Investigation and Identification of the Bromination Products of Dimethoxyamphetamines

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The qualitative analysis of the aromatic bromination products of the 6 isomeric dimethoxyamphetamines and their hydrochloride or hydrobromide salts is described. Their ultraviolet, mass, and proton magnetic resonance spectra are not sufficiently different for distinction but infrared spectra allow a positive identification to be made and reference spectra are provided for the bromination products of 2,4-, 2,5-, 2,6-, 4,5-, and 3,5-dimethoxyamphetamines. The application of gas-liquid and thin layer chromatography for the analysis of these products is discussed. The bromination of 2,3-dimethoxyamphetamine consistently gave mixtures which could not be separated satisfactorily; spectra are included for completeness of the comparison of products.

4-Bromo-2,5-dimethoxyamphetamine has been shown to be hallucinogenic (1, 2) and, in recent years, has been subject to abuse (3). Recently this compound, its salts, isomers, and salts of its isomers were placed in the *Federal Register* in the United States of America as Schedule 1 substances. Consequently it is important that an unambiguous structural identification be made for monobrominated dimethoxyamphetamines (DMAs) and that isomers be distinguished.

There are 16 possible isomers of the DMAs monobrominated in the aromatic ring. The isomers described in this paper are those obtained by direct bromination of the 6 DMAs with bromine. They are therefore the more likely isomers to appear on the illicit market from synthetic operations in clandestine laboratories.

Experimental

The amphetamines were prepared from the corresponding dimethoxybenzaldehyde via reduction of the corresponding β-methyl-β-nitrostyrene with lithium aluminum hydride (4). The individual DMA bases were brominated by treatment with one equivalent of bromine in methylene chloride.

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Bromination of 2,3-DMA gave a product which had a correct elemental analysis for the monobrominated substance (Table 1) but which proton magnetic resonance (PMR) spectroscopy indicated to contain 2 components in a molecular ratio of about 10:1. They could not be separated by the usual procedures (recrystallization of salts, distillation, or chromatography). However, pertinent data are included for the product obtained, since they represent the results which would probably be obtained on illicit material. The major component is believed to be 6-bromo-2,3-DMA and the minor component 5-bromo-2,3-DMA, based on an analysis of PMR spectra and the positional reactivities toward aromatic bromination established in our laboratories for the other members of the series.

Bromination of 3,5-DMA under different conditions always resulted in a mixture of 2 compounds. Only preparative thin layer chromatography was found useful for isolating one of the substances, which proved to be identical with the single dibrominated product of the reaction of 3,5-DMA with an excess of bromine. Chromatographic and spectral data indicate that the second component was monobrominated. The other substances were purified either as the hydrobromide or the hydrochloride salt by recrystallization from isopropanol-hexane mixtures. Elemental analyses and melting points (uncorrected, measured on a Koffler hot stage) are shown in Table 1.

The spectra of free bases were recorded from the base which had been 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 nitrogen. Thin layer chromatograms were developed 15 cm in saturated tanks under ambient conditions, using precoated plates and sheets as received. They were examined under 254 nm ultraviolet (UV) light. Mass spectra were determined on a Hitachi Perkin-Elmer magnetic deflecting 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 (IR) spectra were recorded on a Perkin-Elmer Model 621 instrument and UV spectra on a Beckman Model BD GT spectrophotometer. PMR spectra were recorded on a Varian A-60A spectrometer. Gas-liquid chromatograms were obtained on a Hydro-flow Series 3000 instrument.

Table 1. Melting point and analytical data for the products of molecular bromination of the dimethoxyamphetamines

Compound	Found, % C	H	N	Melting point, °C
6-Bromo-2,3-DMA.HBr	37.17[a]	4.84	3.92	115–117[b]
5-Bromo-2,4-DMA.HBr	37.24[a]	4.90	3.96	180–181
4-Bromo-2,5-DMA.HCl	42.56[c]	5.53	4.52	197–198
3-Bromo-2,6-DMA.HBr	37.37[a]	4.77	4.01	166–168
2-Bromo-4,5-DMA.HBr	37.24[a]	4.84	3.95	196–197
2-Bromo-3,5-DMA[d]				240–244
2,6-Dibromo-3,5-DMA.HBr	30.35[e]	3.53	3.18	261

[a] Calculated for hydrobromide salt (%) $C_{11}H_{17}Br_2NO_2$: C, 37.21; H, 4.83; N, 3.95.
[b] An impurity was indicated by PMR.
[c] Calculated for hydrochloride salt (%) $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.52; N, 4.51.
[d] Intimate mixture with dibromo compound.
[e] Calculated for hydrobromide salt (%) $C_{11}H_{16}Br_3NO_2$: C, 30.44, H, 3.48; N, 3.23.

