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Comparative Determination of 2-Carbomethoxy-3-Alkyloxy- and Heteroaroyloxy-Substituted Tropanes in Illicit South American Cocaine Using Capillary Gas Chromatography-Single Ion Monitoring*

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ABSTRACT: Methodology is presented for the isolation and comparative determination of 16 alkyloyl and 2 heteroaroyl ecgonine methyl esters in illicit cocaine samples. These trace-level alkaloids, five of which are reported for the first time, were partially isolated from cocaine using alumina column chromatography and recrystallization and determined using capillary gas chromatography-mass spectrometry using selected ion monitoring. Acetoxy-, propionoyl-, isobutyroyl-, butyroyl-, 2-methylbutyroyl-, isovaleroyl-, valeroyl-, senecioyl-, trans-4-hexenoyl-, tigloyl-, hexanoyl-, 3′-furanoyl-, trans-2-hexenoyl-, 2′-furanoyl-, trans-3-heptenoyl-, cis-, trans-; trans-, cis-; and trans-, trans-2,4-hexadienoyl- ecgonine methyl esters were detected at levels less than 1×10^{-5} % (w/w relative to cocaine).

KEYWORDS: forensic science, cocaine, tropane alkaloids, gas chromatography, mass spectrometry

This report describes new methodology for the isolation, detection and comparative determination of a new class of coca-leaf alkaloids found in illicit cocaine, including acetoxy-, valeroyl-, trans-4-hexenoyl- and 2′-furanoylecgonine methyl ester. They were determined by capillary gas chromatography - mass spectrometry (GC-MS), using selected ion monitoring (SIM) and a structurally related internal standard (ISTD). This methodology was applied to a survey of 30 illicit cocaine exhibits seized in four South American countries for comparative purposes.

The processing of coca leaves in clandestine laboratories yields refined cocaine that is contaminated with numerous trace-level tropane alkaloids at levels below one percent (w/w relative to cocaine) (1). The detection and determination of these alkaloids in illicit cocaine may be used for sample-to-sample comparisons and/or origin determinations. Previous studies by us have included the isolation, structural characterization and determination of new coca alkaloids in illicit cocaine. We recently described the isolation and characterization of over 40 new tropane alkaloids (including heterocyclic and alkane/alkene esters of cocaine) found in crude coca leaf and its extracts (2,7–13). That work resulted in the development of methods for the comparative determination of four classes of tropane alkaloids; namely, the trimethoxyphenyl- substituted (2), the truxillines (3,4), the hydroxycocaines (5), and the major alkaloids (and their manufacturing by-products) (6).

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Experimental

Reagents, Solvents, and Standards

All chemicals, solvents, and materials utilized in this study have been previously reported (10). The precursor acid chlorides and carboxylic acids were products of Aldrich Chemical or TCI America. The title alkaloids and 2,2-dimethylbutyroyl ecgonine methyl ester (ISTD) were synthesized and isolated from unreacted ecgonine methyl ester using previously reported procedures (10–12).

Capillary Gas Chromatography-Mass Spectrometry (GC-MS)

A Hewlett-Packard Model 5972 Quadrupole Mass-Selective Detector (MSD) interfaced with a Hewlett-Packard 5890 Series II Gas Chromatograph (GC) was used under the following parameters. The MSD was operated in the electron ionization (full scan) mode with an ionization potential of 70 eV, a secondary electron multiplier voltage of 1800 and at 1.2 scans/s; those conditions were used for the characterization of new alkaloids. For comparative determination, the MSD was operated in the selected ion monitoring (SIM) mode. The fragment ion 182.1 Daltons was monitored using a dwell time of 100 msec. The GC was fitted with a 30 m by 0.25 mm I.D. fused-silica capillary column coated with DB-1 (0.25 μm). The oven temperature was programmed as follows: (level 1) initial temperature, 80°C; initial hold, 2.8 min; program rate, 4°C/min; final temperature, 110°C; final hold, 0 min; (level 2) program rate, 15°C/min, final temperature, 300°C; final hold 7.0 min. Injector and detector temperatures were maintained at 230 and 280°C, respectively.

