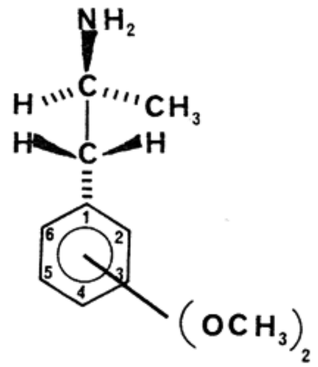
DRUGS

Spectroscopic and Chromatographic Identification of Dimethoxyamphetamines

KEITH BAILEY, DONALD LEGAULT, and DENISE VERNER
Research Laboratories, Health Protection Branch, Tunney's Pasture, Ottawa K1A 0L2, Ontario, Canada

The qualitative analysis of the 6 isomeric dimethoxyamphetamines and their hydrochloride salts is described. Their ultraviolet spectra are insufficiently different for distinction, but mass, proton magnetic resonance, and infrared spectra allow a positive identification to be made, and reference spectra are provided. The application of gas-liquid and thin layer chromatographic systems for the analysis is discussed.

The hallucinogenic dimethoxyamphetamines (DMAs) (1) are formed by dimethoxy substitution in the aromatic ring of amphetamine. In Canada the DMAs and their salts are Restricted Drugs, subject to the same legislative control as the structurally related 2,5-dimethoxy-4-methylamphetamine (STP or DOM), 3,4-methylenedioxyamphetamine (MDA), and others. 2,5-Dimethoxyamphetamine (2,5-DMA) as its hydrobromide has been identified in police exhibits in both Canada (H. D. Beckstead, unpublished data, 1973) and the United States (2). It is important that an unambiguous structural identification be made, and considerable effort has been made to develop analytical methods for abused drugs of the amphetamine type (3). This report describes the mass, ultraviolet (UV), infrared (IR), and proton magnetic resonance (PMR) spectra of the 6 DMAs and their hydrochloride salts. Melting point and thin layer and gas-liquid chromatographic data are also presented.



Structure of DMAs (only S form shown).

Experimental

The amphetamines were prepared from the corresponding dimethoxybenzaldehydes via reduction of the corresponding β-methyl-β-nitrostyrenes with lithium aluminum hydride (4). They were purified as the hydrochloride salts, all of which were recrystallized from isopropanol-hexane mixtures (Table 1). The hydrochlorides are more or less hygroscopic, and consequently their melting points may vary, depending on the drying conditions. Thus, 2,5-DMA.HCl had a melting point of 105–106°C which increased to 110–113°C after a few days' exposure to humid air, and the salt eventually deliquesced. The IR spectra (KBr disk) of samples having mp 105–106°C and 110–113°C could not be differentiated. 3,4-DMA.HCl was obtained as the monohydrate, determined by combustion analysis, and apparent in the PMR spectrum. Thin layer chromatograms were examined under 254 nm UV light and sprayed with ninhydrin.

Results and Discussion

Mass Spectra

The mass spectra of the DMA hydrochlorides have been presented and discussed elsewhere (7). The weakness of the spectra and their general similarity indicate that although dimethoxyamphetamines may be recognized easily, mass spectrometry alone might not allow identification of the substitution pattern. The parent ion (m/e = 195) is of low relative intensity, and the 2 most intense ions observed in all of the spectra are at m/e = 152 and m/e = 44 (the base peak) (7).

Ultraviolet Spectra

Table 2 lists UV data for the 6 compounds. The $\pi - \pi^*$ transition for 2,5-DMA.HCl is at a distinctly longer wavelength than it is for its isomers, and the spectrum is virtually indistinguishable from that of 2,4,5-trimethoxyamphetamine hydrochloride (λ_{max}^{EtOH} 290 (ξ 4400) and 231 (ξ 7700) nm). The data in Table 2 indicate that once an isomer has been identified

Table 1. Analytical and melting point data for dimethoxyamphetamine hydrochlorides

Compound	Found, %[a] C	H	N	Mp, °C[b]	Lit. mp, °C
2,3-	56.8	7.8	6.0	154–155	154–156 (5)
2,4-	56.9	7.9	6.0	149–150	
2,5-	56.95	7.9	6.1	105–106	111.5–112.5 (5)
2,6-	56.8	7.8	6.25	185–186 (subl.)	185–186 (6)
3,4-.H_2O	53.2	7.8	5.95	145–146	147.5–148 (5)
3,5-	57.2	7.75	6.2	161–162	160–161[c] (5)

[a] Calcd for (%) $C_{11}H_{18}ClNO_2$: C, 57.0; H, 7.8; N, 6.05. Calcd for (%) $C_{11}H_{18}ClNO_2.H_2O$: C, 52.9; H, 8.1; N, 5.6.
[b] Corrected, samples were recrystallized from isopropanol-hexane mixtures.

Table 2. Ultraviolet data for dimethoxyamphetamine hydrochlorides[a]

Compound	$\lambda_{max.}$, nm	ϵ	$\lambda_{max.}$, nm	ϵ
2,3-	274–278[b]	1660	218	8040
2,4-	278–283[b]	3000–2680	227	9000
2,5-	291	3930	228	8130
2,6-	272–279	1440–1440	221	7820
3,4-[c]	280	3230	232	9430
3,5-	272–282	1260–1330	224	8210

[a] Solutions in ethanol.
[b] Peak with "saddle."
[c] ϵ calculated as monohydrate (see Experimental).

qualitatively, UV spectroscopy may be used for the quantitative analysis.

