Identification of 2-, 3-, and 4-Methoxyamphetamines and 2-, 3-, and 4-Methylamphetamines

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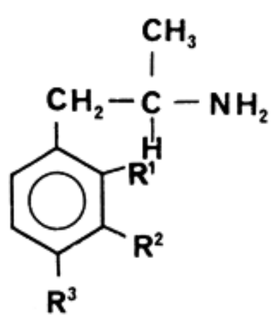
The identity of samples of 2-, 3-, and 4-methoxyamphetamine and 2-, 3-, and 4-methylamphetamine is conclusively established by comparison of their spectra. Ultraviolet, proton magnetic resonance, and mass spectra distinguish and identify the 2 series and infrared spectra differentiate isomers; reference spectra and data are provided. Thin layer and gas-liquid chromatographic systems suitable for distinguishing these compounds are described.

A number of ring-substituted amphetamines are hallucinogenic (1) and subject to abuse. Some are subject to legislative control in Canada, the United States, and other countries, and they may represent health hazards. Methods for their incontrovertible identification are therefore necessary and important. Thus the spectroscopic and chromatographic methods used for the identification of hallucinogenic dimethoxyamphetamines (2) are applied here to the isomeric 2-methoxy- (IA), 3-methoxy- (IIA), and 4-methoxyamphetamines (IIIA) and the isomeric 2-methyl- (IB), 3-methyl- (IIB), and 4-methylamphetamines (IIIB), and the data are presented. 4-Methoxyamphetamine ("PMA", IIIA) and 4-methylamphetamine (IIIB) are appearing on the illicit drug market. The former has marked hallucinogenic properties (1, 3).



Structure of ring-substituted amphetamines.
IA: $R^1 = OCH_3$, $R^2 = R^3 = H$; IIA: $R^2 = OCH_3$, $R^1 = R^3 = H$; IIIA: $R^3 = OCH_3$, $R^1 = R^2 = H$; IB: $R^1 = CH_3$, $R^2 = R^3 = H$; IIB: $R^2 = CH_3$, $R^1 = R^3 = H$; IIIB: $R^3 = CH_3$, $R^1 = R^2 = H$.

Experimental

The amphetamines were prepared as described in ref. 4. They were converted into their hydrochloride salts, all of which were recrystallized from isopropanol-hexane. Since the melting points of similar salts are considerably affected by the degree of hydration (2, 4), this was assessed by obtaining elemental analyses of the samples (Table 1); they appear to be essentially anhydrous. Melting points were taken on a Koffler hot stage and are not corrected (Table 1). Pure samples of the bases were obtained from the salts as follows: About 7 mg salt was thoroughly mixed in a beaker with water (0.5 ml), sodium bicarbonate (1 g), chloroform (1 ml), and Celite (1 g). The mixture was transferred to a small chromatographic column. The beaker was scrubbed with Celite (0.5 g) which was added to the column. The column was eluted with chloroform (20 ml) and the eluate was extracted twice with 0.1*N* H_2SO_4 (1 ml). The aqueous phase was made alkaline with concentrated ammonia solution and the base was extracted twice with chloroform (0.2 and 0.1 ml). The chloroform was removed by warming the solution under a stream of dry nitrogen and the infrared spectrum was then recorded. Thin layer chromatography was carried out under ambient conditions, using precoated plates and sheets as received. The chromatograms were developed for 15 cm, examined under 254 nm ultraviolet light, and exposed to iodine vapor or sprayed with ninhydrin. Gas-liquid chromatography was performed

Table 1. Analytical and melting point data for some amphetamine hydrochlorides

Compd	Found, % C	H	N	mp, °C
IA[a]	59.2	7.7	7.0	108–110
IIA[a]	59.4	7.8	7.1	115–116
IIIA[a]	59.3	7.5	6.95	206–207
IB[b]	64.5	8.6	7.4	165–167
IIB[b]	64.8	8.6	7.6	130–132
IIIB[b]	64.6	8.8	7.6	151–152

[a] Calculated for $C_{10}H_{16}ClNO$ (%): C, 59.5; H, 8.0; N, 6.95.
[b] Calculated for $C_{10}H_{16}ClN$ (%): C, 64.7; H, 8.7; N, 7.5.

either on a Varian Aerograph Series 1520 or a Bendix Model 2500 gas chromatograph with flame ionization detectors. The infrared spectra were recorded on a Beckman 1R 20A spectrophotometer and ultraviolet spectra on Beckman DBGT and Beckman DK2 spectrophotometers. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6L instrument, using the direct inlet system and operating at 160°C and 70 ev. Proton magnetic resonance spectra were measured at 40°C with a Varian A-60A spectrometer.

Results and Discussion

Mass Spectra

The methoxyamphetamine series (A) and the methylamphetamine series (B) give weak molecular ions at m/e 165 and 149, respectively. Both series have their base peak at m/e 44 ($CH_3CH{=}\dot{N}H_2$) and follow the fragmentation pattern established for similar β-phenylethylamines (5–7). Isomers have closely similar relative intensities, and the normalized spectra of 4-methoxyamphetamine (Fig. 1) and 4-methylamphetamine (Fig. 2) are presented as being typical. The methyl isomers of series B have the same formula ($C_{10}H_{15}N$) as methamphetamine ("speed"), which is the most commonly found street drug of this chemical class, but the mass spectrum of methamphetamine has its base peak at m/e 58 ($CH_3CH{=}\dot{N}HCH_3$) and is clearly different from those of series B. It is concluded that mass spectra may be used to provide corroborative evidence of identification.

Ultraviolet Spectra

The ultraviolet spectra of the hydrochloride salts in ethanol show maxima near 280 and 275 nm for the methoxy series A and near 271 and 263 nm for the methyl series B (Table 2). The extinction coefficients of series A are approximately 10 times those of series B at these wavelengths. Thus the 2 series are easily distinguishable, but the spectra of series A resemble those of some dimethoxyamphetamines (2) and those of series B resemble one another and those of the dimethylamphetamines (K. Bailey, 1974, unpublished results).

