Table III summarizes the results of the study of the two test formulations in preventing nausea and vomiting in subjects receiving ipecac syrup. Because of the small number of subjects, it was necessary to pool the results in Groups II–IV for Treatment A or B. Pooling of the data was determined to be permissible since sequential testing revealed that no differences in response existed among Groups II–IV and, according to the binomial theorem of analysis, these groups were not significantly different. However, Group I was significantly different from each of the other groups and was not pooled with the three groups. The high dose of ipecac syrup in Group I caused severe GI irritation along with other marked side effects.

When the results of Groups II–IV were combined, 66.7% of the subjects failed to experience nausea following bismuth subsalicylate while only 7% were not nauseated by the ipecac syrup after the placebo administration. The act of vomiting in response to ipecac syrup was completely prevented in 80% of the subjects (Groups II–IV) treated with the bismuth subsalicylate formulation, and the placebo formulation afforded 20% protection. χ-Square statistical evaluation for the difference between patients receiving bismuth subsalicylate and those receiving the placebo formulation indicated that bismuth subsalicylate is significantly superior in its ability to control nausea and vomiting compared to the placebo formulation.

DISCUSSION

The mechanism of action of ipecac, or its principal alkaloid emetine, with respect to the induction of vomiting is poorly understood, although standard pharmacology texts generally agree that both a local and a central component are involved. In the present study, ipecac syrup was used to induce vomiting in dogs and nausea and vomiting in humans. After establishing the dose of ipecac syrup necessary to meet the criteria of a reliably effective, but not overwhelmingly drastic, emetic, it was found that bismuth subsalicylate formulation elicited a dose-related protective effect against ipecac syrup-induced emesis in the dog.

The laboratory evidence was corroborated by clinical evidence, in which it was revealed that the bismuth subsalicylate formulation was capable of arresting both nausea and vomiting in response to doses of ipecac syrup capable of inducing mild GI upset in humans. In the clinical study, it was necessary to adjust the dose of ipecac syrup to avoid the severe and harsh symptoms induced by the emetic. When utilizing the doses (5.0 and 7.5 ml) of ipecac syrup that appeared to mimic the symptoms of nonspecific GI upset and irritation in humans, the signs and symptoms of ipecac syrup ingestion were easily reproducible. Bismuth subsalicylate, unlike the placebo suspension, successfully controlled the nausea and vomiting in 66.7 and 80% of the subjects, respectively, in response to ipecac syrup.

Thus, both laboratory and clinical findings concur that bismuth subsalicylate provides antiemetic protection against the effects of ipecac syrup and that the decrease in the incidence of emesis in humans and dogs parallels the decreased incidence of nausea noted in humans and the nausea suspected to occur prior to vomiting in the dog.

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Solid-State Anomalies in IR Spectra of Compounds of Pharmaceutical Interest

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Abstract □ Solid-state anomalies in the IR spectra of lysine monohydrochloride, etoxadrol hydrochloride, thiamine hydrochloride, and L-histidine in a potassium bromide matrix were noted. With the first three compounds, the anomalies were due to metathetical exchange of the halide anion between the compound and the matrix. The anomaly seen with L-histidine was related to the crystal structure.

Keyphrases □ IR spectroscopy—solid-state anomalies, lysine monohydrochloride, etoxadrol hydrochloride, thiamine hydrochloride, and L-histidine □ Lysine monohydrochloride—IR spectra, solid-state anomalies □ Etoxadrol hydrochloride—IR spectra, solid-state anomalies □ Thiamine hydrochloride—IR spectra, solid-state anomalies □ L-Histidine—IR spectra, solid-state anomalies

It is well known that IR absorption spectra of solids depend on both structure and crystalline form. Variations between mull and pellet spectra are due either to an induced physical isomerization or to the samples having been rendered amorphous in the alkali halide pellet (1). In addition, the observed spectra from dif-

