DRUGS

Identification of the *N*-Methylated Analogs of the Hallucinogenic Amphetamines and Some Isomers

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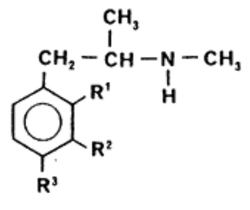
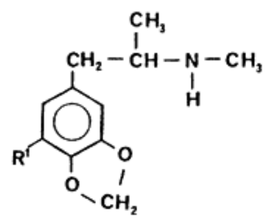
The drugs 2-, 3-, and 4-methoxy-*N*-methylamphetamine, 3-methoxy-4,5-methylenedioxy-*N*-methylamphetamine, and 3,4-methylenedioxy-*N*-methylamphetamine are identified by spectroscopic techniques. The ultraviolet and mass spectra of isomers are similar, but proton magnetic resonance and infrared spectra are distinctly different, and reference spectra and data are provided. Gas-liquid and thin layer chromatographic systems for the analysis are discussed.



I–III



IV–V

I: $R^1 = OCH_3$, $R^2 = R^3 = H$
II: $R^2 = OCH_3$, $R^1 = R^3 = H$
III: $R^3 = OCH_3$, $R^1 = R^2 = H$
IV: $R^1 = H$
V: $R^1 = OCH_3$

Drugs of the amphetamine class have a high potential for abuse, and occur frequently on the illicit market. Some of them are used for their reported (1) hallucinogenic effects, e.g., 4-methoxyamphetamine (PMA), 3-methoxy-4,5-methylenedioxyamphetamine (MMDA), and 3,4-methylenedioxyamphetamine (MDA), and some for their properties as central stimulants, e.g., *N*-methylamphetamine (methamphetamine, speed). 3,4-Methylenedioxy-*N*-methylamphetamine (also known as 3,4-methylenedioxymethamphetamine, MDMA) has been encountered on the illicit market. It is chemically very similar to both methamphetamine and MDA, having the structural features of both, but pharmacological data are not available. 2-Methoxy-*N*-methylamphetamine (methoxyphenamine, I) is in this structural class; it is a sympathomimetic drug with legitimate use in the relief of bronchial asthma.

There is an obvious need for methods which provide an unequivocal identification of these closely related compounds. This paper describes chromatographic and spectroscopic methods for identifying 5 *N*-methylamphetamines in this class: 2-methoxy- (I), 3-methoxy- (II), 4-methoxy- (III), 3,4-methylenedioxy- (IV), and 3-methoxy-4,5-methylenedioxy-*N*-methylamphetamine (V).

Experimental

Compound I was obtained by recrystallization of commercial methoxyphenamine HCl. Compounds II–V were obtained from the corresponding phenylacetone by a Leuckart reaction with *N*-methylformamide and hydrolysis of the intermediate *N*-formyl derivative (2). The compounds were purified as the hydrochloride salts by recrystallization from mixtures of isopropanol with *n*-hexane. Melting points were measured on a Koffler hot stage and are uncorrected, and elemental analysis indicated that the salts were essentially anhydrous (Table 1). The spectra of free bases were recorded on the amphetamine regenerated from the salt with Na_2CO_3 solution and extracted into $CHCl_3$; the $CHCl_3$ was removed by warming the solution under a stream of dry nitrogen. Thin layer chromatograms were developed 15 cm under ambient conditions, using precoated plates and sheets as received. They were examined under 254 nm ultraviolet light and sprayed with ninhydrin or a solution of chromotropic acid (1,8-dihydroxynaphthalene-3,6-disulfonic acid) (3). (This reagent cannot be used with plastic-based sheets, because they darken and distort when heated to develop the spot.) Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6L instrument, operating at 160–180°C, ionization voltage 70 ev, and acceleration voltage 4–5 v. Samples were introduced via the probe. Infrared spectra were recorded on a Unicam SP 1000 spectrophotometer, and ultraviolet spectra were recorded on a Beckman DB GT spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian A-60A spectrometer. Gas-liquid chromatograms were obtained on Varian Aerograph instruments.

