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Differentiation of Side Chain Positional Isomers of Amphetamine

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ABSTRACT: The eleven side chain positional isomers of amphetamine can be distinguished using a combination of color tests, thin-layer chromatography, and mass spectrometry. The primary amines, 1-phenylpropylamine and β-methylphenethylamine, exhibited chromatographic behavior similar to amphetamine but were readily differentiated using mass spectrometry. The mass spectra of *N*-methylphenethylamine was very similar to amphetamine, but using color tests and chromatography it was readily differentiated from amphetamine.

KEYWORDS: toxicology, amphetamine, chromatographic analysis, positional isomers, mass spectrometry

For the routine forensic science identification of arylalkylamines there have been methods reported for differentiating sympathomimetic amines [*1*], phenylalkylamines [*2-5*], and ring substituted phenylisopropylamines [*5-10*]. However, there have been limited discussions [*4, 7*] on differentiating positional isomers of arylalkylamines, that is, where the aromatic position of the molecule is held constant and the alkylamine side chain is varied. Therefore, it was questioned within the laboratory (Drug Examination Section, Bureau of Forensic Science, Commonwealth of Virginia) what routine test or combination of tests were responsible for differentiating the isopropylamine side chain from the other side chain positional isomers. Because of the large number of possible isomers for the arylalkylamine class the initial study was limited to amphetamine and its eleven side chain positional isomers (Fig. 1). This series was used to determine if some structure specific trends might be observed that would be generally applicable to characterization of arylalkylamine side chain isomers.

Experimental Procedure

The α-methylbenzeneethanamine, *I* (*d*-amphetamine, Chemical Abstracts Registry Number 60-15-1), β-methylbenzeneethanamine, *III* (β-methylphenethylamine, 582-22-9), *N*-ethylbenzenemethanamine, *VI* (*N*-ethylbenzylamine, 14321-27-8), benzenepropanamine, *VII* (3-phenyl-1-propylamine, 2038-57-5), *N*-methylbenzeneethanamine, *VIII* (*N*-methyl-

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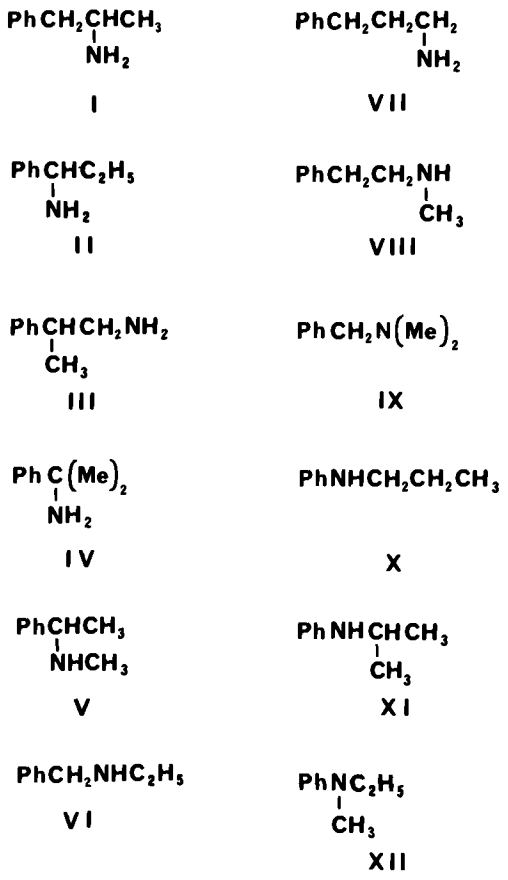

FIG. 1—*Phenylalkylamine side chain positional isomers of* $C_9H_{13}N$.

phenethylamine, 589-08-2), *N,N*-dimethylbenzenemethanamine, *IX* (*N,N*-dimethylbenzylamine, 103-83-3), and *N*-ethyl-*N*-methylbenzenamine, *XII* (*N*-ethyl-*N*-methylaniline, 613-97-8) were obtained from Aldrich Chemical Co. (Milwaukee, WI). The *N*-(1-methylethyl)-benzenamine, *XI* (*N*-phenylisopropylamine, 768-52-5) was obtained from ICN Pharmaceuticals, Inc. (Plainview, NY). The *N*-propylbenzenamine, *X* (*N*-propylaniline, 622-80-0) was obtained from Pfaltz and Bauer, Inc. (Stamford, CT). The *N*,α-ethylbenzenemethanamine, *II* (1-phenylpropylamine, 2941-20-0) was synthesized from propiophenone using the method of Smith et al [*11*]. The *N*,α-dimethylbenzenemethanamine, *V* (*N*-methyl-α-phenethylamine, 32512-24-6) was synthesized from acetophenone using the method of Borch et al [*12*]. The α,α-dimethylbenzenemethanamine, *IV* (1,1-dimethylbenzenemethylamine 582-32-0) was synthesized from 2-phenyl-2-propanol using the method of Ritter et al [*13*].