Determination of 2-Carbomethoxy-3-Alkyloxy- and Heteroaroyloxy-Substituted Alkaloids in Routine Cocaine Samples

Cocaine hydrochloride—Approximately 500 mg of the unadulterated cocaine hydrochloride sample was accurately

weighted into a 13-mL screw-cap centrifuge tube and dissolved in 2.0 mL of water. An aqueous solution saturated with sodium bicarbonate (3.0 mL) was added, followed by 5.0 mL of chloroform containing 5.00 μg of 2,2-dimethylbutyroylecgonine methyl ester (ISTD). After vigorous mixing, the organic layer was passed through anhydrous sodium sulfate into another tube. The aqueous solution was extracted once again with 5.0 mL of chloroform (no ISTD), passed through anhydrous sodium sulfate and combined with the first extract. The chloroform was evaporated at 75°C under a stream of nitrogen to approximately 1 mL and then transferred to a glass chromatographic column (11 by 250 mm) packed with 10.0 g of basic alumina (4.0% water). The column was then eluted with sufficient chloroform to collect 10.0 mL in a centrifuge tube. The eluate was evaporated at 75°C under a stream of nitrogen to a residue. The residue was reconstituted in 4.0 mL of hot hexane and allowed to cool. After cocaine base crystallization was complete (30–60 min), the mother liquor was transferred to another tube and evaporated to a residue. This residue was reconstituted in 1.0 mL of hot hexane and again allowed to cool and crystallize. Approximately 2 μL of the mother liquor was injected into the GC-MSD under SIM conditions previously described.

Cocaine Base—Cocaine base exhibits were dissolved directly into 1.00 mL of chloroform containing 5.00 μg of ISTD and placed onto the alumina column. The column was eluted with sufficient chloroform to collect 10.0 mL in a centrifuge tube; and the eluate treated in the same manner as cocaine hydrochloride samples.

Isolation and Characterization of New Minor Alkaloids from Refined Cocaine

The titled alkaloids were isolated from the bulk cocaine matrix using a modification of the methodology reported previously (10). Approximately 1 kg of illicit cocaine hydrochloride was used, giving a final mother liquor which was submitted to GC-MS analysis.

Results and Discussion

Alumina Column Chromatography and Recrystallization

Alumina column chromatography was used for the removal of alkaloids, such as the truxillines and other polar alkaloids, from the cocaine extract containing the target alkaloids. The eluate from the alumina column held mostly cocaine, the cinnamoylcocaines and trace levels of the target alkaloids.

The recrystallization of the alumina eluate markedly enhanced the concentrations of the minor alkaloids in the mother liquors. Cocaine was the major crystallization product. The mother liquors were subjected to capillary GC-MS and found to contain up to 15 tropane alkaloids previously characterized in crude coca leaf extracts (10,12); these alkaloids are illustrated in Fig. 1. Five new alkaloids were also found; their structures are presented in Fig. 2.

Gas Chromatography-Mass Spectrometry

Figure 3 illustrates a partial reconstructed chromatogram (ion m/z 182) for this methodology. Peaks 4–6 and 8–19 have been previously characterized (10,12), while new alkaloids are repre-

