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Identification of Primary, Secondary, and Tertiary Pharmaceutical Amines by the Infrared Spectra of Their Salts

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

The spectra of 80 pharmaceutically active amine salts have been analyzed in the range of 4000–2000 cm.$^{-1}$. The amine salts have characteristic absorption bands in this region. The wave numbers at which these absorption bands occur are specific for each given class of amine. Spectra-structure correlations and assignments of these bands are given and discussed.

OVER THE past several years the authors have recorded the infrared spectra of several hundred amine salts of varying structure and class. The amines were typical of those usually encountered in the pharmaceutical industry in that they were large, asymmetrical molecules. In most cases, these were combined with small negative ions such as chloride or bromide. During this time we have had occasion to search the literature for assignments and interpretations of the absorption bands due to the amine ions NH_3^+, NH_2^+, NH^+. We have found reports indicating that much work and assignments have been made on these ions (2, 4). Most of the studies made were on a specific ion, *e.g.*, NH_2^+, or aspect of amine salt absorption, *e.g.*, hydrogen bonding. To our knowledge there has been no comprehensive study of amine salt absorption data relative to the type of molecule on which we are reporting.

This article gives the results of an infrared spectral study of 80 amine salts—55 tertiary, 15 secondary, and 10 primary. It shows that these classes of amines possess characteristic frequencies in the range of 4000–2000 cm.$^{-1}$. The frequencies may be used to establish the class of amine present.

PRIMARY AMINE SALTS

Bellamy (1) reports that the hydrochlorides of primary amines have been little studied, and this statement is essentially correct. There have been a few reports (2, 3, 5) that primary amine salts absorb in the range of 3200–2000 cm.$^{-1}$. The absorption bands are generally reported to be a series of weak peaks. Some authors (2, 3) have mentioned an isolated band near 2000 cm.$^{-1}$ whose intensity is variable. Table I lists the primary amine salts studied here and their characteristic absorption bands.

It has been found that these bands are remarkably consistent and unique for the primary amine ion, NH_3^+. The band in the area of 2000 cm.$^{-1}$ which was reported (2, 3) is present in all cases. The authors find the location of this band to be between 1960 and 2080 cm.$^{-1}$. It is a broad band in most cases. There has been some discussion as to the nature of the vibration giving rise to this absorption. It has variously been assigned as an NH_3^+ stretching vibration and as a combination band of the NH_3^+ torsional vibration at about 500 cm.$^{-1}$ and the asymmetrical NH_3^+ deformation (2, 3). That it involves the NH_3^+ ion is evident from its presence in all of the primary amine salts listed in Table I. The other distinguishing feature of the spectra of primary amine salts is a series of weak peaks between 2770 and 2380 cm.$^{-1}$ which are assignable to the NH_3^+ overtone and combination bands (6).

TABLE I.—PRIMARY AMINE SALTS

	Series of Peaks (Weak)	Peak (Broad)
Aminacrine hydrochloride	2770–2500 cm.$^{-1}$	2000 cm.$^{-1}$
d-Amphetamine sulfate	2770–2500	2000
Glutamic acid hydrochloride	2770–2500	2000
Hydroxyamphetamine hydrobromide	2630–2440	1960
Methoxamine hydrochloride	2770–2500	1960
Nordefrin hydrochloride	2770–2500	1960
Phenylpropanolamine hydrochloride	2770–2380	1960
Tuaminoheptane sulfate	2770–2090	2000
dl-Amphetamine sulfate	2700–2040	2090
p-Methoxyamphetamine hydrochloride	2770–2380	1960

SECONDARY AMINE SALTS

The secondary amine salt absorption bands are listed in Table II. It should be noted that there is a series of three bands between 2860 and 2040 cm.$^{-1}$.

