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3′,4′,5′-Trimethoxy-Substituted Analogs of Cocaine, *Cis-/Trans*-Cinnamoylcocaine and Tropacocaine: Characterization and Quantitation of New Alkaloids in Coca Leaf, Coca Paste and Refined Illicit Cocaine

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ABSTRACT: Four new alkaloids have been detected in South American coca leaf, coca paste and refined illicit cocaine. The compounds 3′,4′,5′-trimethoxycocaine (TMC), 3′,4′,5′-trimethoxytropacocaine (TMT), 3′,4′,5′-trimethoxy-*cis*-cinnamoylcocaine (cTMCC) and 3′,4′,5′-trimethoxy-*trans*-cinnamoylcocaine (tTMCC) were isolated from the coca leaf matrix and other alkaloids by toluene extraction followed by trap and ion-pair column chromatography. The identity of each alkaloid was verified via comparison of its mass spectrum with a synthesized standard. All four alkaloids were quantitated in leaf, paste and refined samples at levels of less than 0.1% relative to cocaine via capillary gas chromatography—flame ionization detection (cGC-FID).

KEYWORDS: criminalistics, illicit cocaine, coca alkaloids, cocaine impurities, gas chromatography, chromatographic analyses

In recent years considerable attention has focused on chromatographic signature profile analyses of illicit cocaine exhibits [*1–16*]. These techniques specifically examine trace level impurities in cocaine, including both naturally occuring alkaloids and/or additional by-products resulting from the chemical manipulation of coca leaf, coca paste, or refined cocaine. The resulting chromatograms have been predominantly used in sample/sample comparisons for use as corroborative evidence. Two such methodologies were recently used in the successful prosecution of two separate drug conspiracy investigations [*13,17*]. An additional objective of these analyses is the development of methods that can be used for geographic origin determinations.

Recently, we observed an unidentified, low intensity, late eluting peak in 10 to 20% of our chromatograms. The compound was tentatively identified as 3′,4′,5′-trimethoxycocaine (TMC). It has been previously reported that differing species of coca produce diverse tropane alkaloids [*18–24*]. In two such investigations [*18,20*], several 3′,4′,5′-trimethoxy-substituted tropane alkaloids were characterized in the root-bark of two dif-

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fering species of *Erythroxylum*. In contrast to cocaine, those alkaloids possessed the C-3 substituent in an *axial* (opposed to equatorial in the case of cocaine) position. However, trimethoxy-substituted alkaloids have not been previously reported in *Erythroxylum* coca, the cultivar believed to be most prevalent in illicit cocaine production.

Following identification of TMC, we identified three additional trimethoxy-substituted tropane alkaloids, including 3',4',5'-trimethoxytropacocaine (TMT), 3',4',5'-trimethoxy-*cis*-cinnamoylcocaine (cTMCC) and 3',4',5'-trimethoxy-*trans*-cinnamoylcocaine (tTMCC). The four alkaloids are illustrated in Fig. 1. Herein, methodology is presented for preparative and analytical isolation of these alkaloids from coca leaf, illicit coca paste, and refined illicit cocaine using "trap" and ion-pair column chromatography. Detection and quantitation of the isolated alkaloidal impurities was accomplished using cGC-FID. The identity of each alkaloid was verified by comparison of their retention time and mass spectra with authentic standards.

Experimental

Capillary Gas Chromatography-Flame Ionization Detection

A Hewlett Packard Model 5890 Series II gas chromatograph was used to generate all standard and sample chromatograms. A 30 m × 0.25 mm i.d. fused-silica capillary column coated with DB-1 (J & W Scientific) at a film thickness of 0.25 μm was employed. Hydrogen (99.999, UHP) was the carrier gas at a linear velocity of 35 cm/s. The injection port and flame ionization detector were maintained at 230°C and 280°C, respectively. Samples were injected (2 μL injection) in the split mode (20:1). The oven temperature was programmed as follows: initial temperature, 150°C; initial hold, 1.0 min;