Table 1. Melting point and analytical data for some *N*-methylamphetamine derivatives as their hydrochlorides

Compd	mp, °C	Found, % C	Found, % H	Theoretical, % C	Theoretical, % H
I	129–130.5	60.80	8.73	61.24	8.41
II	88–90	60.80	8.71	61.24	8.41
III	177–178	60.76	8.74	61.24	8.41
IV	147–148	57.81	7.04	57.50	7.02
V	127–128.5	55.52	7.17	55.50	6.99

Table 2. Ultraviolet data[a] for some *N*-methylamphetamine derivatives

Compd	λ Max. (ε)	λ Max. (ε)
I	277 (2010)	272 (2130)
II	280 (1870)	274 (2000)
III	282 (1440)	276 (1660)
IV	286 (3843)	
V	283 (inflexion)	276 (1216)

[a] Solutions of the hydrochloride in ethanol, λ max. in nm.

Results and Discussion

Mass Spectra

The compounds as salts follow the established (4) fragmentation pattern on electron impact. All have their base peak at m/e 58 ($CH_3CH{=}\overset{+}{N}H.CH_3$) and have only weak molecular ions. The isomers I, II, and III have very similar mass spectra, and Fig. 1 shows the normalized spectrum of methoxyphenamine (I) which is representative of the series. The mass spectra of the methylenedioxy derivatives IV and V are also presented in Fig. 1. From these and other data (5, 6) it is concluded that mass spectra may not unequivocally differentiate isomeric amphetamine derivatives, but that they may be used to provide corroborative evidence of identification.

Ultraviolet Spectra

Ultraviolet absorption data on the 5 compounds as salts are listed in Table 2. The wavelengths and extinction coefficients of the maxima in the spectra closely resemble those of the corresponding non-*N*-methylated derivatives (5) and may not alone be used for unequivocal identification.

Proton Magnetic Resonance Spectra

The 5 compounds have distinctly different spectra as free bases examined in $CDCl_3$ solution or as hydrochloride salts examined in D_2O. Data from the spectra are given in Table 3, and the aromatic proton signal patterns are reproduced in Fig. 2. The presence of the strong singlet from the NCH_3 group at about 2.38 ppm for the bases and 2.66 ppm for the salts immediately distinguishes the compounds and their corresponding "nor" derivatives which have otherwise similar spectra (5).

Infrared Spectra

Infrared spectra of the free bases (films between NaCl plates) and of the hydrochlorides (0.75% in KBr disks) are presented in Figs. 3–6. The spectra of the hydrochlorides are clearly distinct from one another and from those of closely related isomers and homologs (5, 6). The spectra of the free bases are similar to those of the corresponding non-*N*-methylated homologs (5), and the spectra of II and its non-

Table 3. Proton magnetic resonance data[a] for some *N*-methylamphetamine derivatives

Compd	β-CH_3	Ar-OCH_3	OCH_2O	α-H_2		β-H	NCH_3	Ar-H
I	1.05	3.81		2.5	—	3.0	2.39	Fig. 2A
II	1.06	3.81		2.5	—	3.0	2.38	Fig. 2B
III	1.03	3.80		2.5	—	3.0	2.38	Fig. 2C
IV	1.05		5.93	2.4	—	3.0	2.39	Fig. 2D
V	1.06	3.90	5.94	2.4	—	3.0	2.38	Fig. 2E
I.HCl	1.21	3.81		2.91		3.50	2.65	Fig. 2F
II.HCl	1.21	3.78		2.90		3.50	2.66	Fig. 2G
III.HCl	1.19	3.76		2.85		3.42	2.66	Fig. 2H
IV.HCl	1.20		5.92	2.83		3.45	2.66	Fig. 2J
V.HCl	1.21	3.82	5.90	2.85		3.45	2.66	Fig. 2K

[a] δ-Value measured at 60 MHz, using ca 10% solutions at 40°C. The spectra of free bases were recorded with deuterium exchange in $CDCl_3$ containing trimethylsilane (TMS) as internal standard, and of hydrochlorides in D_2O with external TMS. The β-CH_3 signal was a doublet (J ca 6.5 Hz), the Ar-OCH_3, NCH_3, and OCH_2O signals were singlets, and the α-methylene protons and the β-proton signals were overlapping multiplets whose individual band centers are given for the salts and approximate ranges for the bases.

