4.06	11	18

continued on next page

TABLE I.—(*Continued*)

Compd.	Structural Formula	U. V. Data[a] $\lambda_{max.}$ mμ	Log ε	$\lambda_{min.}$ mμ	Log ε	I.R. Spec. No. of Free Base	NMR Spec. No. of Free Base
Methdilazine hydrochloride		304 254	3.61 4.50	276 222	3.17 3.93	7	21
Pipamazine hydrochloride		312 257	3.65 4.57	280	3.22	19	10
Triflupromazine hydrochloride		308 258	3.57 4.53	280 224	3.21 4.01	17	6
Promethazine hydrochloride		302 252	3.58 4.49	274 220	3.21 3.97	4	7
Acetophenazine dimaleate		280 243	4.35 4.44	255 230	4.19 4.32	13	14
Thiopropazate hydrochloride		310 257	3.66 4.57	280 226	3.26 4.12	18	16

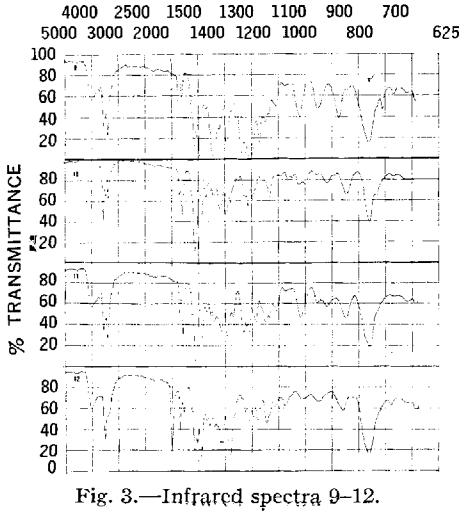


Fig. 3.—Infrared spectra 9–12.

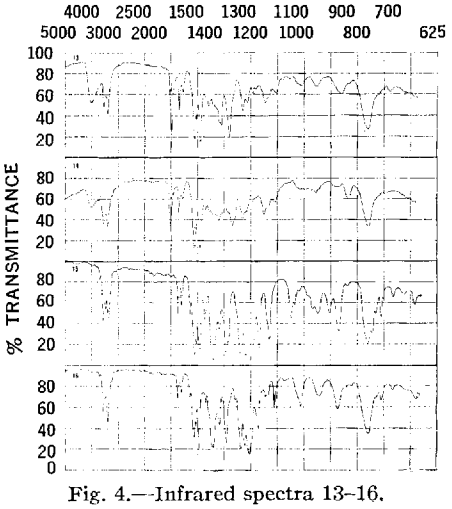
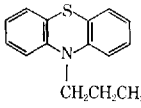
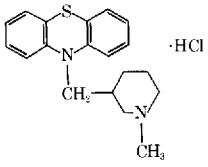
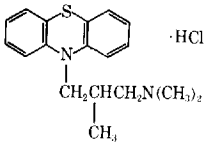
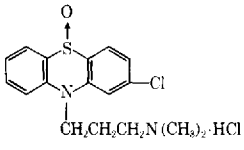
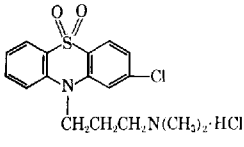


Fig. 4.—Infrared spectra 13–16.

TABLE I.—(*Continued*)

Compd.	Structural Formula	U. V. Data[a] $\lambda_{max.}$ mμ	Log ε	$\lambda_{min.}$ mμ	Log ε	I.R. Spec. No. of Free Base	NMR Spec. No. of Free Base
Promazine		306 254	3.64 4.53	277 222	3.20 3.95	3	8
Mepazine hydrochloride		304 254	3.59 4.48	276 221	3.15 3.96	6	11
Trimeprazine hydrochloride		308 255	3.67 4.53	278 222	3.22 3.95	5	4
Chlorpromazine sulfoxide hydrochloride		240 275 298 342.5	4.52 4.03 3.88 3.72			22	22
Chlorpromazine sulfone hydrochloride		233 271 294 332	4.54 4.16 3.89 3.76			23	23

[a] U.V. spectra run in 95% ethanol.

