J. Ass. Off. Anal. Chem. 54(5), 1179-1191 (1971)

DRUGS

Identification of Amphetamines and Related Sympathomimetic Amines

By R. J. WARREN, P. P. BEGOSH, and J. E. ZAREMBO (Smith Kline & French Laboratories, 1500 Spring Garden St., Philadelphia, Pa. 19101)

The IR, UV, and NMR spectral data as well as the pKa′ values of a series of 18 phenyl-propyl amines are presented and discussed. The series includes the amphetamines and many of the commercially available phenyl-propyl amines being used in the field of medicine as sympathomimetic agents. These data provide a basis for rapid identification of samples from biological, forensic, and medical research.

The amphetamines and related phenyl-propyl amines have been established as useful and important therapeutic agents for years. Their effectiveness is so widely recognized that it is not necessary to make further mention of it here. There is, however, some confusion as to just how many compounds are classified as "amphetamines." Strictly speaking, there are only 3 commercially available amphetamines: amphetamine sulfate (Benzedrine), dextroamphetamine sulfate (Dexedrine), and methylamphetamine sulfate (Desoxyn). There are, however, many additional compounds which are often listed under the heading of amphetamines because of their pharmacological action. In addition to the amphetamines there are about 20 amines which are grouped together because of this sympathomimetic pharmacological action. The entire group is often referred to as "The Amphetamines." Of the 20 compounds so listed, 14, in addition to the 3 amphetamines, are phenyl-propyl amine derivatives, and it is this series of compounds we will concern ourselves with in this paper. In view of the wide consumption of amphetamines and the attention recently focused on them as a result of the abuse of these drugs, a report of the kind offered here should be of help to those seeking to identify and characterize unknown amphetamines or materials suspected of being amphetamines. The information should also be of assistance to those engaged in medical research dealing with amphetamine and/or related compounds.

In the past, one of the principal difficulties in spectroscopic analysis of materials from biological systems was the paucity of sample usually isolated. However, it is now possible by the use of techniques such as internal reflectance spectroscopy (ATR) to obtain infrared (IR) spectra on samples in the microgram range. Likewise, time-averaging computers and newer nuclear magnetic resonance (NMR) instrumentation provide NMR spectra on micro samples. In addition, the techniques involved in this report—IR, UV, NMR—are all nondestructive so that it is possible to obtain spectra by all 3 techniques and still have the sample intact for additional testing, if required.

The purpose of this report is to provide the necessary spectral data with structural correlations that will permit identification of samples from biological, forensic, and medical research. In addition, the pKa′ values of the amines are presented as an aid to medical and pharmaceutical research and in structure elucidation.

Experimental

The IR spectra were recorded from 4000 to 625 cm^{-1} on a Perkin-Elmer Model 21 spectrometer with a NaCl prism. The amines were prepared as natural films of the free bases with one exception. The exception was No. 13, whose spectrum was recorded as a mineral oil mull of the hydrochloride salt. No. 15 is shown as both free base and sulfate salt (15a) because of solubility problems in isolating the free base.

The UV spectra were recorded between 200 and 400 nm on a Cary Model 14 recording spectrophotometer, using matched fused silica cells with a 1 cm light path.

The NMR spectra were recorded in $CDCl_3$ and in trifluoroacetic acid. Tetramethylsilane was used as internal standard. The spectra were obtained on a Varian Associates Model A-60 spectrometer.

The pKa′ data were obtained by the method of Albert and Serjeant (1).

All data were obtained on the same samples. These

were analytical standards with a purity of 98% or greater.

Results and Discussion

Infrared Spectra

The IR spectra of the phenyl-propyl amines are shown in Figs. 1–4. The amines have been grouped according to the type of substitution on the basic phenyl-propyl amine structure. Group I includes those amines with no substituents on the phenyl ring and only aliphatic groups as substituents on the side chain. Group II is that with no substituent on the ring and an —OH group on the side chain. Group III has —OCH_3 groups as substituents on the ring. Group IV contains compounds with —OH groups on the phenyl ring and, in some cases, on the side chain also.

The spectra of Group I are distinguished by 2 strong absorption bands in the area 690–750 cm^{-1}, which is the expected pattern for a monosubstituted phenyl (2). Overtones and combination bands of these are found in the 1700–2000 cm^{-1} range and the overall pattern is the classical one for a monosubstituted phenyl system (2).

The spectral characteristics of Group II are similar to those of Group I as pertains to the aromatic substitution pattern. The appearance of an —OH absorption band in the vicinity of 3.0 μm indicates the presence of this group. Since the substitution pattern for the aromatic portion of the ring has not materially changed, we may assume that the —OH is on the side chain.

Group III compounds include those materials with an —OCH_3 group on the phenyl *ortho* or *para* to the aliphatic side chain. In one amine having 2 —OCH_3 groups, the substitution is in the 1, 2, and 4 positions. The *ortho* substitution results in absorptions in the 770–735 cm^{-1} region. The *para* and the 1,2,4-trisubstitution absorption is in the range of 860 to 800 cm^{-1}.

Group IV spectra contain those compounds with an —OH group on the phenyl ring. In all cases, the —OH group is *para* to the aliphatic side chain, giving rise to an absorption in the 800–860 cm^{-1} region, which is consistent with a 1,4-disubstituted phenyl (2).

The spectra shown here, with one exception (No. 13), have all been taken on free bases because the amines are usually isolated in this state from biological systems. Before leaving the IR data, it would be well to mention that the *d*-, *l*-, and *dl*-amphetamines cannot be distinguished by this method, since the spectra of these optical isomers are identical as free bases. In order to make positive identification of one of these isomers by IR, it is necessary to prepare a salt, such as the hydrochloride or sulfate salt. The salts of these isomers have different crystalline forms and therefore different crystalline lattice vibrations with resultant different IR spectra.

Ultraviolet Spectra

The UV spectra of Groups I and II are all similar and give the typical pattern for a monosubstituted phenyl, i.e., a series of sharp absorption peaks between 240 and 270 nm (Fig. 5). Group III spectra are lacking in the fine structure shown by Groups I and II. The absorption bands are also insensitive to changes in pH (Fig. 6). Group IV spectra are characterized by a loss of fine structure and absorption bands which are pH-sensitive, due to formation of the phenolate ion in basic solution (Fig. 7).

From these UV data, it is possible to place an unknown material in one of the groups described solely on the basis of its UV spectrum. Presence or absence of fine structure and shift of maxima on change of pH are clear indications of the type of material one has to identify.

The UV data for the various phenyl-propyl amines are given in Table 1.

Nuclear Magnetic Resonance

NMR is probably the most important single spectroscopic tool available for the determination of molecular structure of organic materials. It is extremely useful for choosing among possible configurations and its application to certain of these phenyl-propyl amines has already been reported (3). The ability to observe H nuclei, their orientation, and quantity makes NMR an invaluable technique in a study such as this where differences in molecular structure involve aliphatic chain branching and proton-bearing substituents on the aromatic ring system.

The NMR of the compounds presented here have been taken in deuterated chloroform and in trifluoroacetic acid. The dependence of the NMR spectra of N-substituted amines on hydrogen ion concentration and the proton exchange rate in aqueous solutions is well known. Lowenstein and Meiboom (4), Jackman (5), and Pople, Schneider,