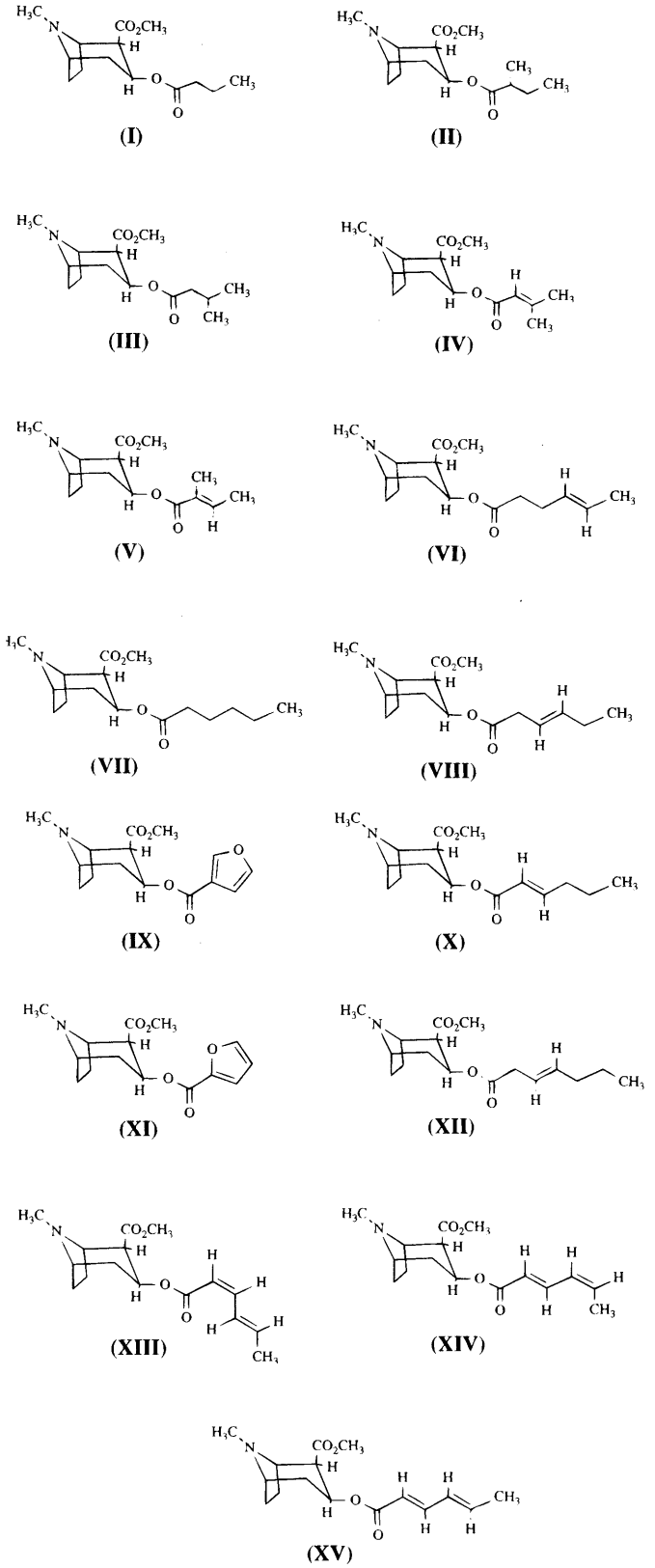

FIG. 1—*Structural formulas of alkaloids previously characterized.*

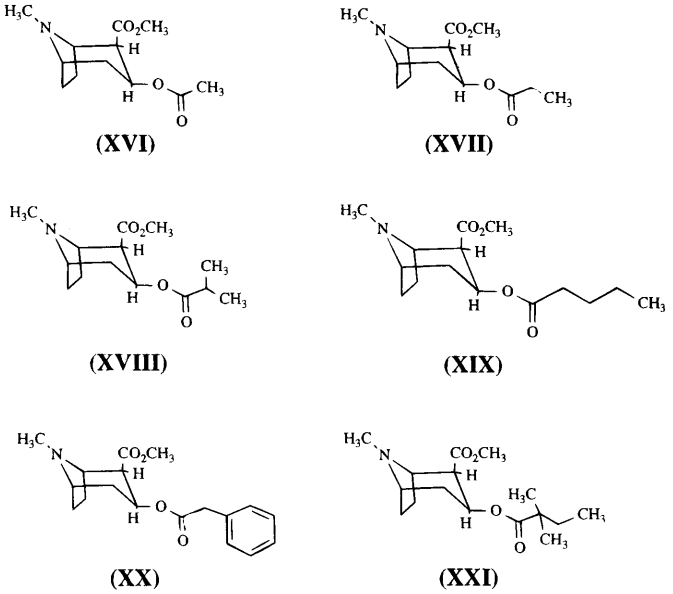

FIG. 2—*Structural formulas of new alkaloids.*

sented by peaks 1–3, 7 and 21. All compounds are identified in Table 1.