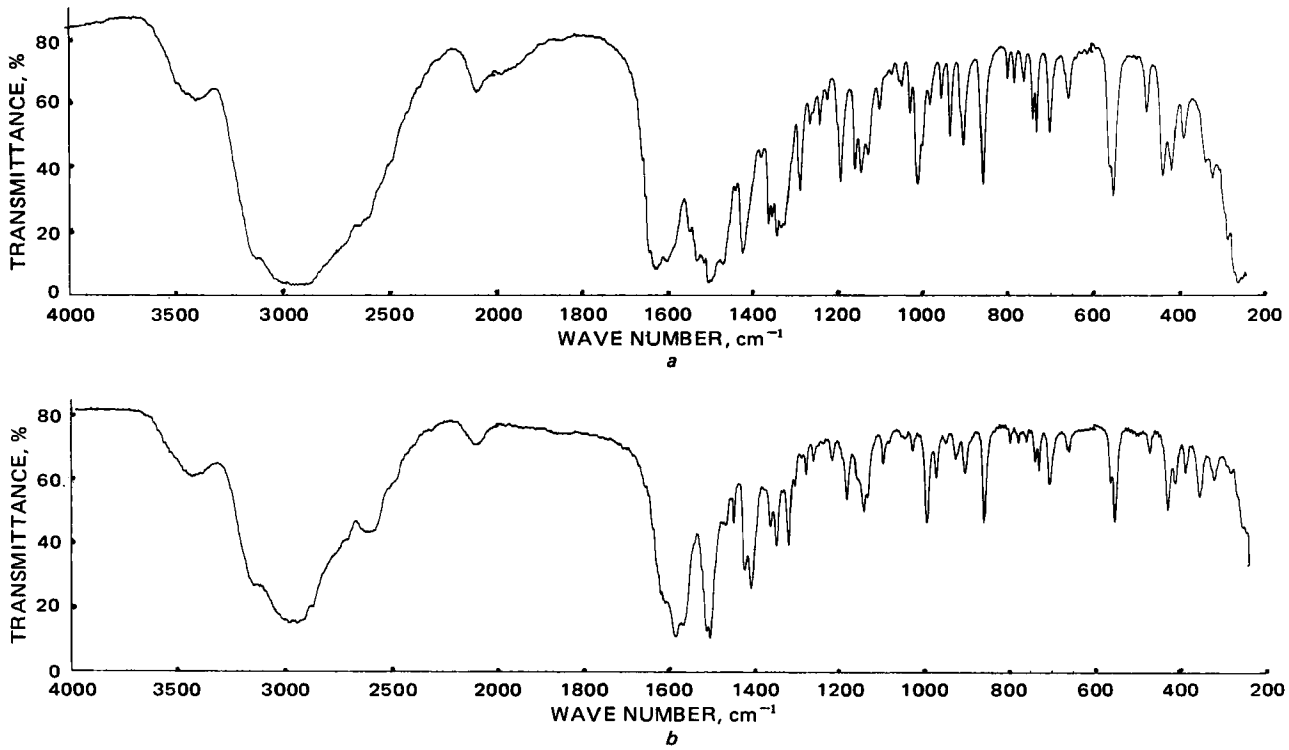

Figure 1—*IR spectra of:* (a) L-*lysine monohydrochloride in potassium chloride pellet (20,000 psi), and* (b) L-*lysine monohydrochloride in potassium bromide pellet (20,000 psi).

ferent dispersion media may not be identical because of anion exchange between the sample and the matrix. Several anomalies of these types have been noted in the IR spectra of compounds of pharmaceutical interest. This paper reports three cases demonstrating the importance of a matched matrix and one case where crystal structure is dependent on the solvent of crystallization.

EXPERIMENTAL

Materials—The following compounds were used: L-lysine monohydrochloride[1], etoxadrol hydrochloride[2] [(+)-2-(2-ethyl-2-phenyl-1,3-dioxolan-4-yl)piperidine hydrochloride] (I), etoxadrol hydrobromide[3] (II), thiamine hydrochloride[4], and L-histidine[5].

Equipment—All IR spectra were recorded on a grating spectrophotometer[6].

Procedures—Pellets of these compounds, using a potassium bromide or potassium chloride matrix, were prepared. Where necessary, spectra were obtained in mineral oil mulls between potassium bromide disks. Histidine was crystallized by the following procedures.

Water Recrystallization—One gram was dissolved in 5 ml of distilled water, heated on a steam bath until dissolved, and then cooled.

80% Ethanol Recrystallization—About 0.5 g was dissolved in 2 ml of hot distilled water, and 8 ml of absolute alcohol was added. Crystals were collected on filter paper[7] and dried overnight under vacuum at 60°

RESULTS AND DISCUSSION

L-Lysine Monohydrochloride, Etoxadrol Hydrochloride, and Thiamine Hydrochloride—Spectra of L-lysine monohydrochloride (Fig. 1*a*), I (Fig. 2*a*), and thiamine hydrochloride (Fig. 3*a*) were recorded in a potassium chloride pellet. Spectra of these compounds were also obtained in a mineral mull. No differences were noted in these two types of spectra in the window region of the mineral mull. However, when potassium bromide pellets of these compounds were prepared at 20,000 psi and spectra were recorded, significant changes were noted compared to the corresponding potassium chloride pellet spectra (Figs. 1*b*–3*b*). If the pressure used in the preparation of potassium bromide pellets was decreased to 10,000 psi, the spectra were identical to the corresponding spectra in the potassium chloride pellet.

