with the red cell membrane. The remaining 19% was associated with the red cell sap and represented ~51 μg of I.

It was reported that membrane-associated urushiol or I (red blood cell or lymphocyte membrane associated) will induce blastogenesis of peripheral blood lymphocytes *in vitro* (24). Urushiol was shown to be highly soluble in, but not covalently bound to, the cell membrane since the urushiol was not removed from the membrane with aqueous washes but was removable with dimethyl sulfoxide. Haptenated membranes were shown to induce contact sensitivity to picryl chloride *in vitro* when administered subcutaneously (25), while intravenous administration of the haptenated membranes induced specific immunological tolerance. Thus, the administration route of the membrane-associated hapten appears to be important in determining whether contact sensitivity or tolerance will result.

Since haptenated membranes can induce hapten-specific tolerance as well as contact sensitivity, it is unlikely that the haptenated membrane is the tolerogen and sensitizer. The membrane probably serves as a physiological vehicle that carries the lipophilic substance until the immune system intercepts the hapten. Whether contact sensitivity or tolerance results probably depends on the prevalence of the interceptor cell type (macrophage, Langerhans cell, T-lymphocyte, B-lymphocyte) that initially reacts with the hapten. The route of hapten administration likely would favor a higher incidence of interaction of the hapten with one of these cell types.

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Laser Raman Investigation of Pharmaceutical Solids: Griseofulvin and Its Solvates

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Received July 24, 1980, from the *Department of Chemistry, State University of New York at Buffalo, Buffalo, NY 14214.* Accepted for publication December 16, 1980.

Abstract □ Laser Raman spectroscopy is convenient for characterizing griseofulvin solvates and investigating solute–solvent interactions and desolvation. The spectra of both lattice and intramolecular vibrations were monitored. A new solvate of griseofulvin with bromoform was characterized by Raman spectroscopy. A temperature-dependence study of the solvates of griseofulvin with chloroform, bromoform, and benzene revealed no phase transformation or chemical change. In the benzene solvate, only weak Van der Waals interactions existed between the solute and solvent. However, in solvates with chloroform and bromoform, a weak hydrogen bonding existed between the proton of the solvent and the C=O group of the benzofuran ring in griseofulvin. Examination of desolvation in these solvates revealed that the crystal did not go through any intermediate structure during desolvation. As the solvent molecule escaped, the lattice reverted to the structure of unsolvated griseofulvin.

Keyphrases □ Griseofulvin—unsolvated and solvate forms, laser Raman spectroscopy, physicochemical stability, desolvation □ Spectroscopy, laser Raman—investigation of griseofulvin and its solvates, physicochemical stability, desolvation □ Pharmaceutical solids, polymorphic—griseofulvin and its solvates, investigation using laser Raman spectroscopy, physicochemical stability, desolvation □ Antifungal agents—griseofulvin and its solvates, investigation with laser Raman spectroscopy, physicochemical stability, desolvation

Many drugs in the solid state exhibit polymorphism, in which the same compound exists in several crystalline modifications at the same temperature (1, 2). Interest in polymorphism stems from the fact that different crystalline modifications of the same drug have different physical and, in some cases, chemical properties that may be a serious consideration in the manufacture of the dosage form (1, 2). For example, differences in the solubility of polymorphic forms can cause serious bioavailability problems.

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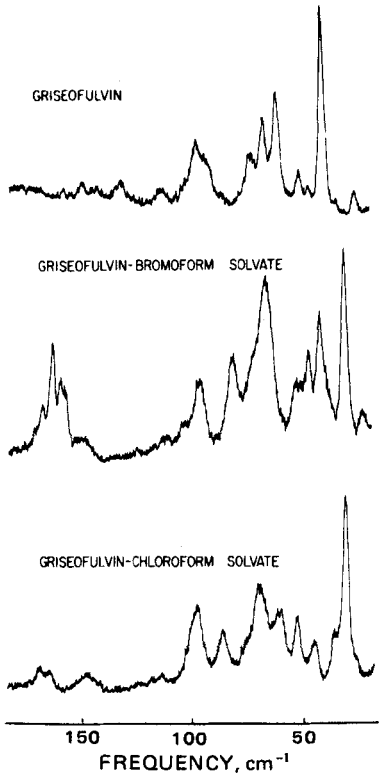

