Association of
Official
Analytical
Chemists

INFRARED AND ULTRAVIOLET SPECTRA OF SOME COMPOUNDS OF PHARMACEUTICAL INTEREST

(Revised Edition)

FOREWORD

This volume of spectra of pharmaceutical compounds supersedes the three separate publications previously distributed singly and as a set, under the various titles "Infrared, Ultraviolet, and Visible Absorption Spectra of Some USP and NF Reference Standards and Their Derivatives" and "Infrared Spectra of Some Compounds of Pharmaceutical Interest, Part I and Part II." These three monographs have now been combined under a single cover with a unified index and with several corrections. To them have been added several related publications, published in the Journal of the Association of Official Analytical Chemists but not previously available as monographs, namely, "Infrared and Ultraviolet Spectra of Some Pharmaceutical Compounds," "Infrared Spectra of Some Antibiotics of Interest," and "An Index of Electronic Spectra." The last title in the series refers the reader to a number of infrared, ultraviolet, and visible spectra of pharmaceuticals published in various books and journals or in collections of the Food and Drug Administration.

Contributors to this volume include T. G. Alexander, Carolyn N. Andres, W. L. Brannon, J. Carol, F. R. Fazzari, Alma L. Hayden, T. Kram, A. Major, Jr., O. R. Sammul, G. B. Selzer, Margaret F. Sharkey, Susan W. Snow, V. Warner, Lola Wayland, P. J. Weiss, and Charlotte A. Yaciw.

Altogether, 817 infrared spectra are presented, plus a smaller number of ultraviolet and visible spectra. A few of the spectra have been found to be duplicates, namely, sitosterols (Nos. 171 and 490), *beta*-sitosterol (Nos. 491 and 492), and hydrochlorothiazide (No. 646) and dihydrochlorothiazide (No. 309), which are actually the same compound. Other cases which appear to be duplications represent the same compound run under different conditions.

It should be noted that doxylamine succinate (No. 41) is the hydrate. Moreover, several names appeared incorrectly on the spectra and could not be corrected because of mechanical difficulties; the names appear correctly in the index.

Helen L. Reynolds

Infrared and Ultraviolet Spectra of Some Compounds of Pharmaceutical Interest

PART I

Infrared, Ultraviolet, and Visible Absorption Spectra of Some USP and NF Reference Standards and Their Derivatives*

By ALMA L. HAYDEN, OSCAR R. SAMMUL, GEORGE B. SELZER, and JONAS CAROL (Food and Drug Administration, Washington 25, D.C.)

Over two hundred Reference Standards are available at present from the United States Pharmacopeia and the National Formulary. These substances, of established purity, include many of the important pharmaceuticals which are in general commercial use. A compilation of the infrared, ultraviolet, and visible absorption spectra of these compounds should be of value for ready identification. However, this collection of absorption spectra should *not* replace the use of standards in quantitative analyses. Analyses should be made by comparing the absorption of samples and standards under the same experimental conditions.

The absorption spectra of 175 Reference Standard compounds, which are presented in this publication, were obtained under uniform and carefully controlled conditions to facilitate their reproduction in other laboratories. The remaining Reference Standards, which are mixtures or materials of unknown molecular structure, were not included in this study. Diethyltoluamide and Phytonadione are liquids, and they were studied in carbon disulfide and in tetrachloroethylene solutions. As most of the solid standards were poorly soluble in carbon disulfide or carbon tetrachloride, their infrared absorption was recorded from potassium halide disks. In addition, spectra were obtained of organic nitrogenous bases which were derived from some of the Reference Standard salts. These compounds were examined in carbon disulfide and in tetrachloroethylene solutions, as films between sodium chloride plates, or in potassium bromide disks.

The experience of many workers has shown that infrared absorption spectra of solids depend on both structure and crystalline form (1). The crystalline form may depend on the solvent, temperature, and rate of crystallization. In addition, the observed spectra from different dispersion media may not be identical. The conditions of recrystallization and the crystalline forms of the Reference Standards were not known. Therefore, when possible, the authors crystallized the solids from solutions of known concentrations before the disks were prepared. To avoid anion exchange between the Reference Standard and the matrix, halide salts were dispersed in the corresponding potassium halide. The acid sulfate salts[1] and all other standards were dispersed in potassium bromide.

Ultraviolet and visible absorption spectra are useful supplements to infrared data in identifying compounds. For this reason, the spectra of the Reference Standards which absorb in the ultraviolet and visible regions are included in this report.

Experimental

The infrared spectra were measured between 2 and 15μ on a Perkin-Elmer Model 21 double-beam spectrophotometer which had a linear wavelength scale. The instrument was equipped with a sodium chloride prism and a disk holder which fitted the micro-cell adapter. Qualitative instrument settings of resolution 927, gain 5.5, response 1, suppression 0, and pen speed of 3 seconds

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Presented as the report of the Associate Referee on Infrared Spectrophotometric Methods for Drugs, Jonas Carol, at the Seventy-fifth Annual Meeting of the Association of Official Agricultural Chemists, Oct. 30–Nov. 1, 1961, at Washington, D.C.

[1] In earlier work, the authors found that metathetical reactions with organic sulfates occurred less readily with potassium bromide than with the other potassium halides.

for full scale deflection were used. The original curves were recorded on a per cent transmission scale which was 20 cm in length, and a wavelength scale of 5 cm per μ. For publication, the data were recorded at a speed of about 2 minutes per μ, on reduced scales of 10 cm and 2 cm per μ. Wavelength measurements were accurate to within $\pm$ 0.02μ as determined with a polystyrene film.

Diethyltoluamide and Phytonadione were studied in carbon disulfide and in tetrachloroethylene solutions in 1 mm sodium chloride cells. The concentration of each solution was 10 mg per ml. A matched cell which contained the appropriate solvent was placed in the reference beam to compensate for solvent absorption. Composite spectra were obtained by recording the carbon disulfide solutions between 2 and about 5.5μ and between 7.2 and 15μ. The tetrachloroethylene solutions were recorded over the range of about 5.5 to 7.2μ. The exact regions over which these solutions were scanned are indicated on the spectra.