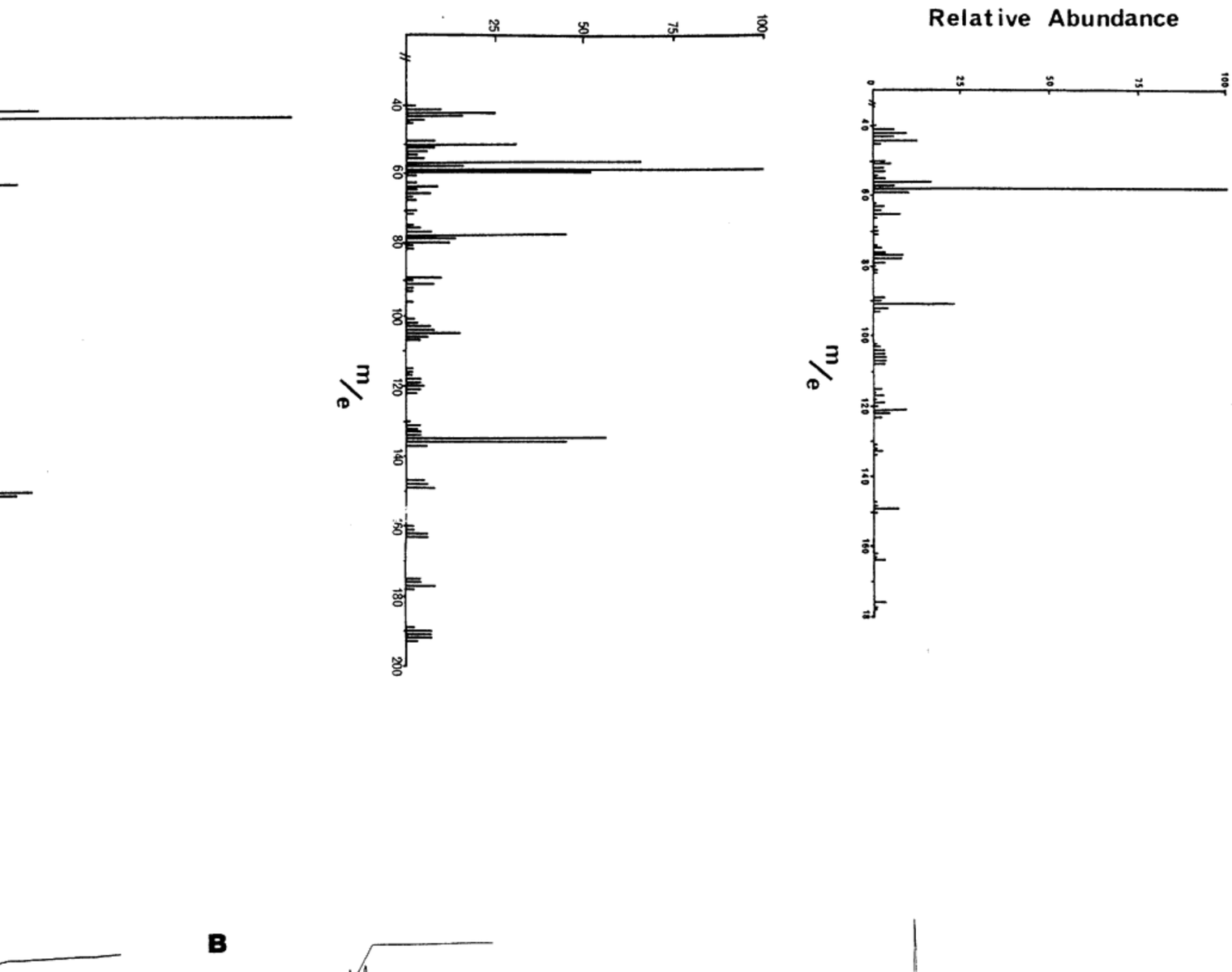