Methodology Internal Standard

An internal standard (ISTD), 2,2-dimethylbutyroylecgonine methyl ester (XXI) was incorporated into this method. The utility

TABLE 1—*Retention times of 2-carbomethoxy-3-oxo substituted tropane esters.*

Alkaloid*	PEAK #	GC Rt	MS Figure
Acetoxy- (XVI)	1	16.80	6a
Propionoyl- (XVII)	2	17.55	6b
Isobutyroyl- (XVIII)	3	17.85	6c
Butyroyl- (I)	4	18.22	—
2-Methylbutyroyl- (II)	5	18.53	—
Isovaleroyl- (III)	6	18.58	—
2,2-Dimethylbutyroyl- (XXI)	IS	18.70	—
Valeroyl- (XIX)	7	18.93	6d
Senecioyl- (IV)	8	19.18	—
Tigloyl- (V)	9	19.23	—
trans-4-Hexenoyl- (VI)	10	19.54	—
Hexanoyl- (VII)	11	19.61	—
trans-3-Hexenoyl- (VIII)	12	19.63	—
3′-Furanoyl- (IX)	13	19.76	—
trans-2-Hexenoyl- (X)	14	19.99	—
2′-Furanoyl- (XI)	15	20.19	—
trans-3-Heptenoyl- (XII)	16	20.25	—
cis-, trans-Hexadienoyl-† (XIII)	17	20.35	—
trans-, cis-Hexadienoyl-† (XIV)	18	20.41	—
trans-, trans-Hexadionoyl- (XV)	19	20.46	—
Benzoyl- (cocaine)	20	21.36	—
Phenylacetoxy- (XX)	21	21.45	6e
cis-Cinnamoyl-	22	22.25	—
trans-Cinnamoyl-	23	23.25	—

*Substitution at C-3 of ecgonine methyl ester.
†The order of these alkaloids may be reversed.