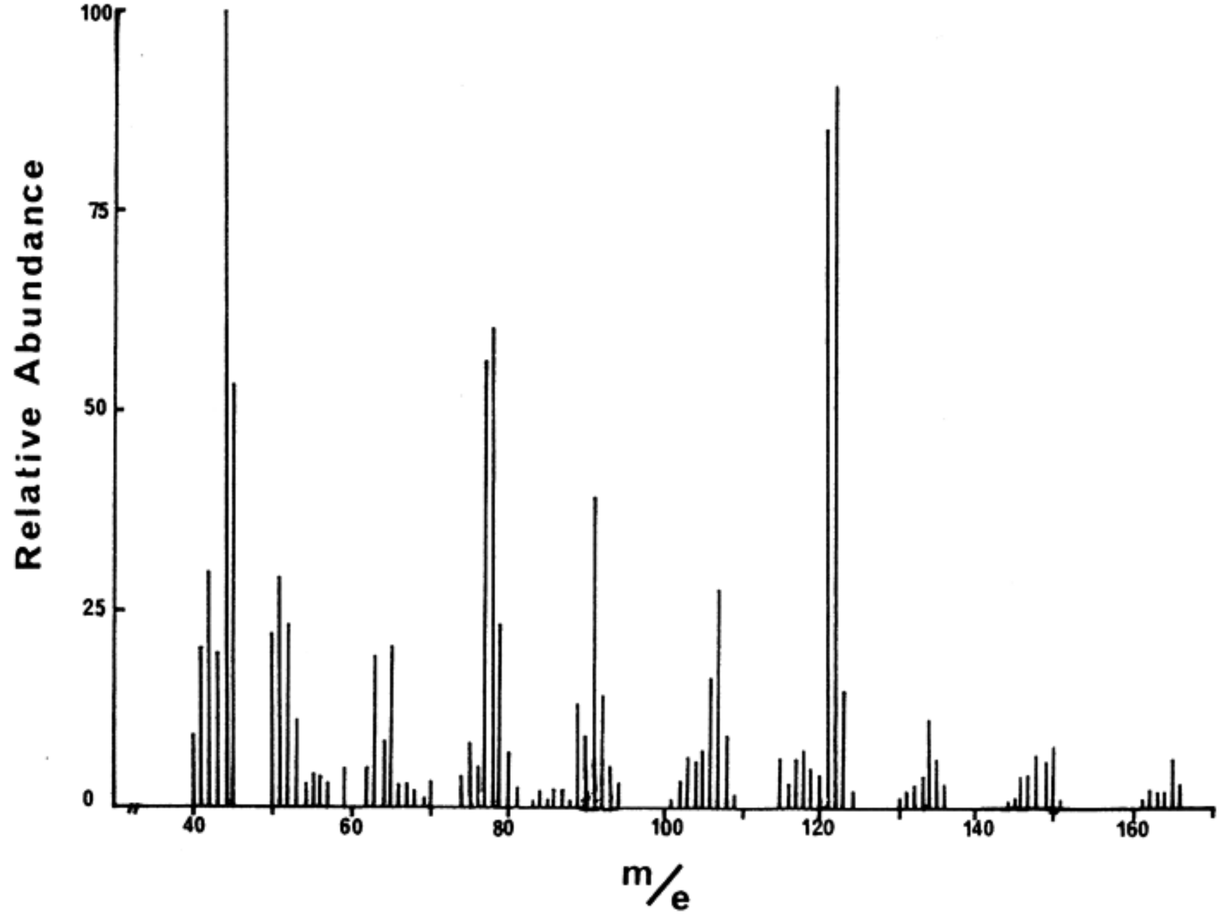


FIG. 1—Normalized mass spectrum of 4-methoxyamphetamine hydrochloride.