All of the amines were tested as the free base. Color test and spray reagents were of standard composition [*14*]. Fluram® was obtained from Roche Diagnostics (Nutley, NJ). Thin-layer chromatographic (TLC) analysis were performed using 250-μm thick layers of Silica Gel GF on 10-cm glass plates precoated by Analtech, Inc. (Newark, DE). Gas chromatography was performed on a Bendix Model 2600 instrument (dual column) with a dual flame ionization detector (FID) (Lewisburg, West VA). A coiled glass column (2-m by 2-mm inner diameter) packed with 5% OV-7 or 10% OV-1 on Gas Chrom Q, 100–120 mesh, was used. The operating conditions were as follows: nitrogen was the carrier gas (30 mL/min), the oven temperature was 150°C (5% OV-7 and 10% OV-1), the injection port was 260°C, and the

detector temperature was 285°C. Gas chromatography/mass spectrometry (GC/MS) was carried out using a Hewlett-Packard Model 5993 GC/MS system which uses probability based matching for library search routines (Palo Alto, CA). The gas chromatographic separation used a coiled glass column, 1.2-m by 2-mm inside diameter, packed with 3% GE-GC-SE 30 on Gas Chrom Q, 100–120 mesh. The isomers were chromatographed using temperature programing, 70 to 100°C at 10°/min (injection port, 270°C; splitter, 350°C) with helium (30 mL/min) as carrier gas.

Results

The analytical tests routinely used within the laboratory for screening of all drug samples include color tests, thin-layer chromatography followed by visualization with specific reagents, gas chromatography, and mass spectrometry. Each of the twelve isomers were evaluated in all of the analytical systems.

The results of the color tests are reported in Table 1. Additional tests evaluated include the Van Urk, Liebermann, Sanchez, and Mandelin, however, no significant color changes were observed with these tests. The color test often considered characteristic for amphetamine is the Marquis in which an orange-brown color is observed. Of the eleven isomers tested all compounds except *V* and *XII* gave an orange color similar to amphetamine. The nitroprusside test gave a positive intense blue color for all the secondary amines (*V*, *VI*, and *VIII*) except for the aniline isomers (*X* and *XI*). The primary and tertiary amines gave no color.

The analysis of the isomers using thin-layer chromatography in six different solvent systems is given in Table 2. Compounds *X*, *XI*, and *XII* are clearly differentiated from the remaining isomers using any of the solvent systems tested. Compounds *II*, *III*, and *V* had TLC properties that were quite similar to amphetamine. None of the solvent systems evaluated differentiated all twelve isomers.

Visualization of the isomers after TLC development was evaluated with a number of reagents that are listed in Table 3. None of the reagents showed specificity for amphetamine. As expected, Fluram and 366-nm ultraviolet (UV) light was specific for detecting the primary amines (*I*, *II*, *III*, *IV*, *VII*).

The retention times T_R of the isomers using gas chromatography are presented in Table 4. All of the isomers exhibited a very short retention time (< 102 s), with Isomers *II*, *VI*, *VIII*, and *XI* having retention times comparable to amphetamine.