When possible, the solid standards were crystallized under controlled conditions to obtain reproducible crystalline forms. The standards, as received, were not dried before use, unless so directed in the official monographs or as noted in the legends to the spectra. In general, the compounds were weighed on a Cahn microbalance and were dissolved in selected solvents at concentrations of about 1 mg per ml. Aliquots of 1 ml each of the solutions were evaporated to dryness at 25–30°C under a stream of nitrogen. The crystalline residues were dried in vacuum at room temperature for 30 minutes unless otherwise directed in the official monographs or in the following procedures.

Many of the standards crystallized from solutions in absolute ethyl alcohol (A) at concentrations of 1 mg per ml under the conditions described. However, when a glassy or amorphous residue was deposited from solvent A, one of the following solvent systems was substituted: (B) absolute ethyl alcohol-heptane (1:3), (C) chloroform, (D) chloroform-heptane (1:3), (E) alcohol-chloroform-heptane (1:1:3), (F) diethyl ether, or (G) acetone. Solutions B and D were obtained by diluting 1 ml of the alcohol or chloroform solution with 3 ml of *n*-heptane. Solution E was obtained by diluting 1 ml of solution A of the standard with 1 ml of chloroform and 3 ml of *n*-heptane. In each case, the total solution was evaporated as described above. The evaporations required between 2 and 10 minutes per ml and varied with the solvents. For most of the compounds, these systems produced crystalline residues.

Because of solubility limitations, some of the amino acids and related compounds were crystallized from (H) 90% ethyl alcohol (L-Tyrosine from 70% alcohol). One mg of the solid was dissolved in 0.5 ml of water, and 4.5 ml of absolute ethyl alcohol was added. (L-Tyrosine was dissolved in 3 ml of water and 7 ml of absolute ethyl alcohol was added.) The solvents were evaporated as described above. The crystalline residues were dried at 105°C for 30 minutes.

The Reference Standards that were insoluble or unstable in the above solvents, or were not crystallized by the above methods, were studied in the crystalline forms as received (I).

For most of the compounds, about 1 mg of the crystalline material was hand-ground for 1 minute under moderate force together with 200 mg of potassium bromide (Harshaw infrared quality, 200/325 mesh), potassium chloride (reagent grade, 20/140 mesh), or potassium iodide (reagent grade, 40/200 mesh). (The oily residue from the Choline Chloride in ethyl alcohol solution was hand-ground with potassium chloride and the mixture was dried at 105°C. The mixture of 0.5 mg of Urethan and 200 mg of potassium bromide was ground in a mechanical vibrator for 2 minutes.) Unless otherwise directed in the official monographs, the mixtures were pressed into disks without additional drying. A Beckman evacuable die, which produced disks 12.7 mm in diameter, was employed. After preliminary evacuation at a pressure of about 1 mm of Hg for 1 minute under 2000 lb of force, a force of 20,000 lb was applied to the mixtures for 3 minutes with continued evacuation. Blank potassium halide disks (220 mg) (2) were pressed in the same manner and were used in the reference

beam to compensate for absorption of water. In order to obtain distinctive spectra, it was necessary to heat the disks of Digitoxin and Digoxin at 105°C for 2 hours. The disks of the other standards were not heated prior to the spectral scan.

The absorption spectra were recorded on the standard scale within 24 hours of the preparations of the disks. The disks were stored for periods of 2 weeks to 6 months. Spectra of these stored disks were recorded on a reduced scale for publication with an appropriate blank disk in the reference beam. Those disks whose spectra revealed significant changes during storage were discarded, and duplicate disks were prepared. Compensated spectra of the Reference Standards which are included in this publication were recorded within 24 hours of the preparations of the disks.

In most analytical procedures, organic nitrogenous bases are isolated instead of the salts of these compounds. Therefore, to aid in their identification, some of these bases were extracted from the Reference Standard salts, and their infrared absorption spectra were measured in solutions, films, or disks.

About 50 mg of the Reference Standard salts were dissolved in 25 ml of water and the solutions were made alkaline with 2–5 ml of 10% ammonium hydroxide, 1*N* sodium carbonate, or 1*N* sodium hydroxide. Duplicate alkaline suspensions of the tertiary bases were prepared. One suspension was extracted with 4 ml of carbon disulfide; the second suspension was extracted with 4 ml of tetrachloroethylene. The extracts were passed through dry filters. Infrared absorption measurements were made immediately in 1 mm sodium chloride cells with the appropriate solvent in a matched reference cell. Composite spectra were recorded as described earlier.

To avoid reactions in carbon disulfide and tetrachloroethylene, the primary and secondary nitrogenous bases were extracted from the alkaline suspensions with about 50 ml of benzene or ether. The extracts were washed with water and filtered. The extracts of Benoxinate, Mecamylamine, and Tetracaine were evaporated under nitrogen and were dried in vacuum as described earlier. Infrared absorption spectra were obtained of the residues as films between sodium chloride plates. The remaining extracts in total, or 1 ml aliquots which were diluted (1:3 or 1:6) with *n*-heptane or cyclohexane, were evaporated as described for the Reference Standards. The extract residue of Pipradrol was recrystallized from *n*-propyl alcohol-water (1:2). The residues were dried at room temperature in vacuum for at least 30 minutes. Potassium bromide disks were prepared of 1 mg of the solids as described earlier. The infrared absorption spectra were recorded immediately after preparation of the disks.