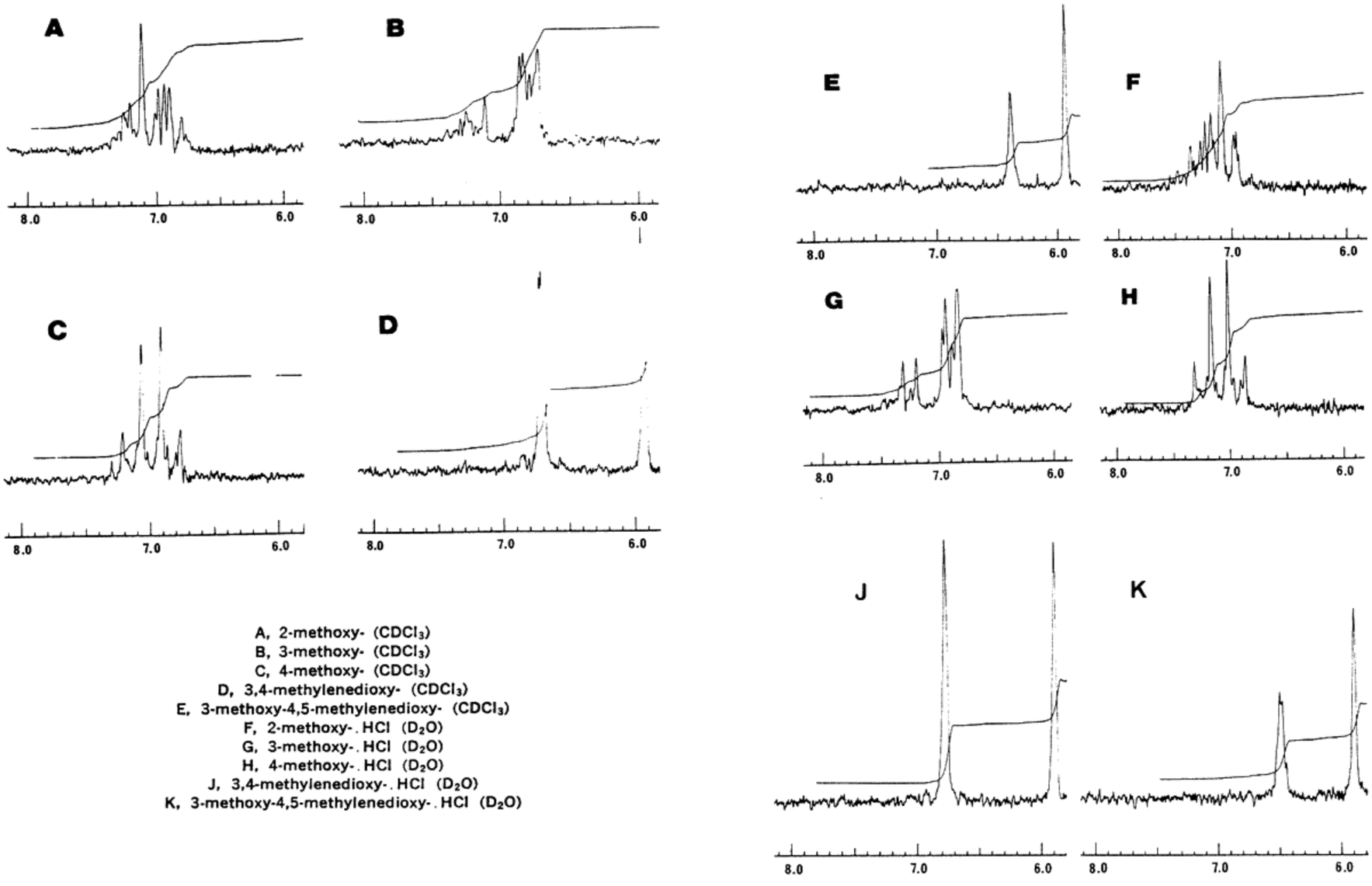