Infrared Spectra

Infrared spectra of the free bases (films on NaCl plates) and of the hydrochlorides (KBr disks) are presented in Figs. 1–12. The spectra are distinct from one another and have sufficient detail for identification. None resemble the spectra of the monomethoxyamphetamines (8), but the spectrum of 2,5-DMA (Fig. 5) is similar to that of methoxamine, its α-hydroxylated derivative (2, 8). 2,3- and 2,6-DMA have "1,2,3-type" aromatic proton substitution patterns, and 2,4-, 2,5-, and 3,4-DMA have "1,2,4-type" substitution. Although there are guidelines for determining aromatic substitution patterns from IR bands (9), the spectra show that such determinations should be made cautiously.

Proton Magnetic Resonance Spectra

The PMR spectra of the DMAs and their hydrochlorides have been reported (4), with the exception of 2,6-DMA which has signals at δ 1.10 (doublet, β-CH_3), 2.69 (multiplet, α protons), 3.15 (multiplet, β proton), 3.79 (singlet, 2 overlapping $-OCH_3$ groups), 6.54 ("doublet," protons 3 and 5), and 7.14 ("double doublet," proton 4) ppm in $CDCl_3$ at 60 MHz. The hydrochloride in $CDCl_3$ has the corresponding signals at δ 1.42, 3.05, ca 3.60, 3.83 (singlet, 2 overlapping $-OCH_3$ groups), 6.53, and ca 7.15 ppm. The aromatic protons give rise to typical AB_2 patterns (9) (*see* Figs. 13G and 13H).

The spectra of 2,6-DMA and 2,4,6-trimethoxyamphetamine resemble one another and differ from the other compounds (4) in that the 2 α and β protons give a complex signal in $CDCl_3$ at 60 MHz which approximates the A_2B case (9).

Integrated spectra enable one to immediately recognize a dimethoxyamphetamine, and the pattern of the aromatic proton signals allows their distinction from one another. Figure 13A–M shows the aromatic proton signals from the free bases and their salts. The solvent was $CDCl_3$, except for 13F and 13K, and the small signal with "ringing" at 7.24 ppm is due to the small amount of $CHCl_3$ present. Solutions of 2,5- and 3,4-DMA hydrochlorides in $CDCl_3$ gave aromatic proton signals which were almost singlets (both at about 6.76 ppm) and for these 2 compounds, information on the aromatic substitution is apparent by comparing the spectra determined in D_2O (Figs. 13F and 13K).

Thin Layer Chromatography

Kaistha and Jaffe (10) and Cartoni *et al.* (11) recommended several solvent systems for the thin layer chromatographic differentiation of amphetamine, methamphetamine, and other psychotropic drugs. The results from the dimethoxyamphetamines (Table 3) show that their R_f values are generally between those of amphetamine and methamphetamine. The spots were somewhat elongated, and with the exception of 3,4-DMA, these isomers may not be definitely distinguished using these systems.

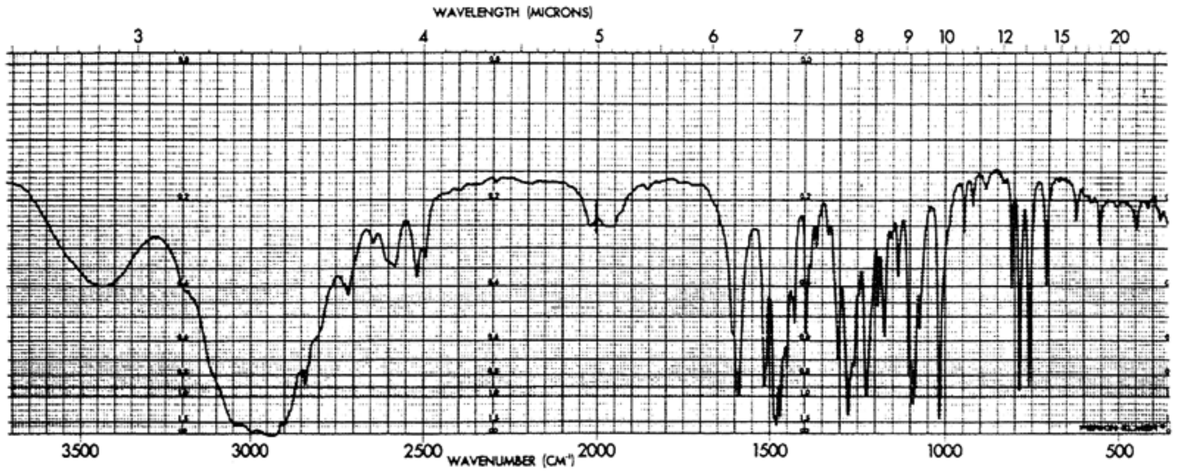


FIG. 1—2,3-Dimethoxyamphetamine hydrochloride, KBr disk.