Table 1. Wavelengths and slit widths

Ultraviolet		Visible	
Wavelength, mμ	Slit Width, mm	Wavelength, mμ	Slit Width, mm
360	0.30	700	0.21
340	0.33	600	0.04
320	0.36	550	0.02
300	0.41	500	0.03
280	0.48	400	0.09
260	0.56	350	0.20
240	0.83		
220	1.53		

The ultraviolet and visible spectra of Reference Standards were measured on a Beckman DK-2 recording spectrophotometer with a linear wavelength scale. The solutions were measured in silica cells 1 cm in thickness. Compensation was effected with the appropriate solvent in a matching cell in the reference beam. A hydrogen discharge tube and a tungsten lamp were used for the ultraviolet and visible regions, respectively. The ultraviolet data were recorded between 360 and 220 mμ; the visible curves were obtained between 700 and 350 mμ. Wavelength measurements were accurate to within ± 2 mμ as determined with a holmium oxide glass. Some wavelengths and the corresponding slit widths are given in Table 1.

In general, the ultraviolet and visible absorption spectra were obtained as directed in the identification tests of the USP and NF monographs. In some cases, the solutions specified in assay procedures were measured.

Other procedures were modified to allow measurements in both acidic and basic solutions to determine the effect of pH on the spectra. The spectra of other compounds were recorded from solutions in water, 95% ethyl alcohol, methyl alcohol, chloroform, 0.1*N* hydrochloric acid, or 0.1*N* sodium hydroxide. When necessary, the concentrations of the solutions were adjusted so that the absorption maxima exhibited absorbance values in the range of 0.2 to 0.9. The ultraviolet and visible spectra of the organic nitrogenous bases were not determined.

Results and Discussion

The absorption spectra are presented alphabetically with the USP Reference Standards first and those of the NF last. The visible and/or ultraviolet curves are shown on the page opposite the infrared curves. The names and structures of the compounds, methods of crystallization, and dispersion medium or solvent for the infrared spectra are included in the legends which accompany the ultraviolet and visible spectra. The infrared absorption spectra of the organic nitrogenous bases are grouped alphabetically and are separate from those of the Reference Standards.

The infrared spectra of the liquid and of most of the solid Reference Standards are well-defined and reproducible. The spectra of the unheated disks of Digitoxin and Digoxin were very similar. However, distinct differences between the spectra were observed when the disks of these two compounds were heated. No significant spectral changes, except in resolution and slight relative intensity reversals, were observed when the disks of 150 of the standards were remeasured after periods of 2 weeks to 6 months. However, the compounds in Table 2 displayed significant spectral variations after standing.

The changes exhibited by these compounds are attributed primarily to crystalline form transitions. The conditions of crystallization, force of grinding, and the disk storage period influenced the crystalline forms and spectra.

The disks of Calciferol, Activated 7-dehydrocholesterol, and Riboflavin exhibited the formation of very weak absorption (about 1–5%) in the carbonyl region (5.5–5.9μ) on standing. These compounds are light-sensitive and are easily oxidized. These observations emphasize the need for examining standard and sample under the same experimental conditions.

Table 2. Compounds showing absorption changes on standing

Betazole hydrochloride
Calcium pantothenate
Carbinoxamine maleate
Dihydrostreptomycin sulfate
Epinephrine bitartrate
Ergonovine maleate
Estradiol
Estradiol benzoate
Hydroxystilbamidine isethionate
Menadione
Mercaptopurine
Nifuroxime
Nitrofurantoin
Oxytetracycline
Phenindamine tartrate
Phentolamine methanesulfonate
Probenecid
Pyrilamine maleate
Sodium diatrizoate
Sulfamethazine
Sulfamethoxypyridazine
Tetracaine hydrochloride
Thiamine hydrochloride
Trimethaphan camphorsulfonate
Zoxazolamine

The names of the organic nitrogenous bases, solvents of extraction, infrared media, and solvent(s) of crystallization are given in Table 3. Because of the apparent instabilities of some of the tertiary bases in carbon disulfide and in tetrachloroethylene, the infrared spectra of these compounds were obtained immediately after extraction. When solutions of Phenindamine and of Promethazine in carbon disulfide were allowed to stand for an hour or more, spectral variations occurred in the 3–4μ region. The spectra of Hydroxychloroquine (m.p. 89–91°C) and of Phentolamine (m.p. 174–175°C) in disks are poorly resolved and probably represent amorphous materials.

The absorption maxima of the ultraviolet and visible spectra agree with those which

Table 3. Data on organic nitrogenous bases

Nitrogenous Base	Extraction		Infrared	
	Alkalizing Agent	Solvent	Medium	Crystallization Solvent
176. Amodiaquine	10% NH_4OH	C_6H_6	KBr	C_6H_6-C_7H_{16}(1:3)
177. Atropine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
178. Azacyclonol	1*N* NaOH	C_6H_6	KBr	C_6H_6-C_7H_{16}(1:3)
179. Benoxinate	10% NH_4OH	Et_2O	film	
180. Carbetapentane	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
181. Carbinoxamine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
182. Chlorcyclizine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
183. Chlorpheniramine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
184. Chlorpromazine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
185. Cyclizine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
186. Dibucaine	10% NH_4OH	Et_2O	KBr	Et_2O-C_7H_{16}(1:3)
187. Dimethisoquin	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
188. Diphenhydramine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
189. Doxylamine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
190. Hydroxychloroquine	1*N* NaOH	Et_2O	KBr	Et_2O-C_6H_{12}(1:6)
191. Hydroxyzine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
192. Levallorphan	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
193. Mecamylamine	1*N* NaOH	Et_2O	film	
194. Meclizine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
195. Phenindamine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
196. Phentolamine	1*N* Na_2CO_3	C_6H_6	KBr	C_6H_6-C_7H_{16}(1:3)
197. Pipradrol	1*N* NaOH	C_6H_6	KBr	*n*-C_3H_7OH-H_2O(1:2)
198. Pramoxine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
199. Prochlorperazine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
200. Promethazine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
201. Propoxyphene	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
202. Pyrilamine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
203. Tetracaine	1*N* NaOH	Et_2O	film	
204. Thenyldiamine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
205. Tolazoline	1*N* Na_2CO_3	C_6H_6	KBr	C_6H_6-C_7H_{16}(1:3)
206. Trihexyphenidyl Base	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	
207. Tripelennamine	1*N* NaOH	CS_2, C_2Cl_4	CS_2, C_2Cl_4	

are given in the USP and NF monographs. The absorption maxima of the standards are given in the legends of the spectra.