FIG. 1—Normalized mass spectra of top, 2-methoxy-*N*-methylamphetamine HCl; middle, 3,4-methylenedioxy-*N*-methylamphetamine HCl; bottom, 3-methoxy-4,5-methylenedioxy-*N*-methylamphetamine HCl.



A, 2-methoxy- ($CDCl_3$)
B, 3-methoxy- ($CDCl_3$)
C, 4-methoxy- ($CDCl_3$)
D, 3,4-methylenedioxy- ($CDCl_3$)
E, 3-methoxy-4,5-methylenedioxy- ($CDCl_3$)
F, 2-methoxy-. HCl (D_2O)
G, 3-methoxy-. HCl (D_2O)
H, 4-methoxy-. HCl (D_2O)
J, 3,4-methylenedioxy-. HCl (D_2O)
K, 3-methoxy-4,5-methylenedioxy-. HCl (D_2O)

FIG. 2—Proton magnetic resonance spectra of some *N*-methylamphetamine derivatives and their hydrochlorides in the region 6.0–8.0 ppm downfield of TMS, recorded at 60 MHz. The solvent used is shown in parentheses.

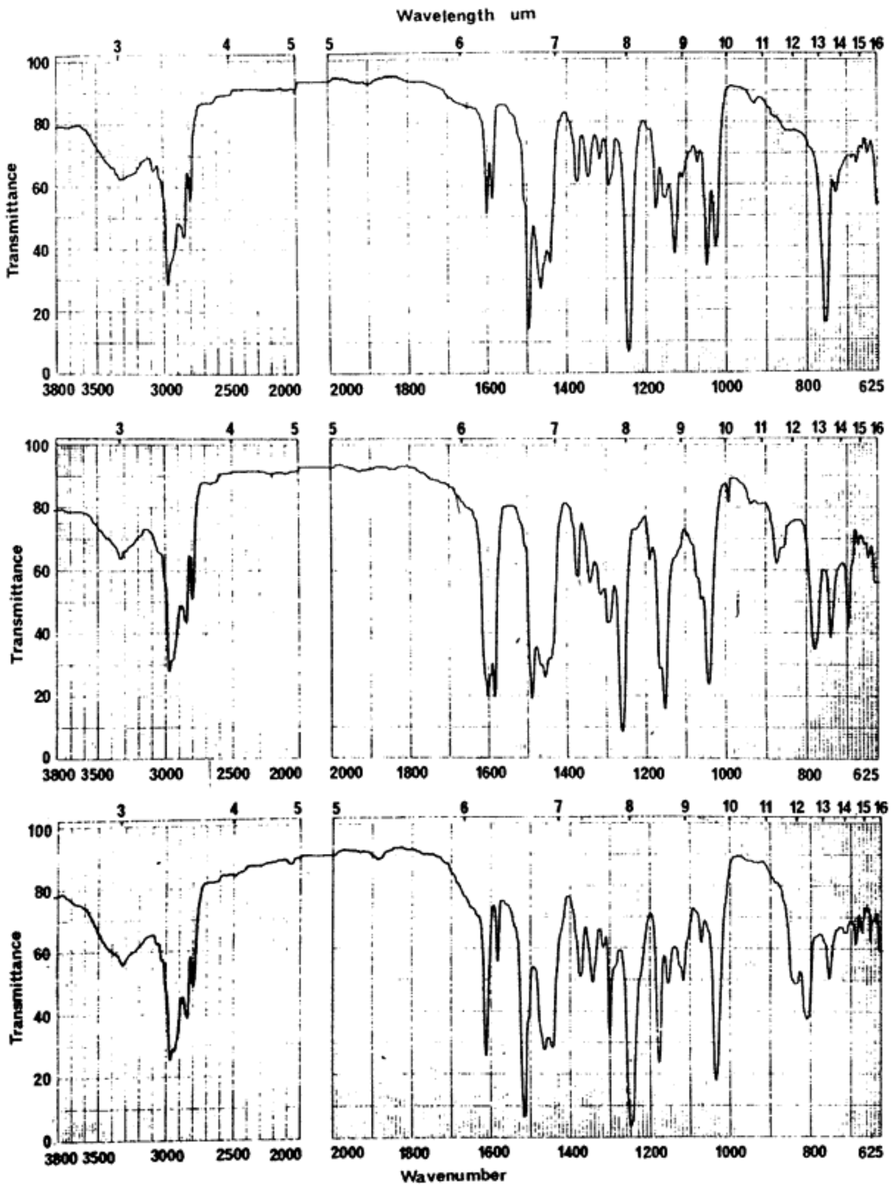


FIG. 3—Infrared spectra of top, 2-methoxy-*N*-methylamphetamine base, NaCl film; middle, 3-methoxy-*N*-methylamphetamine base, NaCl film; bottom, 4-methoxy-*N*-methylamphetamine base, NaCl film.

methylated homolog bear close resemblances to one another, except in the regions 1400–1300 and 1000–800 cm^{-1}.