Results and Discussion

Mass Spectra

The spectra of the brominated DMAs, like those of the parent DMAs (5), were weak and, although the "isotopic clusters" due to the 2 bromine isotopes allow brominated DMAs to be recognized and distinguished from the dibrominated compounds, mass spectrometry alone does not allow identification of the substitution pattern. The intensity of the molecular ions varies from 0.5 to 10% of the base peak (m/e 44). The 2 most intense signals after the base peak are at m/e 230 and 232, due to the ion $C_9H_{10}BrO_2$ resulting from the fission of the β-bond and the expulsion of C_2H_6N.

Ultraviolet Spectra

The UV data shown in Table 2 indicate that the maxima are shifted to a slightly longer wavelength than those for the parent DMAs (6) and that the molar absorptivities are somewhat greater. It is apparent that once an isomer has been identified qualitatively, UV spectroscopy may be used for the quantitative analysis.

Table 2. Ultraviolet data for the products[a] of molecular bromination of the dimethoxyamphetamines

Compound	$\lambda_{max.}$, nm	ϵ
6-Bromo-2,3-DMA[b]	280	2213
5-Bromo-2,4-DMA	285	4020
4-Bromo-2,5-DMA	293	5412
3-Bromo-2,6-DMA	279	1733
2-Bromo-4,5-DMA	283	3214
2,6-Dibromo-3,5-DMA	294	3794

[a] Solutions of salts in 0.1*N* H_2SO_4.
[b] An impurity was indicated by PMR.

Infrared Spectra

IR spectra of the free bases (films of NaCl plates) and of the salts (KBr disks) are presented in Figs. 1–12. The spectra are distinct from one another and have sufficient detail for identification. As noted for the DMAs (6), the aromatic C—H bending bands cannot be used to deduce the aromatic substitution pattern with reliability.

Proton Magnetic Resonance Spectra

The PMR spectra of all of the free bases were recorded from their solutions in $CDCl_3$ and the spectra of their salts were recorded in D_2O solutions except for 5-bromo-2,4-DMA and 2,6-dibromo-3,5-DMA, which were isoluble in D_2O. The integrated spectra are very similar to those published for the parent compounds (6) apart from the signals due to the aromatic protons, and allow the immediate recognition of either mono- or disubstituted DMAs. The pattern of the aromatic proton signals distinguishes 3 groups, the members in each group having a common aromatic proton substitution pattern: *para* for 5-bromo-2,4-DMA, 4-bromo-2,5-DMA, and 2-bromo-4,5-DMA; *ortho* for 6-bromo-2,3-DMA and 3-bromo-2,6-DMA; *meta* for 2-bromo-3,5-DMA, although the last compound always occurs as a mixture containing a little of the corresponding dibromo derivative. Distinction within these groups is possible by recourse to the accurate measurement of chemical shifts. The differences are extremely small