Figure 1—*Raman spectra of the lattice vibrations of the unsolvated griseofulvin and the griseofulvin solvates with chloroform and bromoform at 135°K.*

BACKGROUND

The present study examined polymorphism exhibited by griseofulvin, which is used in the treatment of fungus infection (3). This compound in the solid state exists in the unsolvated form, and its solvates with chloroform (4, 5) and benzene (6) have been studied by various techniques. Reducing the particle size of griseofulvin enhances its GI tract absorption (3, 4). Particle-size reduction can be obtained by desolvating the solvates of griseofulvin. Thus, study of the stability of the solvates, the solute–solvent interaction, and the desolvation process is of great importance.

Normally, the methods used to characterize polymorphs are X-ray diffraction, optical and electron microscopy, thermal methods (differential thermal analysis, differential scanning calorimetry, and thermal gravimetric analysis), and IR spectroscopy of the internal vibrations (1, 2). Recently, Raman spectroscopy of lattice vibrations was introduced to study the polymorphism of pharmaceutical solids (7). The lattice vibrations (also called phonons) correspond to librations and translations of the entire molecule in the lattice. These vibrations are of low frequency (10–150 cm^{-1}) and are easily observed in the Raman spectra. The lattice vibrations are characteristic of the crystal structure and interactions. Thus, the Raman spectra of the lattice vibrations can be used to characterize the solid states of a drug and to study the stabilities of various crystalline modifications (8–10).

The Raman spectra of intramolecular vibrations also can be obtained in the same experimental arrangement. Intramolecular vibrations can be used to study both the specific nature of the solute–solvent interaction and the chemical stability of the various forms. The present study was based on the principle that a physical transformation in the solid state shows a dominant effect on the phonon spectra but only a small effect on intramolecular vibrations. On the other hand, a chemical change leads to a large change in both the phonon spectra and the spectra of intramolecular vibrations.

Laser Raman spectroscopy was used for the following investigations on griseofulvin: (*a*) the characterization and identification of unsolvated griseofulvin and its various solvates, (*b*) the physical and chemical stability of these solvates with changes of external conditions such as temperature, (*c*) the effect of chemical perturbation (*e.g.*, change of a substituent group) on the crystal structure, (*d*) the nature of solute–solvent interactions in a solvate, and (*e*) the process of solvate desolvation.

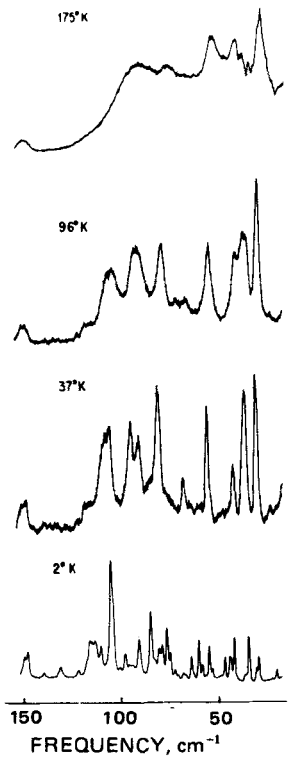

Figure 2—*Lattice vibration Raman spectra of the benzene solvate at several temperatures.*

EXPERIMENTAL

The griseofulvin[1] solvates were grown from benzene (protonated and deuterated), chloroform (protonated and deuterated), and bromoform[2]. The chloroform and bromoform solvates were readily formed by slow solvent evaporation and were air stable for days. To obtain the benzene solvates, between 0.06 and 0.08 g of griseofulvin was added to 5 ml (±5%) of benzene. While the 5-ml volume was maintained, the solution was heated to boiling (~75°). When all of the griseofulvin was dissolved, the solution was transferred to a warmed beaker and checked for any visible matter. This hot solution was cooled rapidly in an ice bath to 10–15°. When this temperature was maintained for 24 hr, only the benzene solvate of griseofulvin was formed. This solvate was stable in air for only a few hours.