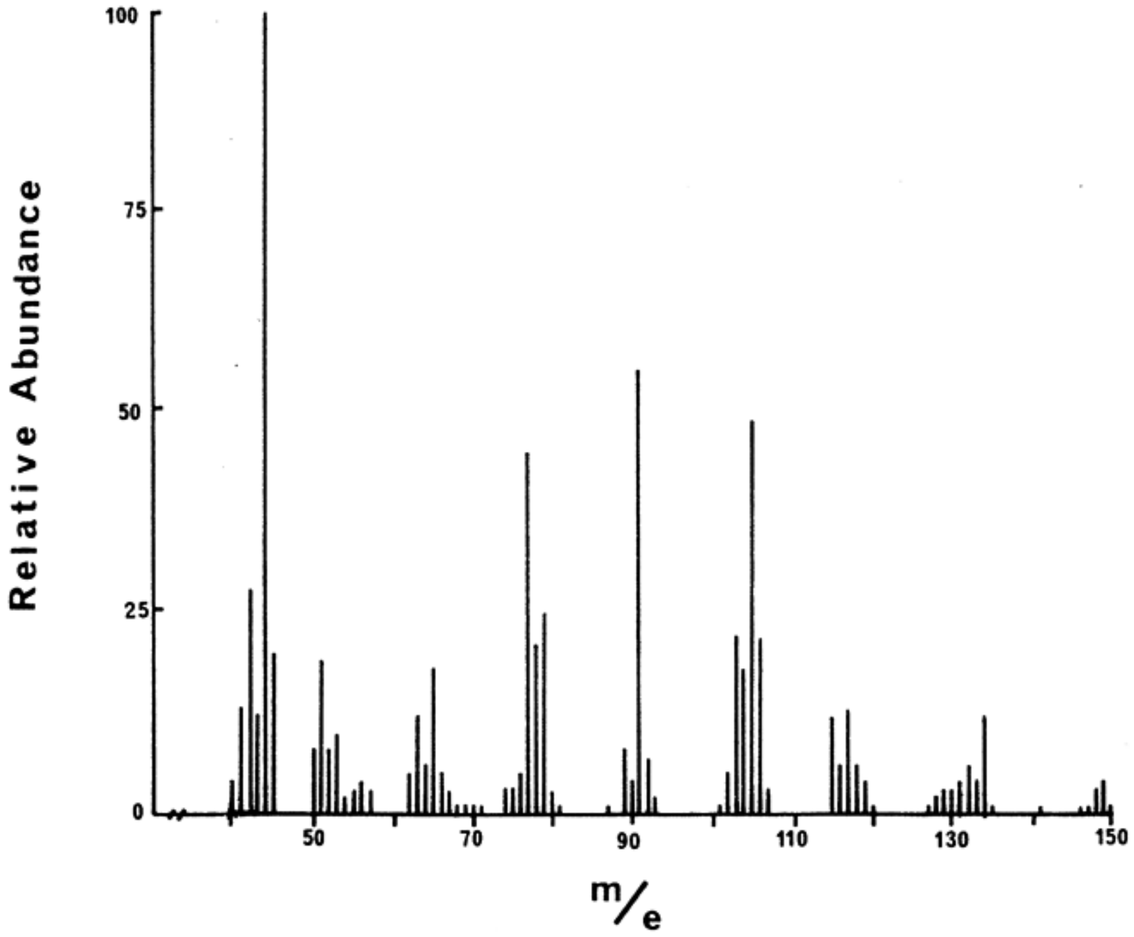


FIG. 2—Normalized mass spectrum of 4-methylamphetamine hydrochloride.

Table 2. Ultraviolet data for some amphetamine hydrochlorides[a]

Compd	$\lambda_{max.}$ (ε)	$\lambda_{max.}$ (ε)
IA	279 (1930)	272 (2180)
IIA	280 (1900)	273 (2070)
IIIA	284 (1410)	277 (1640)
IB	271 (205)	262 (256)
IIB	271 (236)	263 (280)
IIIB	272 (285)	263 (325)

[a] Solutions in ethanol, wavelengths in nm.

Proton Magnetic Resonance Spectra

Some features of the free base spectra of these compounds have been described (4). Data are given in Table 3 for the salts in deuterium oxide and the free bases in deuterochloroform. The aromatic proton signals of 2- and 4-methylamphetamine are singlets at 60 MHz, and the spectra are not suitable for distinguishing between these isomers. For the remaining compounds, examination of the distinctive, complex aromatic proton signals, in conjunction with the observation of an aromatic methyl or methoxyl signal, readily identifies their structures (*see* Figs. 3A-H and Table 3).

Infrared Spectra

The spectra of the substituted amphetamine hydrochlorides (0.3% in KBr disks) are presented in Figs. 4–9 and the free bases (films between KBr plates) in Figs. 10–15. Apart from the aromatic C—H bands at about 700–900 cm^{-1}, the spectra of the free bases are somewhat featureless, especially in the methyl series B. Broadening of the absorption bands in the liquid film state is pronounced in the methyl series B (and still more so in the case of the dimethylamphetamine free bases; K. Bailey, 1974, unpublished results). Nevertheless, the 6 compounds as bases or salts are clearly differentiated by infrared spectrophotometry. The features of the free base spectra of IIA and IIIA presented here correspond with those published (8).