Acknowledgments

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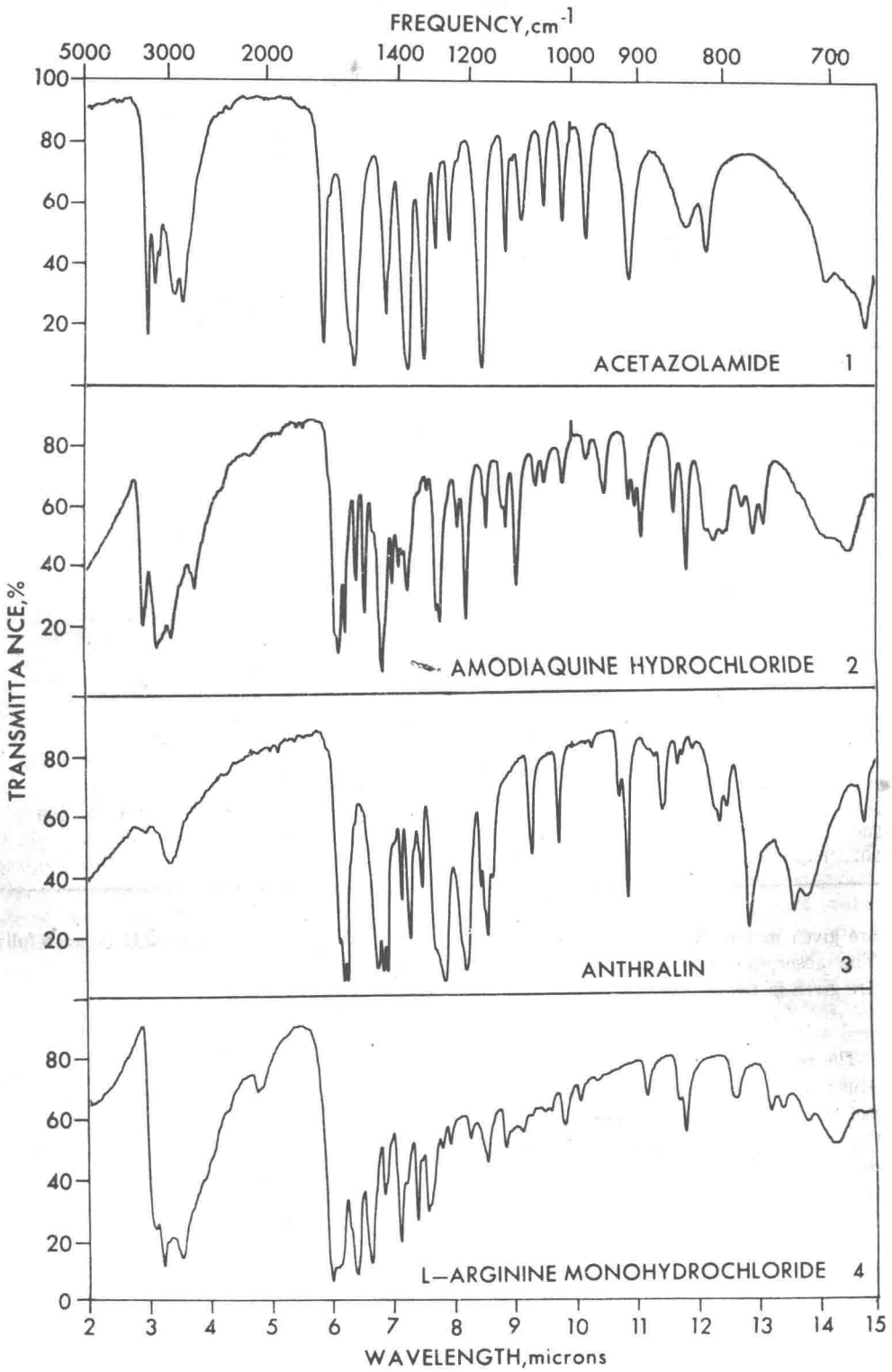
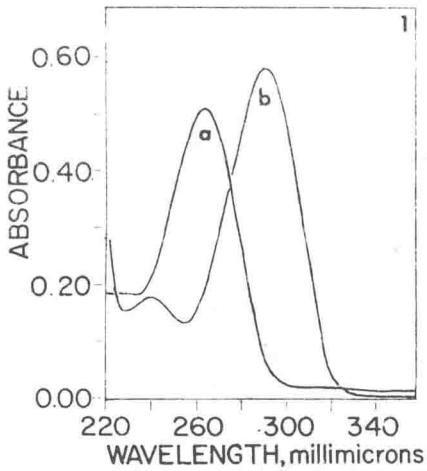
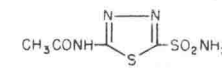
References

(1) Jones, R. N., and Sandorfy, C., in Chapter 4 of *Chemical Applications of Spectroscopy*, edited by W. West, Vol. 9, of *Techniques of Organic Chemistry*, Interscience Publishers, Inc., New York, 1956, p. 294.

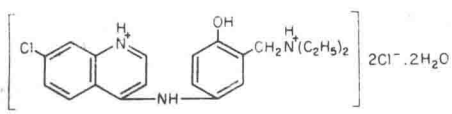
(2) Hayden, Alma L., *J. Pharm. Sci.*, **51**, 617 (1962).