Raman spectra were obtained using a double monochromator[3] and the 5145-Å line of a coherent radiation argon-ion laser. Most samples were studied below room temperature because of the improved spectral resolution. Spectra were taken with the sample in liquid nitrogen or by cooling the sample with a flow of nitrogen vapor that provided an effective bath of ~125°K or higher. To obtain spectra below the liquid nitrogen temperature, crystals were cooled in a cryostat[4] using a flow of helium vapor. The spectra of the benzene solvates were taken at 2°K. To obtain this temperature, a vacuum was pulled on liquid helium, forming a superfluid state. The temperature was measured with a chromel-constantan thermocouple referenced at an ice bath. Direct-current detection was used. The band positions were measured relative to the laser line and were accurate to ±1.0 cm^{-1}.

RESULTS AND DISCUSSION

The following discussion emphasizes the aspects rather than the specific system investigated.

Characterization of Various Solvates—Raman spectra of the phonon region provide unambiguous characterization of the various crystalline modifications of a given substance. For this purpose, the observed phonon spectral patterns were used. The spectral pattern is defined by the number of peaks observed and their frequencies and relative intensities. Although relative intensities may show some variations de-

[1] McNeil Laboratories.
[2] Aldrich Chemical Co.
[3] Spex model 14018.
[4] 10 DT Janis Research Supervaritemp.

pendent on crystal orientation, use of a polycrystalline or powdered sample helps minimize this problem and provides reproducible spectral patterns that can identify and distinguish between various polymorphs. On the other hand, the internal vibration region (which also can be investigated using IR techniques) generally shows only small shifts in frequencies and only in selected regions.

The results of phonon spectral studies to characterize griseofulvin and its chloroform and benzene solvates were reported previously (7); the present study investigated other solvates. Griseofulvin also was reported to form a solvate with dioxane (6); however, the phonon spectra obtained on crystals grown from dioxane solution were identical to those of unsolvated griseofulvin. Thus, no evidence of solvate formation with dioxane was found.

An attempt was made to form a solvate with bromoform. As shown in Fig. 1, the Raman phonon spectra of the samples obtained from chloroform and bromoform solutions clearly are different from those of the unsolvated griseofulvin. Again, the low temperature (135°K) spectra provided improved resolution of peaks (Fig. 1) and assisted in the comparison. Thus, the crystalline modification obtained from bromoform was different from that of the unsolvated griseofulvin. The presence of the solvent (bromoform) internal vibration in the internal vibration region also confirmed the formation of a solvate between bromoform and griseofulvin. This solvate was never reported previously.

Temperature Study of Crystalline Forms—The phonon spectra of griseofulvin and its solvates were studied from room temperature down to liquid helium temperature (2°K). As the temperature was lowered, more structures became resolved due to the reduced linewidth of the peaks, and the phonon frequencies shifted to higher values. Figure 2 shows the spectra at several temperatures for the benzene solvate in the 10–150-cm^{-1} spectral region. In this region the benzene solvate showed nine resolved peaks at 96°K and 33 resolved peaks at 2°K. On the other hand, 12 peaks were observed for the chloroform solvates at 136°K, but only 31 peaks were observed for the same solvate at liquid helium temperature.

Except for the increased number of peaks due to improved resolution, the number of spectral features of each crystalline form remained the same as the temperature was varied; *i.e.*, there was no spectra discontinuity. This result clearly indicates absence of any structural phase transitions or any chemical change for either griseofulvin or any of the solvates studied. A phase transition or a chemical change will clearly reveal itself by a change in the spectral pattern of the phonon region (9, 10).

The reduction in linewidths of the peaks and the shift of frequencies with temperature are general phenomena that arise primarily from the anharmonicity of the lattice (11, 12). The temperature dependence of the phonon frequencies is derived mainly from thermal expansion of the lattice which, in turn, is a consequence of lattice anharmonicity (11). The observed effect clearly indicates a considerable degree of lattice anharmonicity for these crystals. The linewidths of the peaks reflect the contribution from disorders in the lattice as well as from anharmonic phonon–phonon interactions (12). The line broadening derived from disorder can be assumed to be temperature independent, but the broadening due to anharmonic phonon–phonon interactions is highly temperature dependent. Thus, a temperature-dependence study of the linewidth can be used to investigate the presence of disorder in the lattice (12). For griseofulvin and its solvates, the linewidths were highly dependent on temperature. At 2°K, the lines were narrow, indicating highly-ordered lattices.