Thin Layer Chromatography

Several systems were investigated (Table 4). Amphetamine and methamphetamine were included in order to compare data for these compounds at least qualitatively with those presented (5, 6) for closely related amphetamine derivatives. The use of a chromotropic acid spray reagent (3) allowed the positive, rapid differentiation of IV and V from I, II, and III—it gave a blue spot only with the methylenedioxy compounds. It appears that the general trend of the change in R_f values with position of methoxyl substitution for isomers I–III (R_f II > R_f I > R_f III) parallels that found for the non-methylated isomers (5).

Gas-Liquid Chromatography of Bases

The results obtained with several phases are presented in Table 5. Their order of emergence from these columns is the same as that for the non-*N*-methylated derivatives (5). The general appearance of the chromatograms obtained on

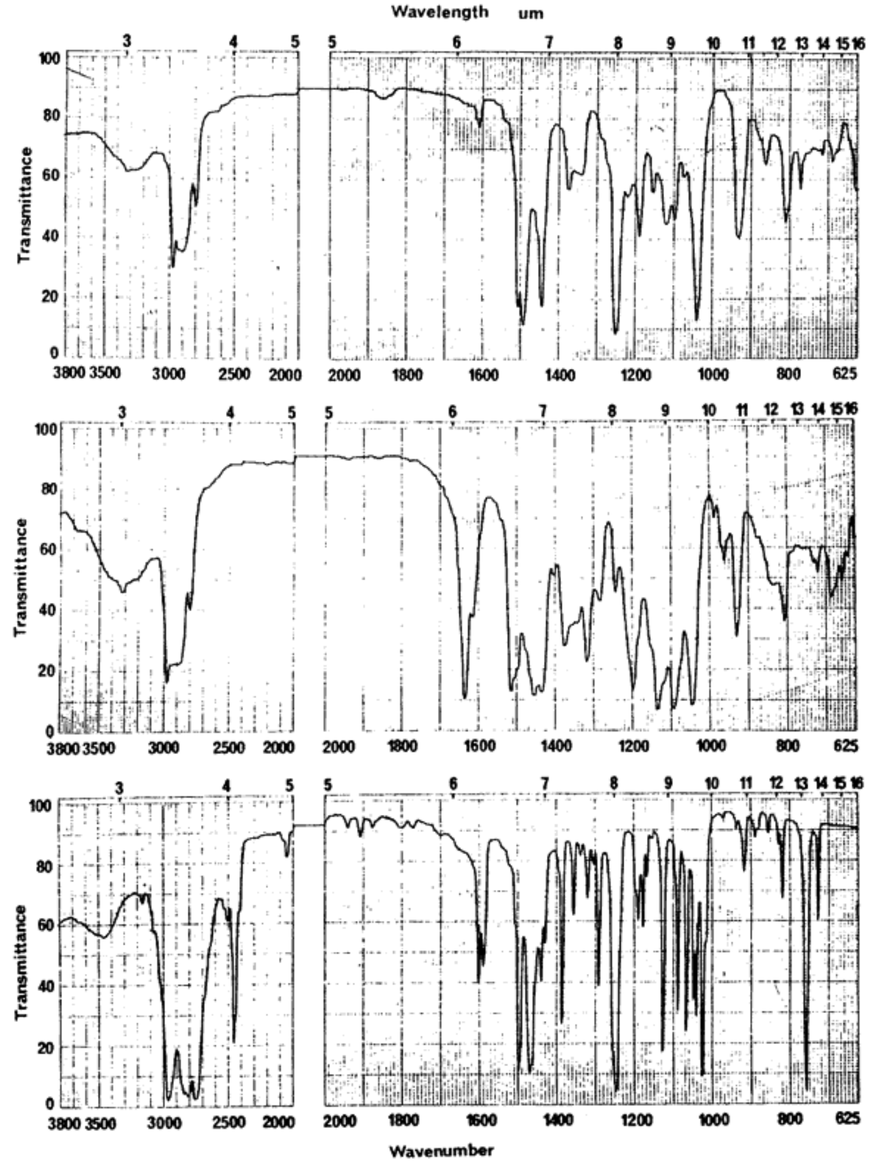


FIG. 4—Infrared spectra of top, 3,4-methylenedioxy-*N*-methylamphetamine base, NaCl film; middle, 3-metho 4,5-methylenedioxy-*N*-methylamphetamine base, NaCl film; bottom, 2-methoxy-*N*-methylamphetamine HCl, K disk.