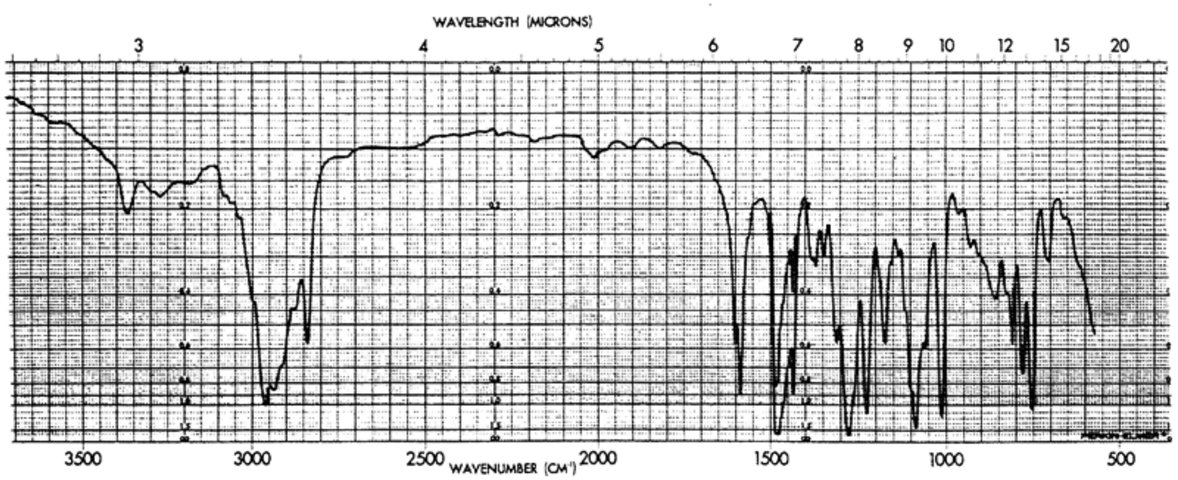


FIG. 2—2,3-Dimethoxyamphetamine base, NaCl film.

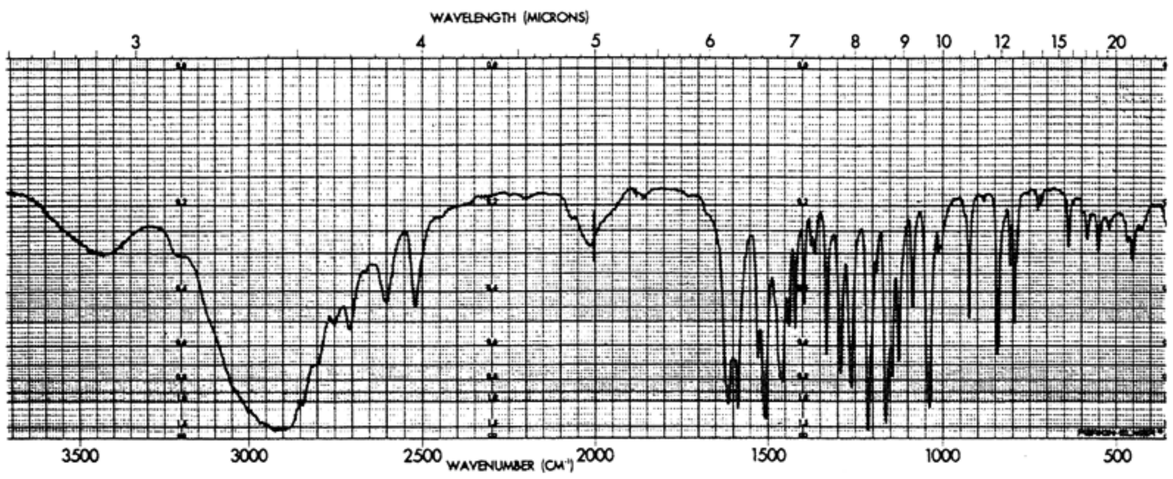


FIG. 3—2,4-Dimethoxyamphetamine hydrochloride, KBr disk.

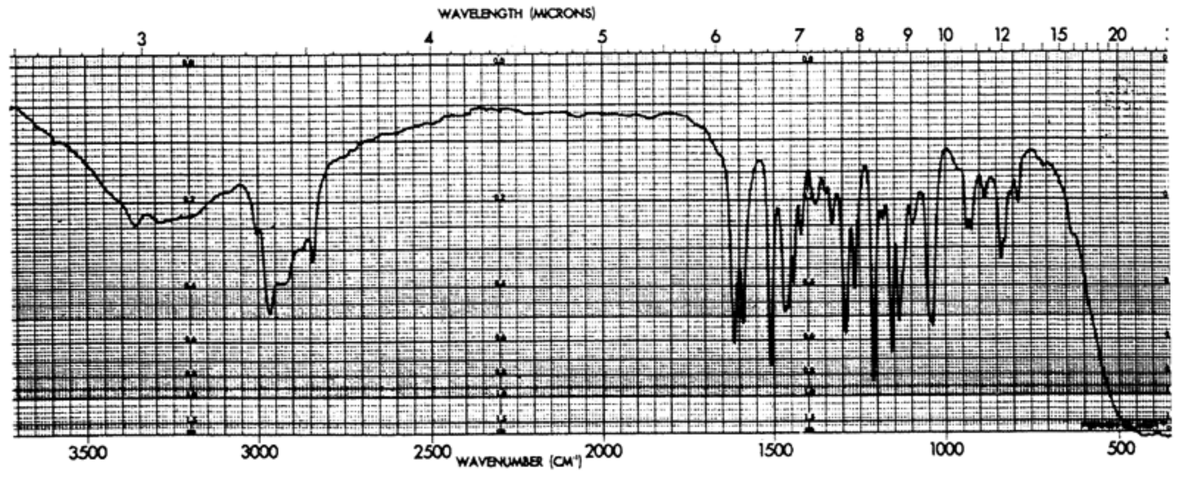


FIG. 4—2,4-Dimethoxyamphetamine base, NaCl film.