FREQUENCY, cm-1
5000
3000
2000
1400
1200
1000
900
800
700
TRANSMITTANCE, %
ACETAZOLAMIDE 1
AMODIAQUINE HYDROCHLORIDE 2
ANTHRALIN 3
L—ARGININE MONOHYDROCHLORIDE 4
WAVELENGTH, microns

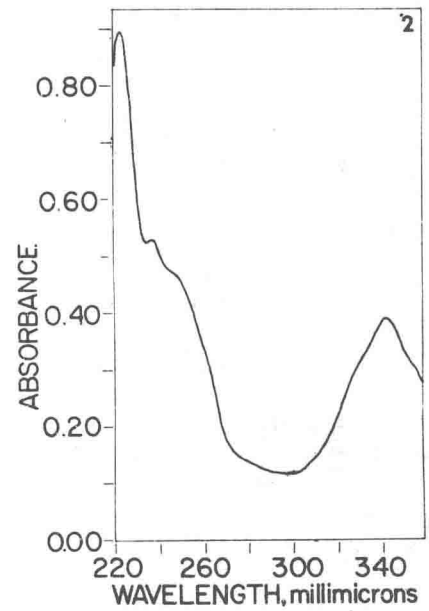


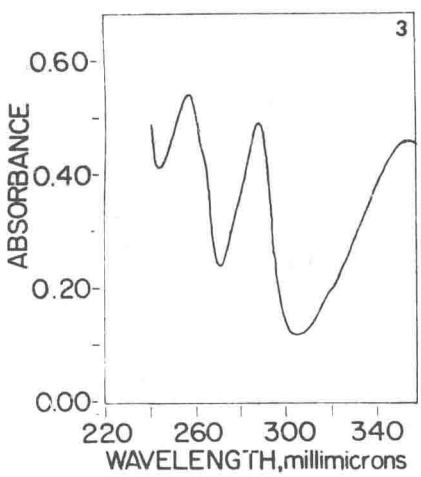


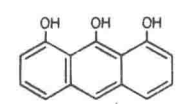
1. Acetazolamide: IR-A, KBr. UV: a. 10 μg per ml in 0.1*N* HCl, λ_{max} 264 mμ; b. 10 μg per ml in 0.1*N* NaOH, λ_{max} 239, 291 mμ.