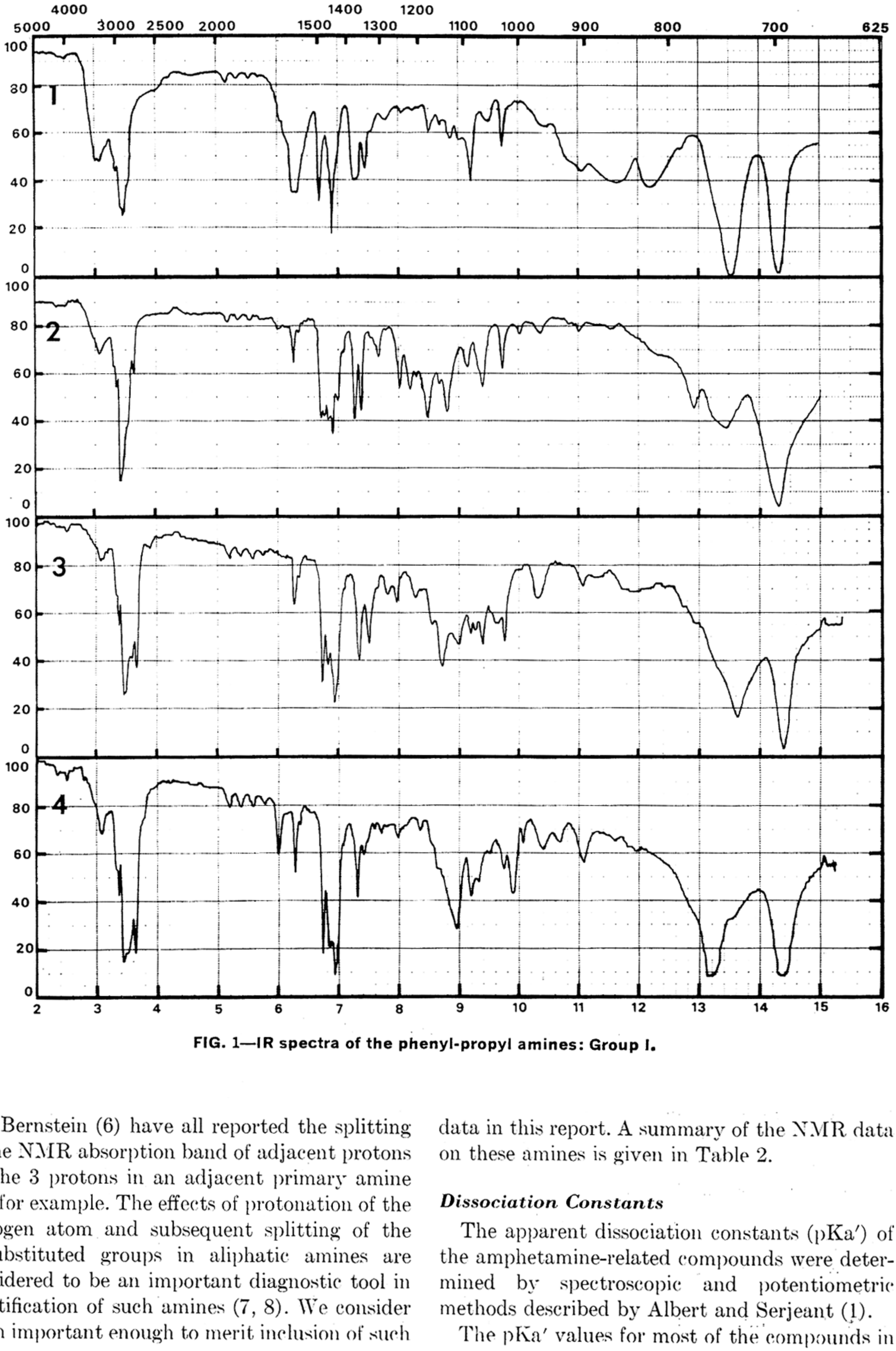


FIG. 1—IR spectra of the phenyl-propyl amines: Group I.

and Bernstein (6) have all reported the splitting of the NMR absorption band of adjacent protons by the 3 protons in an adjacent primary amine ion, for example. The effects of protonation of the nitrogen atom and subsequent splitting of the N-substituted groups in aliphatic amines are considered to be an important diagnostic tool in identification of such amines (7, 8). We consider them important enough to merit inclusion of such data in this report. A summary of the NMR data on these amines is given in Table 2.

Dissociation Constants

The apparent dissociation constants (pKa′) of the amphetamine-related compounds were determined by spectroscopic and potentiometric methods described by Albert and Serjeant (1).

The pKa′ values for most of the compounds in

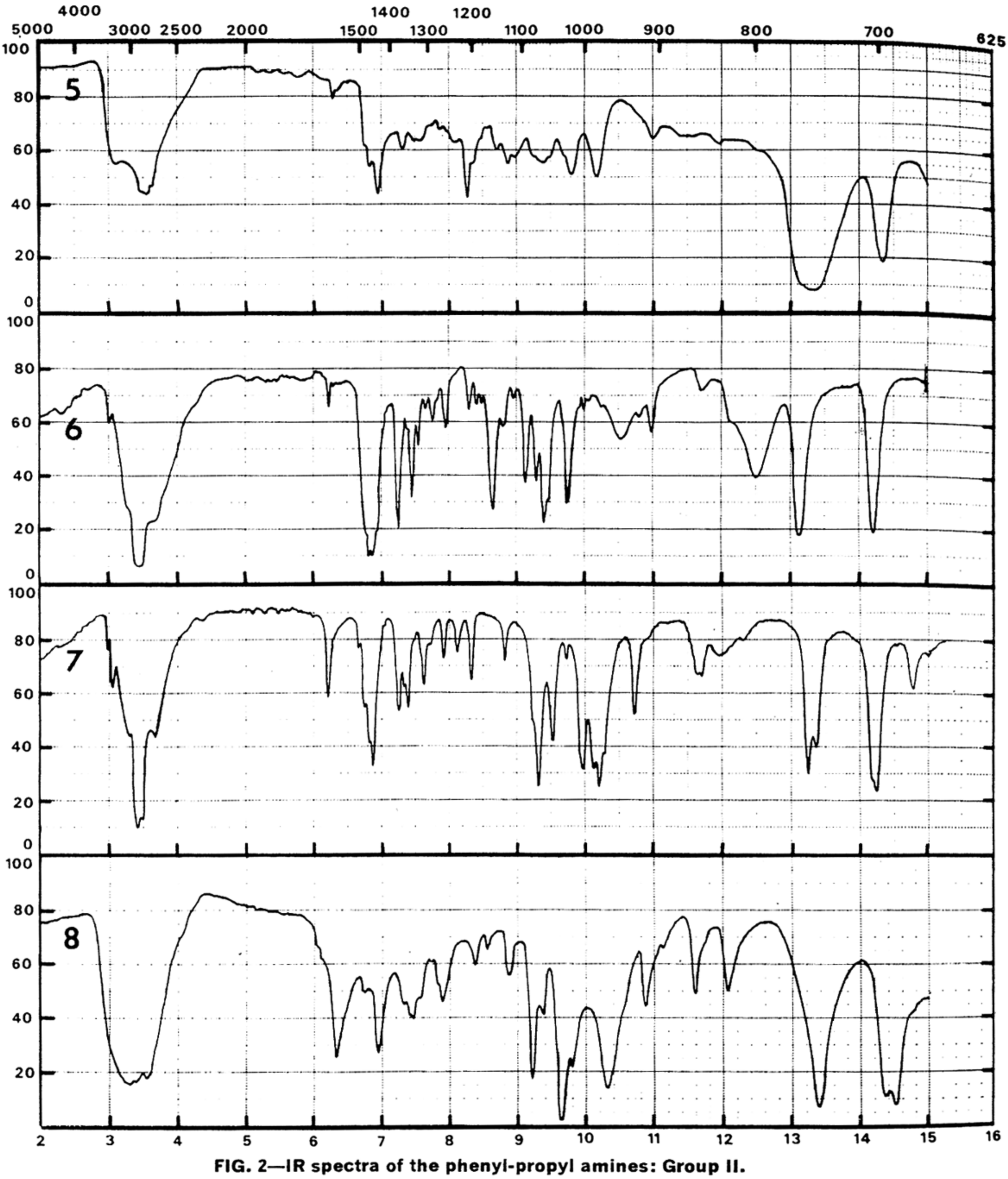


FIG. 2—IR spectra of the phenyl-propyl amines: Group II.

this study are being reported for the first time; a few have been reported previously (9–12). These pKa′ values for the same compounds reported by different workers have not always been in very good agreement; procedural and/or conceptual errors can account for these differences (13). We have spared no effort to achieve a high degree of reliability in this study; every effort was made to eliminate or minimize experimental error. For example, the compounds were all of pharmaceutical grade purity, dissolved in carbon dioxide-free, deionized water, and titrated with carbonate-free potassium hydroxide solution, using a pH meter whose stability was checked before and after titrations with 2 different buffers (pH 8.48 and 10.00).

When available, both amine salt and free base were titrated and duplicate titrations, done on

