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TECHNICAL NOTE

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Gas Chromatographic Analysis of Amphetamine Derivatives and Morpholine-Related Drugs

Forensic chemists are constantly evaluating various techniques for the identification and isolation of large classes of drugs of similar chemical structure. Because of increased abuse, of particular interest are the amphetamine derivatives and morpholine-related drugs either clandestinely synthesized or manufactured in licit form. The twelve drugs studied in this paper, some of which have been recently controlled by law as dangerous substances, are routinely encountered in crime laboratories; thus, the chromatographic separation and identification of these substances is important to practicing forensic drug chemists.

The common method for screening amphetamine-related drugs has been a combination of color tests and microcrystalline reagents [*1,2*] for the structurally similar members of the amphetamine family such as amphetamine and methamphetamine. This is followed by further spectrophotometric and chromatographic analysis for confirmation. Although miscellaneous chemical data is available for many of these drugs, a comprehensive gas chromatographic analysis would be an effective method for confirmation. Infrared analysis, although generally specific, is not readily applicable in those cases which the drug is encountered in highly adulterated form.

Experimental Procedure

Drug Standards

The following drugs were obtained from the manufacturers as the hydrochloride salts: *d*,l-phenylpropanolamine, *d*-benzphetamine, and ephedrine. Other drugs studied were proprietary forms as follows: Pre-Sate® (chlorphentermine HCl), Pondimin® (fenfluramine HCl), Voranil® (clortermine HCl), and two morpholine drugs, Preludin® (phenmetrazine HCl) and Plegine® (phendimetrazine bitartrate). Mescaline, 3,4-methylenedioxyamphetamine (MDA), 4-methyl-2,5 dimethoxyamphetamine (STP), and 4-bromo-2,5 dimethoxyamphetamine were obtained from clandestine sources.

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Apparatus

The instrument used was a Varian dual column 2400 gas chromatograph with a flame ionization detector at a temperature of 250°C. Inserted in the instrument were two 6-ft (1.8-m) by ¼-in. (6.35-mm) outside diameter, 2-mm inside diameter glass columns purchased from Analabs, Inc. The column packings were 10% Apiezon L plus 2% KOH and Carbowax 20M plus 2% KOH, both on the same support, Chromosorb W/AW 80–100 mesh, available from Supelco, Inc., Bellefonte, Pa. The carrier gas was medical-grade nitrogen at a flow rate of 30 ml/min, and the detector gases were hydrogen at 30 ml/min and compressed air at 300 ml/min. All injections were made with an 801-μl syringe in concentrations of 1 to 5 mg/ml, depending on the drug. The injection port temperature was 210°C. A graphical representation of the chromatographic separation was accomplished on a Hewlett-Packard 3380A integrator-recorder.

Preparation of Column Packings

Apiezon L is dissolved in chromatographic-grade toluene, then KOH is added to the solution. Methanol absolute is added to this solution until the KOH is just solubilized. The solid support Chromosorb W/AW is placed in a 250-ml Erlenmeyer flask with a two-holed rubber stopper with two glass tubes inserted so that the longer tube is slightly above the support. Nitrogen is introduced through the longer glass tube, and the support is flushed for 5 min. The stopper is then removed, the Apiezon L solution is added, and the flask is restoppered and dried with gentle agitation. Ideally, the column should be packed under nitrogen; however, using vacuum and gentle vibration has proven effective.

Carbowax 20M is dissolved in chromatographic-grade chloroform and KOH is added to the chloroform solution, followed by small aliquots of methanol absolute to solubilize the KOH. The solid support Chromosorb W/AW is prepared in the same manner as Apiezon L. Treatment of the column with KOH and drying over nitrogen has proven effective in reducing tailings which result in poor resolution of individual components [*3,4*].

Results and Discussion

The Apiezon L column system, a branched polyalkane hydrocarbon, if treated with KOH, has been successful in the separation of amphetamine and methamphetamine [*5–7*]. This column packing, adopted for the separation of amphetamine derivatives and morpholine-related drugs, was found to be stable with time and to exhibit reproducible data and resolve the simpler amphetamines at 115°C in the order of amphetamine, phentermine, and methamphetamine [*7*].