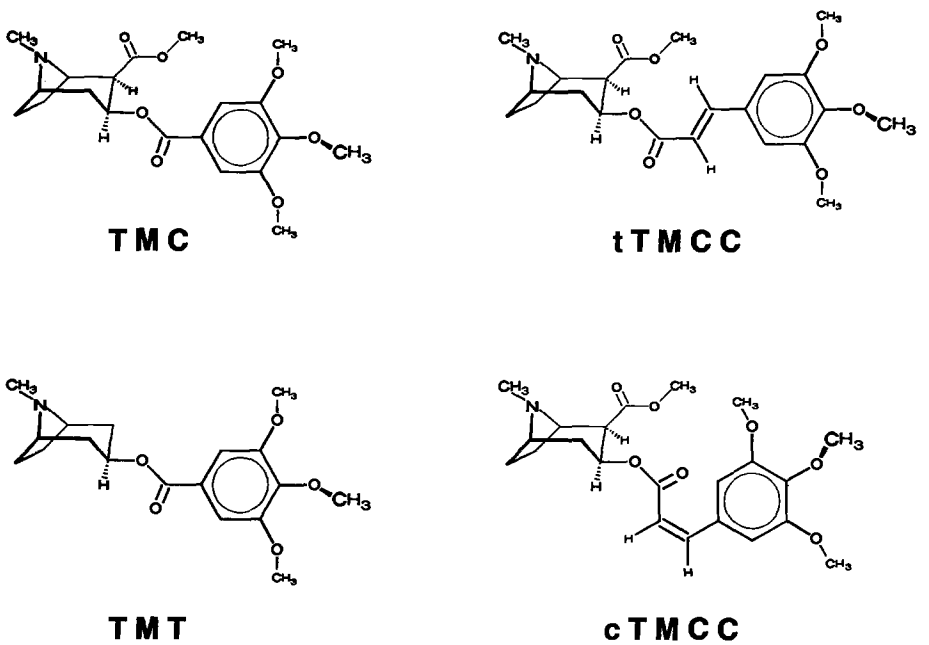

FIG. 1—*Structural formulae.*

program rate, 6.0°C/min; final temperature, 275°C; final hold, 8.0 min. All chromatograms were recorded at an attenuation of 2^{-1}, unless otherwise noted.

Mass Spectrometry

Mass spectra for all compounds were obtained on a Hewlett Packard Model 5971A Mass Selective Detector (MSD) interfaced with a Hewlett Packard 5890 Series II gas chromatograph. The MSD operated under electron ionization (EI) conditions at 70 eV and in full scan mode. The column and oven temperature parameters were identical to those utilized for the cGC-FID analyses, except that the final temperature and hold were 285°C and 11.0 min, respectively.

Materials

The glass chromatographic columns used for analytical separations were products of Lurex (Vineland, NJ, USA), and were 260 mm × 22 mm i.d. with a stem length of 50 mm. The Celite 545 stationary phase was purchased from J. T. Baker (Jackson, TN) and was used without any pre-treatment. All solvents used for column chromatography were water-saturated and were prepared as previously described [*25*].

Coca Leaf, Coca Paste and Refined Cocaine

The coca leaf, coca paste and refined cocaine samples examined in this study were collected in South America from the countries of Peru, Bolivia, Columbia, and Brazil.

Reagents and Standards

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI, USA). Standards of TMT, TMC, tTMCC, 2′,3′,4′-TMC, 2′,4′,5′-TMC, 2′,4′,6′-TMC, 2′,3′,4′-tTMCC, 2′,4′,5′-tTMCC, 2′,4′,6′-tTMCC and 3′,4′,5′-trimethoxyethylcocaine (internal standard, ISTD) were synthesized in this laboratory. The synthesis of TMT and TMC was accomplished by acylation of pseudotropine and ecgonine methyl ester, respectively, with 3,4,5-trimethoxybenzoyl chloride. The syntheses of tTMCC was accomplished by acylation of ecgonine methyl ester with 3,4,5-trimethoxycinnamoyl chloride. The syntheses of the 2,3,4-, 2,4,5- and 2,4,6-trimethoxy-substituted analogs of TMC and tTMCC were accomplished by the condensation of ecgonine methyl ester with the respective trimethoxy- benzoic or cinnamic acid using dicyclohexylcarbodiimide (DCC) [*26*]. The internal standard was diluted with chloroform to give a solution containing 0.10 mg/mL.