The result of the mass spectral study is tabulated in Table 5 in which the base peak, inten-

TABLE 1—*Color test data.*[a]

Compound	Marquis	Nitroprusside	Mecke	Nitric Acid	Froehde	Cobalt Thiocyanate	Sulfuric Acid	Ehrlich
I	OR/BR	NR	BR	NR	NR	BL	NR	NR
II	Pink/OR	NR	NR	NR	NR	NR	YEL	NR
III	OR/BR	NR	NR	NR	NR	PU/BL	NR	NR
IV	OR	NR	NR	NR	NR	BL	NR	NR
V	NR	BL	NR	NR	NR	BL	NR	NR
VI	OR/BR	BL	YEL/BR	YEL/BR	YEL/BR	BL/GR	YEL/OR	PU/Rose
VII	RED/OR	NR	GR	BR	Olive	BR/GR	YEL/OR	PU
VIII	OR/BR	BL	GR	NR	YEL	BL	YEL	NR
IX	OR/BR	NR	NR	NR	NR	BL	NR	NR
X	YEL/OR	NR	YEL	BR/BK	YEL	BL	YEL	BR/OR
XI	OR/Red	NR	YEL	NR	YEL	NR	NR	YEL
XII	YEL	NR	YEL	YEL	YEL	NR	YEL	NR

[a]YEL = yellow, OR = orange, BR = brown, WT = white, GR = green, BL = blue, PU = purple, BK = black, and NR = no reaction.

TABLE 2—*Thin-layer isomer chromatography on silica (rf).*

Solvent System	Isomer											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
A $CHCl_3/CH_3OH$(9/1)	0.22	0.22	0.19	0.39	0.19	0.13	0.07	0.07	0.35	0.83	0.83	0.83
B NH_3Sat$CHCl_3/CH_3OH$(18/1)	0.41	0.51	0.41	0.49	0.41	0.49	0.25	0.30	0.59	0.79	0.82	0.82
C $CHCl_3/CH_3OH$(1/1)	0.33	0.35	0.25	0.47	0.33	0.21	0.08	0.15	0.44	0.86	0.88	0.88
D NH_4OH/CH_3OH(1.5/100)	0.48	0.59	0.44	0.63	0.51	0.45	0.23	0.26	0.63	0.85	0.85	0.85
E $CH_3COCH_3/CHCl_3$(2/1)	0.31	0.44	0.26	0.28	0.20	0.10	0.17	0.04	0.24	0.81	0.81	0.81
F $C_6H_{14}/CH_3COCH_3/CHCl_3$(5/1/2)	0.07	0.04	0.03	0.08	0.04	0.00	0.01	0.00	0.04	0.60	0.63	0.69

TABLE 3—*Visualization of isomers after TLC.*

Method of Visualization	Isomer											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
UV light, 254 nm[a]	+	+	+	+	+	+	+	+	+	+	+	+
Iodine vapors	+	+	+	+	+	+	+	+	+	+	+	+
Fluram and 366-nm UV light[a]	+	+	+	+	−	−	+	−	−	−	−	−
Iodoplatinate	−	−	−	−	−	−	+	+	+	−	−	−
1% ceric sulfate in 1*N* H_2SO_4	−	−	−	−	−	−	−	−	−	+	+	+
Iodoplatinate oversprayed with ceric sulfate	+	+	+	+	+	+	+	+	+	+	+	+
1% $KMnO_4$	+	+	+	+	+	+	+	+	+	+	+	+

[a]Silica plate contains fluorescent indicator.

TABLE 4—*Gas chromatography.*

Compound	5% OV-7, 145°C (t_R, s)	10% OV-1, 145°C (t_R, s)	Boiling Point[a] (°C, 760- or 765-mm Hg)[b]	Melting Point, HCl,[a] °C
I	61	61	203	145–147
II	66	67	204–6	194
III	74	77	210	123–4
IV	52	56	196–7	235.5
V	46	51	184	178–9
VI	61	65	199	184
VII	97	99	221	218
VIII	70	73	205	152–4
IX	42	43	181	175
X	101	97	222	196–198(150)
XI	67	71	206–8	102
XII	76	76	203–5	114

[a]All boiling points and melting points are taken from Ref *20*.
[b]Conditions are described in the Experimental Procedure section.