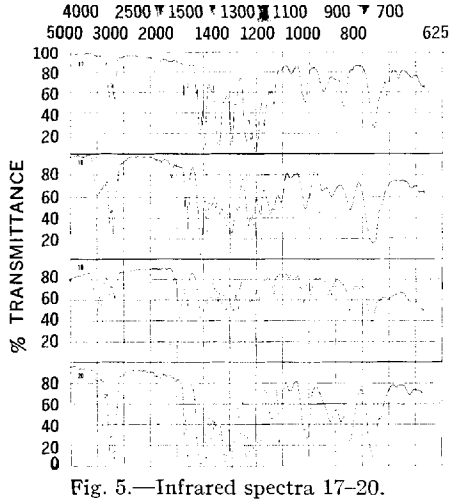


Fig. 5.—Infrared spectra 17–20.

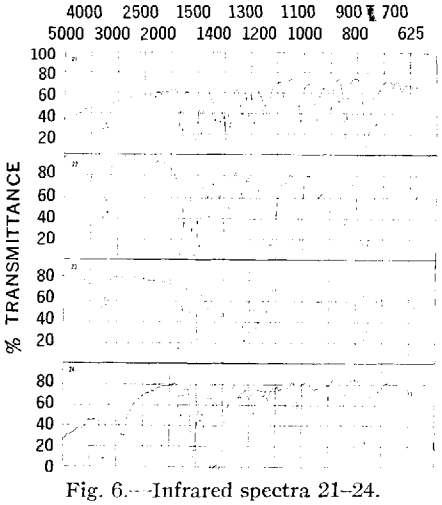


Fig. 6.—Infrared spectra 21–24.

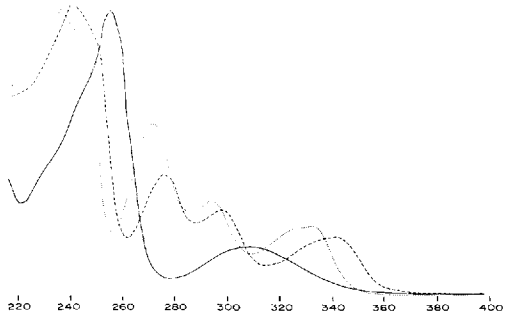


Fig. 7.—Ultraviolet spectra. Key: ——, phenothiazine; ---, sulfoxide; . . ., sulfone.

2,10-positions. These 2,10-disubstituted phenothiazines have a characteristic and unique over-all pattern in the infrared spectrum. There are 4 bands in the region 1000–700 cm.$^{-1}$ which are common to all. These bands occur at 915–928 cm.$^{-1}$, 840–870 cm.$^{-1}$, 785–800 cm.$^{-1}$, and 730–755 cm.$^{-1}$. The band at 785–800 cm.$^{-1}$ exhibits some splitting in certain cases, but it is steady in location. The bands listed are all strong and comprise a definite over-all pattern which dominates the fingerprint range of the spectrum. The bands are assignable to the phenothiazine ring system and the substitution in the 2-position. Bellamy (1) gives the range 770–735 cm.$^{-1}$ for the out-of-plane bending vibration of 4 adjacent hydrogens in an aromatic ring and the 900–800 cm.$^{-1}$ for 1,2,4-trisubstitution.

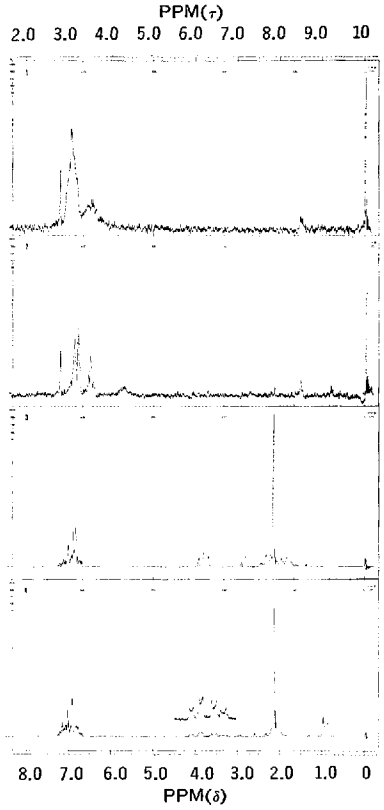


Fig. 8.—NMR spectra 1–4.