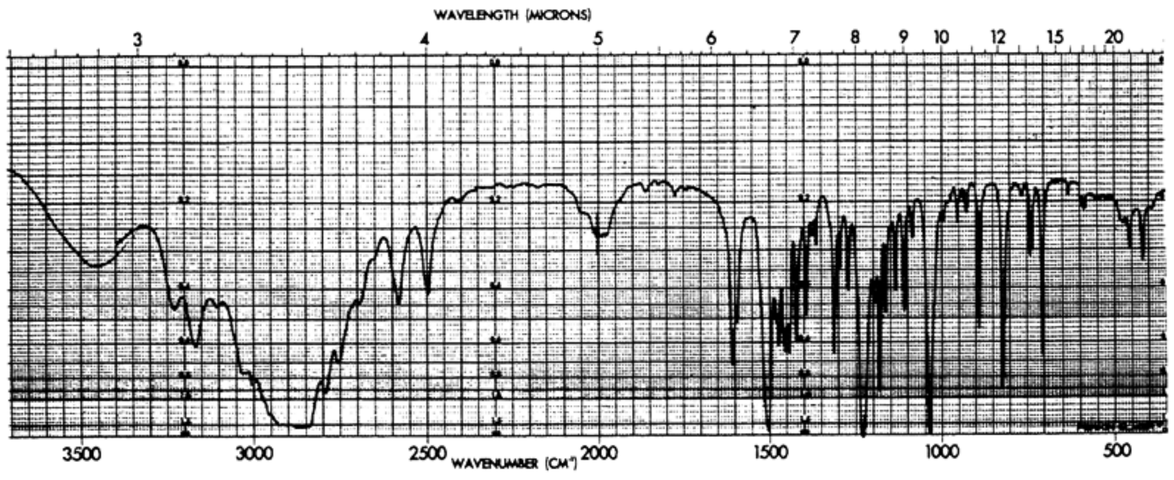


FIG. 5—2,5-Dimethoxyamphetamine hydrochloride, KBr disk.

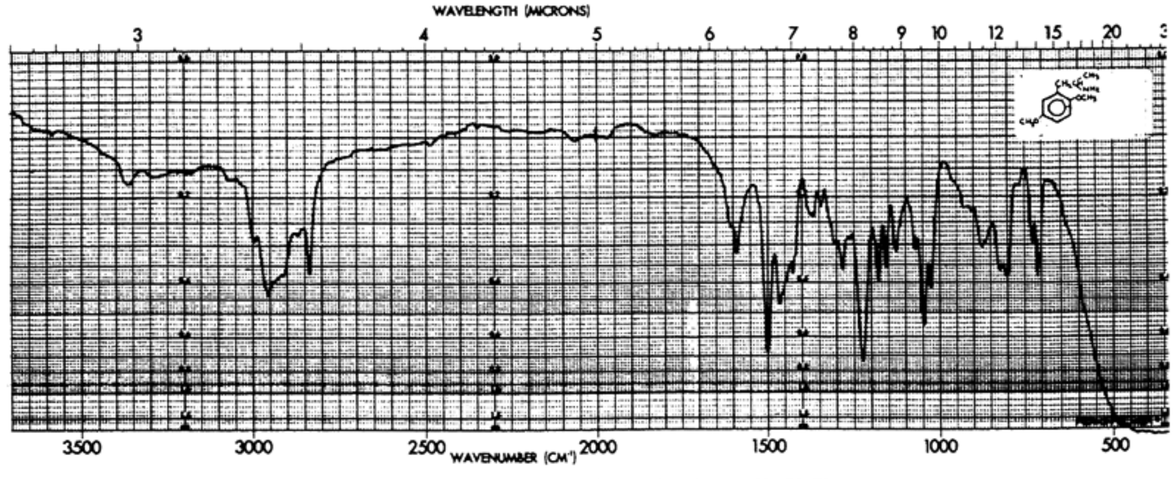


FIG. 6—2,5-Dimethoxyamphetamine base, NaCl film.

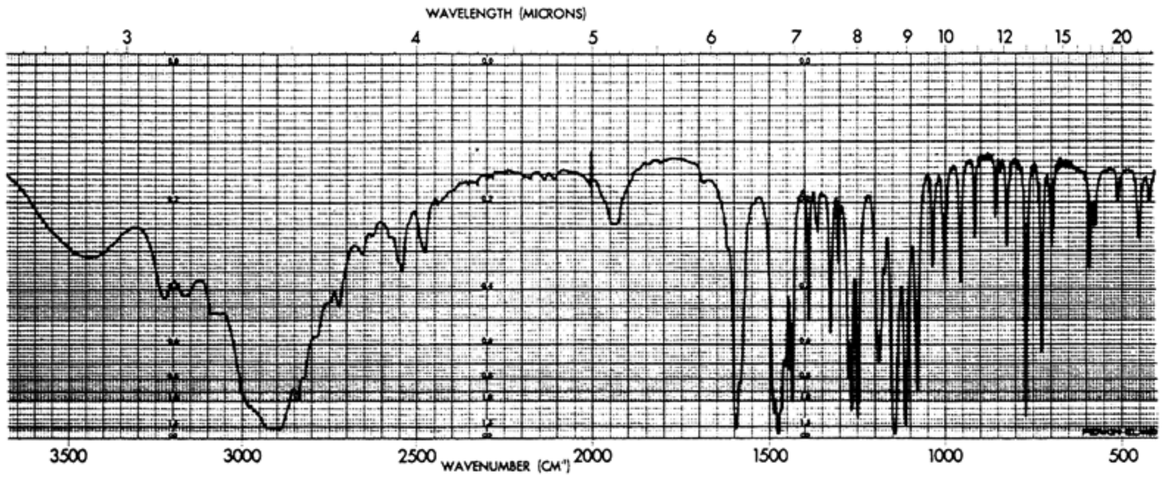


FIG. 7—2,6-Dimethoxyamphecamine hydrochloride, KBr disk.