Isolation of Trimethoxy-Substituted Alkaloids from Bulk Coca Leaf for Mass Spectral Characterization

The preparative isolation of the four trimethoxy-substituted alkaloids was accomplished using recently developed methodology [*25*]. To a mixture of 50 g powdered Bolivian leaf and 100 g powdered Peruvian leaf was added 75 mL of saturated aqueous sodium bicarbonate. After trituration, the basified leaf was separated into 10 g samples and each extracted with toluene (3 × 30 mL) at 65–70°C for 1 h. The toluene extracts were combined and evaporated in vacuo to ca. 200 mL. The concentrated extract was saturated with water and passed through a column packed with a mixture of 8 g Celite 545 and 4.0 mL of 0.36N sulfuric acid. The column was then washed with an additional 30 mL water-saturated toluene. All eluates were discarded. The alkaloids were then

liberated from the column by elution with 60 mL water-saturated chloroform containing 200 μL of diethyl amine. The eluate was evaporated in vacuo to an oily residue. This residue was reconstituted in ca. 500 μL of water-saturated chloroform and transferred to a column packed with: bottom layer, 1 g Celite 545 mixed with 0.5 mL saturated aqueous sodium bicarbonate; top layer, 4 g Celite 545 mixed with 2.0 mL of 2N NaCl/1N HCl solution. The first 9–10 mL of eluate were collected and concentrated under a stream of nitrogen to ca. 1 mL for GC/MSD analyses.

Isolation and Quantitation of Trimethoxy-Substituted Alkaloids in Coca Leaf, Coca Paste and Refined Cocaine

All exhibits were air dried prior to analysis. The coca leaf was ground to a fine powder to pass through a 2 mm sieve prior to analysis.

Coca Leaf—One gram of dry, freshly ground leaf was accurately weighed into a 13 mL glass centrifuge tube, and 0.50 mL of ISTD and 0.5 mL of saturated aqueous sodium bicarbonate added. After one minute of vigorous shaking, ca. 10 mL of water-saturated toluene was added and the tube was heated in a water bath at 65–70°C for 1 h. The tube was centrifuged at 2000 rpm for 10 min and the toluene extract set aside. The procedure was repeated twice more and the combined toluene extracts passed through a chromatographic column packed with: bottom layer, 1.0 g Celite 545 mixed with 0.5 mL saturated aqueos sodium bicarbonate solution; top layer, 4.0 g Celite 545 mixed with 2.0 mL of 2N NaCl/1N HCl solution. The column was then eluted with 5.0 mL water-saturated toluene followed by 6.0 mL water-saturated hexane. Both eluates were discarded. The column was then eluted with 22 mL of water-saturated chloroform. The first 9–10 mL of eluate (column dead volume) were discarded and the following 10 mL collected in a tube. This latter fraction was evaporated to dryness under a stream of nitrogen, and the isolated alkaloids reconstituted in 1.0 mL of chloroform for GC analysis.

Coca Paste and Refined Cocaine—1) A 100 mg equivalent of cocaine base was placed into a 13 mL centrifuge tube containing 0.50 mL of ISTD solution and 0.5 mL aqueous saturated sodium bicarbonate. After vigorous mixing, the chloroform extract was triturated with 0.5 g of Celite 545, which was then set aside; 2) A chromatographic column was prepared as follows: bottom layer—packed mixture of 0.5 mL saturated aqueous sodium bicarbonate +1 g Celite 545; top layer—packed mixture of 2.0 mL of 1N HCl/ 2N NaCl + 4 g Celite 545. After preparation, 10 mL of water-saturated chloroform is passed into the column; 3) the chloroform/Celite triturate from Step 1) is packed atop the column and then eluted with 22 mL of water-saturated chloroform, discarding the first 9–10 mL of eluate and collecting the remainder. This eluate is evaporated to dryness and the residue reconstituted in 1.0 mL of chloroform for chromatographic analysis.

For the quantitative analysis of TMT, TMC, cTMCC and tTMCC, 2 μL of the reconstituted solutions were injected in duplicate as described in the Experimental Section. All quantitative calculations were based on multiple injections of two freshly prepared mixed standards at concentrations for each alkaloid at ca. 0.10 mg/mL and 0.010 mg/mL.