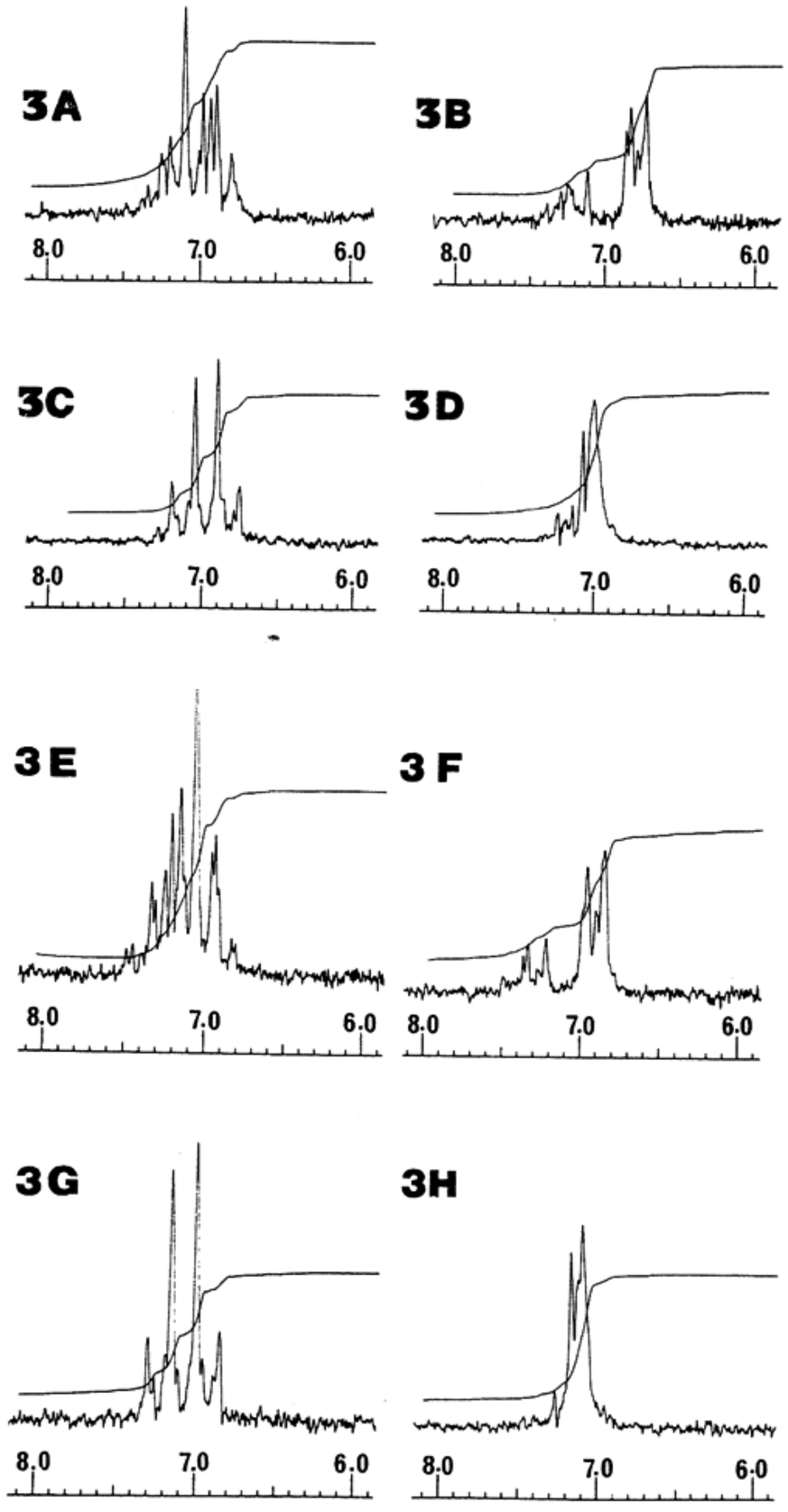


FIG. 3—Proton magnetic resonance spectra of some amphetamine derivatives and their hydrochlorides in the region 6.0–8.0 ppm downfield from TMS, recorded at 60 MHz. Solvent used is shown in parentheses.
A, 2-Methoxyamphetamine ($CDCl_3$); B, 3-methoxyamphetamine ($CDCl_3$); C, 4-methoxyamphetamine ($CDCl_3$); D, 3-methylamphetamine ($CDCl_3$); E, 2-methoxyamphetamine.HCl (D_2O); F, 3-methoxyamphetamine.HCl (D_2O); G, 4-methoxyamphetamine.HCl (D_2O); H, 3-methylamphetamine.HCl (D_2O).

Table 3. Data[a] from the proton magnetic resonance spectra of some amphetamine derivatives

Compd	β-CH_3(d)	Ar-CH_3(s)	Ar-OCH_3(s)	α-CH_2(m)	β-H(m)	Ar-H
IA	1.12		3.80	2.63	3.20	see Fig. 3A
IIA	1.12		3.79	2.59	3.17	see Fig. 3B
IIIA	1.08		3.77	2.55	3.12	see Fig. 3C
IB	1.13	2.31		2.61	3.15	7.11(s)
IIB	1.12	2.32		2.55	3.15	see Fig. 3D
IIIB	1.10	2.31		2.55	3.12	7.08(s)
IA.HCl	1.22		3.78	2.85	3.60	see Fig. 3E
IIA.HCl	1.25		3.79	2.87	3.60	see Fig. 3F
IIIA.HCl	1.22		3.77	2.82	3.55	see Fig. 3G
IB.HCl	1.24	2.25		2.88	3.55	7.18(s)
IIB.HCl	1.24	2.26		2.82	3.55	see Fig. 3H
IIIB.HCl	1.22	2.25		2.83	3.54	7.16(s)

[a] δ-values, measured at 60MHz using solutions at 40°C, 10–15% in $CDCl_3$ containing TMS for the bases and 10–15% in D_2O (external TMS) for the hydrochlorides. Signals were singlets (s), doublets (d), or complex multiplets (m).

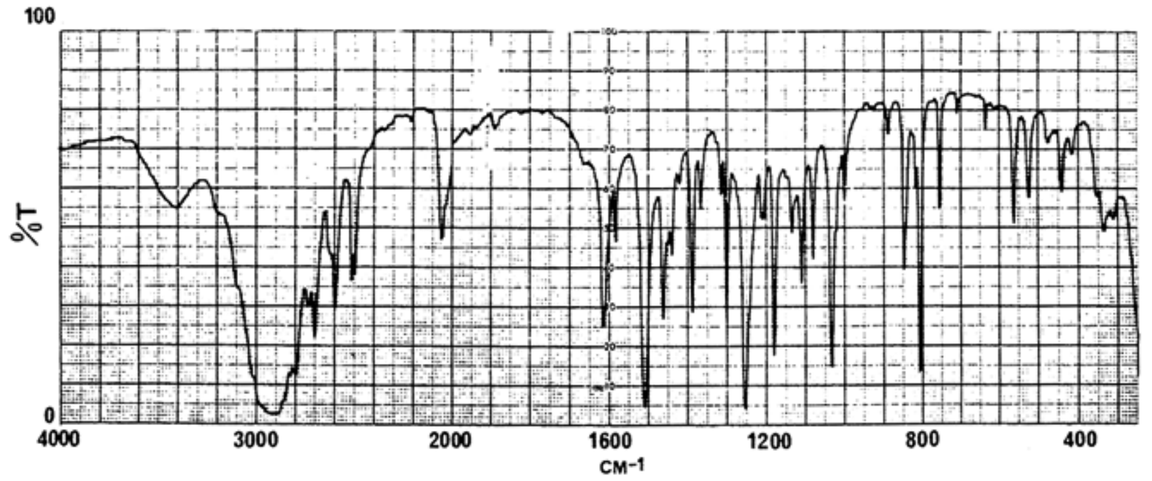


FIG. 6—4-Methoxyamphetamine hydrochloride, KBr disk.

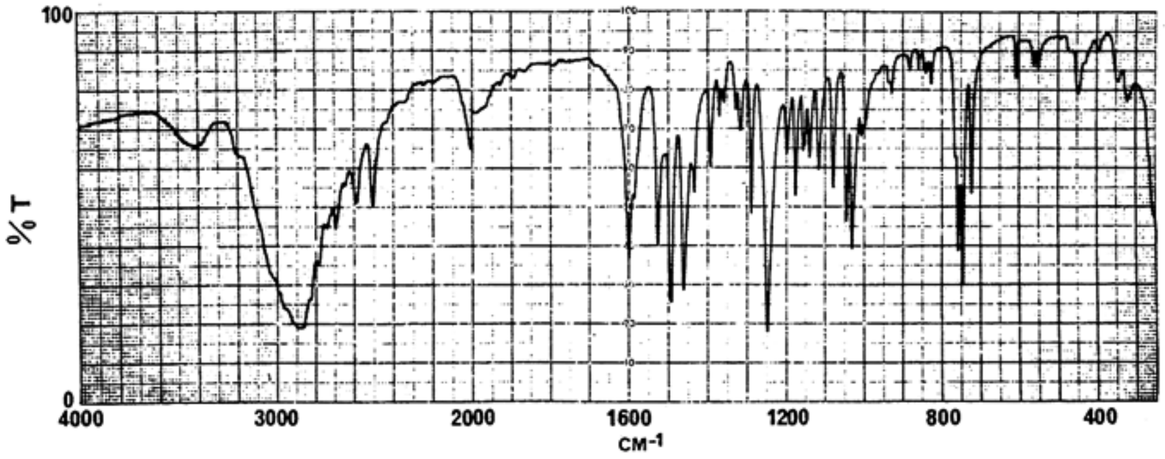


FIG. 4—2-Methoxyamphetamine hydrochloride, KBr disk.