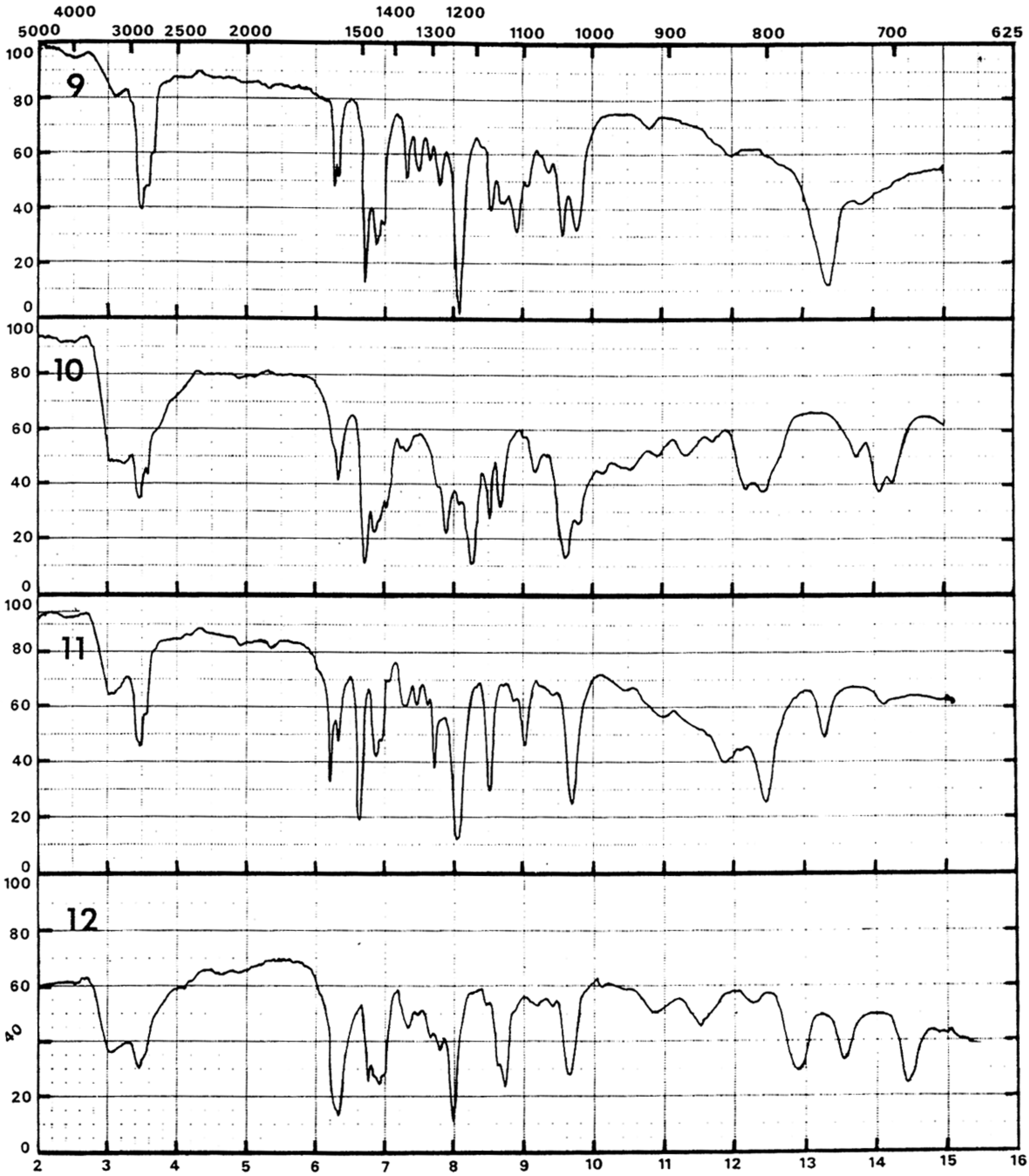


FIG. 3—IR spectra of the phenyl-propyl amines: Group III.

different days, were performed at 0.01 meq./ml at 25±0.5°C.

Although the effects of altered chemical structure on pKa′ values are apparent from inspection of the data, some of the relationships warrant further comment.

(*a*) N-Methylation raises the pKa′ of amphetamine by 0.1 unit.

(*b*) *p*-Hydroxylation of the ring raises amphetamine pKa′ by 0.6 unit.

(*c*) Hydroxylation of the propyl side chain lowers amphetamine pKa′ by 0.9 unit. This decrease in basicity is probably caused by intramolecular hydrogen bonding between the alcohol and amine groups with some contribution from the inductive effect (−I) of the hydroxyl group.

(*d*) N-Methylation of compounds containing

Received December 30, 1970.

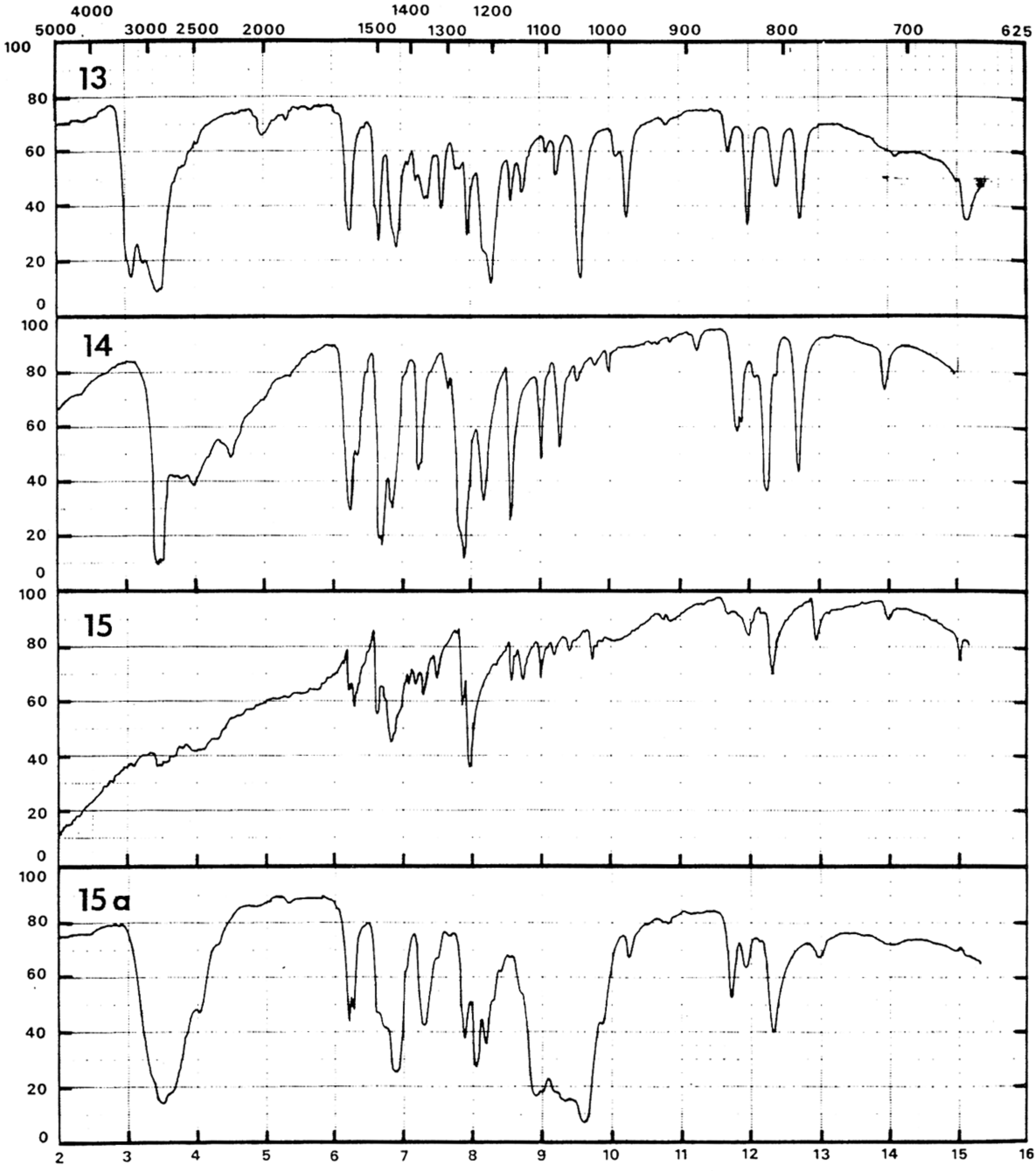


FIG. 4—IR spectra of the phenyl-propyl amines: Group IV.

such a propyl hydroxyl group raises the pKa′ by 0.6 unit rather than the expected 0.1 unit (compare No. 5 with No. 7).

(*e*) Stereochemical effects are apparent in a comparison of the isomeric pairs norephedrine/pseudonorephedrine and ephedrine/pseudoephedrine. Kanzawa (14) and Hyne (15) have used IR and NMR methods, respectively, to study the ephedrines and they both concluded that pseudoephedrine is more strongly hydrogen bonded than ephedrine. This conclusion can be applied to the corresponding norephedrine isomers. Our data show that the more strongly intramolecular hydrogen-bonded pseudo-isomers have pKa′ values 0.1 unit higher than their corresponding isomers. This is in agreement with the thermodynamic (pKa′) values reported by Everett and Hyne (9) for ephedrine and pseudoephedrine.