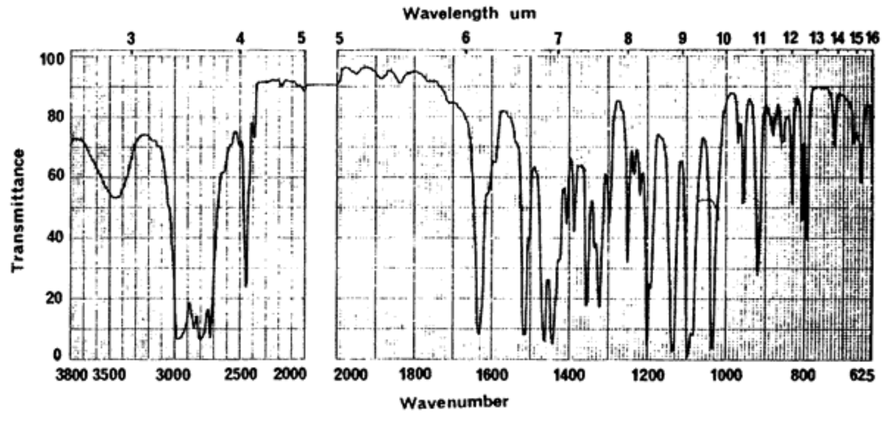


FIG. 5—Infrared spectrum of 3-methoxy-4,5-methylenedioxy-*N*-methylamphetamine HCl, KBr disk.