Chemical Perturbation of Crystal Structure—It often becomes necessary to improve a drug by changing a substituent group in the molecular structure. However, since bioavailability is dependent on the crystal structure of the compound, it is helpful to know how the parent compound's crystal structure is affected by chemical substitution. A previous investigation on organic solids suggested that Raman spectroscopy can provide useful information in this area (13, 14). If a small chemical perturbation (changing only a small substituent group in the parent structure) yields a crystal structure that is identical (in space group) to the parent crystal structure, the phonon spectral pattern bears a close correspondence with that of the parent material.

For griseofulvin, this criterion was used to obtain information regarding the crystal structure of the new bromoform solvate. The bromoform solvate can be visualized as being derived from the chloroform solvate by chemical substitution of the chloroform. The phonon spectra of these two solvates at 135°K are compared in Fig. 1. Except for the shifts in phonon frequencies, there appeared to be close correspondence between the phonon peaks in the spectra of the two solvates, suggesting that they have the same crystal structures. The phonon frequencies in the bromoform solvate were lower than those for the chloroform solvate. This shift to lower frequencies was perhaps a result of a larger unit cell required by a larger solvent molecule (bromoform compared to chloroform).

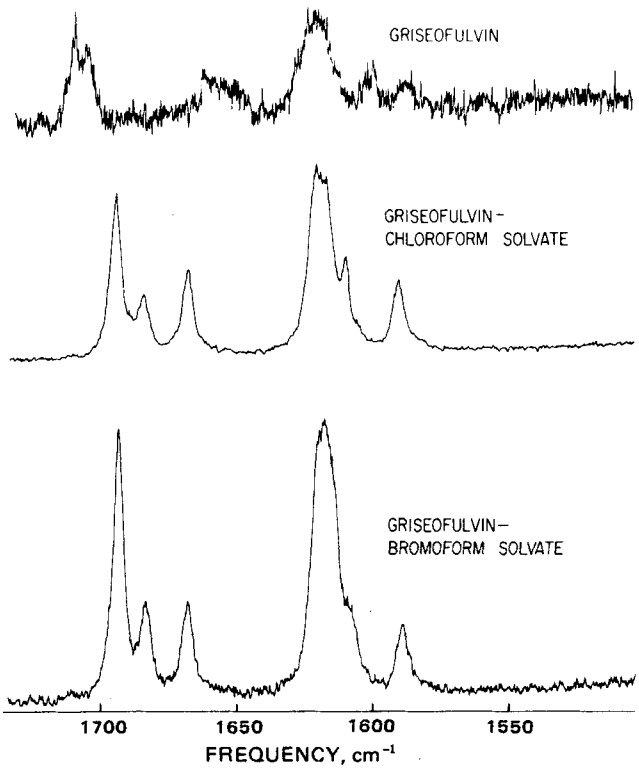

Figure 3—*Raman spectra of the chloroform and bromoform solvates obtained for the 1550–1800-cm^{-1} spectral region.*

Solute–Solvent Interactions—To investigate the interaction between the griseofulvin molecule and the solvents involved in solvate formation, a comparative study of the internal vibrational frequencies of various functional groups of the drug and the solvent molecule was needed in the solvate as well as in the pure states.

The internal vibrational spectra of the benzene solvate appeared to be essentially a superposition of the spectra of pure griseofulvin and benzene. The frequency shifts of the vibrations of both components were <3 cm^{-1}. The solvate spectra contained no additional bands other than those observed for the pure components. Since these shifts were small, the interaction between griseofulvin and benzene was weak and of a Van der Waals type. A manifestation of this weak interaction was the loss of benzene when the griseofulvin–benzene solvate was exposed to the atmosphere. After 24 hr, an unsealed sample exhibited a spectrum identical to that of the unsolvated griseofulvin.

In the 200–1550-cm^{-1} region, the chloroform and bromoform solvates exhibited a behavior similar to that of the benzene solvate. The spectra were essentially a superposition of those of the pure components. Two spectral regions showed changes: 1550–1800 and 2800–3200 cm^{-1}. Figure 3 shows that the 1703.5- and 1708.5-cm^{-1} bands of pure griseofulvin shifted to 1684.0 and 1694.5 cm^{-1} in the chloroform solvate. A similar observation was noted for the bromoform solvate where a slightly larger shift occurred. These vibrational frequencies correspond to the C=O stretching modes of the benzofuran ring of griseofulvin.