These changes in the IR spectra were due to the exchange of halide anions between the compound and the potassium halide matrix. This result is best illustrated in the case of I. Spectra of I (Fig. 2*b*) and II (Fig. 2*c*) were obtained in the potassium bromide matrix. The pressure used in the preparation of the pellet in both cases was 20,000 psi. The spectra thus obtained were identical.

The spectrum of I obtained in the potassium chloride (Fig. 2*a*) matrix was dramatically different from the one obtained in potassium bromide (Fig. 2*b*). The potassium bromide pellets of I, prepared at 15,000 psi, contained all corresponding maxima for hydrochloride and hydrobromide salts, indicating an equilibrium situation. When the pressure was changed from 10,000 to 20,000 psi in preparing the potassium chloride pellets, no such changes were noted.

L-Histidine Base—The spectrum of L-histidine[8] was obtained in the potassium bromide pellet (Fig. 4*a*). This spectrum did not match with the in-house standard[9] spectrum (Fig. 4*b*). This lot passed all other tests, such as specific rotation, assay, nitrogen content, and TLC homogeneity, so the compound certainly was histidine. The difference seen could have been due to crystal structure.

Two common solvents used for the crystallization of amino acids are water and 80% ethanol. When L-histidine was recrystallized from 80% ethanol, it gave a spectrum identical to the in-house standard. Similarly, when the in-house reference standard was crystallized from water, it gave a spectrum identical to the L-histidine.

Conclusions—Both USP and NF recommend that the IR spectra of all hydrochlorides be obtained in potassium bromide pellets. Hayden *et al.* (2) recommended that the spectra of halide salts be obtained in the matched matrix. Three of the examples noted here

[1] Ajinomoto lot 19590 and USP reference standard.
[2] CL 1848C, Cutter Laboratories, Berkeley, Calif.
[3] Cutter Laboratories, Berkeley, Calif.
[4] Hoffmann–La Roche lot 030091 and USP reference standard.
[5] Ajinomoto lot 19060 and Calbiochem A grade lot 64418 used as the in-house standard.
[6] Perkin-Elmer model 457.
[7] Whatman No. 2.
[8] Ajinomoto lot 19060.
[9] Calbiochem A grade lot 64418.