The drugs chromatographed using 10% Apiezon L plus 2% KOH at 165°C in two groups (Table 1) produced reasonable separation of all twelve drugs of interest (Figs. 1*a* and *b*). Certain drugs of close structural resemblance resolve extremely well, namely clortermine and chlorphentermine, ephedrine and phenylpropanolamine, as well as the morpholines phenmetrazine and phendimetrazine. The methoxyamphetamine derivatives and benzphetamine, a high molecular weight amphetamine, also resolve well when chromatographed at 165°C (Fig. 1*b*).

Alkaline-treated Carbowax, investigated by Lebish et al [*8*] as a column packing, was used by Blasof and Fasanello [*7*] for the separation of amphetamine and methamphetamine. The retention order for Carbowax 20M plus 2% KOH at 115°C was methamphetamine, phentermine, and amphetamine. This is the reverse order as compared to Apiezon L and reproduces Blasof's work.

TABLE 1—*Gas chromatography data for amphetamines and morpholines at 165°C.*

Drug	10% Apiezon L + 2% KOH on Chromosorb W/AW			10% Carbowax 20M + 2% KOH on Chromosorb W/AW		
	Retention Time, min	Relative Time[a]	Order	Retention Time, min	Relative Time[a]	Order
Clortermine	4.13	0.61	3	4.83	0.37	2
Chlorphentermine	4.78	0.71	5	5.22	0.45	3
Ephedrine	4.41	0.65	4	11.44	0.99	5
Fenfluramine	1.77	0.26	1	1.38	0.12	1
Phendimetrazine	7.66	1.13	8	8.08	0.70	4
Phenylpropanolamine	3.65	0.54	2	15.91	1.38	6
Phenmetrazine	6.77	1.00	6	11.57	1.00	5
Benzphetamine	49.81	7.36	12	36.06	3.12	9
Mescaline	16.24	2.40	10	~50.0	~4.3	10
3,4-methylenedioxyamphetamine	7.34	1.08	7	17.50	1.51	7
4-methyl-2,5 dimethoxyamphetamine	12.35	1.82	9	22.50	1.95	8
4-bromo-2,5 dimethoxyamphetamine	34.57	5.11	11	~60.0	~5.2	11

[a] Based on phenmetrazine.

At 165°C, the amphetamine and morpholine-related drugs (Table 1) resolve with greater separation in time with 10% Carbowax 20M plus 2% KOH than with Apiezon L (Fig. 2*a*). The only two drugs which did not resolve, phenmetrazine and ephedrine, can be easily separated on the Apiezon L column. Figure 2*b* shows that the amphetamine derivatives also resolve easily, except that mescaline and 4-bromo-2,5 dimethoxyamphetamine exhibit unusually long retention times at 165°C and are not illustrated. The retention order for the amphetamine hallucinogenic derivatives is the same on both columns, namely, MDA, STP, mescaline, and 4-bromo-2,5 dimethoxyamphetamine.

The drugs of similar chemical structure also resolve on Carbowax 20M plus 2% KOH with even greater retention time differences than on Apiezon L. Of particular interest is the reversal of retention order for ephedrine and phenylpropanolamine and the morpholines phenmetrazine and phendimetrazine; clortermine and chlorphentermine do not reverse. This reversal in elution order is significant when gas chromatography is used as a confirmatory tool in qualitative analysis.

In selecting stationary phases for confirmatory analysis, one should use substances of diverse polarities as exhibited by the McReynolds constants [*9*]. The McReynolds constants based on pyridine as the alkaline material representing amphetamine-like drugs are 42 for Apiezon L and 510 for Carbowax 20M, indicating the divergent nature between the phases.

Summary

A gas chromatographic column system has been evaluated for the separation and confirmation of twelve amphetamine-related drugs, including the morpholine drugs phenmetrazine and phendimetrazine.