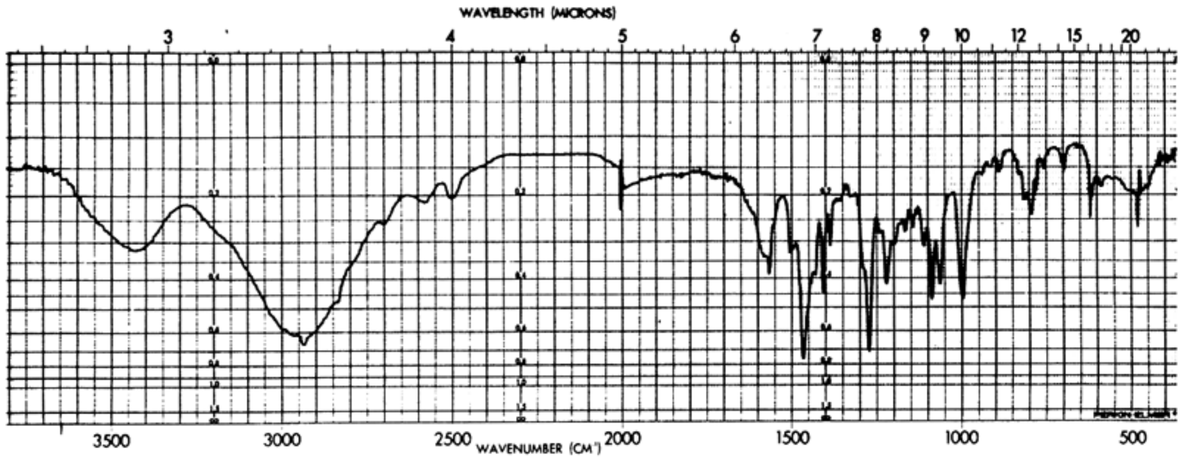

FIG. 1—IR spectrum of 6-bromo-2,3-dimethoxyamphetamine hydrobromide, KBr disk.

FIG. 2—IR spectrum of 6-bromo-2,3-dimethoxyamphetamine base, NaCl film.

FIG. 3—IR spectrum of 5-bromo-2,4-dimethoxyamphetamine hydrobromide, KBr disk.

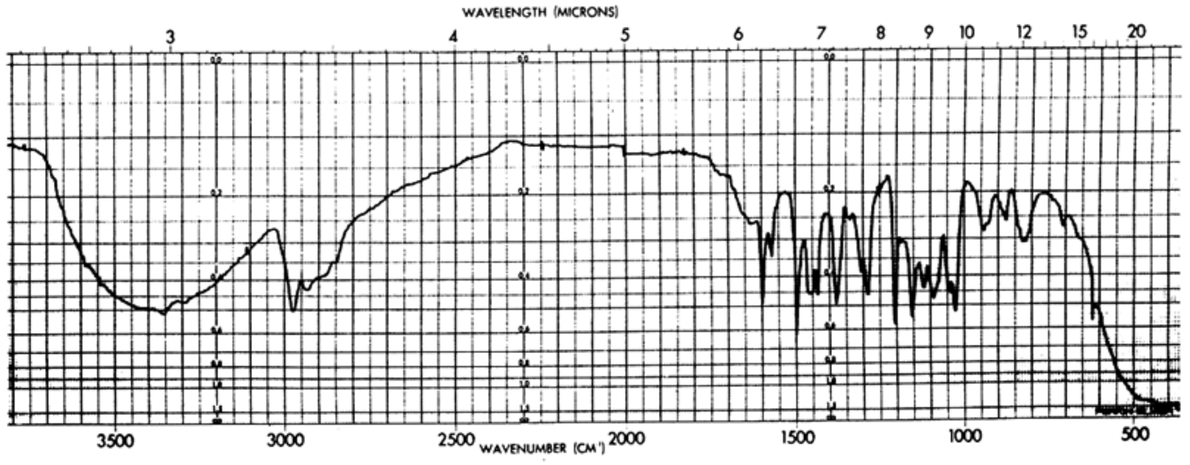

FIG. 4—IR spectrum of 5-bromo-2,4-dimethoxyamphetamine base, NaCl film.

FIG. 5—IR spectrum of 4-bromo-2,5-dimethoxyamphetamine hydrochloride, KBr disk.

FIG. 6—IR spectrum of 4-bromo-2,5-dimethoxyamphetamine base, NaCl film.