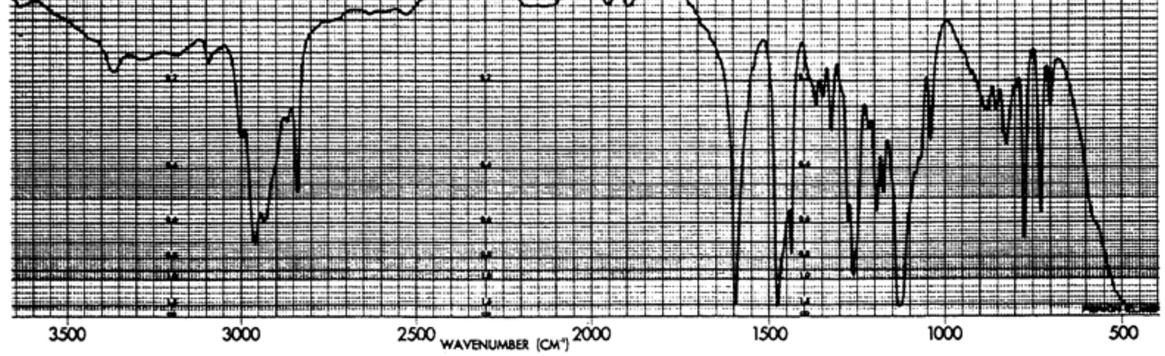


FIG. 8—2,6-Dimethoxyamphetamine base, NaCl film.

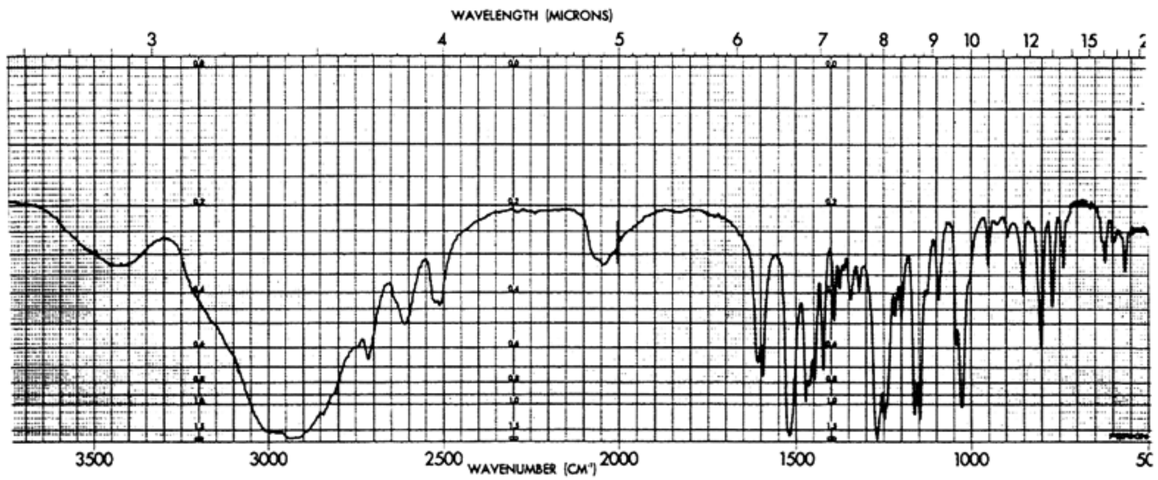


FIG. 9—3,4-Dimethoxyamphetamine hydrochloride, KBr disk.

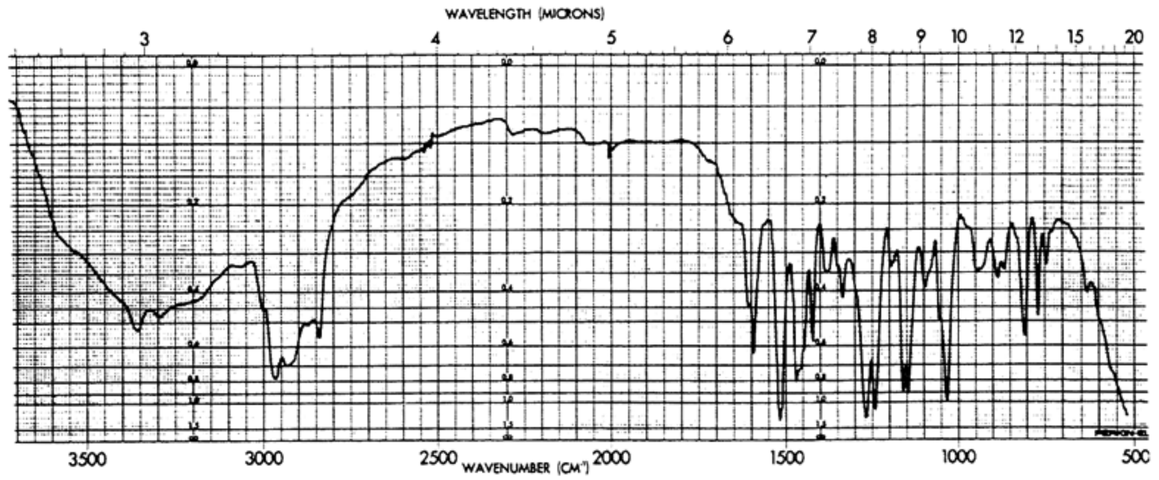


FIG. 10—3,4-Dimethoxyamphetamine base, NaCl film.