Table I shows the analysis of the C–H stretching region (2800–3200 cm^{-1}) of the bromoform solvate and the chloroform (deuterated and protonated) solvates. Except for the transitions at 2998 cm^{-1}, there was a 1:1 correlation between the three solvates. The pure chloroform-*h* solvent transition at 3011.0 cm^{-1} shifted by 13 cm^{-1} to 2998.0 cm^{-1} in the solvate. Pure bromoform solvent transition at 3023.0 cm^{-1} shifted by 24 cm^{-1} to 2999.5 cm^{-1}. In both cases, there was a shift of the C–H stretching mode of the solvent in the solvate.

These results indicate a specific interaction between the C–H group of the solvents and the C=O group of griseofulvin and, possibly, a weak hydrogen bonding between H– –O. This result is consistent with the X-ray diffraction work of Cheng and Shefter (15) who also found a short H– –O distance.

This additional interaction tends to make these solvates more stable than the benzene solvate. When exposed to air for several days, the

Table I—Analysis of the C–H Stretching Region (2800–3200 cm^{-1}) of the Bromoform Solvate and Chloroform (Deuterated and Protonated) Solvates [a]

Griseofulvin–Chloroform-*d*		Griseofulvin–Chloroform-*h*		Griseofulvin–Bromoform	
Frequency	Intensity	Frequency	Intensity	Frequency	Intensity
2899.5	m	2899.5	m	2894.0	w
2912.5	vw	2914.0	vw	2911.5	w
2940.5	w-Br	2941.5	w	2938.5	w-Br
2949.0	w	2950.0	w	2944.5	vw
2960.0	w	2959.0	w	2955.5	w-Br
2973.0	w	2974.0	w	2970.5	vw
2987.5	m	2988.0	m	2986.5	w-Br
		2998.0	vw	2999.5	w
3012.0	w-m	3012.5	w-m	3010.0	w
3025.5	w	3025.5	s	3025.5	s
3033.0	w	3033.5	w-m		
3074.0	w	3075.0	w-Br	3076.5	vw-Br

[a] The following abbreviations are used: s = strong, m = medium, w = weak, vw = very weak, and Br = broad.

griseofulvin–chloroform or bromoform solvate showed no degradation.

Desolvation—As a crystalline solvate undergoes desolvation, the solvent molecule makes an exit due to an external perturbation (*e.g.*, rise in temperature) and the lattice can suffer several consequences. Three possibilities define the modes of desolvation:

1. The lattice still exists in the same crystalline form even in the absence of the solvent molecule.
2. Desolvation produces an intermediate structure, which eventually reverts to that of the unsolvated griseofulvin.
3. As the solvent molecule escapes, the lattice immediately (or in an extremely short period) reverts to the structure of the unsolvated griseofulvin.

Phonon spectra were used to investigate desolvation in the chloroform and benzene solvates. A crystal of the stable, deuterated chloroform solvate was washed with ethanol, air dried, and ground to a powder. A small sample of this crystal was heated uniformly with a flow of warm nitrogen vapor at 60°. After each 15-min interval, the sample was removed and cooled to 135°K, and a spectrum of the phonon region was obtained. After 1 hr, the phonon spectra (Fig. 4) appeared to be the superimposed spectra of the chloroform solvate and unsolvated griseofulvin. Additional solvate heating showed that only unsolvated griseofulvin was present. As the solvent diffused out, the solvate lattice collapsed. Since the crystal structure returned to that of unsolvated griseofulvin, the structures of these solvates were not stable without the solvent.

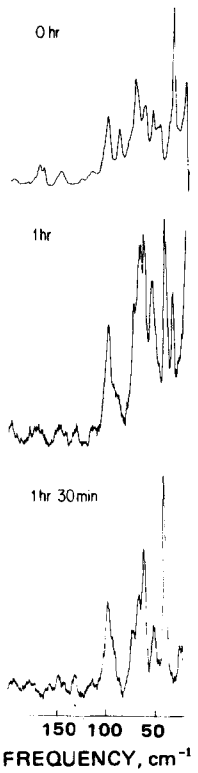

Figure 4—*Raman spectra of the lattice vibrations of the deuterated chloroform solvate obtained as a function of the desolvation process.*