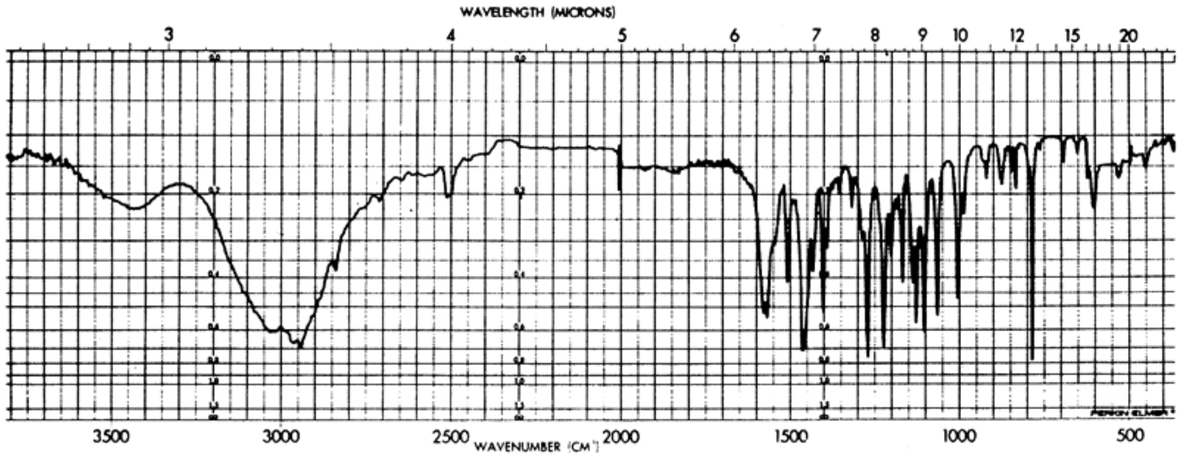

FIG. 7—IR spectrum of 3-bromo-2,6-dimethoxyamphetamine hydrobromide, KBr disk.

FIG. 8—IR spectrum of 3-bromo-2,6-dimethoxyamphetamine base, NaCl film.

FIG. 9—IR spectrum of 2-bromo-4,5-dimethoxyamphetamine hydrobromide, KBr disk.

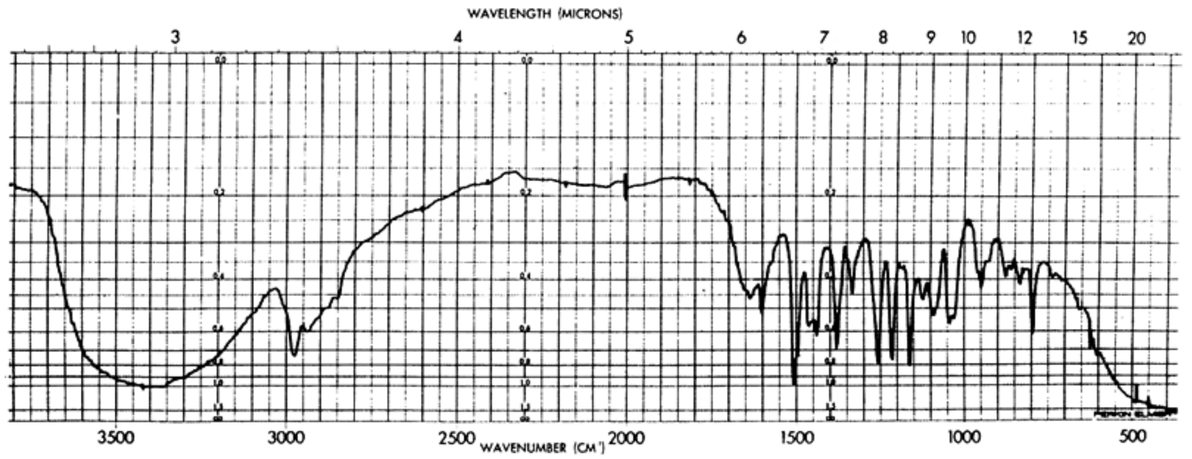

FIG. 10—IR spectrum of 2-bromo-4,5-dimethoxyamphetamine base, NaCl film.

FIG. 11—IR spectrum of 2,6-dibromo-3,5-dimethoxyamphetamine hydrobromide, KBr disk.

FIG. 12—IR spectrum of 2,6-dibromo-3,5-dimethoxyamphetamine base, KBr disk.