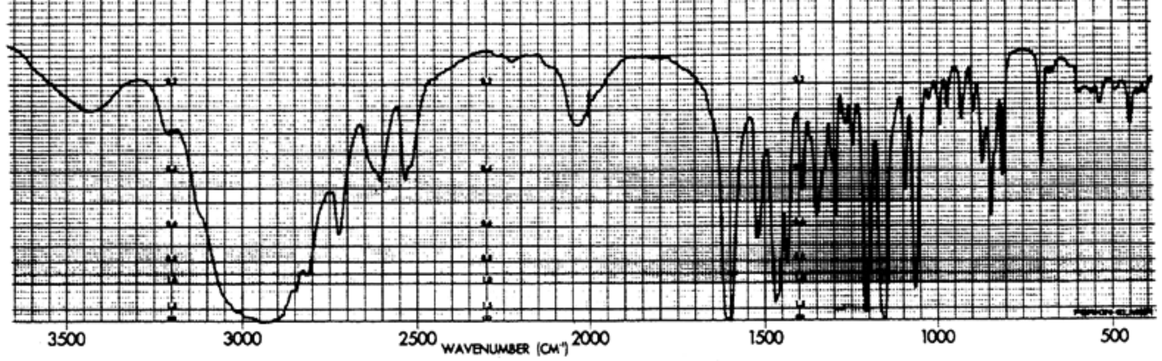


FIG. 11—3,5-Dimethoxyamphetamine hydrochloride, KBr disk.

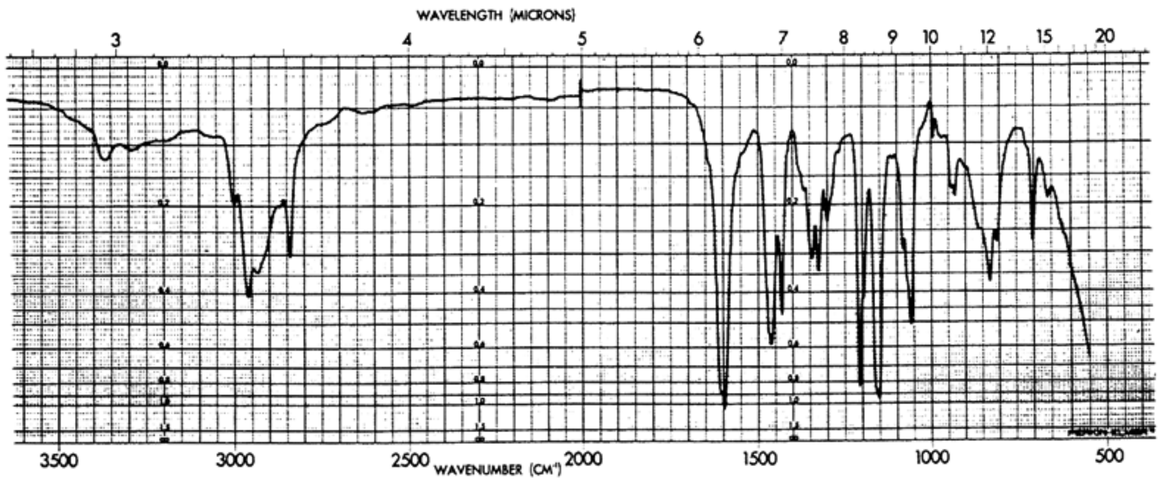
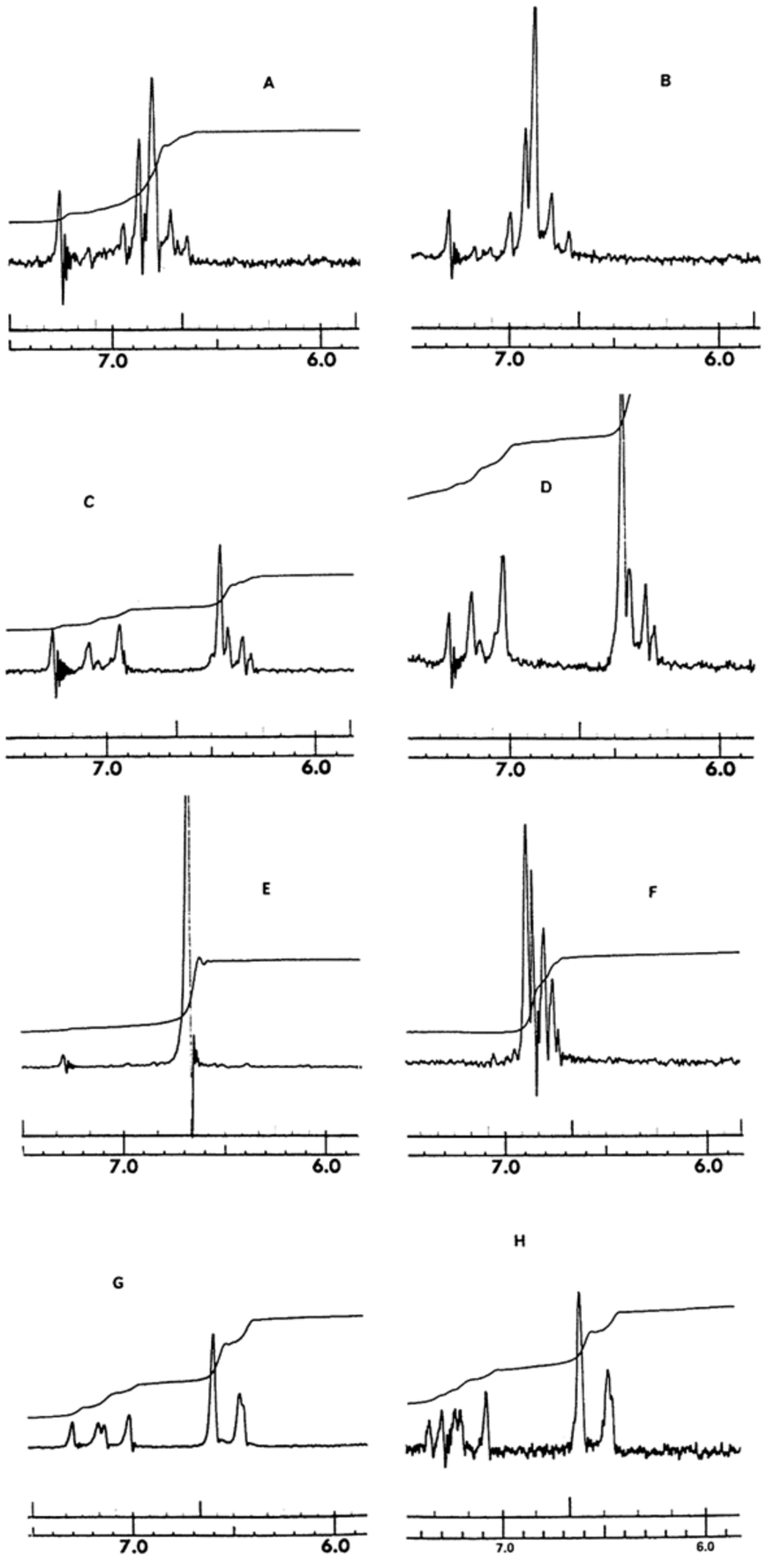