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TABLE II.—SECONDARY AMINE SALTS

	Strong	Weak	Strong and Sharp
Ephedrine sulfate	2860	2740	2440
Hexylcaine hydrochloride	2770	2510	2440
Isoproterenol hydrochloride	2770		2380
Mecamylamine hydrochloride	2770		2440
Mephentermine sulfate	2770	2560	2440
Meprylcaine hydrochloride	2770	2500	2410
Methamphetamine hydrochloride	2770	2040	2440
Methoxyphenamine hydrochloride	2770		2440
Nylidrin hydrochloride	2770	2702	2440
Phenylephrine hydrochloride	2770		2440
Phenylpropylmethylamine hydrochloride	2770	2500	2410
Pipradol hydrochloride	2770	2500	2380
Propylhexedrine hydrochloride	2770	2040	2440
Protokylol hydrochloride	2770	2380	2440
Racephedrine hydrochloride	2770		2440

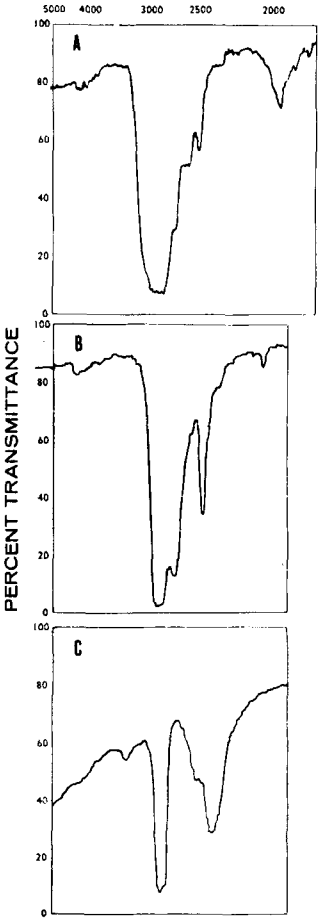

Fig. 1.—Key: spectrum A, primary amine salt; spectrum B, secondary amine salt; spectrum C, tertiary amine salt.

TABLE III.—TERTIARY AMINE SALTS

	Broad Peak
Alphaprodine hydrochloride	2560 cm.$^{-1}$
Apomorphine hydrochloride	2630
Arecoline hydrobromide	2630
Atropine sulfate	2560
Benactyzine hydrochloride	2700, 2670(s)
Benoxinate hydrochloride	2630
Biallylamicol hydrochloride	2630
Biperiden hydrochloride	2330, 2560(s)
Chlorcyclizine hydrochloride	2500
Chloroprocaine hydrochloride	2700, 2500(w)
Chlorphenoxamine hydrochloride	2700
Chlorpromazine hydrochloride	2560, 2440(s)
Cocaine hydrochloride	2770, 2500(s)
Cyclomethylcaine hydrochloride	2560
Cyclopentolate hydrochloride	2630
Cycrimine hydrochloride	2700, 2560(m)
Dextromethorphan hydrobromide	2500, 2440(w)
Diamethazole hydrochloride	2630
Dicyclomine hydrochloride	2645
Diethylpropion hydrochloride	2630
Diphenhydramine hydrochloride	2630
Diphenylpyraline hydrochloride	2410
Ethopropazine hydrochloride	2500
Eucatropine hydrochloride	2630
Homatropine hydrochloride	2700, 2560(w)
Hydroxyzine hydrochloride	2440
Hyoscyamine hydrobromide	2700, 2560(w)
Meclizine hydrochloride	2560
Mepazine hydrochloride	2560
Meperidine hydrochloride	2560
Methadone hydrochloride	2560
Methapyrilene hydrochloride	2630, 2500(w)
Methdilazine hydrochloride	2630
Orphenadrine hydrochloride	2560, 2440(w)
Phenazocine hydrobromide	2630
Phenoxybenzamine hydrochloride	2500
Piperidolate hydrochloride	2560
Piperocaine hydrochloride	2560
Pipethanate hydrochloride	2630, 2500(w)
Pramoxine hydrochloride	2560, 2500(w)
Procyclidine hydrochloride	2630, 2500(w)
Promazine hydrochloride	2630
Promethazine hydrochloride	2560, 2440(w)
d-Propoxyphene hydrochloride	2630, 2500(w)
Pyrathiazine hydrochloride	2440
Quinine hydrochloride	2600
Thiopropazate hydrochloride	2380
Thioridazine hydrochloride	2650, 2440(w)
Thonzylamine hydrochloride	2630, 2500(w)
Trifluoperazine hydrochloride	2440
Tripelennamine hydrochloride	2630, 2500(w)
Fluphenazine hydrochloride	2500, 2410(s)
Prothipendyl hydrochloride	2560, 2440(m)
Triflupromazine hydrochloride	2560, 2440(s)