2. Amodiaquine Hydrochloride: IR-I, KCl. UV: 10 μg per ml in 0.1*N* HCl, λ_{max} 223, 237, 247, 343 mμ.

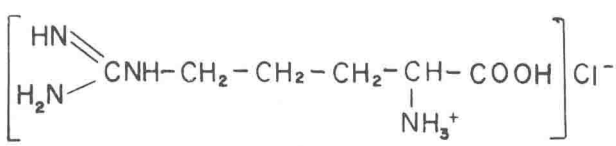




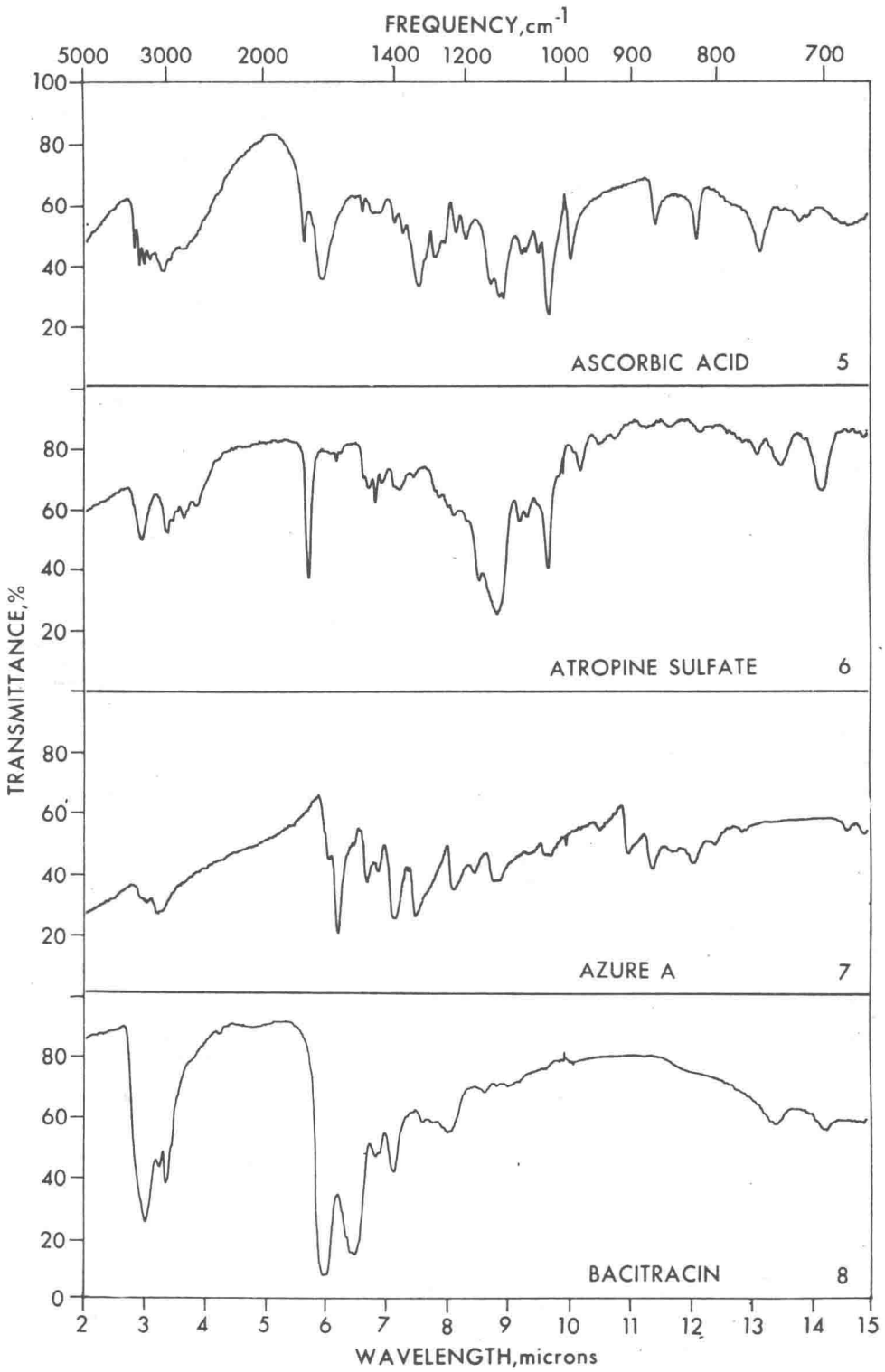


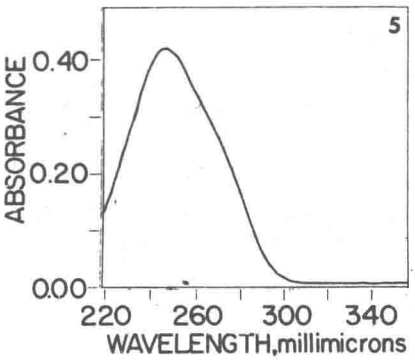
3. Anthralin: IR-A, KBr. UV: 10 μg per ml in $CHCl_3$, λ_{max} 256, 288, 355 mμ.

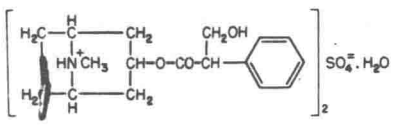
4



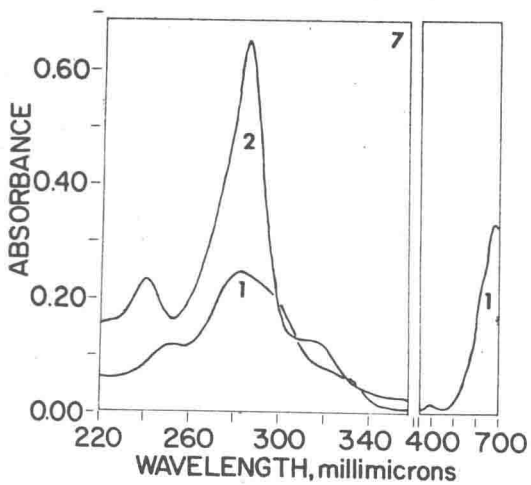
4. L-Arginine Monohydrochloride: IR-I, KCl.



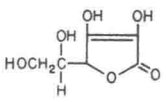




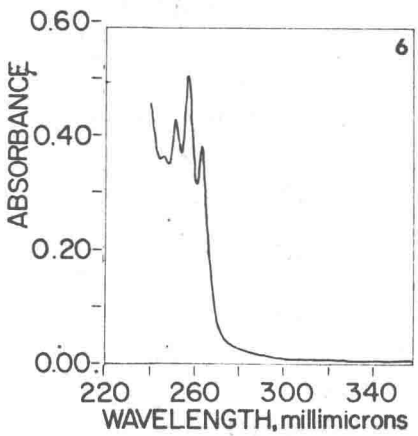
6. Atropine Sulfate: IR-C (crystals dried at 105°C for 1 hr), KBr. UV: 1 mg per ml in 95% EtOH, λ_{max} 246, 251, 257, 263 mμ.