Results and Discussion

Trap and Ion-Pair Chromatography

Toluene has been shown previously to be the solvent of choice for extraction and isolation of coca alkaloids from leaf [*25*]. The dilute sulfuric acid/Celite 545 column "traps" alkaloids from the leaf/toluene extract, while the bulk of acidic and neutral compounds are removed in the eluate. The alkaloids are subsequently liberated from the

column with water-saturated chloroform containing diethylamine. Ion-pair chromatography is used to isolate trace levels of the trimethoxy-substituted compounds from the bulk cocaine matrix [25].

Gas Chromatography of TMC, TMT, cTMCC and tTMCC

The cGC-FID chromatogram for cocaine impurities isolated in the ion-pair extract of a refined cocaine HCl exhibit seized in South America is illustrated in Fig. 2. Included in the chromatogram are peaks (#'s 6, 7, 9 and 10) for the four trimethoxy-substituted alkaloids as well as the ISTD (peak #8). It is also believed that, with some minor modifications, this methodology may be suitable for the quantitation of tropacocaine (peak #1) and N-norcocaine (peak #2). Finally, it is believed that a substantial number of the unenumerated peaks in Figure 2 may be additional uncharacterized coca alkaloids.

Characterization of Trimethoxy-Substituted Alkaloids from Coca Leaf

As seen in Fig. 3, the mass spectrum of suspected TMC exhibited ions at m/z 82 and m/z 182 (base peak), suggesting the presence of a 2-carbomethoxytropane moiety. The difference between its molecule ion and that of cocaine is 90 daltons, suggesting trimethoxy substitution on the aromatic ring. The mass spectrum and retention time of the unknown and synthesized 3',4',5'-TMC were virtually identical.

Mass spectral analysis of the bulk coca leaf isolate revealed three additional suspected

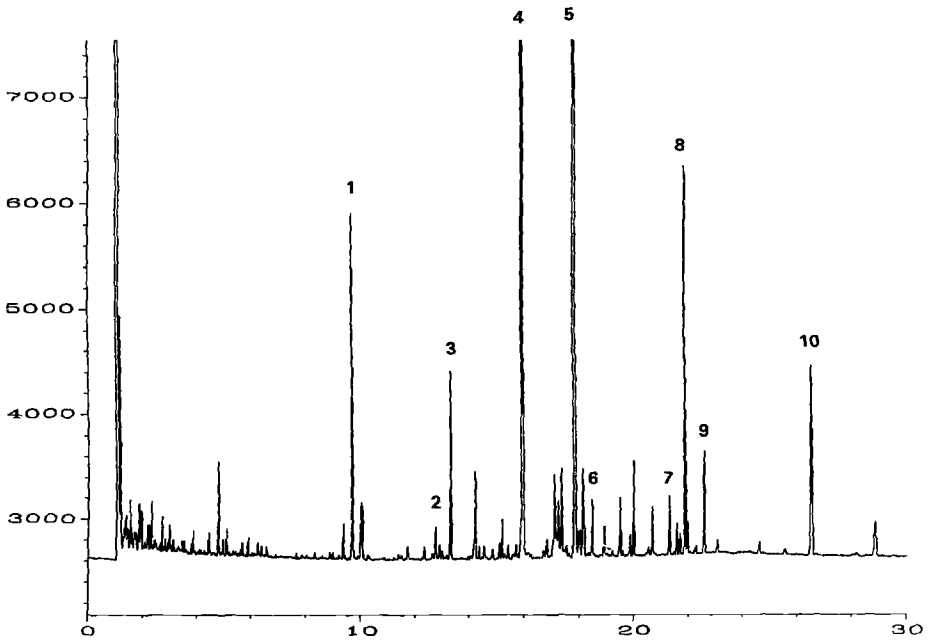

FIG. 2—*Capillary gas chromatogram of ion-pair eluate from a refined cocaine HCl exhibit containing trimethoxy-substituted alkaloids. Peak identification (min)—1 = tropacocaine (9.7 min), 2 = norcocaine (12.4 min), 3 = cocaine (13.3 min), 4 =* cis-*cinnamoylcocaine (16.0 min), 5 =* trans-*cinnamoylcocaine (17.9 min), 6 = trimethoxytropacocaine (18.49 min), 7 = trimethoxycocaine (21.4 min), 8 = trimethoxy-ethylcocaine internal standard (21.9 min), 9 = trimethoxy-*cis-*cinnamoylcocaine (22.6 min) and 10 = trimethoxy-*trans-*cinnamoylcocaine.*