TABLE 5—*Mass spectral data for the isomers.*

Compound	Base Peak, *m/z*	Parent Ion, *m/z* (%)	Prominent Ions, *m/z* (%)			
I	44	135 (0.0)	51 (3.7)	65 (5.5)	91 (5.2)	...
II	106	135 (0.0)	51 (7.3)	77 (14.3)	79 (28.1)	...
III	30	135 (3.1)	77 (6.7)	91 (6.6)	105 (6.4)	...
IV	120	135 (0.2)	42 (50.6)	58 (15.2)	77 (8.1)	104 (4.7)
V	120	135 (2.5)	42 (30.0)	58 (18.8)	77 (11.7)	105 (9.8)
VI	91	135 (14.4)	65 (15.7)	120 (31.3)	44 (14.3)	...
VII	30	135 (3.5)	91 (24.7)	117 (26.5)	118 (41.5)	44 (11.6)
VIII	44	135 (1.2)	51 (3.2)	65 (7.1)	91 (9.7)	...
IX	58	135 (61.9)	91 (61.6)	134 (42.9)	44 (12.3)	...
X	106	135 (24.5)	51 (9.5)	77 (17.6)	...	...
XI	120	135 (23.3)	39 (9.4)	77 (10.2)	44 (1.1)	...
XII	120	135 (28.5)	77 (18.7)	104 (12.0)	44 (0.8)	...

sity of parent peak and other prominent fragment ions are recorded. All of the samples give distinctly different spectra from amphetamine except for Compound *VIII*.

Discussion

Many of the original analytical methods used for the identification of simple arylalkylamines utilized the preparation of derivatives and matching of melting points. For example, a very simple derivative, the hydrochloride salt of the amines, allows differentiation of amphetamine from all of the other amines (Table 3). Other analytical tests that are useful in differentiating positional isomers include infrared (ir) and nuclear magnetic resonance (nmr), however, the disadvantage of all these techniques is that they require a rather large amount of sample and time, as well as excellent technique in sample isolation and purification. Although the chromatographic techniques (thin-layer, paper, and gas chromatography) do not provide as much structural information as ir and nmr, many of the above problems are circumvented in that chromatography simultaneously purifies and identifies very small quantities of sample. In general, however, these chromatographic techniques were developed for differential identification of central nervous system stimulants such as amphetamine, methamphetamine, ephredrine, phentermine, phenylpropanolamine, and so forth [*1-10*]. Frequently, these tests were not evaluated against their positional isomers (possibly as a result of limited availability) even though color tests, chromatographic separation, and even ir are primarily based on functional group differences or molecular weight differences or both.

Because of the large number of positional isomers available with the formula $C_9H_{13}N$, it was necessary to limit this study to isomers in which the phenyl ring is held constant and only the side chain arrangement is varied. This approach was chosen for three reasons: (1) the commercial availability of most of the isomers; (2) mass spectrometry is used in all analysis and placement of nitrogen in the ring or disubstitution of the phenyl ring would preclude the characteristic cluster of ions at *m/z* 77, 78, and 79 characteristic of the monoalkylbenzenes [*15*]; and (3) the chromatographic and spectral traits observed with these simple isomers could possibly be extrapolated and applied to the side chain differentiation of ring modified amphetamines.

The color test (Table 1) considered characteristic for amphetamine is the Marquis test in which an orange-brown color is produced. It was observed that nine of the other isomers gave a color reaction that was identical or very similar. Since only Compounds *V* (a secondary amine) and *XII* (a tertiary amine) gave no color it would appear no conclusion relative to structure can be made for the color reaction. This is also true for the other color reactions

except for the nitroprusside test. As expected this gave a color response for the secondary amines (*V*, *VI*, and *VIII*) and was negative for the anilines, primary, and tertiary amines.

Separations using thin-layer chromatography are dependant on partitioning which is usually based on structural or functional group differences [*16,17*]. In Table 2 it is seen that the aniline isomers (*X*, *XI*, and *XII*) were well resolved from the other amines in all of the solvent systems evaluated, probably as a result of the decreased basicity of the nitrogen. For the remaining amines there was no trend associated with the separation of the primary, secondary, and tertiary amines in any of the solvent systems. Isomers *II*, *III*, and *V* had TLC properties similar to amphetamine in the solvent systems. Overspotting each of these isomers on amphetamine and developing in the solvent systems, indicated Isomer *II* was resolved from amphetamine (solvent Systems B, D, and E) while Isomers *III* and *V* were not resolved. Visualization of the plate with Fluram and 366-nm light (a test specific for primary amines), is necessary for differentiating Isomer *V* from amphetamine (Table 3). Using only color tests and TLC, Compound *III* has not been differentiated from amphetamine.