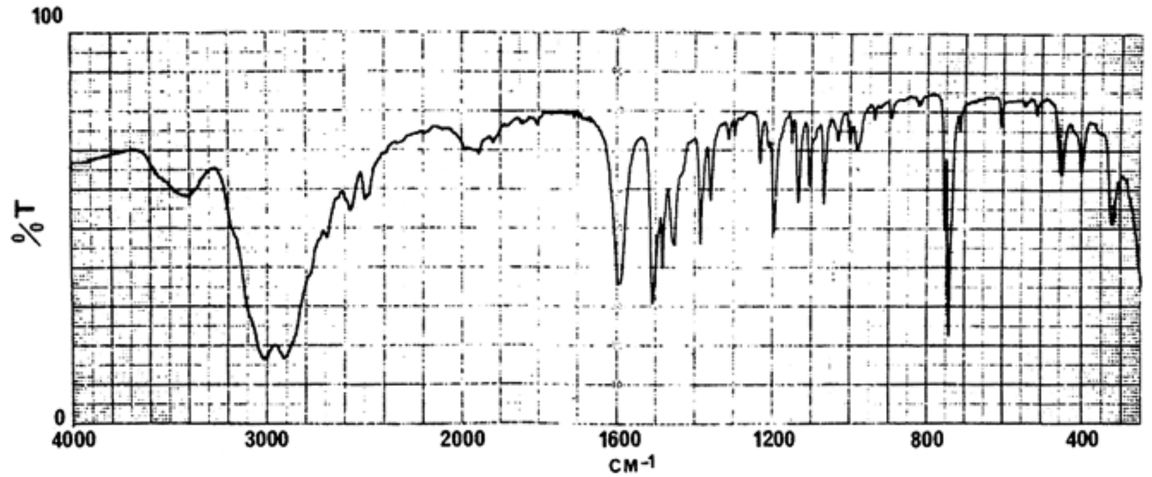


FIG. 7—2-Methylamphetamine hydrochloride, KBr disk.

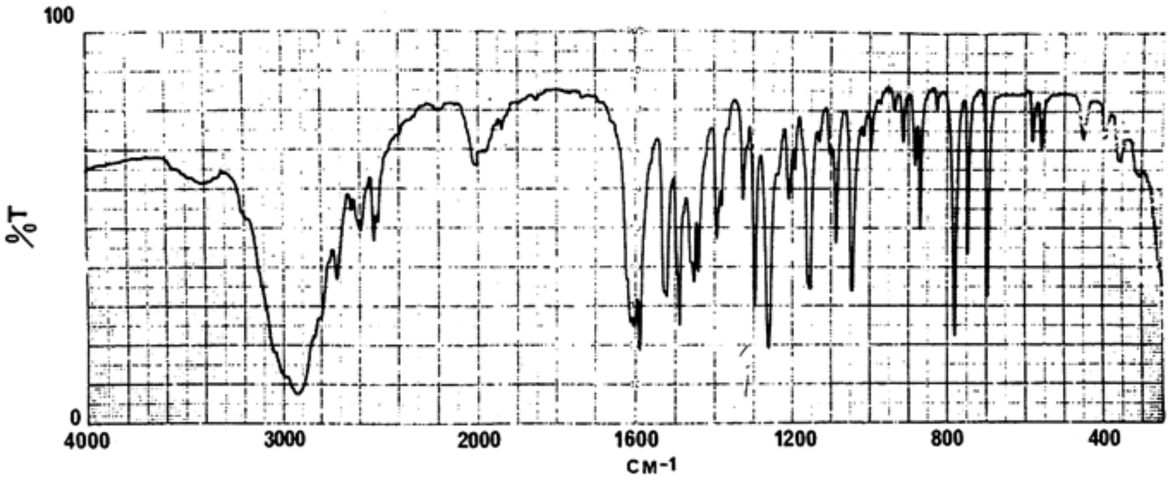


FIG. 5—3-Methoxyamphetamine hydrochloride, KBr disk.

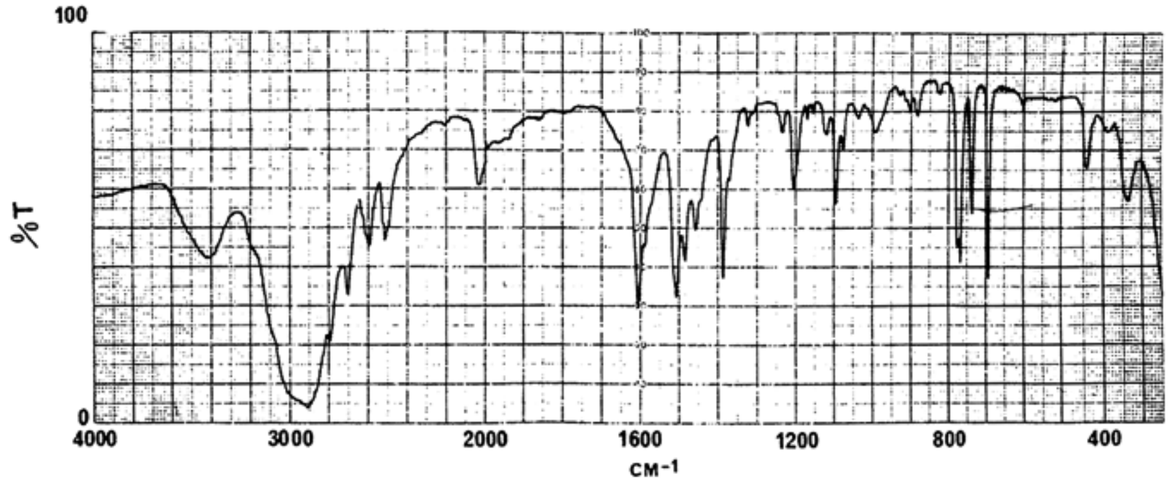


FIG. 8—3-Methylamphetamine hydrochloride, KBr disk.