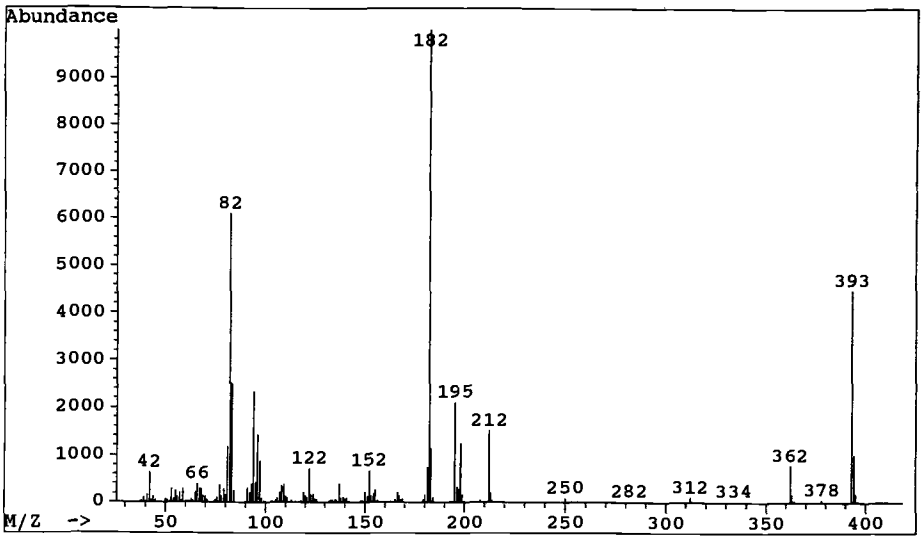

FIG. 3—*Electron ionization mass spectrum of TMC.*

trimethoxy-substituted alkaloids. Two of these compounds gave spectra that also contained ions at m/z 82 and m/z 182 (base peak). Both spectra were markedly similar to TMC, but each had a molecule ion of m/z 419. In addition, both compounds gave virtually identical mass spectra, suggesting the compounds were isomers of each other. A representative spectrum depicting both isomers is shown in Fig. 4. The mass difference of 28 daltons between the unknown compounds and TMC suggested the presence of cinnamoyl moieties. Synthesis of 3′,4′,5′-trimethoxy-*trans*-cinnamoylcocaine (tTMCC) gave a mass spectrum and retention time virtually identical to the second "419" com-