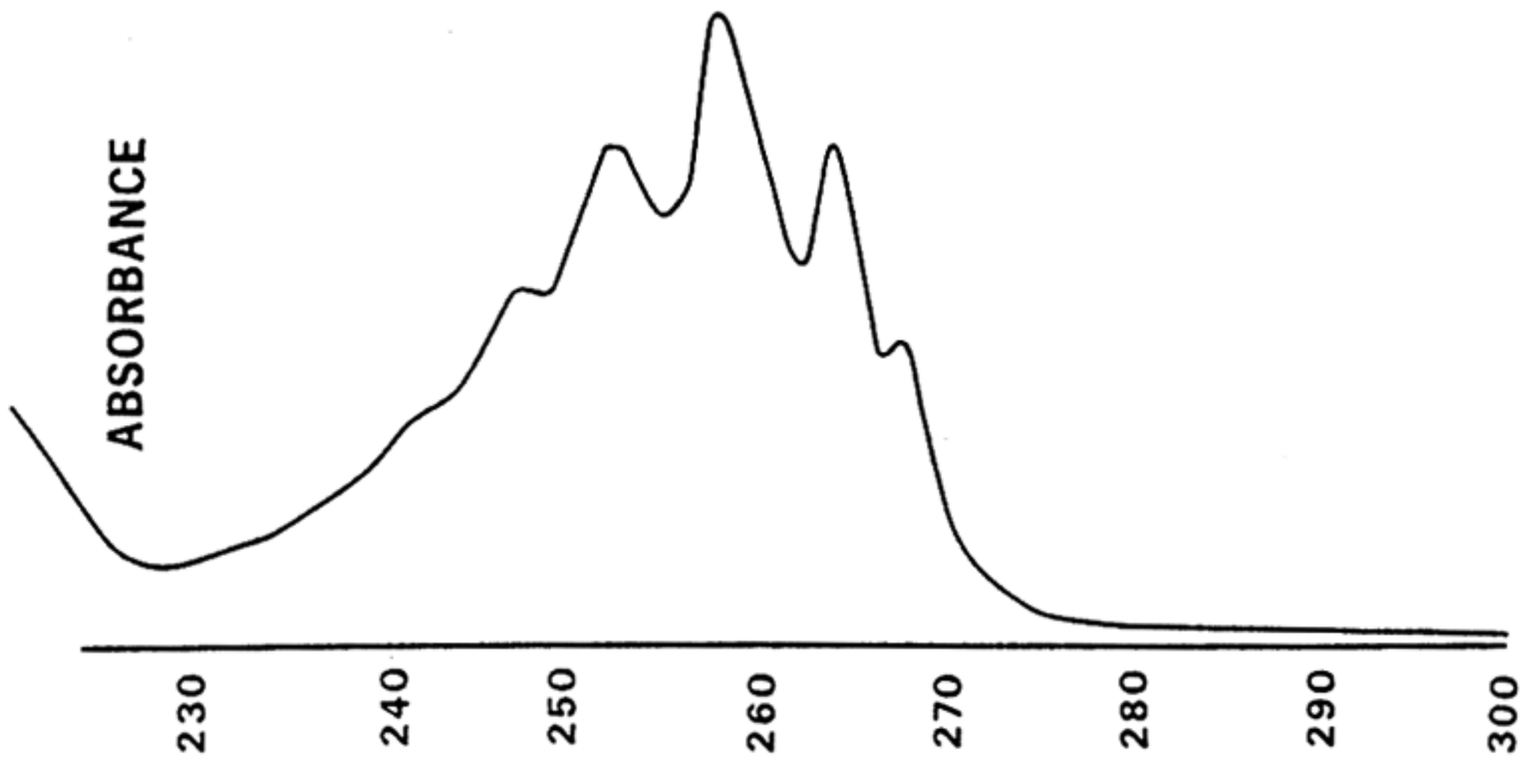


FIG. 5—UV spectrum of Groups I and II phenyl-propyl amines.

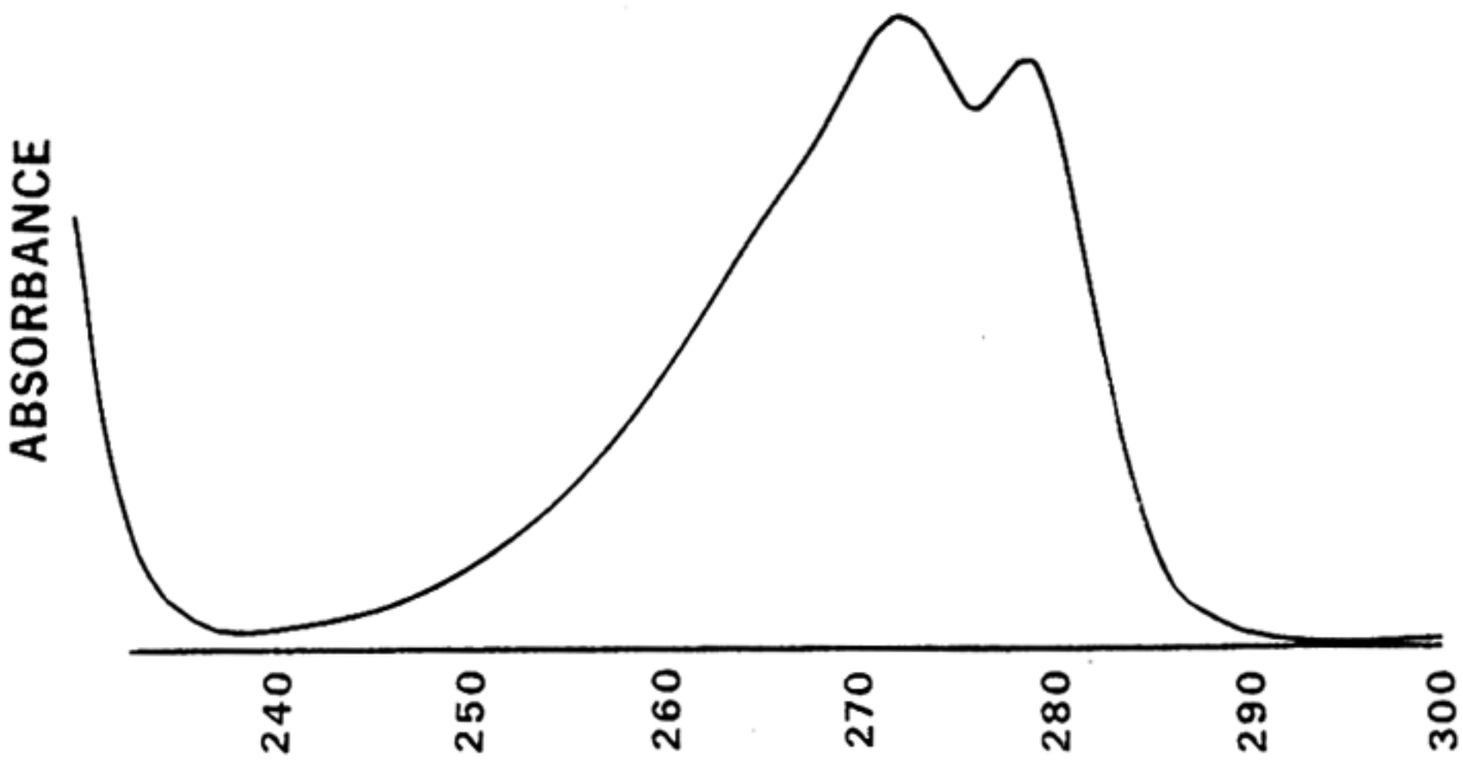


FIG. 6—Typical UV spectrum of Group III phenyl-propyl amines.