Separations using gas chromatography are mainly dependant on partitioning differences in boiling point, molecular weight, and functional group variation. As shown in Table 4 the isomers with the lower boiling points (*IV*, *V*, and *IX*) eluted much earlier than the isomers with the highest boiling points (*VII* and *X*). However, in the boiling point range of 199 to 210° the GC retention times were not directly related to either boiling point or functional group variation. Although retention times are quite short, only Isomers *II*, *III*, *VI*, *VIII*, and *XI* had retention times similar to amphetamine and only Isomers *II* and *VI* were found to co-elute with amphetamine when injected together. Better resolution of the isomers could be obtained by using a more polar phase or lower temperatures [*18*], but these conditions are a compromise which allows rapid sample analysis and reasonable selectivity for identification. It should be noted that in this protocol using TLC and GC all the isomers have been differentiated from amphetamine.

Mass spectrometry is the final method used for conformation of structure within the laboratory. Analysis of a compound using the electron impact (EI) mode provides valuable spectral information as well as a characteristic fragmentation pattern [*1-10*]. Analysis of the fragmentation pattern of these isomers closely follows four characteristic pathways [*15*]. First, the relative height and intensity of the parent ion is greatest for the tertiary amines, decreases for the secondary amines, and is barely detectable for the primary amines. Second, the carbon-carbon bond alpha to nitrogen is usually cleaved as depicted in Fig. 2. Except for Isomer *VI*, this fragment accounts for the base peak. In general, the preferred order of cleavage is R_1 = benzyl · > alkyl · > phenyl · ≥ H · for the isomers. For example, analysis of the intensity of these fragments for Isomer *V* gives *m/z* 120 (100%, M − CH_3·), *m/z* 58 (18.8%, M − phenyl·), and *m/z* 134 (2.7%, M − H·).

Third, another major route of fragmentation is cleavage of the carbon-carbon bond beta to the ring. The relative intensity of these fragments are phenyl-CH_2^+ ≥, phenyl-ChR^+ ≫ phenyl-CR_2^+ (*R* = alkyl or nitrogen or both). Cleavage of a nitrogen-carbon bond beta to the ring (aniline compounds) does not occur, but cleavage of a carbon-nitrogen bond beta to the ring is very fascile and is responsible for the base peak in Isomer *VI*, the only exception to the second rule. Fourth, the unsubstituted phenyl ring gave the characteristic cluster of ions

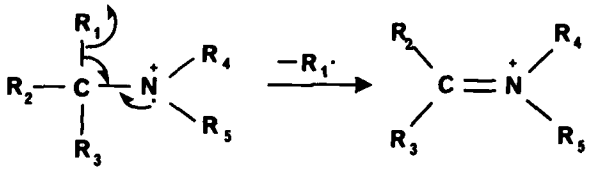

FIG. 2—*Carbon-carbon bond alpha to nitrogen as it is normally cleaved.*

at m/z 77, 78, and 79, however, their intensity and relative ratios were varied and any general parameters in predicting substitution patterns alpha to the ring was not possible.

Comparison of the mass spectra of the isomers to amphetamine, shows that only Isomer *VIII* appeared similar to amphetamine. It was extremely difficult to distinguish the two isomers by visual comparison of the mass spectrum. The computer generated library search of the mass spectrum of Isomer *VIII* gave a similarity index to itself of 0.9707 and to amphetamine of 0.9644. In addition, the K factor [*19*], a computer derived value based on mass and abundance was 37.2 for *VIII* and 31.0 for amphetamine (maximum possible K value was 47.7). Even though *VIII* and amphetamine are difficult to distinguish using EI mass spectrometry, the other analytical test (TLC, visualization with Fluram and GC) clearly differentiates the two compounds. Mass spectrometry also differentiates Isomers *II* and *III* from amphetamine in this series of analytical tests.

One aspect of this paper was to validate the analytical procedure for amphetamine that is used within the laboratory. What is of more significance is that this information facilitates the interpretation of analytical data and identification of other ring modified amphetamines. As clandestinely synthesized drug analogs appear on the "street" this presents a challenge to the analytical chemist to analyze and identify these analogs when authentic standards may not be readily available. Therefore, when confronted with ring modified amphetamine isomers, this initial study would suggest that a base peak in the mass spectrum of m/z 44, a negative nitroprusside color test, and a positive test for a primary amine after TLC would be adequate evidence for the isopropylamine side chain pattern.

Finally, this information now allows us to direct our synthetic efforts to the synthesis of N-methylamphetamine side chain positional isomers ($C_{10}H_{15}N$) which we anticipate would have very similar mass spectral or chromatographic behavior or both for which unambiguous analytical tests can be developed.

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