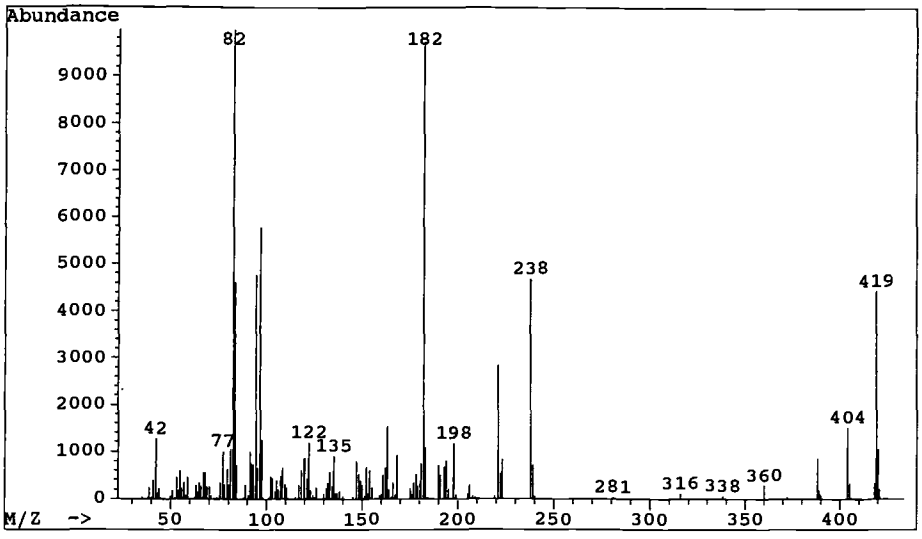

FIG. 4—*Electron ionization mass spectrum of tTMCC or cTMCC.*

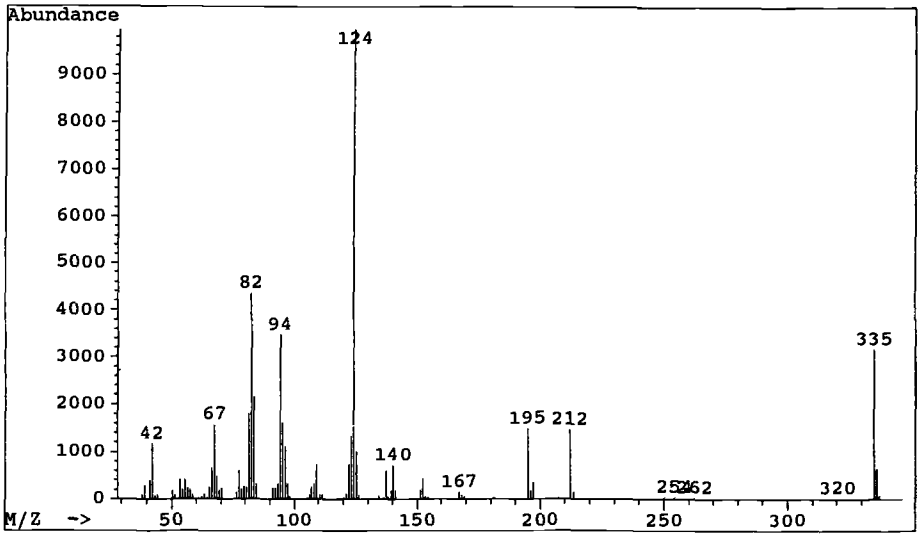

FIG. 5—*Electron ionization mass spectrum of TMT.*

pound. The first "419" compound was therefore identified as 3',4',5'-trimethoxy-*cis*-cinnamoylcocaine (cTMCC) based on its mass spectrum and relative retention time to the *trans* isomer. The third compound gave a mass spectrum, seen in Fig. 5, that contained ions at m/z 82, m/z 124 (base peak) and an apparent molecule ion of m/z 335. The presence of ions at m/z 82 and 124 suggested the presence of a tropane moiety similar to tropacocaine. The mass difference vs. tropacocaine was 90 daltons. Synthesis of 3',4',5'-TMT gave a mass spectrum and retention time virtually identical to this third compound.

Finally, standards of 2',3',4'-, 2',4',6'- and 2',4',5'-TMC were synthesized and gave differing mass spectra and retention times compared to 3',4',5'-TMC. Standards of 2',3',4'-, 2',4',6'- and 2',4',5'-tTMCC were also synthesized and similarly gave differing mass spectra and retention times vs. 3',4',5'-tTMCC. The retention times of the identified trimethoxy-substituted alkaloids are listed in Table 1.

Quantitation of Trimethoxy-Substituted Alkaloids in Coca Leaf

The quantitative data obtained for trimethoxy-substituted alkaloids in coca leaf is given in Table 2. As seen, there are striking differences in the relative content of the trimethoxy-

TABLE 1—*Retention times of trimethoxy-substituted compounds.*[a]

Compound	Retention time
Cocaine	9.05
TMT[b]	11.87
TMC[c]	14.84
cTMCC[d]	16.49
tTMCC	18.97

[a]All data obtained from CGC-MSD analyses.
[b]Trimethoxytropacocaine.
[c]Trimethoxycocaine.
[d]*cis*-Trimethoxycinnamoylcocaine.

TABLE 2—*Trimethoxy-substituted alkaloid content in South American coca leaf.*[a,b]

Country	TMT	TMC	cTMCC	tTMCC
Brazil	...	1.12	...	0.15
Colombia	...	...	...	...
Bolivia-1	...	0.14	0.13	0.74
Bolivia-2	...	0.22	0.11	0.95
Peru	0.18	0.24	0.16	0.83

[a]Results calculated using 3′,4′,5′-trimethoxyethylcocaine as the internal standard.
[b]All data is presented as %w/w relative to cocaine.