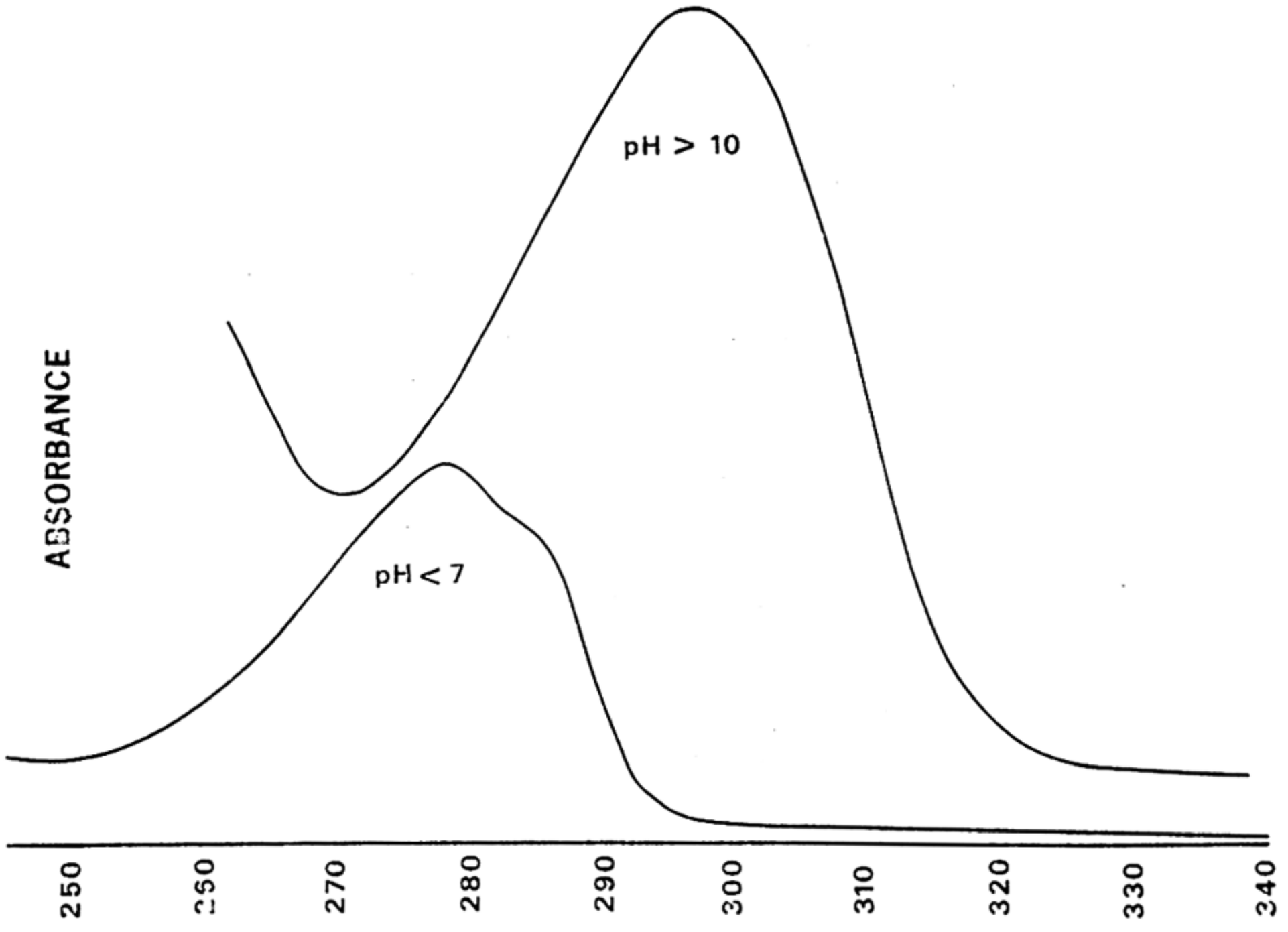
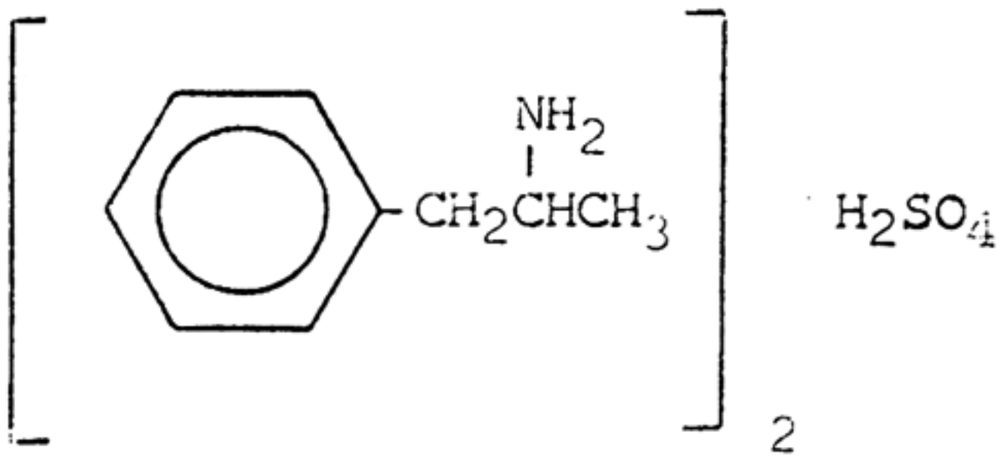
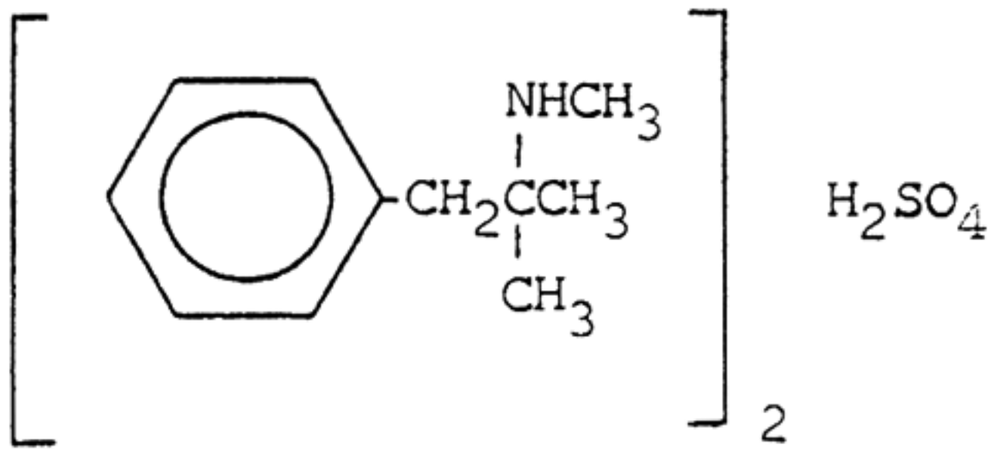
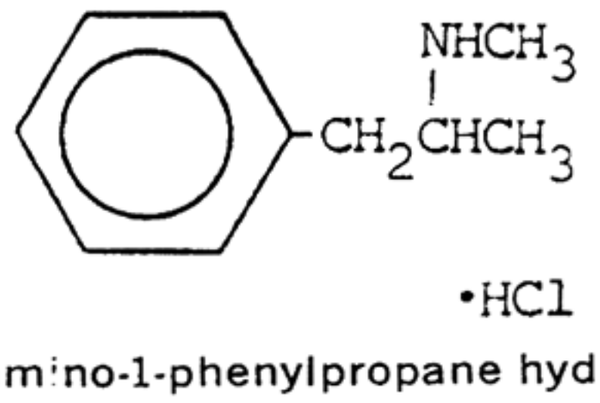
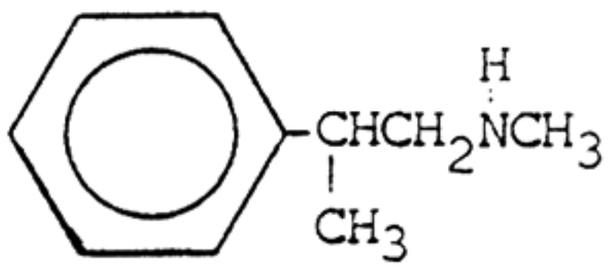
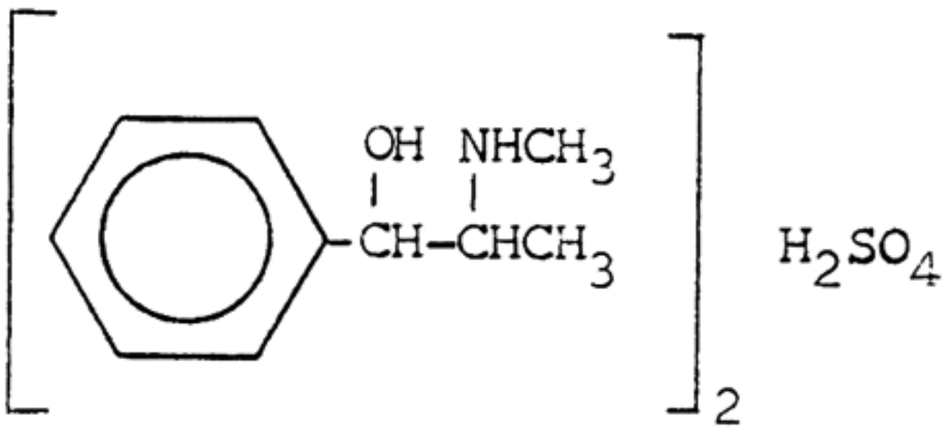
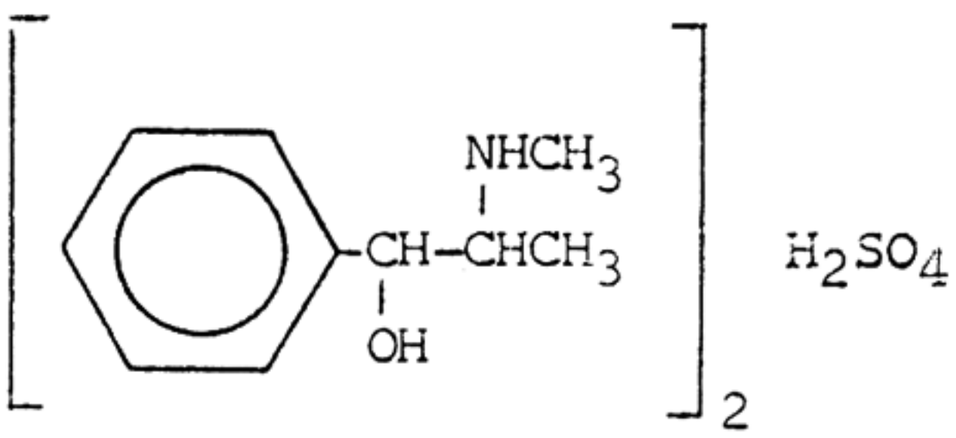