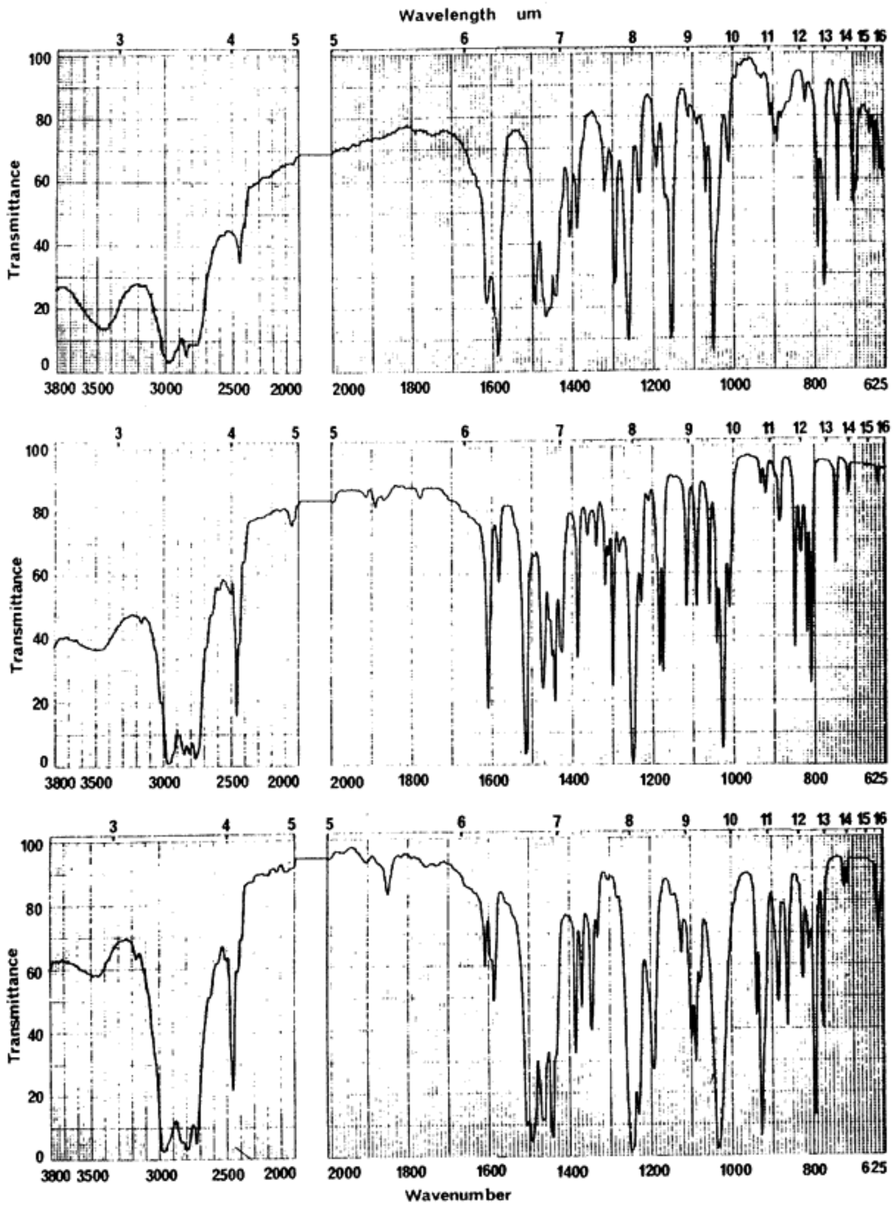


FIG. 6—Infrared spectra of top, 3-methoxy-*N*-methylamphetamine HCl, KBr disk; middle, 4-methoxy-*N*-methylamphetamine HCl, KBr disk; bottom, 3,4-methylenedioxy-*N*-methylamphetamine HCl, KBr disk.

OV-7 and SE-30 columns was superior to those obtained on OV-17 and OV-225 columns.

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Table 4. R_f Values (×100) of some *N*-methylamphetamine derivatives

System[a]	Plate[b]	I	II	III	IV	V	Amph.[c]	Meth.[c]
A	Brinkmann	3	4	2	4	3	8	5
A	Eastman	11	16	10	13	12	25	19
B	Brinkmann	3	3	3	4	6	5	3
B	Eastman	7	13	9	13	10	23	15
C	Brinkmann	17	19	14	17	14	31	22
C	Eastman	38	45	37	42	39	58	48
D	Brinkmann	2	4	3	4	3	3	4
D	Eastman	11	18	10	14	14	55	19
E	Brinkmann	6	8	6	10	8	10	11
E	Eastman	27	37	30	39	35	41	45
F	Brinkmann	23	24	21	23	20	47	27
F	Eastman	45	45	45	43	42	59	47

[a] A = ethyl acetate-cyclohexane-dioxane-methanol-water-ammonium hydroxide (50+50+10+10+1.5+0.5) (7).
B = ethyl acetate-cyclohexane-ammonium hydroxide-methanol-water (70+15+2+8+0.5) (7).
C = ethanol-5*N* ammonia (9+1) (8).
D = acetone-12*N* ammonia (99+1) (9).
E = chloroform-methanol (9+1) (10).
F = chloroform-acetone-triethylamine (5+4+1) (M. LeBelle (1974) private communication).
[b] Brinkmann refers to Brinkmann silica gel G glass plates and Eastman to Eastman Chromagram 6060 silica gel sheets, with a fluorescent indicator.
[c] Amph. = amphetamine; Meth. = methamphetamine.

Table 5. Retention times (min) of some *N*-methylamphetamine derivatives[a] for column packings and oven temperatures indicated

	5% OV-7		5% OV-17		3% SE-30		2.5% OV-225	
Compd	200	175	150	125	150	125	175	125
I	2.4	4.5	5.5	13.5	2.9	6.6	1.2	4.2
II	2.7	5.3	6.4	16.5	3.3	7.8	1.4	5.4
III	2.8	5.5	6.8	17.6	3.4	8.4	1.4	5.7
IV	4.0	8.6	11.2	31.3	4.9	12.7	2.1	10.0
V	9.2	24.1	33.8		10.8	35.4	5.4	40.4

[a] Columns were glass, 6′ long, injector 275°C, nitrogen flow 30 ml/min. Support material was 80–100 mesh Chromosorb W (HP).

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