substituted alkaloids in coca leaf. The Colombian leaf did not contain detectable amounts of any of the four trimethoxy-substituted alkaloids, and is therefore easily differentiated from Brazilian, Peruvian and Bolivian leaf. The Brazilian leaf contained the highest concentration of TMC (>1%) relative to cocaine and contains 4–7× more TMC than Bolivian or Peruvian leaf. Interestingly, no cTMCC was detected in the Brazilian leaf even though a significant amount of tTMCC was found. The amount of tTMCC was approximately 5 times less than that found in Bolivian and Peruvian leaf. TMT was not detected in this sample. As was found for the Brazilian and Colombian leaf, the Bolivian leaf did not contain a detectable amount of TMT. However, this leaf was distinguishable from the Brazilian leaf by the presence of cTMCC, the relatively higher concentration of tTMCC and the relatively lower concentration of TMC. The Bolivian leaf was distinguishable from the Peruvian leaf by the absence of TMT. Finally, the Peruvian leaf was easily distinguished from all other leaves by the presence of TMT. As seen in Fig. 6, this leaf contained all four trimethoxy-substituted alkaloids.

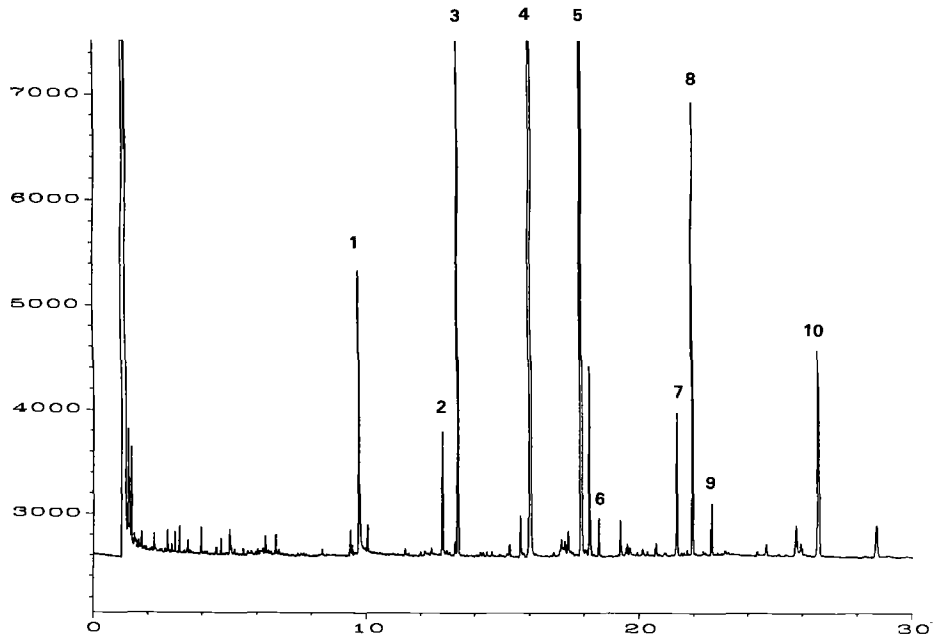

FIG. 6—*Capillary gas chromatogram of Peruvian coca leaf. See Figure 2 for peak enumeration.*

TABLE 3—*Trimethoxy-substituted alkaloid content in coca paste and refined cocaine.*[a,b]

Type cocaine	TMT	TMC	cTMCC	tTMCC
Bolivian HCL	...	0.003	...	...
Bolivian HCL	...	0.017	0.029	0.084
Bolivian base	...	0.006	...	...
Bolivian paste	...	...	0.017	0.038
Peruvian HCL	...	...	...	...
Peruvian HCL	...	...	0.013	0.045
Peruvian paste	...	0.004	0.007	0.040
Peruvian paste	0.103	0.042	0.075	0.267
Peruvian paste	...	0.003	...	0.011
Colombian HCL	...	0.004	0.022	0.046
Colombian HCL	...	0.026	...	...
Colombian base	0.012	0.049	0.005	...
Colombian paste	...	0.005	0.005	0.056
Colombian paste	...	0.006	...	...
Colombian paste	...	...	...	...

[a]Results calculated using 3',4',5'-trimethoxyethylcocaine as the internal standard.
[b]All data is presented as %w/w relative to cocaine.