The column packings of 10% Apiezon L plus 2% KOH and 10% Carbowax 20M plus 2% KOH on Chromosorb W/AW resolved all drugs of interest on each column at 165°C except for phenmetrazine and ephedrine on the Carbowax 20M column. Several drugs that were structurally related reversed their elution order, an important factor in chro-

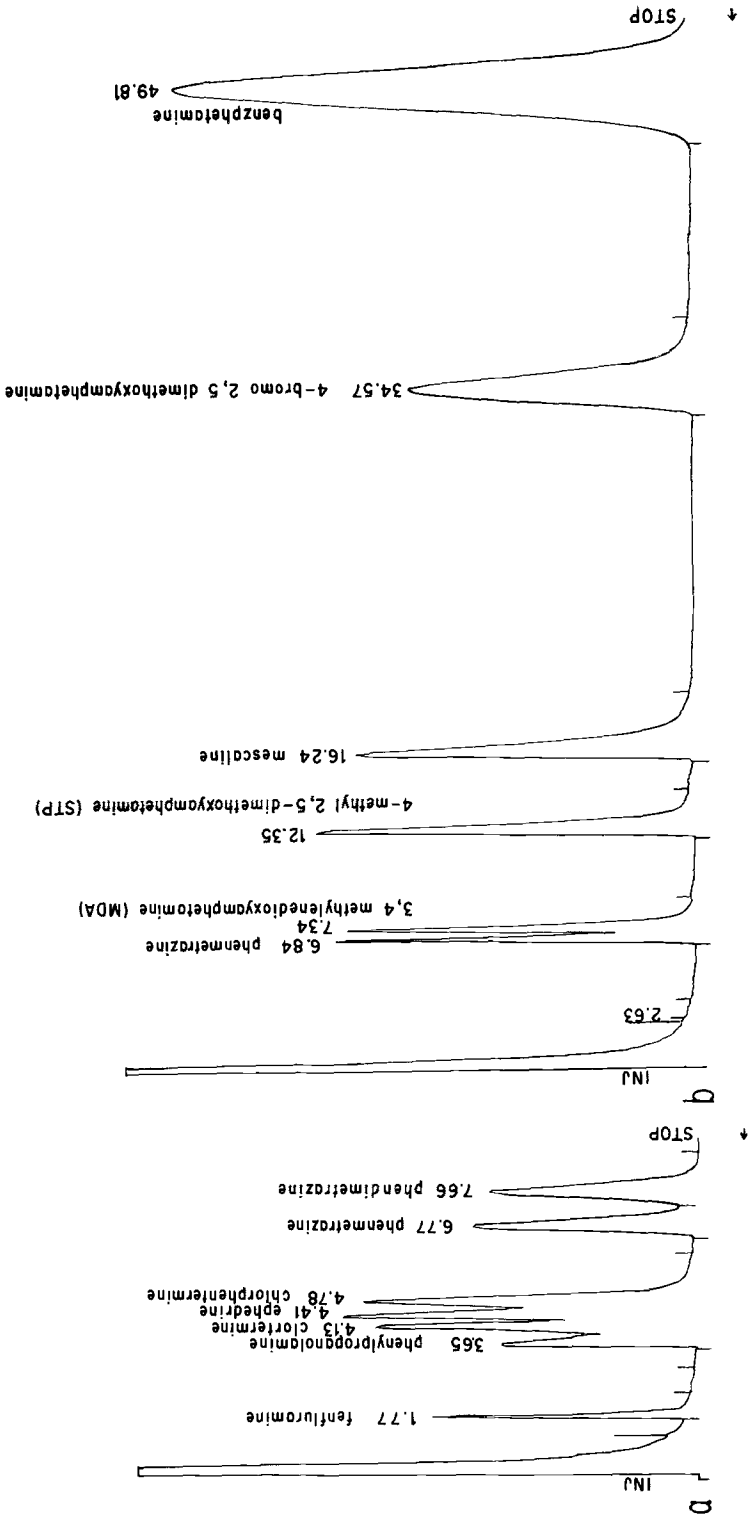

FIG. 1—*Gas chromatographs obtained at 165°C with 10% Apiezon L plus 2% KOH on Chromosorb W/AW; (a) common amphetamines and morpholines; (b) amphetamine derivatives.*