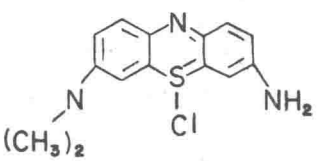


8. Bacitracin: IR-I, KBr. UV: 200 μg per ml in H_2O, λ_{max} 251, 287 mμ.

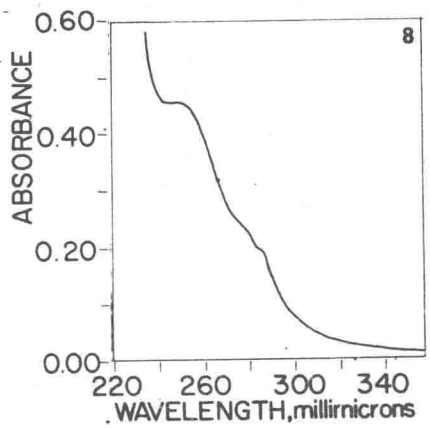


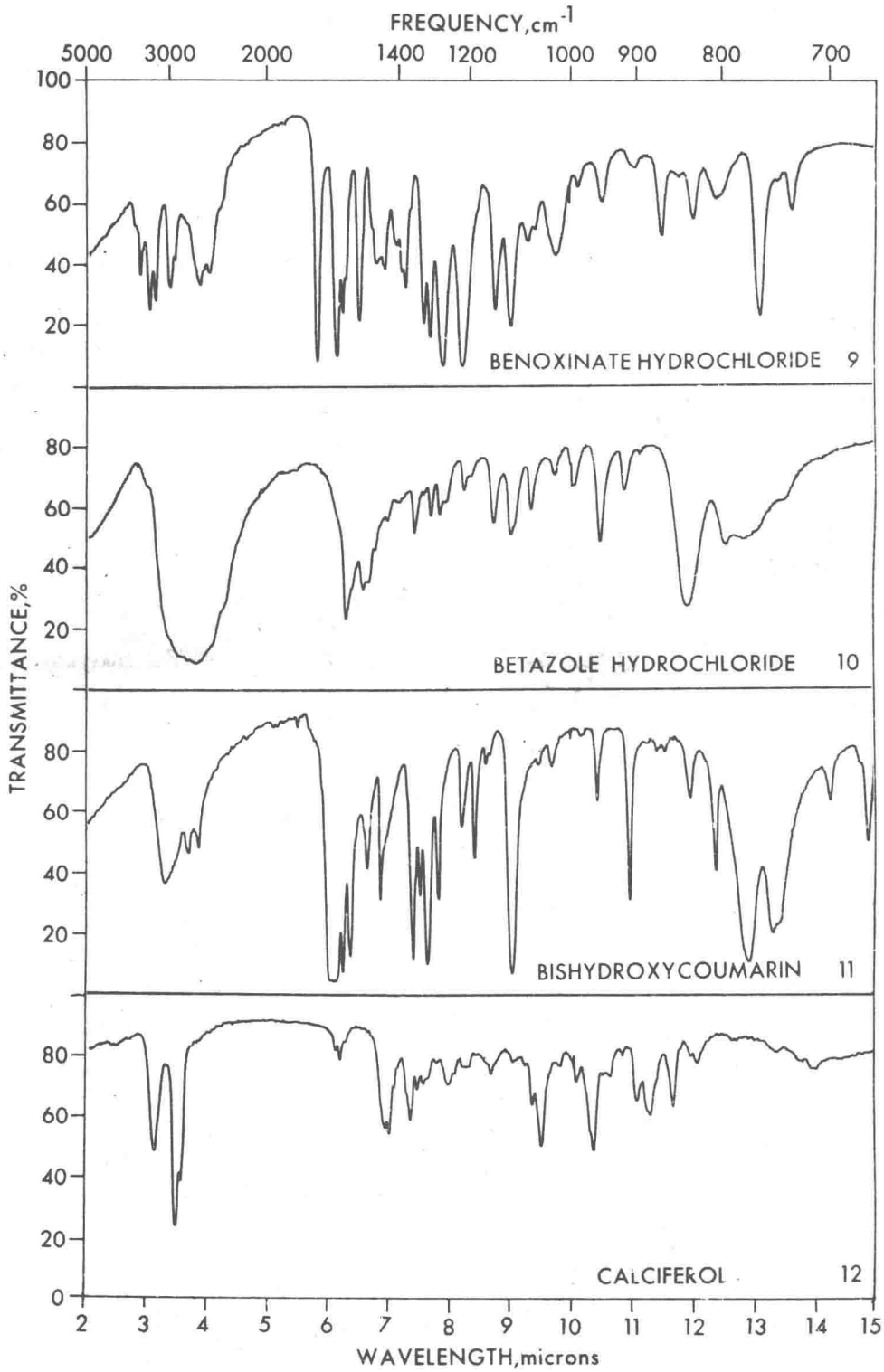
5. Ascorbic Acid: IR-I, KBr. UV: 10 μg per ml in 95% EtOH, λ_{max} 248 mμ.

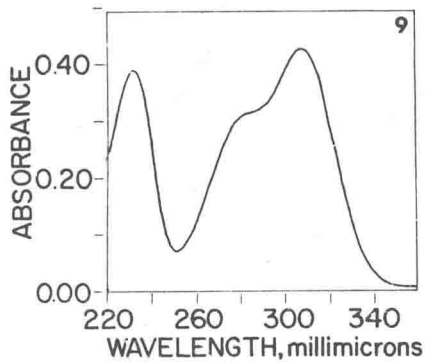




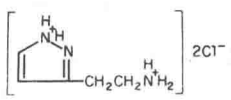
7. Azure A: IR-I, KBr. Visible and UV: 1. 3 μg per ml in 47.5% EtOH + HCl (2 + 1), λ_{max} 252, 285, 690 mμ; 2. 5 μg per ml in 95% EtOH, λ_{max} 241, 287, 318 mμ.



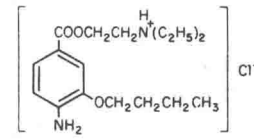

FREQUENCY, cm-1
5000 3000 2000 1400 1200 1000 900 800 700
TRANSMITTANCE, %
BENOXINATE HYDROCHLORIDE 9
BETAZOLE HYDROCHLORIDE 10
BISHYDROXYCOUMARIN 11
CALCIFEROL 12
WAVELENGTH, microns