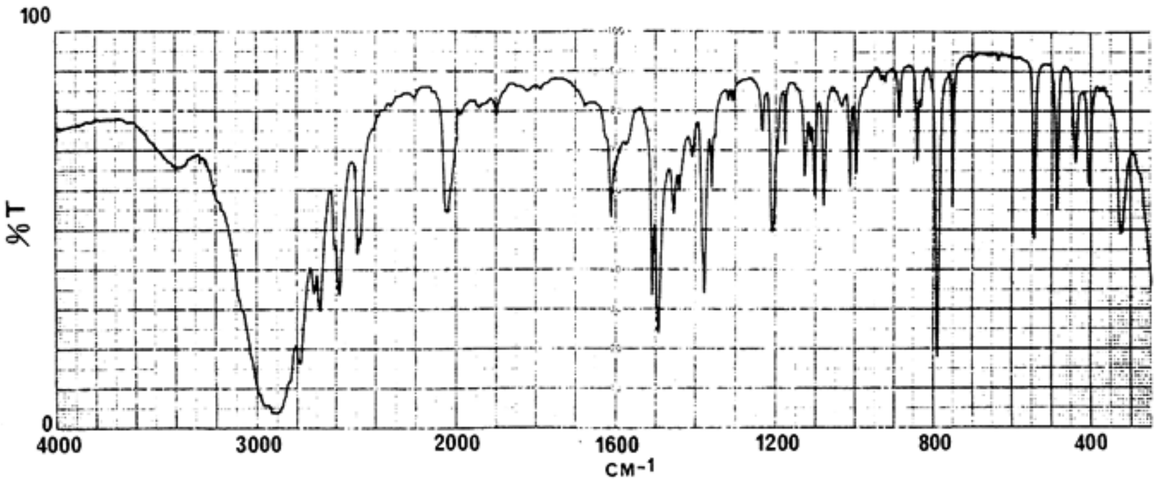


FIG. 9—4-Methylamphetamine hydrochloride, KBr disk.

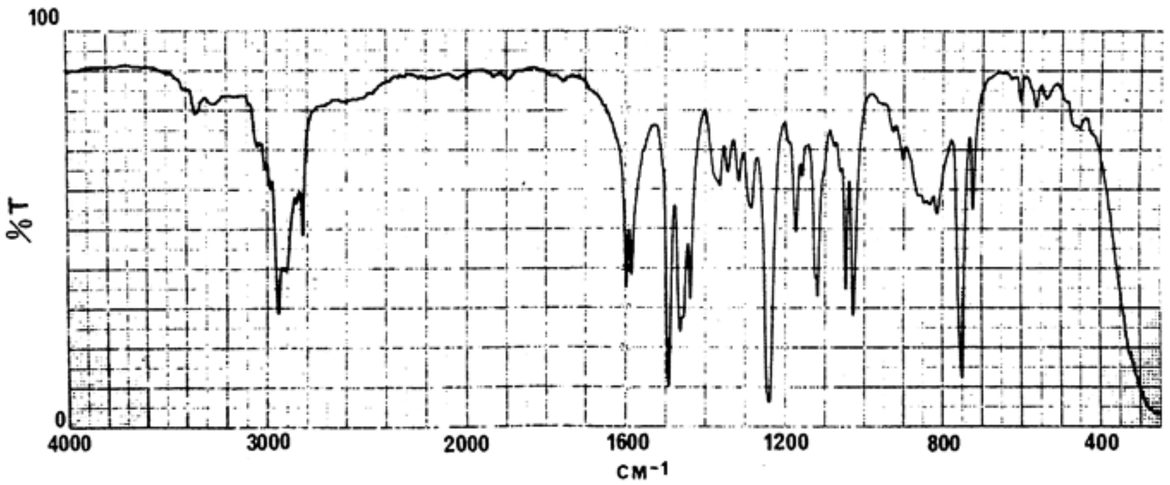


FIG. 10—2-Methoxyamphetamine base, film between KBr plates.

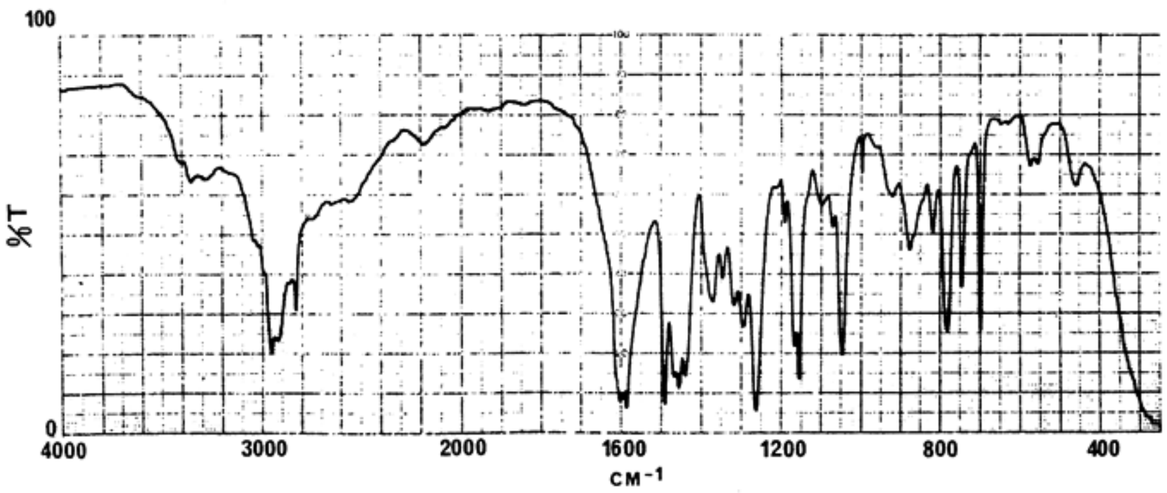


FIG. 11—3-Methoxyamphetamine base, film between KBr plates.