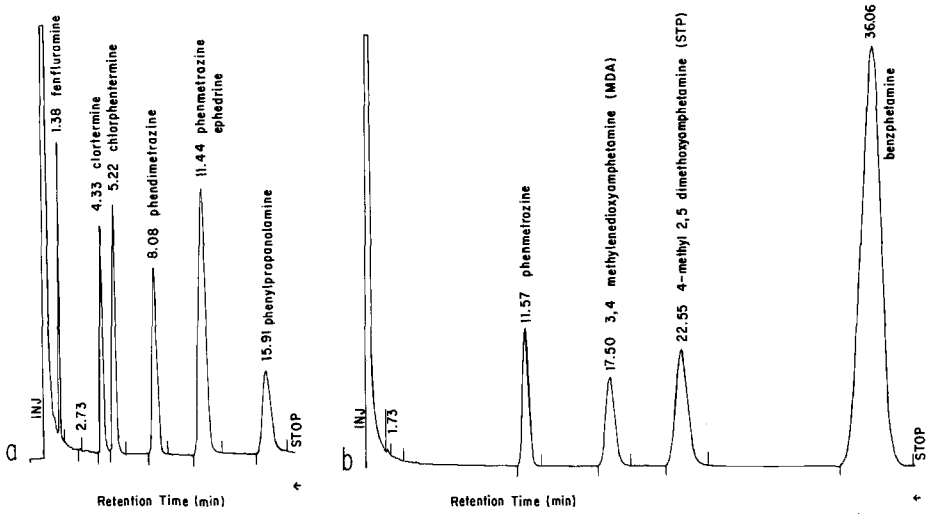

FIG. 2—*Gas chromatographs obtained at 165°C with 10% Carbowax 20M plus 2% KOH on Chromosorb W/AW*; (a) *common amphetamines and morpholines*; (b) *amphetamine derivatives.*

matographic confirmation. These drugs are ephedrine and phenylpropanolamine as well as phenmetrazine and phendimetrazine.

References

[1] Clarke, E. G. C., *Isolation and Identification of Drugs,* Pharmaceutical Press, London, 1971, pp. 192 and 420.

[2] Sunshine, I., *Handbook of Analytical Toxicology,* The Chemical Rubber Co., Cleveland, 1969, p. 464.

[3] Smith, E. D. and Radford, R., "Modification of Gas Chromatographic Substrates for the Separation of Aliphatic Diamines," *Analytical Chemistry,* Vol. 33, No. 9, 1961, pp. 1160–1162.

[4] Supina, W. R., *The Packed Column In Gas Chromatography,* Supelco, Inc., Bellefonte, Pa., 1972, p. 33.

[5] *Chromatography Lipids,* Vol. 6, No. 3, 1972, Supelco, Inc., Bellefonte, Pa.

[6] Jain, N. C., "Rapid Mass Screening and Confirmation of Urinary Amphetamine and Methamphetamine by Gas Chromatography," *Clinical Toxicology,* Vol. 8, No. 2, 1975, p. 211.

[7] Blasof, S. and Fasanello, J., "The Determination of Amphetamine and Methamphetamine Preparations by Gas Chromatography," *Micrograms,* Vol. 7, No. 2, 1974, pp. 22–24.

[8] Lebish, P., Finkle, B. S., and Brackett, J. W., "Determination of Amphetamine, Methamphetamine and Related Amines in Blood and Urine by Gas Chromatography with Hydrogen Flame Ionization Detector," *Clinical Chemistry,* Vol. 16, No. 3, 1970, pp. 195–200.

[9] McReynolds, W. D., "Characterization of Some Liquid Phases," *Journal of Chromatographic Science,* Vol. 8, No. 12, 1970, pp. 685–691.

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