Table 3. R_f values (× 100) of the direct bromination products of the dimethoxyamphetamines

System[a]	Plate[b]	6-Bromo-2,3-DMA[c]	5-Bromo-2,4-DMA	4-Bromo-2,5-DMA	3-Bromo-2,6-DMA	2-Bromo-4,5-DMA	2-Bromo-3,5-DMA	2,6-Dibromo-3,5-DMA[d]	Amphetamine	STP
A	Ea	37	22	21	20	27	23	42	37	11
B	Ea	48	40	38	37	47	47	47	50	25

[a] A = ethyl acetate-cyclohexane-ammonium hydroxide-methanol-water (70+15+2+8+0.5); B = chloroform-methanol (8+1).
[b] Ea = Eastman chromogram 6060 gel sheet with fluorescent indicator.
[c] An impurity was indicated by PMR.
[d] As present in a mixture of mono- and dibromo-3,5-DMA.

Table 4. Retention times (min) of the products of the direct bromination of the dimethoxyamphetamines for column packings and oven temperatures indicated[a]

	3% OV-17		2.5% OV-225		5% OV-7		3% SE-30	
Compound	200°C	175°C	175°C	150°C	175°C	150°C	150°C	125°C
6-Bromo-2,3-DMA[b]	2.3	10.3	2.8	7.8	4.5	13.8	1.4	3.1
5-Bromo-2,4-DMA	3.1	17.5	4.5	16.2	6.5	22.4	1.8	5.0
4-Bromo-2,5-DMA	2.8	14.7	3.5	12.0	5.7	19.1	1.7	4.3
3-Bromo-2,6-DMA	2.4	12.5	2.8	8.2	4.8	14.3	1.5	3.4
2-Bromo-4,5-DMA	2.8	13.5	3.5	12.1	5.8	19.0	1.6	4.5
2-Bromo-3,5-DMA[c]	3.3	17.6	4.5	16.0	6.6	23.3	2.1	5.2
2,6-Dibromo-3,5-DMA	7.9		13.8		20.9		4.3	20.3
STP	1.6	5.7	1.5	4.0	3.0	7.7	1.0	2.1

[a] Columns were glass, 6′ long, injector 275°C, nitrogen flow 30 ml/min. Support material was 80-100 mesh Chromosorb W (HP), except for 3% SE-30 when 60-80 mesh was used.
[b] An impurity was indicated by PMR.
[c] In mixture of mono- and dibromo-3,5-DMA.

in the *para* series and great caution should be exercised in the final assignment.

Thin Layer Chromatography

Two development systems (7, 8) were investigated (Table 3). Amphetamine and 2,5-dimethoxy-4-methylamphetamine (STP) were included to compare data for these compounds and it could be seen that they have similar R_f values. The spots were somewhat elongated and the isomers could not be definitely distinguished with these systems.

Gas-Liquid Chromatography

The 4 columns examined each gave similar results (Table 4). The monobromo isomers of DMA can be grouped into 3 pairs of similar retention times which, in the order of their emergence from the columns, are 6-bromo-2,3-DMA and 3-bromo-2,6-DMA; 4-bromo-2,5-DMA and 2-bromo-4,5-DMA; and 5-bromo-2,4-DMA and 2-bromo-3,5-DMA. It is interesting to note the structural relationships (*see* Fig. 13) within each of these pairs; the first pair has *ortho* hydrogen atoms, one flanked by hydrogen and bromide atoms and the other by hydrogen and methoxyl groups; the second pair has *para* hydrogen atoms, one flanked by bromine and methoxyl groups and the other by alkyl and methoxyl groups; and the third pair has one hydrogen atom flanked by methoxyl groups and the other by bromine and an alkyl group or methoxyl and an alkyl group.

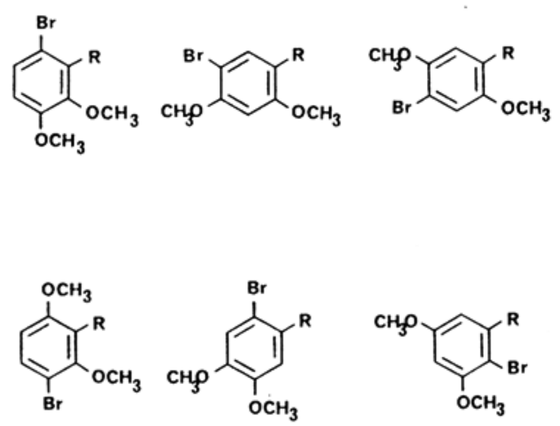

FIG. 13—Structures of 6 isomeric bromo-dimethoxyamphetamines.

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