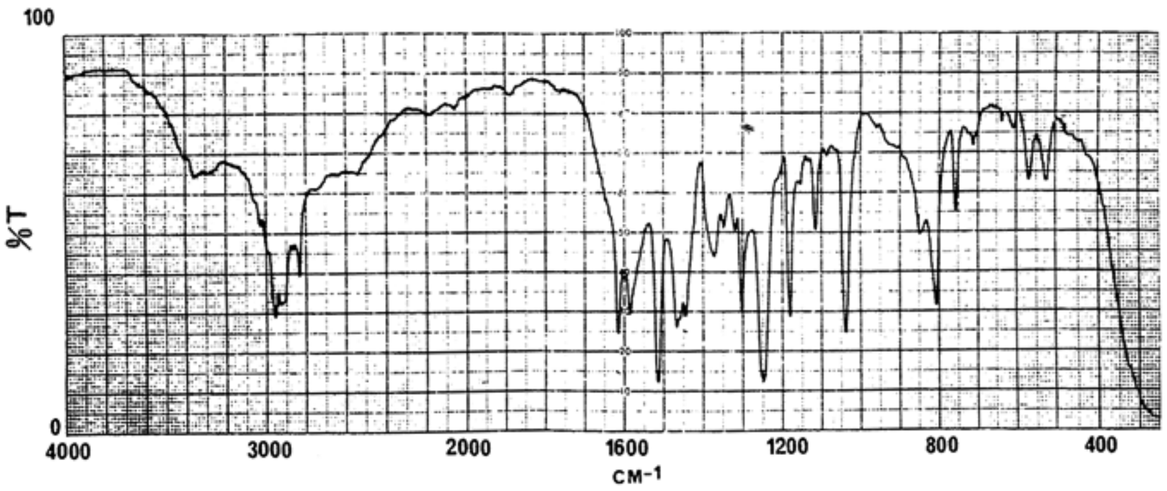


FIG. 12—4-Methoxyamphetamine base, film between KBr plates.

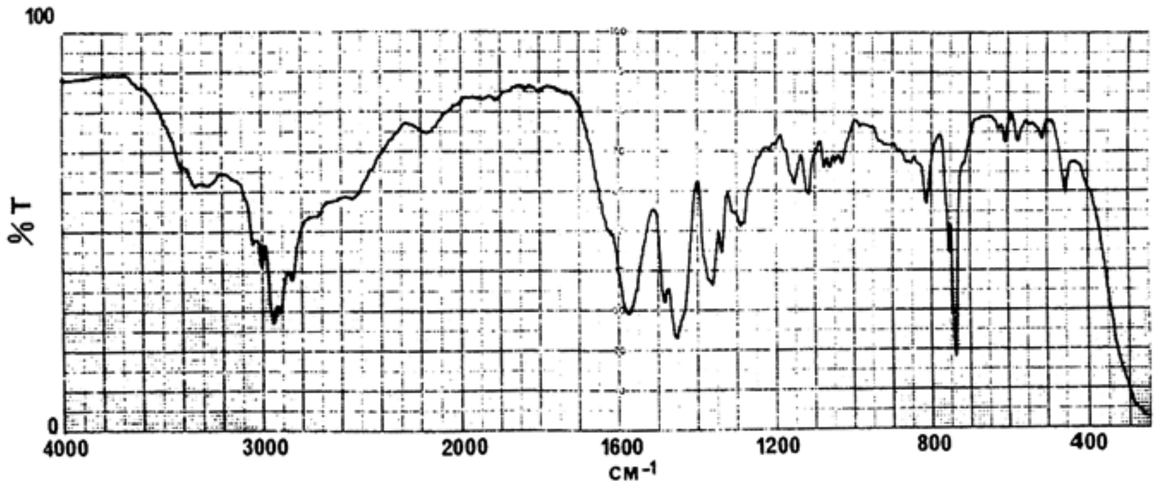


FIG. 13—2-Methylamphetamine base, film between KBr plates.

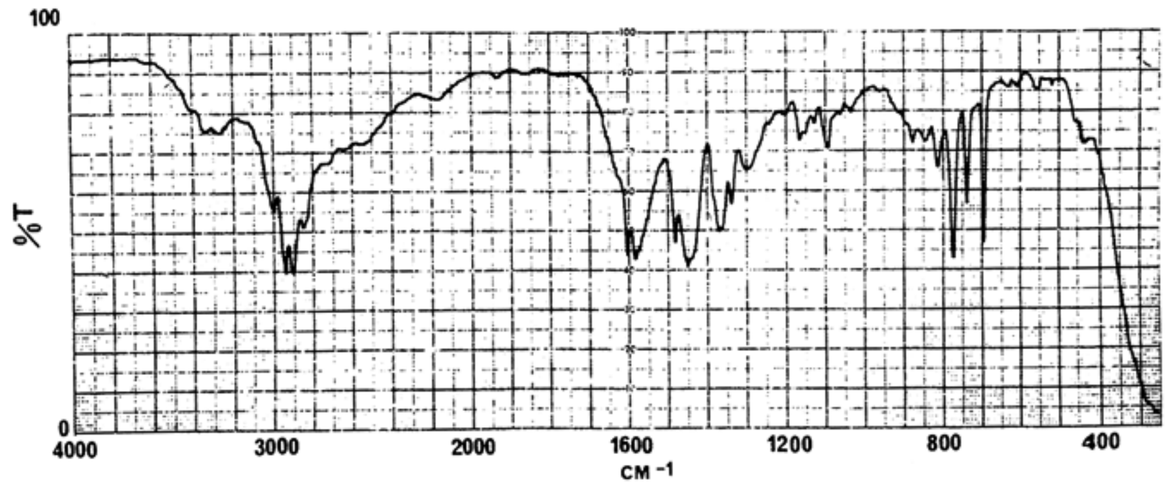


FIG. 14—3-Methylamphetamine base, film between KBr plates.