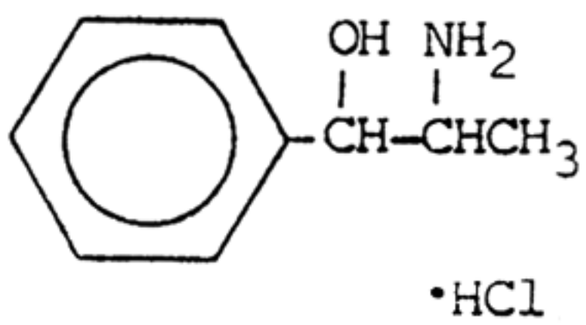
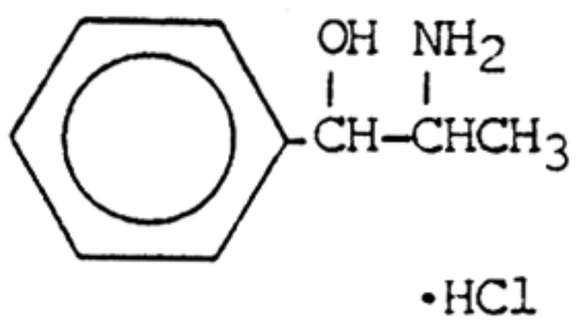
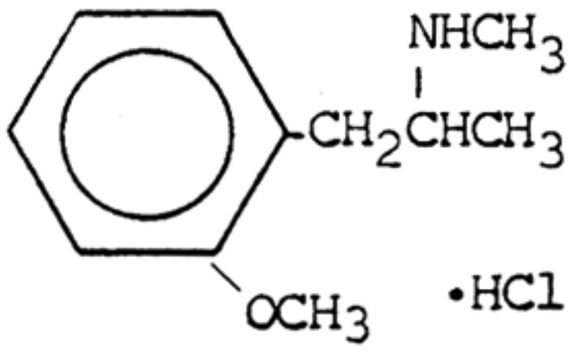
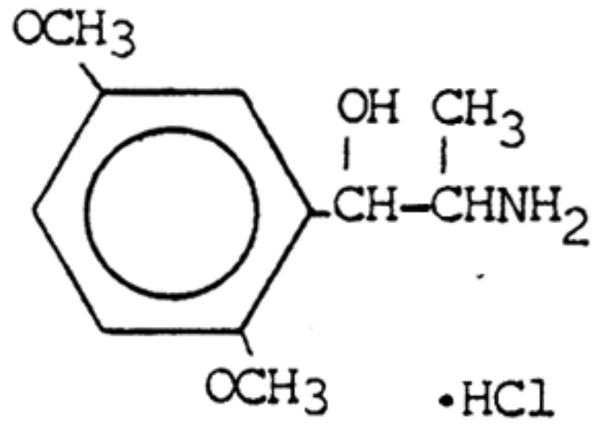
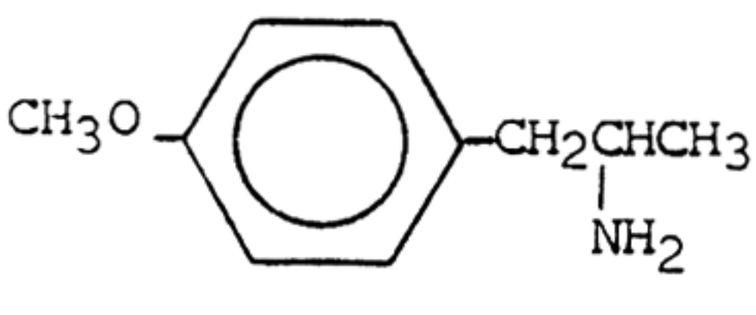
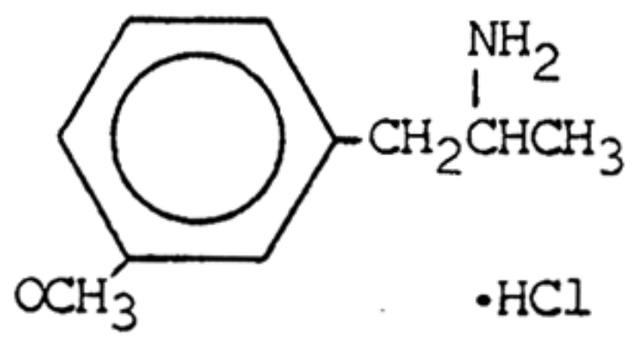
FIG. 7—UV spectrum of Group IV phenyl-propyl amines.

Table 1. UV data for the phenyl-propyl amines (95% ethanol solvent)

Compound	λ_{max}, nm	log ϵ	pKa′	IR Spectrum of Free Base
 2-Amino-1-phenylpropane sulfate	247 252 258 264	2.45 2.55 2.43 2.28	9.94	1
 2-Methylamino-2-methyl-1-phenylpropane sulfate	247 252 258 264	2.45 2.55 2.44 2.28	10.37	2
 2-Methylamino-1-phenylpropane hydrochloride	247 252 258 263 267	2.02 2.16 2.27 2.16 1.88	9.99	3
 2-Methylamino-1-phenylpropane hydrochloride	247 251 257 263	2.30 2.50 2.50 1.90	10.07	4
 Erythro-1-hydroxy-2-methylamino-1-phenylpropane sulfate	247 252 257 263 266	2.11 2.27 2.38 2.27 1.98	9.63	5
 Threo-1-hydroxy-2-methylamino-1-phenylpropane sulfate	247 252 257 263 266	2.11 2.27 2.38 2.27 1.98	9.73	6

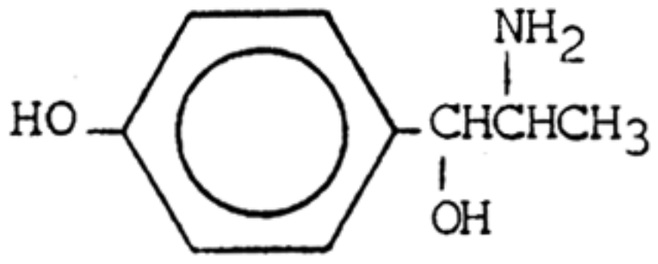
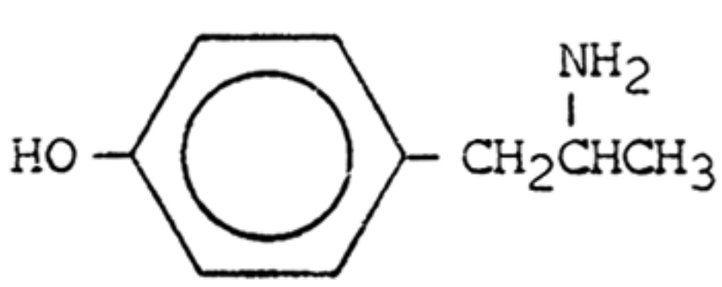
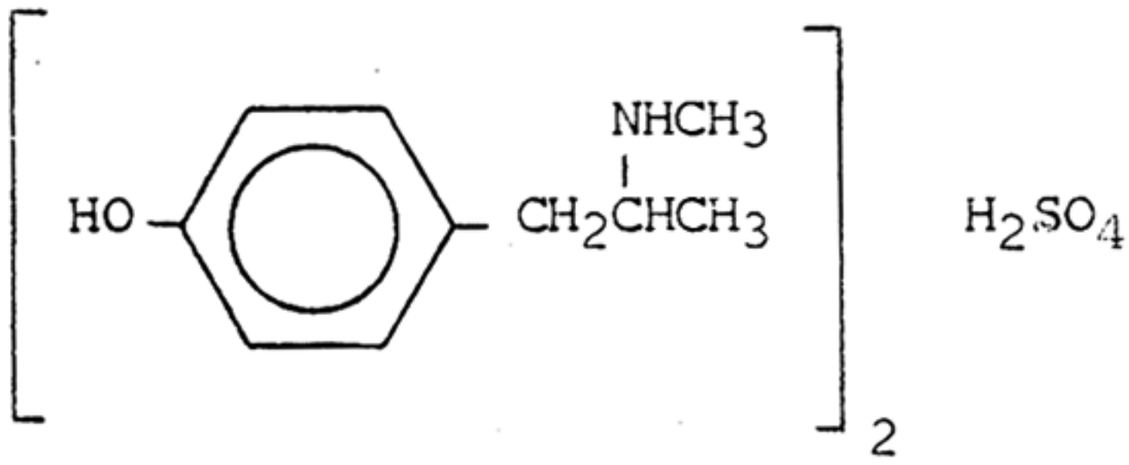
(Continued)

Table 1. (*Continued*)

Compound	λ_{max}, nm	log ϵ	pKa′	IR Spectrum of Free Base
 Erythro-2-amino-1-hydroxy-1-phenylpropane hydrochloride (nor-isomer)	249 251 257 263 267	2.02 2.18 2.29 2.18 1.88	9.05	7
 Threo-2-amino-1-hydroxy-1-phenylpropane hydrochloride (pseudo nor-isomer)	249 251 257 263 266	2.02 2.18 2.29 2.18 1.88	9.19	8
 2-Methylamino-(1-methoxyphenyl)-propane hydrochloride	272 279	3.35 3.34	10.45	9
 2-Amino-1-hydroxy-1-(2,5-dimethoxyphenyl)-propane hydrochloride	290	3.60	9.32	10
 2-Amino-1-(4-methoxyphenyl)-propane hydrochloride	275 282	3.25 3.18	9.99	11
 2-Amino-1-(3-methoxyphenyl)-propane hydrochloride	272 279	3.32 3.28	9.86	12