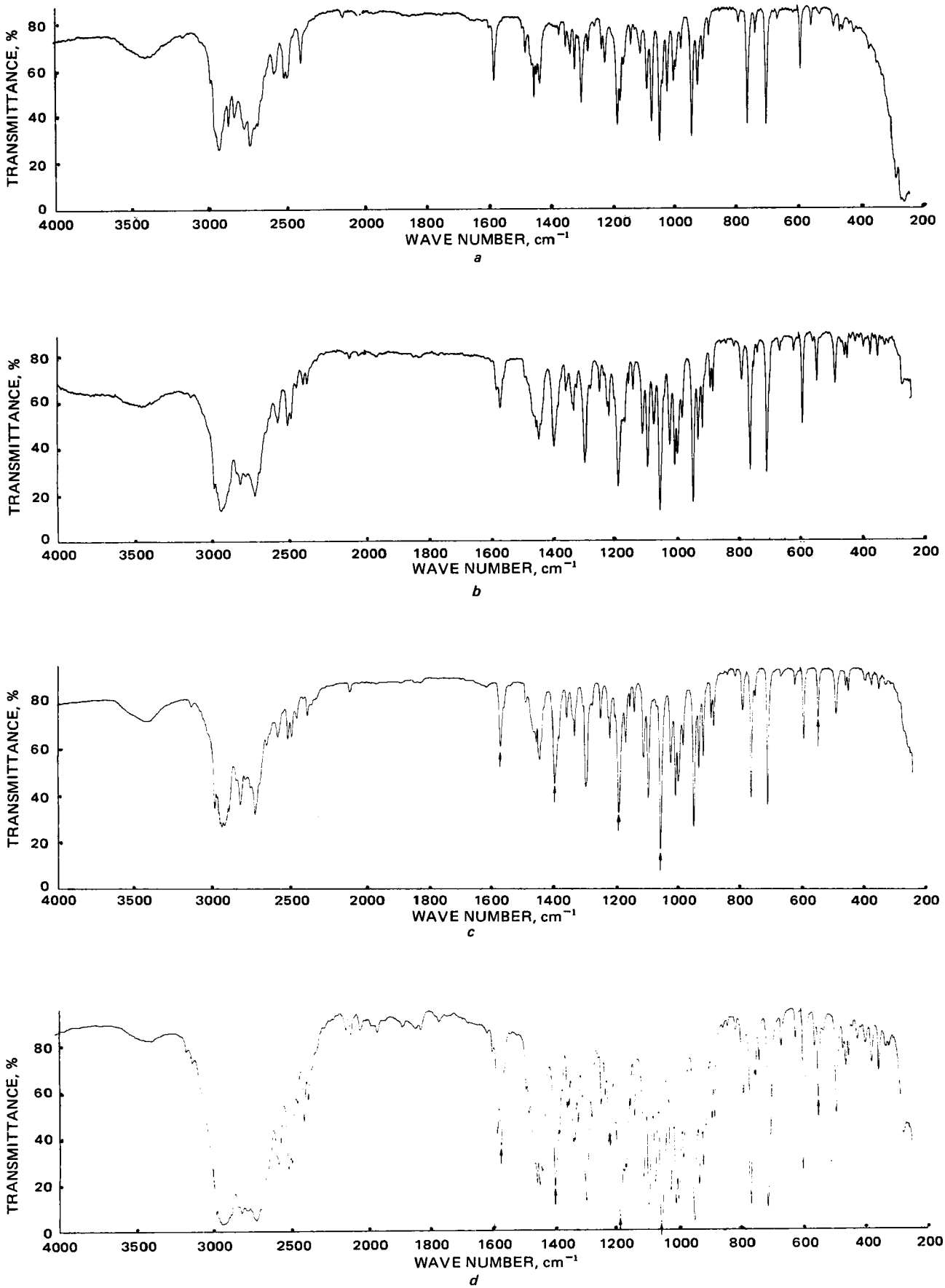

Figure 2—*IR spectra of:* (a) *I in potassium chloride pellet (20,000 psi),* (b) *I in potassium bromide pellet (20,000 psi),* (c) *II in potassium bromide pellet (20,000 psi), and* (d) *I in potassium bromide pellet (15,000 psi).*