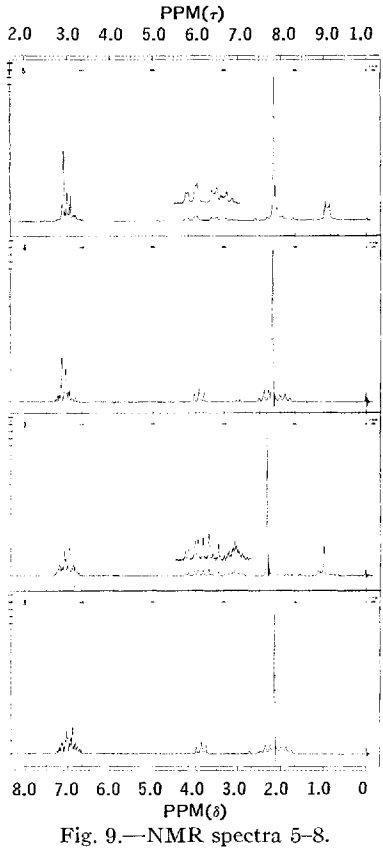


Fig. 9.—NMR spectra 5–8.

Phenothiazines with no substituent in the 2-position all show very strong absorption in the 720–770 cm.$^{-1}$ range which is assignable to the out-of-plane bending vibrations of the 4 adjacent hydrogens of the phenothiazine ring system (1).

Two other characteristic bands for the phenothiazine system are found at 1590 and 1560 cm.$^{-1}$. These bands are quite consistent in location, although they vary as to which is the more intense. They also may be assigned to the aromatic system.

In the case of phenothiazine amine salts (spectrum No. 24, chlorpromazine HCl) a strong, broad band centered between 2300 and 2500 cm.$^{-1}$ is characteristic of the R_3NH^+ ion combined with X^-. The relatively small negative ion X^- can approach the amine cation R_3NH^+ from only one direction, forming the ion pair $R_3NH^+X^-$ with the hydrogen atom bound strongly to the negative ion. Water of hydration tends to raise the frequency and lower the intensity of the absorption (2).

Two of the important oxidation products of phenothiazines are the sulfoxide and sulfone. The presence or absence of these may be determined by examining the spectra for S=O and SO_2 bands. The single S=O band occurs at 1000 cm.$^{-1}$ (±20). The —SO_2 asymmetric stretching band occurs at 1250–1300 cm.$^{-1}$ and the symmetric stretching band at 1140–1160 cm.$^{-1}$. All exhibit strong absorption bands.

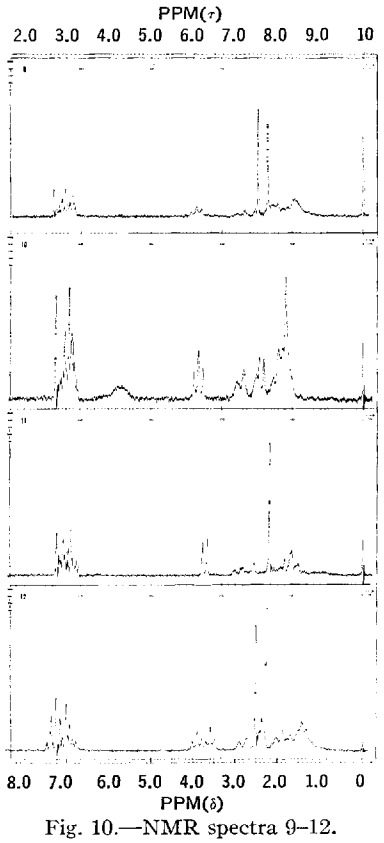


Fig. 10.—NMR spectra 9–12.