The first one, occurring at 2860–2770 cm.$^{-1}$, is a strong absorption band present in all 15 of the amines. It is consistent and occurs within a narrow range. No exceptions to this band were noted here. The second band for NH_2^+ is in the range 2560–2380 cm.$^{-1}$. It is assigned to NH_2^+ stretching and undergoes splitting in some cases due to hydrogen bonding or the presence of water, but even in the case of splitting, there is one sharp band found at 2440 cm.$^{-1}$. The bands listed above have been found in all of the spectra analyzed. One of the spectra also shows a band in the region of 2090–2040 cm.$^{-1}$. This is a weak band, probably a combination band. It is also observable in Fig. 1, spectrum B. Its shape and intensity are not likely to be confused with a primary amine salt absorption

band, as may be seen in spectrum A of the same figure.

TERTIARY AMINE SALTS

The tertiary amine salts are by far the most common class of amines used pharmacologically. It has been possible to draw conclusions concerning correlations from many tertiary amine specta. Table III lists the amine salts used in this study along with their characteristic absorption bands. A tertiary amine salt has the simplest NH^+ absorption spectrum since it contains only one hydrogen. The distinguishing feature of NH^+ spectra is a broad and intense peak located in the range of 2770–2380 cm.$^{-1}$. The exact location of the absorption peak depends on whether the molecule contains water of hydration. Water of hydration affects the bonding between NH^+ and X^- so that the band shifts to higher frequency when hydrated. The band is assigned to an NH^+ stretching vibration. The range of this band may seem large, but the shape of the band and its intensity leave little doubt in assigning it to NH^+ in an unknown material. The peak is of such characteristic shape and intensity that it could not be confused with the primary or secondary amine salts. Figure 1 illustrates the shape and location of the various NH_3^+, NH_2^+, NH^+ absorption bands. Their unique characters can be seen at once.

It might be appropriate to mention at this point that, on the basis of this study, the authors agree with Nakanishi (7) that for identification purposes the solid state spectra are most reliable when reference spectra are available. The absorption bands of these amine salts would be greatly altered by solvent effects in solution spectra, so that those peaks that owe their unique shape and position to their degree of hydrogen bonding and crystal lattice would be changed beyond recognition. It is recommended that similar compounds be run in the solid state as Nujol mulls in preference to potassium bromide disks to avoid ion exchange with the potassium bromide matrix and to avoid alteration of the crystal lattice by pressure exerted during formation of the disk.

SUMMARY

The spectra of 80 pharmaceutical amines of varying structure and class have been analyzed. Spectra-structure correlations have been made on the absorption bands of NH_3^+, NH_2^+, and NH^+ groups which enable one to make a rapid identification of the class of amine present.

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Mannich Reaction at the 4-Methyl Group in Schistosomicidal Agents, Lucanthone and Oxalucanthone

By I. NABIH and M. ELSHEIKH

The schistosomicidal agents lucanthone (I) and oxalucanthone (II), when subjected to reaction with formaldehyde and diethylamine in the presence of concentrated hydrochloric acid, condensation took place to give 1-(2-diethylaminoethylamino)-4-diethylaminoethylthiaxanthone (III) and 1-(2-diethylaminoethylamino)-4-diethylaminoethyl-6-chloroxanthone (IV), respectively. Without the addition of acid, the reaction failed to occur.

THE BIOLOGICAL activity of the schistosomicidal (1) and antitumor agents (2) lucanthone, chemically 1-(2-diethylaminoethylamino)-4-methylthiaxanthone (I) and its analog, oxalucanthone or 1-(2-diethylaminoethylamino)-4-methyl-6-chloroxanthone, lies in the *p*-toluidine moiety common in both molecules which constitutes a methyl group at a *para* position to an amino side chain at the 1-position. Changes involving either or both groups will bring about a loss in chemotherapeutic activity (3).

These facts suggested the authors' studies of the chemical nature of the 4-methyl group.

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In a previous communication, the authors reported that the methyl group at the 4-position in both molecules of I and II can be chlorinated when treated with gaseous chlorine in the presence of an acid binding material to build up the monochlorinated derivatives (4).

In the present work, the behavior of this group toward reaction with formaldehyde and diethylamine known as Mannich reaction was investigated.

DISCUSSION

The Mannich reaction is a condensation between an amine (primary or secondary) or its salt with formaldehyde and a compound containing an active hydrogen which is replaced by a substituted aminomethyl group. The acidic component in the Man-