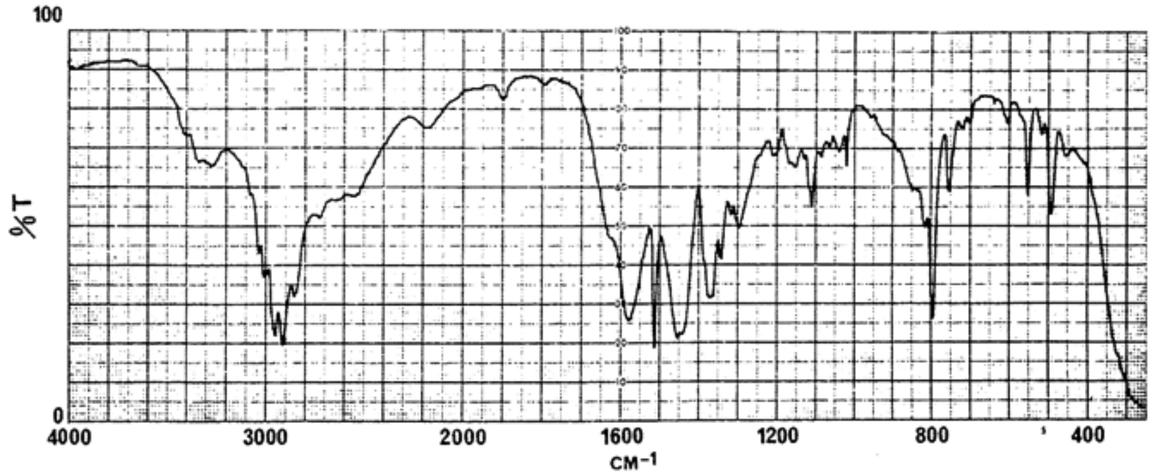


FIG. 15—4-Methylamphetamine base, film between KBr plates.

Table 4. R_f values (×100) of some amphetamine derivatives

System[a]	Plate[b]	IA	IIA	IIIA	IB	IIB	IIIB	Amph.[c]	Meth.[c]
A	Brinkmann	8	9	6	12	10	10	10	8
A	Eastman	20	21	16	25	21	22	24	18
B	Brinkmann	15	15	12	19	18	17	17	11
B	Eastman	26	26	20	32	29	27	29	20
C	Brinkmann	24	27	22	34	31	30	31	18
C	Eastman	51	52	49	51	53	52	53	39
D	Brinkmann	24	25	20	30	26	24	27	7
D	Eastman	50	50	44	57	51	46	55	18

[a] A = ethyl acetate-cyclohexane-dioxane-methanol-water-ammonium hydroxide (50+50+10+10+1.5+0.5) (9).
B = ethyl acetate-cyclohexane-ammonium hydroxide-methanol-water (70+15+2+8+0.5) (9).
C = ethanol-5*N* ammonia (9+1) (10).
D = acetone-12*N* ammonia (99+1) (11).
[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.

Thin Layer Chromatography

The results from several systems are presented in Table 4. Since R_f values are sensitive to ambient conditions, concurrent and co-spotting of authentic samples is highly desirable if an attempt is made to establish identity by thin layer chromatography. In the absence of authentic samples, it is useful to determine the R_f of one or more reference materials concurrently and, in the present instance, amphetamine and methamphetamine were used. This approach also allows more reliable comparisons between these and previous data (2). Isomers could not always be clearly differentiated with the systems examined. The R_f values of the methyl series B were generally greater than those of the methoxy series A.

Gas-Liquid Chromatography

Results obtained with columns packed with 5% OV-7, 5% OV-1, 5% OV-17, or 2.5% OV-225 on 80–100 mesh Chromosorb W (Table 5) show that OV-7 and OV-17 are capable of distinguishing between the 6 amphetamines, but mixed injections are recommended for the definitive identification of isomers. Considerably longer retention times are obtained with the methoxy series A than with the methyl series B. The order of emergence is the same on the various columns, and comparison of series A and B indicates that factors other than the position of ring substitution are important in determining retention characteristics.

Received February 26, 1974.

Table 5. Retention times (min) of some amphetamine derivatives[a]

Compd	5% OV-7[b] 100°C	5% OV-7[b] 150°C	2.5% OV-225[b] 100°C	2.5% OV-225[b] 150°C	5% OV-1[c] 100°C	5% OV-1[c] 150°C	5% OV-17[c] 150°C
IA	18.3	3.0	8.0	1.6		25.0	6.1
IIA	23.0	3.5	11.1	1.9		28.7	7.4
IIIA	24.5	3.7	11.6	2.0		30.1	7.8
IB	8.2	1.8	3.4	ca 1.0	11.5[d]	1.7	3.3
IIB	7.6	1.8	3.1	ca 1.0	11.2[d]	1.7	3.1
IIIB	7.8	1.8	3.1	ca 1.0	11.7[d]	1.7	3.2

[a] Columns were glass, 6′ long, with 80–100 mesh Chromosorb W as support.
[b] Injector 275°C, nitrogen flow 30 ml/min, Varian Aerograph 1520.
[c] Injector 300°C, nitrogen flow 60 ml/min, Bendix 2500.
[d] Peaks tailed, retention times are approximate.

Acknowledgments

The cooperation of H. W. Avdovich in determining the proton magnetic resonance spectra and of J.-C. Ethier and A. W. By in determining the mass spectra is much appreciated.

References

(1) Shulgin, A. T., Sargent, T., & Naranjo, C. (1969) *Nature* 221, 537–541
(2) Bailey, K., Legault, D., & Verner, D. (1974) *JAOAC* 57, 70–78
(3) Smythies, J. R., Johnston, V. S., Bradley, R. J., Benington, F., Morin, R. D., & Clark, L. C. (1967) *Nature* 216, 128–129
(4) Bailey, K., By, A. W., Graham, K. C., & Verner, D. (1971) *Can. J. Chem.* 49, 3143–3151
(5) Beckett, A. H., Tucker, G. T., & Moffat, A. C. (1967) *J. Pharm. Pharmacol.* 19, 273–294
(6) Bailey, K. (1972) *Anal. Chim. Acta* 60, 287–292
(7) Beckett, A. H., Coutts, R. T., & Ogunbona, F. A. (1973) *J. Pharm. Pharmacol.* 25, 708–717
(8) Warren, R. J., Begosh, P. P., & Zarembo, J. E. (1971) *JAOAC* 54, 1179–1191
(9) Kaistha, K. K., & Jaffe, J. H. (1972) *J. Pharm. Sci.* 61, 679–689
(10) Cartoni, G. P., Lederer, M., & Polidori, F. (1972) *J. Chromatogr.* 71, 370–375
(11) Choulis, N. H. (1971) *Biochem. Med.* 5, 311–316