Ultraviolet Spectra.—The ultraviolet spectra of the phenothiazines are characteristic both in wavelength and in intensity. Two peaks are observed, the first and most intense in the range 250–265 mμ and the second in the range 300–325 mμ. The exact location of the peaks in both regions is dependent upon the nature of the group in the 2-position. Halogen substituents such as chloro- or trifluoromethyl appear to exert a slight influence in the form of small bathochromic shifts of 2–4 mμ on the more intense peak in the 250–265-mμ region. The trifluoro effects a slightly stronger shift than the chloro analog. It has been further noted that the alkyl side chain containing an amine group causes slight shifts in the peak locations, and the amount of shift is related to the length of the side chain, which is to say the proximity of the amine group to phenothiazine nucleus. The amine group has been found to exert a slight influence even when located at the end of a 4-carbon chain.

Phenothiazines with a carbonyl group in the 2-position are exceptions to the general rule regarding location of the 3 ultraviolet peaks. This type of phenothiazine exhibits strong absorption peaks in the range 240–245 mμ and 275–285 mμ.

Because of the distinctive ultraviolet spectrum and the intense absorption detectable at low concentrations (0.015 mg./ml.), it is possible to make a qualitative determination quickly and with a minimum amount of sample.

The presence or absence of the sulfone and sulfoxide decomposition products is easily ascertained by examining the ultraviolet spectrum. The spectrum of sulfone or sulfoxide is quite different and easily detected (Fig. 7).

Nuclear Magnetic Resonance.—For NMR study (Figs. 8–13) and correlations the phenothiazine spectra can be separated into 5 groups: 4 groups according to the type of side chain on the nitrogen in the 10-position, a fifth group consisting of the oxidation products (sulfone and sulfoxide). The groups to be considered are: (*A*) those having an aliphatic side chain with no heterocyclic ring; (*B*) those having a side chain containing a piperazine ring; (*C*) those having a side chain containing a piperidine ring; (*D*) those containing a pyrrolidine ring; and (*E*) oxidized phenothiazines.

Group A.—All of the compounds belonging to group *A* have features in common. All contain an *N,N*-dimethyl group, all have a CH_2 group attached to the 10-position of the phenothiazine ring, and, of course, all contain aromatic protons from the phenothiazine nucleus itself. It is, therefore, not surprising that their NMR spectra are similar in many respects, and have characteristic absorbance bands unique to their general group. The *N,N*-dimethyl group is found at 131 c.p.s. for the compounds with straight chain amines and at 138 c.p.s. in the case of branched chain amines. The position of the branched chain amine is influenced by its proximity to the ring N. The CH_2 group on

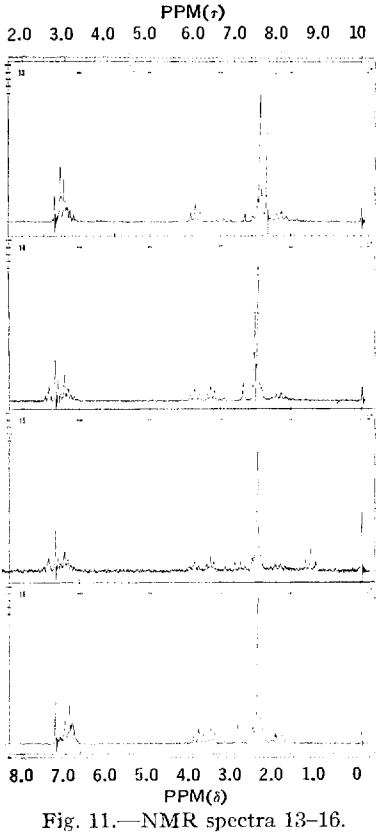


Fig. 11.—NMR spectra 13–16.