Sekiguchi *et al.* (6) studied the desolvation mechanism of the benzene solvate by periodically measuring X-ray powder diffraction patterns. They observed a peak that was not present in the benzene solvate spectrum or in the pure griseofulvin spectrum and concluded that an intermediate structure was formed during desolvation. The benzene solvate desolvation was monitored by placing a single crystal in a focused laser beam, which allowed the monitoring of the phase boundary by periodically obtaining the phonon spectra. As Fig. 4 shows, the desolvation exhibited the appearance of an unsolvated griseofulvin peak (59 cm^{-1}), which grew in intensity upon further desolvation. No new peak was observed during desolvation. While the data show no intermediate structure, additional work with single-crystal X-ray crystallography may be necessary to establish unequivocally the presence or absence of an intermediate structure during desolvation.

Laser Raman spectroscopy has a number of advantages and disadvantages. It is convenient and versatile for investigating pharmaceutical solids, and spectra of both lattice vibrations and intramolecular vibrations in the same arrangement can be obtained. The spectra of lattice vibrations provide valuable information on crystalline interactions and can be used to characterize crystalline modifications, the effect of various perturbations on crystal structures, and the desolvation process. The study of intramolecular vibrations is used to study both the specific nature of the solute–solvent interaction and the chemical stability of the various forms.

From an experimental point of view, Raman spectroscopy offers several advantages over other techniques used to study drugs:

1. No special sample preparation is required, so the grinding required for X-ray powder diffraction or the pressing for IR absorption is eliminated.
2. Because the incident laser radiation can be focused into a very small spot, extremely small amounts of material can be used.
3. Raman spectra of lattice vibrations can be obtained easily in a short time.
4. The internal vibration region is examined easily in the same experiment.
5. The temperature of the sample can be controlled accurately during the experiment, allowing thermal studies of the various forms.
6. The use of a coherent, tunable, and monochromatic dye laser permits tuning of the exciting radiation to some electronic transitions. This resonance Raman technique permits work with very low laser light levels and highly colored materials.

On the other hand, Raman spectroscopy has some disadvantages. The Raman effect is highly inefficient and, thus, is more suitable for the study of concentrated species than for a small amount of impurity. In general, only relative intensities of various Raman peaks are measured, and even then the relative intensities do not easily provide quantitative information on the concentrations of various species. Moreover, with colored samples, the excitation wavelength of the laser and the power levels must be chosen carefully so that the sample does not undergo thermal or photochemical decomposition.

In view of these limitations, Raman spectroscopy cannot be used as a substitute for all other techniques. However, when used with discretion, it can be a powerful technique for the investigation of pharmaceutical solids.

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High-Performance Liquid Chromatographic Analysis of Clorazepate Dipotassium and Monopotassium in Solid Dosage Forms

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Received October 14, 1980, from the *Analytical Research Department, Abbott Laboratories, North Chicago, IL 60064.* Accepted for publication December 16, 1980.

Abstract □ Methodology for the quantitative determination of clorazepate dipotassium and monopotassium in solid dosage forms was developed. Clorazepate was resolved from its degradation products, making the analysis specific and stability indicating. Analytical separation was performed on a octadecylsilylated silica column. Clorazepate was extracted from the dosage forms with 0.04% NaOH and chromatographed with aqueous 0.005 *M* tetra-*n*-butylammonium ion (pH 7.5)–acetonitrile (70:30) as the eluent. The analysis was completed in ~20 min with a precision of <2.4% *RSD*.

Keyphrases □ High-performance liquid chromatography—analysis of clorazepate dipotassium and monopotassium in solid dosage forms □ Clorazepate, dipotassium and monopotassium—high-performance liquid chromatographic analysis, solid dosage forms □ Tranquilizers—clorazepate dipotassium and monopotassium, high-performance liquid chromatographic analysis, solid dosage forms

In the past, clorazepate (I) primarily was determined chromatographically as its primary degradation product and major metabolite nordiazepam (II). Clorazepate decarboxylates to give nordiazepam; in aqueous systems (pH 2–11), the transformation is unimolecular with respect to clorazepate. Nordiazepam can undergo further metabolic transformations to oxazepam and the glucuronide in urine (1).

GLC has been used extensively (2–6) for the analysis of clorazepate as nordiazepam in biological fluids. Similarly, nordiazepam has been determined in plasma and urine by high-performance liquid chromatography (HPLC) in both reversed-phase (7–11) and normal-phase (12, 13) chromatographic modes.