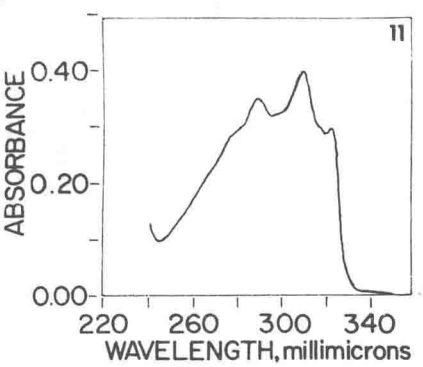
10

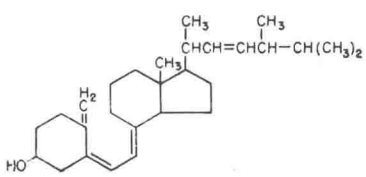


10. Betazole Hydrochloride: IR-B, KCl.

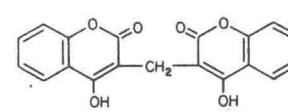


9. Benoxinate Hydrochloride: IR-I, KCl. UV: 10 μg per ml in H_2O, λ_{max} 230, 281, 307 mμ.

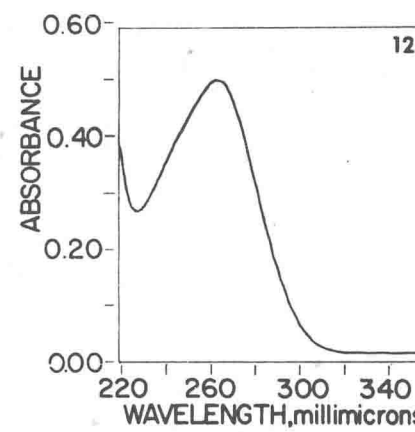


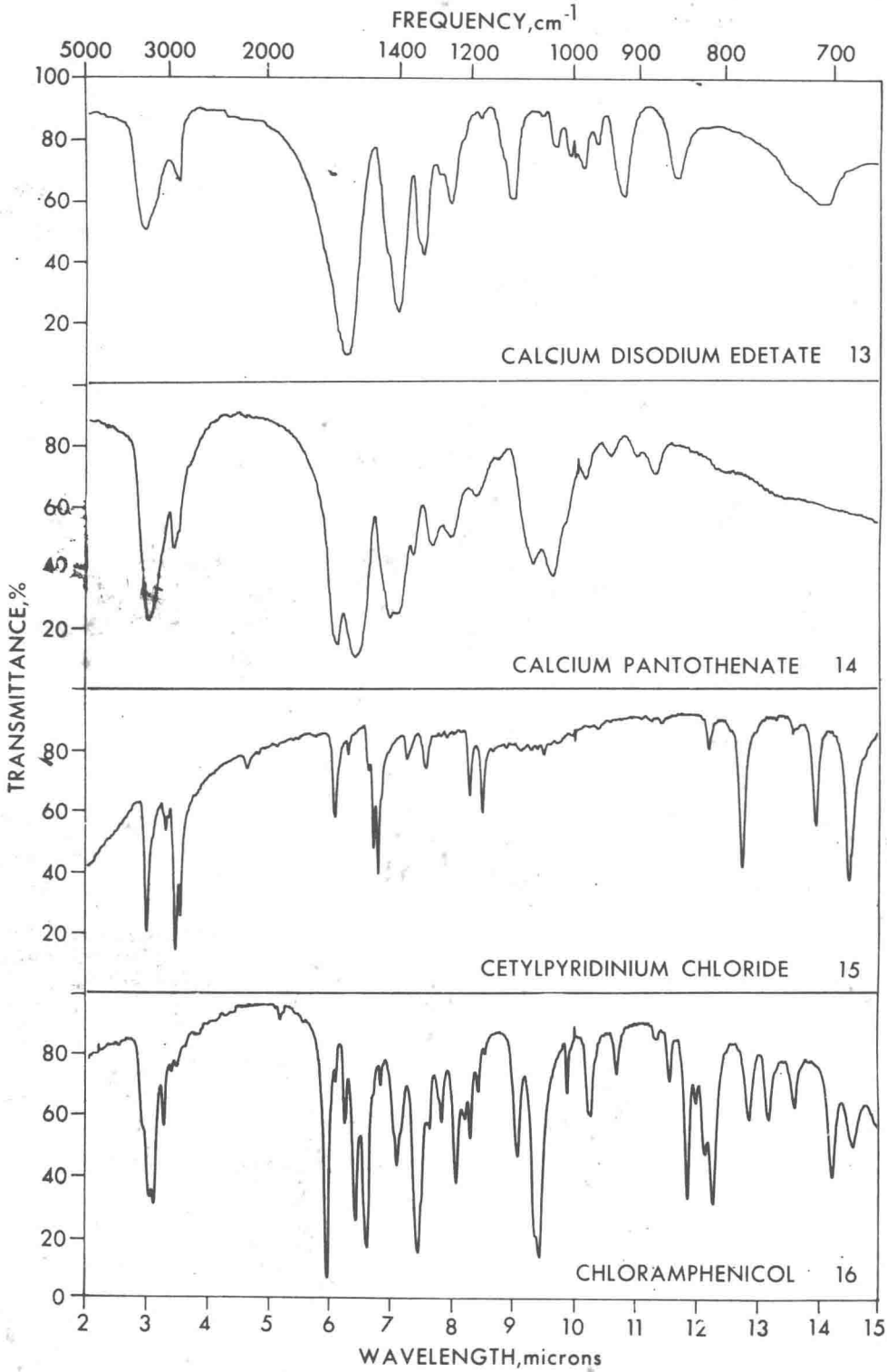


12. Calciferol: IR-I, KBr. UV: 10 μg per ml in 95% EtOH, λ_{max} 265 mμ.

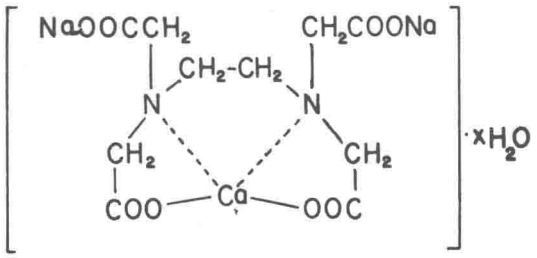


11. Bishydroxycoumarin: IR-C, KBr. UV: 5 μg per ml in $CHCl_3$, λ_{max} 288, 309, 322 mμ.




FREQUENCY,cm-1
5000 3000 2000 1400 1200 1000 900 800 700
TRANSMITTANCE,%
CALCIUM DISODIUM EDETATE 13
CALCIUM PANTOTHENATE 14
CETYLPYRIDINIUM CHLORIDE 15
CHLORAMPHENICOL 16
WAVELENGTH,microns

13

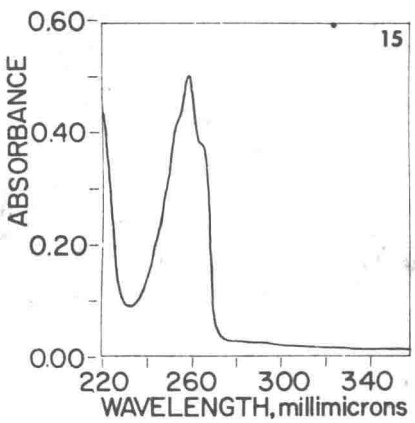


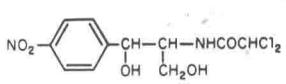
13. Calcium Disodium Edetate: IR-I, KBr.

14

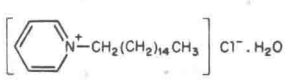
$$[HOCH_2C(CH_3)_2CH(OH)CONH(CH_2)_2COO]_2Ca$$

14. Calcium Pantothenate: IR-I (crystals dried at 105°C for 3 hr), KBr.





16. Chloramphenicol: IR-I, KBr. UV: 20 μg per ml in H_2O, λ_{max} 278 mμ.



15. Cetylpyridinium Chloride: IR-B, KCl. UV: 42 μg per ml in H_2O, λ_{max} 253, 259, 265 mμ.