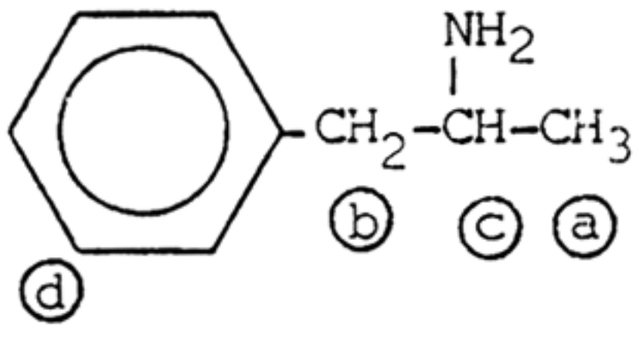
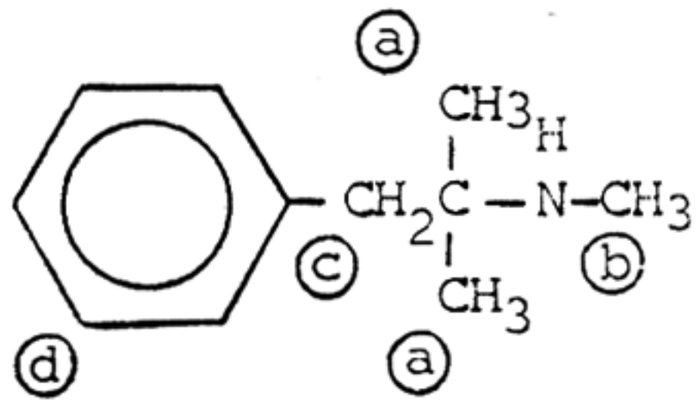
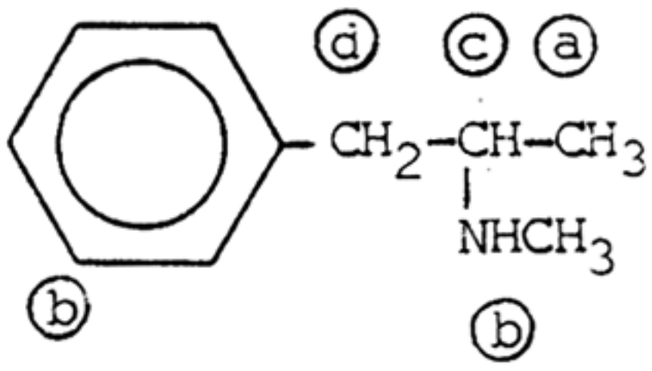
(*Continued*)

Table 1. (*Continued*)

Compound	λ_{max}, nm	log ϵ	pKa′	IR Spectrum of Free Base
	225 276	3.97 3.23	9.62	
•HCl	246[a] 294[a]	4.19[a] 3.43[a]	9.58	13
2-Amino-1-hydroxy-1-(4-hydroxyphenyl)-propane hydrochloride				
	224 278	3.96 3.25	9.70 9.49[b]	
•HBr	297[a]	3.49[a]	10.53 10.66[b]	14
2-Amino-1-(4-hydroxyphenyl)-propane hydrobromide				
	276.5	3.55	9.62 9.49[b] 10.78[b]	
H_2SO_4	295[a]	3.56[a]	10.75	15
1-(4-Hydroxyphenyl)-2-methylaminopropane sulfate				

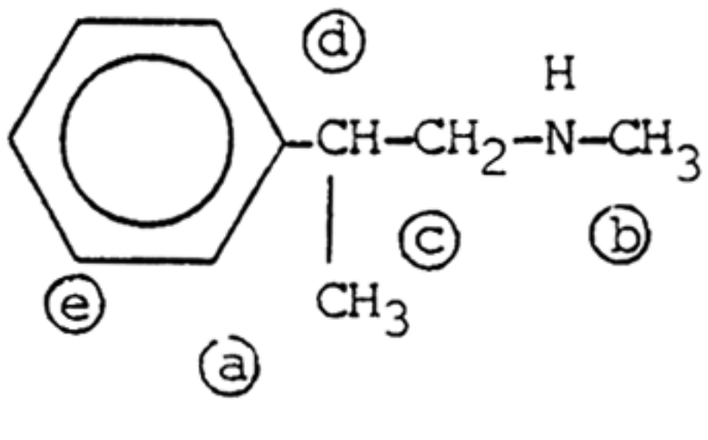
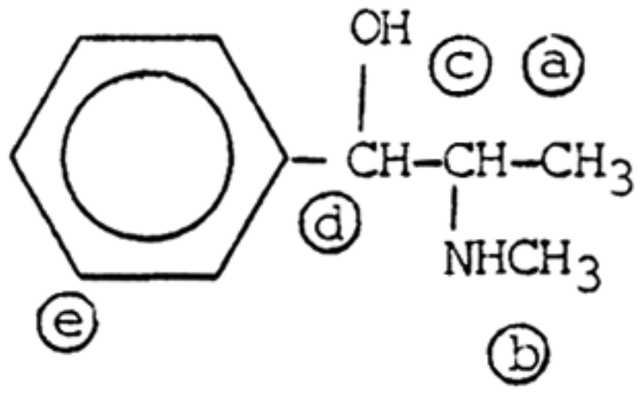
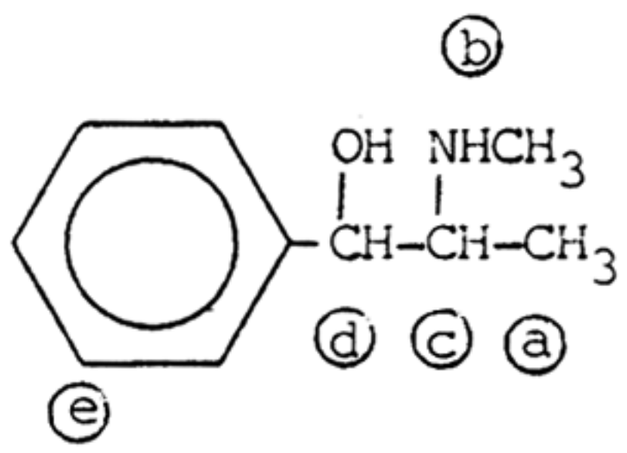
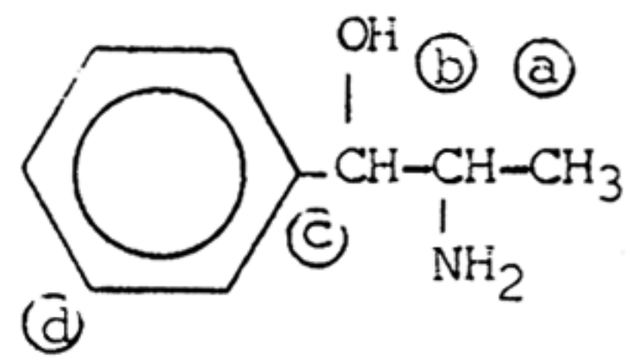
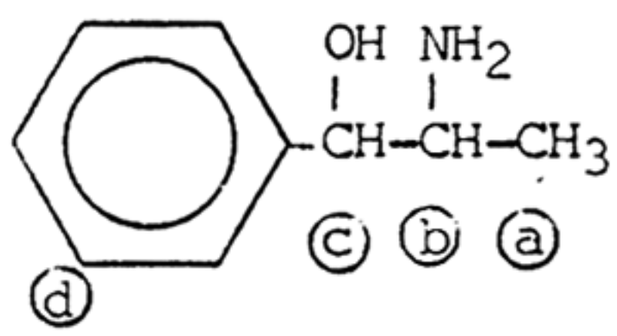
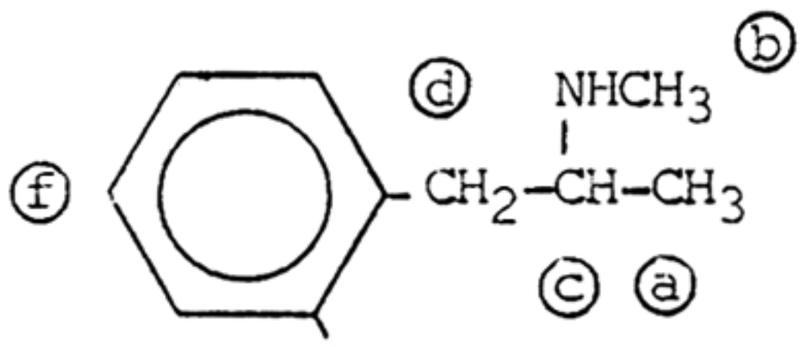
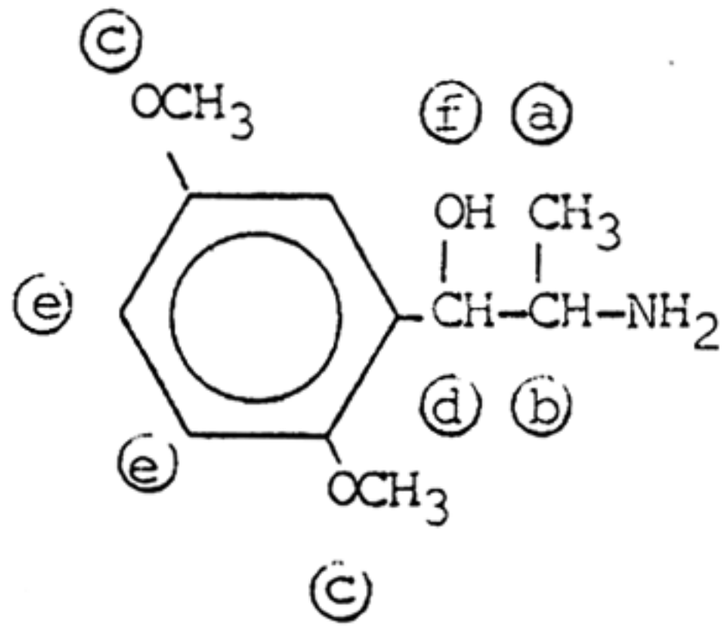
[a] Basic ethanol solvent, pH > 10.
[b] Calculated by method of Noyes in ref. 16.