Recently, a reversed-phase HPLC system for the qualitative identification of clorazepate in oral dosage forms was reported (14). With aqueous phosphate buffer (pH 8) and methanol (1:2 and 3:4) as the eluent, clorazepate was chromatographed intact on an octadecylsilylated column both with and without tetra-*n*-butylammonium ion (0.005 *M*) as an ion-pairing counterion. This paper reports the quantitation of clorazepate in its dosage forms by a similar procedure used in these laboratories for several years. The procedure has been applied to eight formulations of clorazepate (monopotassium and dipotassium), both capsules and tablets, and is specific and stability indicating.

EXPERIMENTAL

Reagents and Chemicals—Acetonitrile[1], tetra-*n*-butylammonium hydroxide[2], phosphoric acid[3], and sodium hydroxide[4] were used as received. 2,6-Dimethylaniline[5] was converted to the hydrochloride by acidification of a hexane[4] solution of the amine (10% v/v) with concentrated hydrochloric acid[6]. The precipitated amine salt was filtered, washed with hexane, and dried for use as the internal standard. Distilled water was used for all aqueous reagent and mobile phase preparations.

Apparatus—The liquid chromatograph consisted of a pump[7], a loop-type injector[8], a variable-wavelength UV detector[9], and a recorder/data handling system[10] for quantitative work. The 30-cm × 4-mm i.d. column contained an octadecylsilylated silica material[11].

Mobile Phase—A 0.005 *M* aqueous solution of tetra-*n*-butylammonium ion was prepared from 5.0 ml of tetra-*n*-butylammonium hydroxide in 1 liter of water, and the pH was adjusted[12] to 7.5 with phosphoric acid. The mobile phase was prepared by diluting 300 ml of acetonitrile to 1 liter with 0.005 *M* tetra-*n*-butylammonium-ion solution. The eluent was filtered[13] through a 0.45-μm membrane filter[14], stirred magnetically, and degassed under vacuum.

Chromatographic Conditions—The temperature was ambient, and the flow rate was ~1.8 ml/min. The detector sensitivity was set at 0.2 au (230 nm). The injector loop size was 20 μl, and the chart speed was 0.2 cm/min.

Sample Solvent—Sodium hydroxide (0.04% w/v) was filtered[13] through a 0.45-μm membrane filter[14].

Internal Standard—2,6-Dimethylaniline hydrochloride (30 mg) was dissolved in, and diluted to 100.0 ml with, the sample solvent.

Reference Standard—A solution containing 50–60 μg of clorazepate reference standard[15]/ml was prepared by dissolving it in, and diluting appropriately with, the sample solvent. An ultrasonic water bath[16] was employed to aid dissolution. A 5.0-ml portion of this solution and 2.0 ml of the internal standard solution were diluted to 10.0 ml with the sample

[1] Distilled-in-glass, Burdick & Jackson Laboratories, Muskegon, Mich.
[2] Titration grade, 1.0 *M* in methanol, Southwestern Analytical Chemicals, Austin, Tex.
[3] Reagent grade (85%), J. T. Baker Chemical Co., Phillipsburg, N.J.
[4] AR grade, Mallinckrodt, Paris, Ky.
[5] Eastman Organic Chemicals, Rochester, N.Y.
[6] Baker analyzed, J. T. Baker Chemical Co., Phillipsburg, N.J.
[7] Model M6000A, Waters Associates, Milford, Mass.
[8] Model 7120, Rheodyne, Berkeley, Calif.
[9] Model 450, Waters Associates, Milford, Mass.
[10] Model 3385A, Hewlett-Packard Corp., Rolling Meadows, Ill.
[11] μBondapak C_{18}, Waters Associates, Milford, Mass.
[12] Model 10 pH meter, Corning Scientific, Medfield, Mass.
[13] Millipore Corp., Bedford, Mass.
[14] Flotronics Division, Selas Corp., Huntingdon Valley, Pa.
[15] Clorazepate dipotassium (lot 72-307-CA) or clorazepate monopotassium (lot 64-922-AL), House Reference Standards, Abbott Laboratories, North Chicago, Ill.
[16] Bransonic 32, Branson Cleaning Equipment Co., Shelton, Conn.

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