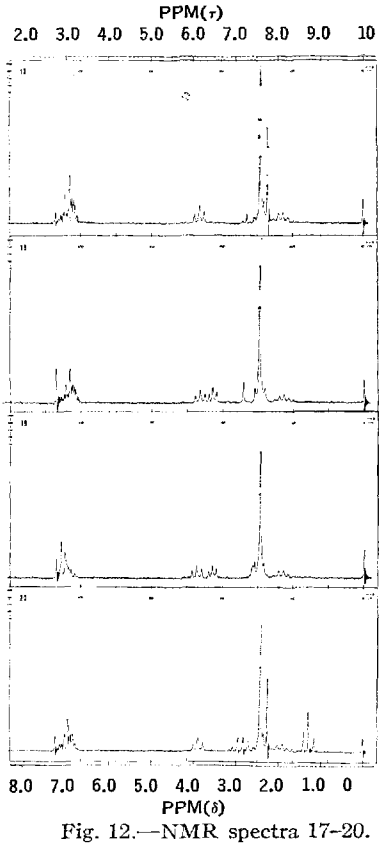


Fig. 12.—NMR spectra 17–20.

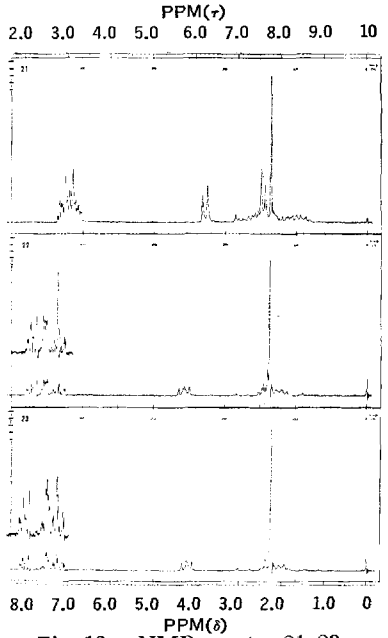


Fig. 13.—NMR spectra 21–23.

the nitrogen atom in the 10-position is found to be a triplet at 232 ± 3 c.p.s. for straight chain amines and in the same area but with more splitting in the case of branched chain amines due to the increased number of adjacent protons. All of the phenothiazine spectra show a complex pattern for the aromatic protons in the area 400–440 c.p.s. (3).

Group B.—Phenothiazines having a piperazine ring in their side chain have common features attributable to their specific group which distinguish them from other phenothiazines. The 8 protons in the piperazine ring being equivalent are found as a single peak at 146 ± 2 c.p.s. This is the strongest peak and the dominant feature of a phenothiazine in this group. The CH_2 attached to the N in the 10-position is found at 234 ± 4 c.p.s. In those piperazine derivatives where the piperazine ring is attached directly to a CH_2 in the chain (6 of the 9 shown) the CH_2 adjacent to the piperazine is located at 215 c.p.s. The complex aromatic pattern is located at 400–450 c.p.s.

Group C.—The phenothiazines containing a piperidine group in the side chain have chemical shifts due to the piperidine ring in the range 90–130 c.p.s., depending on the position and nature of the substitutent. The CH_2 attached to the N at the 10-position is again found at 235 c.p.s. with 1 exception, where the CH_2 is the only link between the N and the piperidine ring. In this case the CH_2 is a doublet located at 220 and 227 c.p.s. The aromatic pattern is found at 400–450 c.p.s.

Group D.—The group containing a pyrrolidine ring shows a chemical shift in the range of 100–180 c.p.s. due to the substitution on the ring. The CH_2 which links the N at 10-position and the pyrrolidine ring is a doublet at 224 and 231 c.p.s.

Group E.—This group contains the sulfoxide and sulfone of chlorpromazine. The effect of the introduction of oxygen into the system is an increase in chemical shift as compared with chlorpromazine. The $N(CH_3)_2$ is shifted 4–6 c.p.s. to 135–137 c.p.s. The CH_2 in position 10 is shifted to 254–256 c.p.s. and the aromatic protons show additional splitting and shift to 490 c.p.s.

SUMMARY

Infrared, ultraviolet, and nuclear magnetic resonance spectral data of phenothiazine compounds have been presented and correlated. On the basis of the information presented here, it is possible to make a rapid identification with a minimum amount of sample of any of the commercially available phenothiazines used in pharmaceutical preparations.

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