Table 2. NMR data (cps) for the phenyl-propyl amines; chemical shift relative to TMS

Compound	Proton	$CDCl_3$	CF_3COOH
	a	67	95
	b	157	195
	c	285	235
	d	435	443
	a	63	92
	b	144	174
	c	162	186
	d	435	437
	a	64	78
	b	139	165
	c	160	196
	d	160	196
	e	437	437

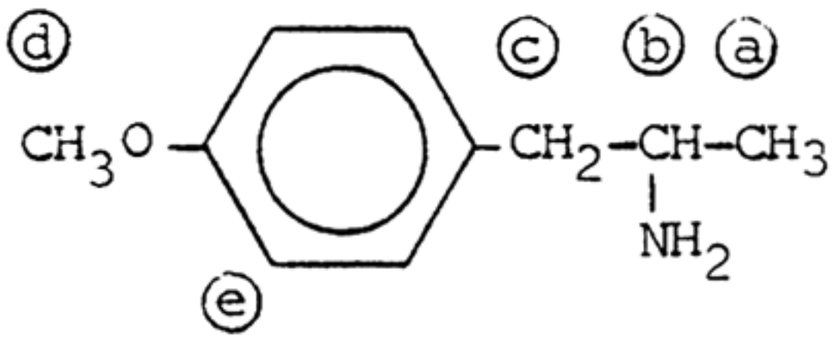
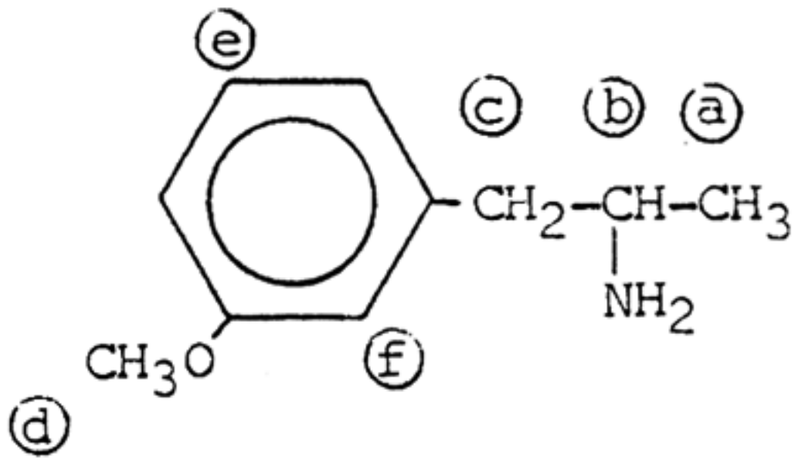
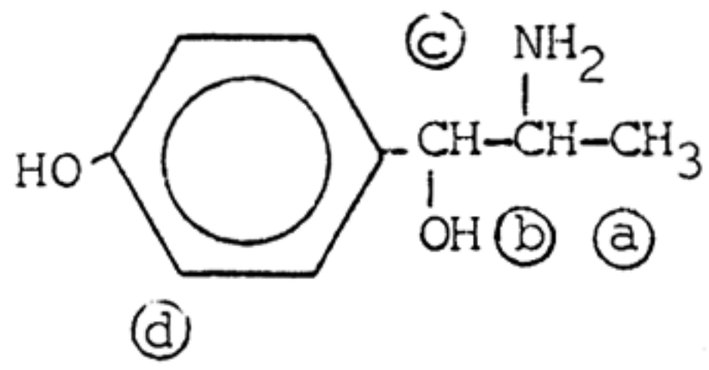
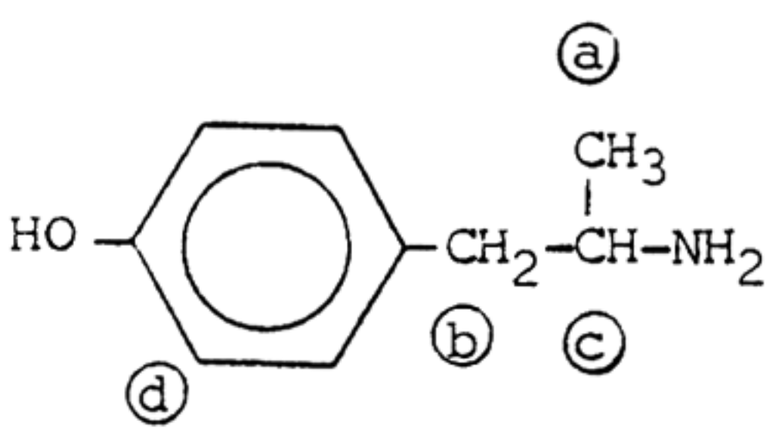
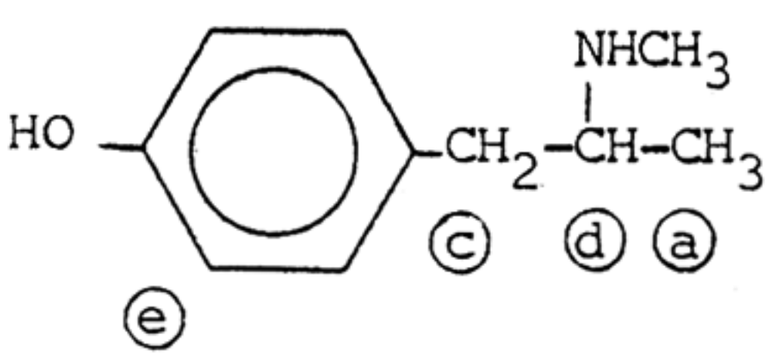
(*Continued*)

Table 2. (*Continued*)

Compound	Proton	$CDCl_3$	CF_3COOH
	a	73	77
	b	138	165
	c	160	196
	d	160	196
	e	433	437
	a	52	81
	b	146	183
	c	170	225
	d	285	323
	e	438	448
	a	53	79
	b	142	183
	c	158	222
	d	253	294
	e	440 (pseudo)	448
	a	56	82
	b	188	240
	c	270	315
	d	440	447
	a	55	82
	b	153	246
	c	252	300
	d	439	449
	a	62	90
	b	145	175
	c	170	190
	d	170	190
	e	229	237
	f	425	430
	a	56	84
	b	158	250
	c	224	237
	d	290	326
	e	406	429
	f	424	429

(*Continued*)

Table 2. (*Continued*)

Compound	Proton	$CDCl_3$	CF_3COOH
	a	64	91
	b	150	180
	c	150	180
	d	223	236
	e	417	429
	a	78	94
	b	160	182
	c	160	189
	d	228	240
	e	408	420
	f	435	440
	insoluble		87
			245
			300–330
			437
	a	69	94
	b	156	181
	c	185	230
	d	410	428
	a	60	89
	b	139	174
	c	155	182
	d	155	219
	e	420	425

(*f*) Our spectroscopically determined pKa's (phenols) are in good agreement with those reported by others (12, 13). However, the potentiometric methods coupled with the Noyes method (16) of calculation for overlapping constants gave results for the phenolic pKa′ that were lower by 0.1 and 0.2 unit for Nos. 14 and 15, respectively, and very imprecise results for No. 13. Consequently, the pKa′ values for these compounds were determined by the same procedure used by Kappe and Armstrong (13) (spectroscopic value used to determine amine value from titration curve).

References

(1) Albert, A., and Serjeant, E. P., *Ionization Constants of Acids and Bases*, John Wiley and Sons, Inc., New York, 1962.

(2) Bellamy, L. J., *Infrared Spectra of Complex Molecules*, 2nd Ed., John Wiley and Sons, Inc., New York, 1958.

(3) Portoghese, P. S., *J. Med. Chem.* **10**, 1057–1063 (1967).

(4) Lowenstein, A., and Meiboom, S., *J. Chem. Phys.* **27**, 1067–1069 (1957).
(5) Jackman, L. M., *Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York, 1959.
(6) Pople, J. A., Schneider, W. G., and Bernstein, H. J., *High Resolution Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, 1959.
(7) Thompson, W. E., Warren, R. J., Zarembo, J. E., and Eisdorfer, I. B., *J. Pharm. Sci.* **55**, 110–111 (1966).
(8) Thompson, W. E., Warren, R. J., Zarembo, J. E., and Eisdorfer, I. B., *J. Pharm. Sci.* **55**, 857–858 (1966).
(9) Everett, D. H., and Hyne, J. B., *J. Chem. Soc.* 1636–1642 (1958).
(10) Leffler, E. B., Spencer, H. M , and Burger, A., *J. Amer. Chem. Soc.* **73**, 2611–2613 (1951).
(11) Prelog, V. Von, and Hafliger, O., *Helv. Chim. Acta* **33**, 2021–2029 (1950).
(12) Lewis, G. P., *Brit. J. Pharmacol.* 9, 488–493 (1954).
(13) Kappe, T., and Armstrong, M. D., *J. Med. Chem.* **8**, 368–374 (1965).
(14) Kanzawa, T., *Bull. Chem. Soc. Japan* **29**, 398–403 (1956).
(15) Hyne, J. B., *Can. J. Chem.* **38**, 125–130 (1960).
(16) Britton, H. T. S., *Hydrogen Ions*, D. Van Nostrand and Co., Inc., Princeton, N. J., 1956, p. 217.