Trimethoxy-Substituted Alkaloids in Coca Paste and Refined Cocaine

The trimethoxy-substituted alkaloid content of coca paste and refined cocaine are presented in Table 3. Close inspection provides some interesting data. It should be noted that because of current cocaine trafficking trends in South America, the coca paste (crude cocaine base that has not been oxidized with potassium permanganate) and refined cocaine exhibits from Peru and especially Colombia may have originated in another coun-

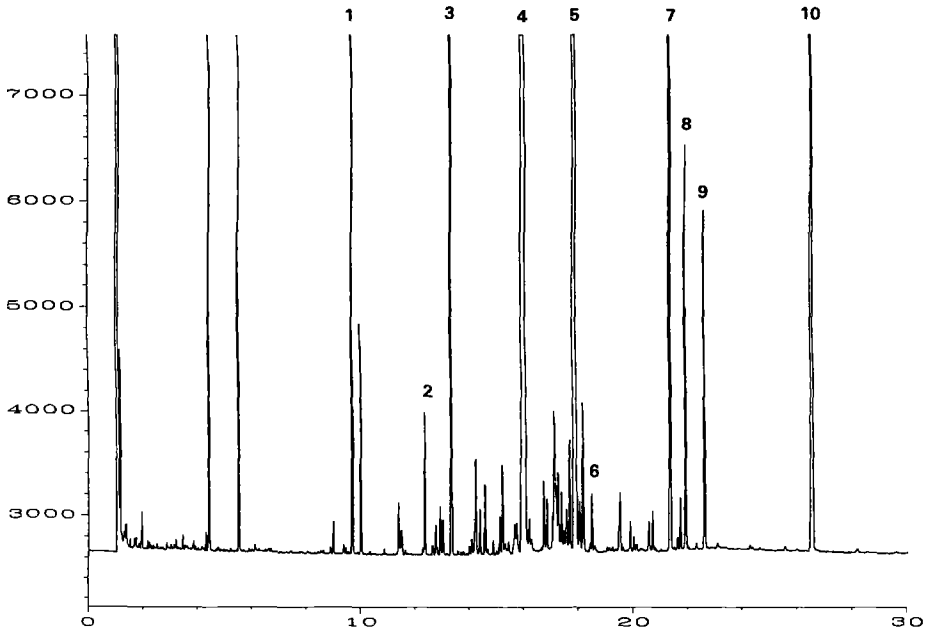

FIG. 7—*Capillary gas chromatogram of a refined cocaine base sample. See Fig. 2 for peak enumeration.*

try; their authenticity (as being derived from coca leaf in that country) is therefore questionable. It should also be noted that cTMCC and tTMCC are reduced or completely eliminated in those refined cocaine exhibits that have been oxidized by potassium permanganate [*6*]. The concentrations of trimethoxy-substituted alkaloids in coca paste and refined cocaine are a full order of magnitude less than found in the leaf exhibits. It was observed during the syntheses of the trimethoxy-substituted standards that these compounds are practically insoluble in diethyl ether and petroleum ether. The marked decrease in concentration of these alkaloids in refined exhibits is therefore most probably due to the crude processing of coca leaf using petroleum distillates of low polarity, such as kerosene, and the use of diethyl ether in the conversion of cocaine base to cocaine hydrochloride. A chromatogram of trimethoxy-substituted alkaloids in refined illicit cocaine base (crack cocaine) seized in the United States is illustrated in Fig. 7.

In order to show a definitive relationship between refined cocaine and the origin of leaf that produced it, substantial numbers of authentic cocaine exhibits which are representative of leaf grown in certain geographic regions must be acquired.

Conclusions

A detailed methodology for the isolation and quantitation of four trimethoxy-substituted tropane alkaloids in coca leaf, coca paste and refined cocaine is presented. The use of ion-pair chromatography effectively removes over 99 percent of the cocaine from the target compounds, thus eliminating cGC column overloading with excessive amounts of cocaine. Quantitation via FID is sufficiently sensitive for exhibits containing less than 0.01 percent of target compounds relative to cocaine. Coca leaf grown in Peru, Bolivia, Colombia, and Brazil gave differing trimethoxy substituted alkaloid profiles. Preliminary data on coca leaf, coca paste and refined cocaine shows promise that trimethoxy substituted coca alkaloids may be used as indicators for comparative purposes and origin determinations.

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