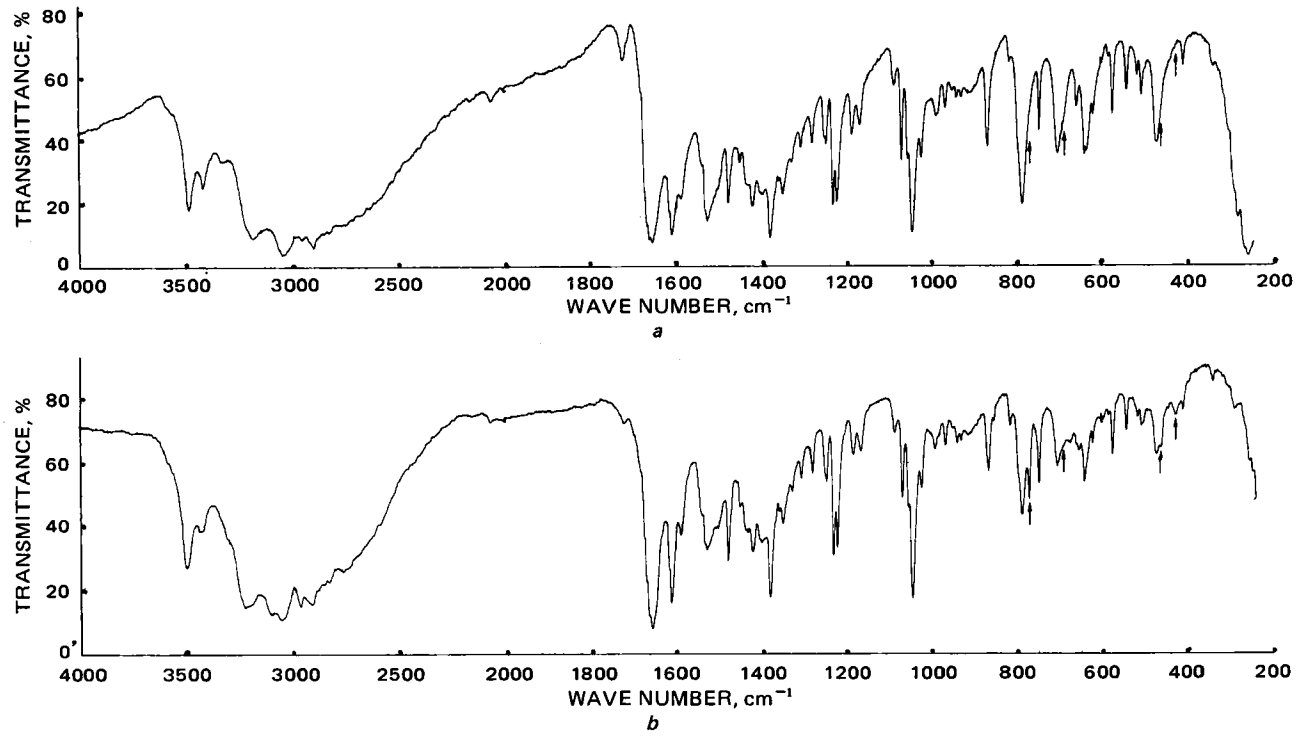

Figure 3—*IR spectra of:* (a) *thiamine hydrochloride in potassium chloride pellet (20,000 psi), and* (b) *thiamine hydrochloride in potassium bromide pellet (20,000 psi).*

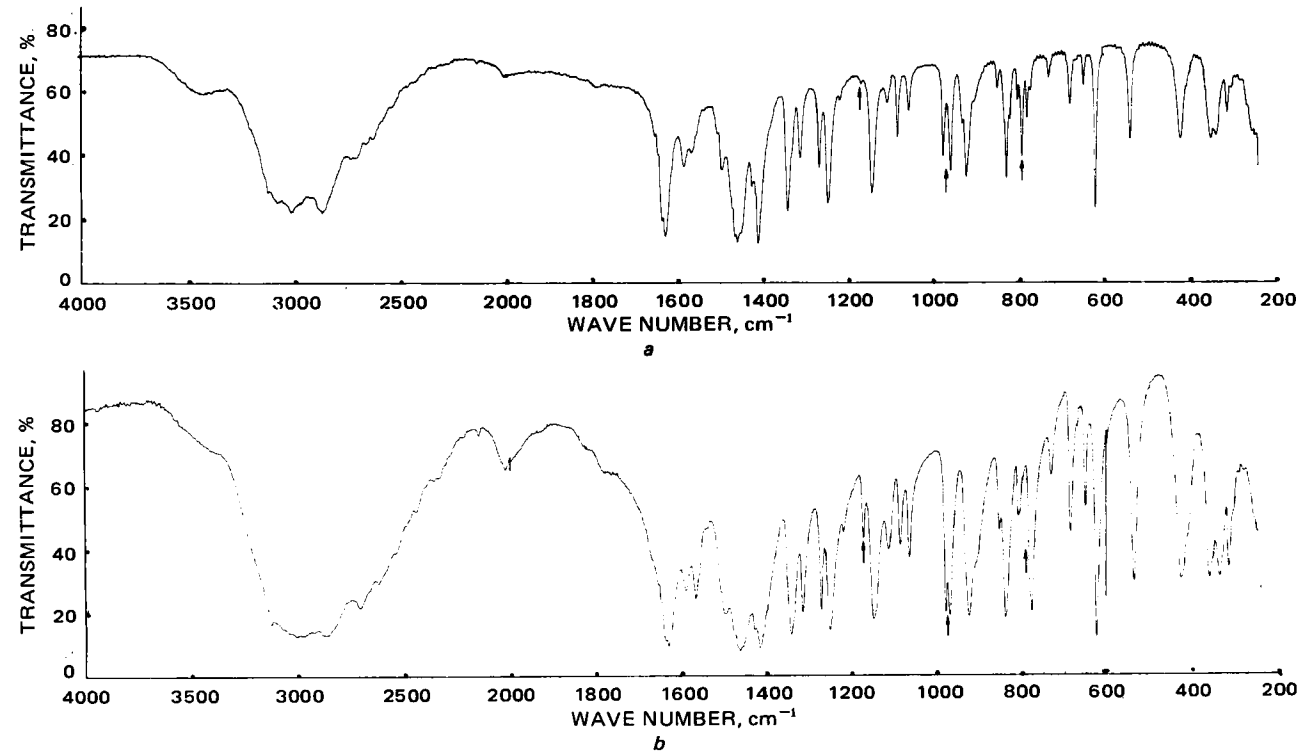

Figure 4—*IR spectra of:* (a) L-*histidine (Ajinomoto) in potassium bromide pellet (crystallized from water), and* (b) L-*histidine (Calbiochem) in potassium bromide pellet [crystallized from 80% (v/v) ethanol].*

also demonstrate that the spectra of halide salts be obtained in the corresponding potassium halide matrix.

IR spectra are dependent on the crystalline form; therefore, the solvent of recrystallization should be noted.

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