FIG. 12—3,5-Dimethoxyamphetamine base, NaCl film.



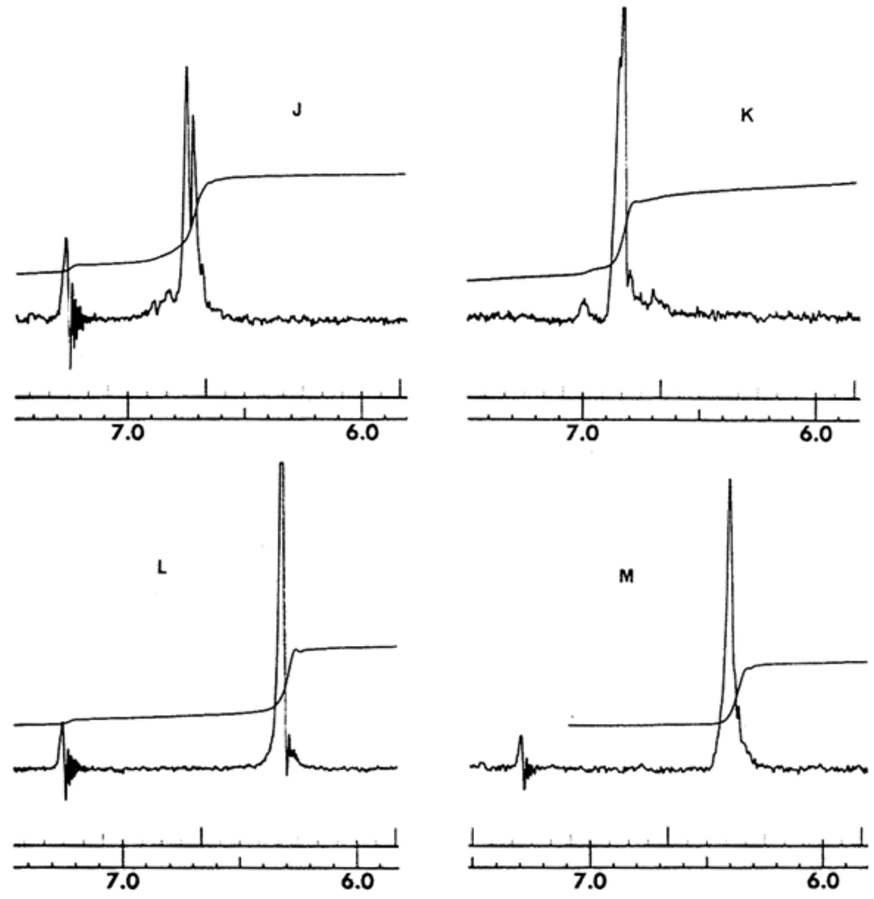


FIG. 13—Proton magnetic resonance spectra of dimethoxyamphetamines (DMAs) and their hydrochlorides in the region 5.8–7.5 ppm downfield of TMS, recorded at 60 MHz on Varian A-60A spectrometer. Solvent used is in parentheses.

A, 2,3-DMA ($CDCl_3$); B, 2,3-DMA.HCl ($CDCl_3$); C, 2,4-DMA ($CDCl_3$); D, 2,4-DMA.HCl ($CDCl_3$); E, 2,5-DMA ($CDCl_3$); F, 2,5-DMA.HCl (D_2O); G, 2,6-DMA ($CDCl_3$); H, 2,6-DMA.HCl ($CDCl_3$); J, 3,4-DMA ($CDCl_3$); K, 3,4-DMA.HCl (D_2O); L, 3,5-DMA ($CDCl_3$); M, 3,5-DMA.HCl ($CDCl_3$).

Table 3. R_f values of dimethoxyamphetamines

System[a]	Plate[b]	2,3–	2,4–	2,5–	2,6–	3,4–	3,5–	Amph.[c]	Meth.[c]
A	Brinkmann	0.26	0.25	0.25	0.23	0.15	0.22	0.28	0.22
A	Eastman S	0.47	0.44	0.45	0.40	0.33	0.44	0.49	0.46
B	Brinkmann	0.30	0.30	0.30	0.23	0.19	0.27	0.32	0.23
B	Eastman S	0.57	0.55	0.61	0.56	0.53	0.58	0.60	0.52
C	Brinkmann	0.48	0.46	0.49	0.43	0.42	0.49	0.50	0.38
C	Eastman A	0.78	0.78	0.78	0.81	0.78	0.78	0.81	0.82
C	Eastman S	0.63	0.60	0.65	0.63	0.58	0.65	0.67	0.58
D	Brinkmann	0.50	0.51	0.49	0.52	0.40	0.49	0.52	0.37
D	Eastman A	0.74	0.72	0.72	0.76	0.64	0.72	0.75	0.84
D	Eastman S	0.63	0.64	0.65	0.66	0.55	0.62	0.66	0.55
E	Eastman A	0.65	0.66	0.66	0.67	0.66	0.65	0.64	0.68
E	Eastman S	0.38	0.27	0.34	0.26	0.32	0.44	0.45	0.44
F	Brinkmann	0.19	0.13	0.18	0.10	0.15	0.18	0.17	0.17

[a] A = ethyl acetate-cyclohexane-dioxane-methanol-water-ammonium hydroxide (50+50+10+10+1.5+0.5) (10).
B = ethyl acetate-cyclohexane-ammonium hydroxide-methanol-water (70+15+2+8+0.5) (10).
C = ethanol-5*N* ammonia (9+1) (9).
D = *n*-butanol-formic acid-water (20+1+2) (9).
E = chloroform-methanol (8+1).
F = chloroform-methanol (1+1).
Developing time (15 cm) for systems C and D was >5 hr.

[b] Brinkmann = Brinkmann silica gel G glass plates, and Eastman A and Eastman S = Eastman Chromagram 6063 alumina and 6060 silica gel sheets, respectively.

[c] Amph. = amphetamine and Meth. = methamphetamine.

Gas-Liquid Chromatography

The results obtained with 5% OV-7 and 2.5% OV-225 (Table 4) were similar. The order of emergence from both columns was the same. However, while mixtures of amphetamine and methamphetamine separated on the OV-7, mixtures of 2,4- and 3,4-DMA did not, but the reverse was found on OV-225. Chloroform solutions of the hydrochlorides injected onto the columns gave the same results, but led to more rapid deterioration of column performance (peak broadening and retention times steadily increasing). The use of OV-225 (recommended for the isothiocyanate derivatives of amphetamines (12)) allows rapid distinction of the dimethoxyamphetamines.

Table 4. Retention times (min) of dimethoxyamphetamines[a]

Compound	5% OV-7	2.5% OV-225
2,3-	5.7	4.6
2,6-	7.5	5.8
2,5-	7.9	6.7
2,4-	8.7	7.2
3,4-	9.0	8.5
3,5-	10.2	9.2
Amphetamine	1.5	2.0[b]
Methamphetamine	1.7	2.1[b]

[a] Columns were of glass, 6′ long, with 80–100 mesh Chromosorb W as support. Injector at 275°, nitrogen flow 30 ml/min. Column temperature 150°C except as noted.

[b] Column temperature 125°C.

Acknowledgments

The cooperation of A. W. By, H. W. Avdovich, J. C. Ethier, and K. C. Graham is much appreciated.

REFERENCES

(1) Shulgin, A. T., Sargent, T., & Naranjo, C. (1969) *Nature* **221**, 537–541
(2) Shaler, R. C., & Padder, J. J. (1972) *J. Pharm. Sci.* **61**, 1851–1855
(3) Kaistha, K. K. (1972) *J. Pharm. Sci.* **61**, 655–679
(4) Bailey, K., By, A. W., Graham, K. C., & Verner, D. (1971) *Can. J. Chem.* **49**, 3143–3151
(5) Ho, B. T., McIsaac, W. M., An, R., Tansey, L. W., Walker, K. E., Englert, L. F., & Noel, M. B. (1970) *J. Med. Chem.* **13**, 26–30
(6) Shamshurin, A. A., & Revenko, Y. M. (1962) *Izv. Akad. Nauk. Mold. SSR* **10**, 86–97
(7) Bailey, K. (1972) *Anal. Chim. Acta* **60**, 287–292
(8) Warren, R. J., Begosh, P. P., & Zarembo, J. E. (1971) *JAOAC* **54**, 1179–1191
(9) Dyer, J. R. (1965) *Applications of Absorption Spectroscopy of Organic Compounds,* Prentice-Hall, Inc., Englewood Cliffs, N.J., pp. 52, 102–107
(10) Kaistha, K. K., & Jaffe, J. H. (1972) *J. Pharm. Sci.* **61**, 679–689
(11) Cartoni, G. P., Lederer, M., & Polidori, F. (1972) *J. Chromatogr.* **71**, 370–375
(12) Narasimhachari, N., & Vouros, P. (1972) *Anal. Biochem.* **45**, 154–163

Received March 7, 1973.