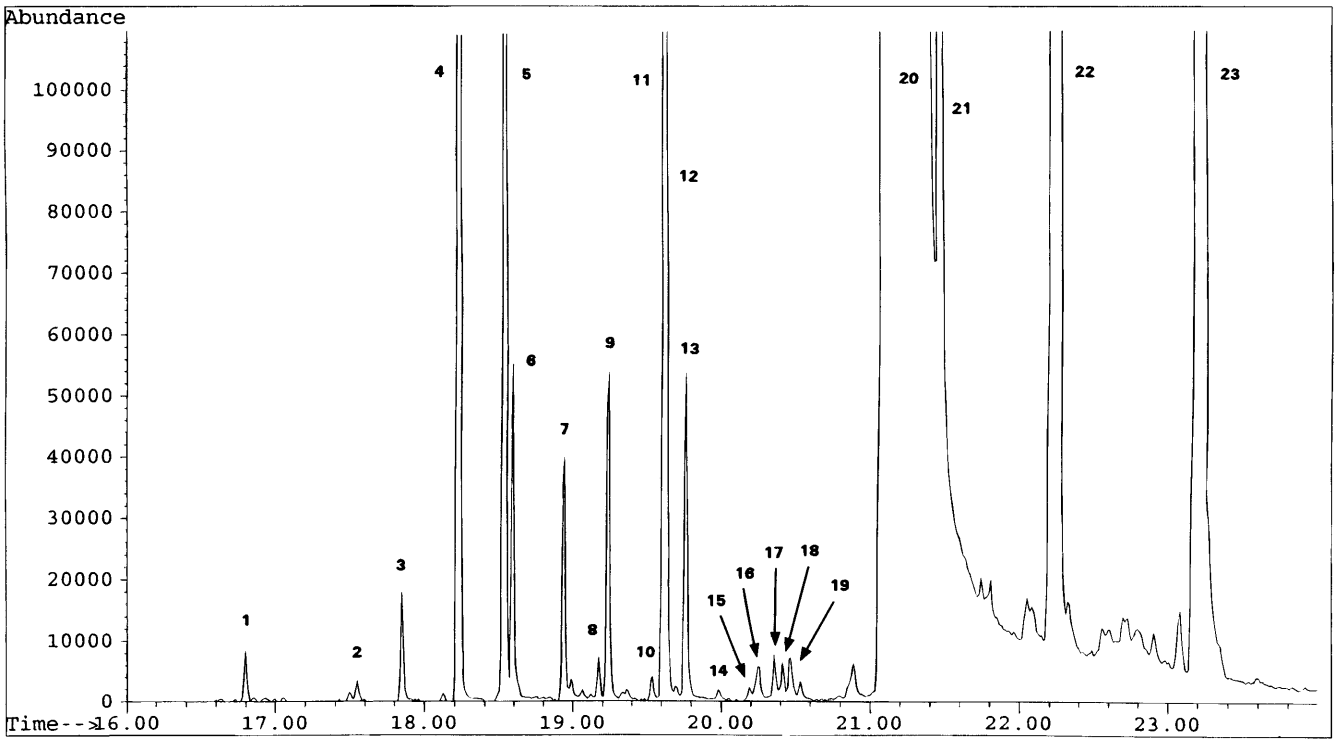

FIG. 3—*Partial reconstructed total electron ionization of chromatogram for m/z 182 from work-up from 1 kg illicit refined cocaine hydrochloride. Peaks: 1 = acetoxy-, 2 = propionoyl-, 3 = isobutyroyl-, 4 = butyroyl-, 5 = 2-methylbutyroyl-, 6 = isovaleroyl-, IS = 2,2-dimethylbutyroyl- (ISTD), 7 = valeroyl-, 8 = senecioyl-, 9 = tigloyl-, 10 = trans-4-hexenoyl-, 11 = hexanoyl-, 12 = trans-3-hexenoyl-, 13 = 3′-furanoyl-, 14 = trans-2-hexenoyl-, 15 = 2′-furanoyl-, 16 = trans-3-heptenoyl-, 17 and 18 = cis-, trans-2, 4-hexadienoyl- or trans-, cis-2, 4-hexadienoyl-, 19 = trans-, trans-2, 4-hexadienoyl-, 20 = benzoyl-, 21 = phenylacetoxy-, 22 = cis-cinnamoyl-, and 23 = trans-cinnamoylecgonine methyl esters.*

TABLE 2—*Reproducibility of alumina column chromatography, recrystallization and cGC-MSD methodology.**

COMPOUND†	MEAN‡	RSD (%)
Acetoxy-(XIV)	ND	—
Propionoyl-(XVII)	0.16	± 7.08
Isobutyroyl-(XVIII)	2.78	± 5.51
Butyroyl-(I)	3.55	± 1.92
2-Methylbutyroyl-(II)	6.34	± 3.84
Isovaleroyl-(III)	12.80	± 6.35
Valeroyl-(XIX)	1.40	± 3.13
Senecioyl-(IV)	ND	—
Tigloyl-(V)	6.66	± 2.81
trans-4-Hexenoyl-(VI)	0.93	± 2.98
Hexanoyl-(VII)	168.9	± 2.98
3′-Furanoyl-(IX)	1.61	± 4.44
trans-2-Hexenoyl-(X)	1.21	± 3.95
2′-Furanoyl-(XI)	0.11	± 5.06
trans-3-Heptenoyl-(XII)	9.55	± 3.39
cis-, trans-Hexadienoyl-(XIII)	0.40	± 3.53
trans-, cis-Hexadienoyl-(XIV)	0.23	± 5.02
trans-, trans-Hexadienoyl-(XV)	0.17	± 13.4

*Repetitive analyses (N = 7) from a uniform exhibit of illicit cocaine. ND = not detected.
†C-3 esters of ecgonine methyl ester.
‡Data is presented as $\times 10^{-5}$ % w/w relative to cocaine.

of this ISTD was found in its close structural relationship to the target alkaloids. This allowed for its coelution with the target alkaloids from the alumina column. Furthermore, it did not coelute by cGC with any of the target alkaloids. Finally, it gave a common major ion (m/z 182) found in all the target compounds and could therefore be utilized for selected ion monitoring, thus increasing the sensitivity and selectivity of the method.

Target Alkaloid Recovery

A recovery study was conducted on a cocaine exhibit containing relatively high concentrations of target compounds via analyses of the remaining alumina column eluate and both crops of crystals from recrystallization. Of the 18 compounds determined in this study, 16 had recoveries of > 95%. This figure includes recovery of the target alkaloids from both the alumina column and recrystallization steps. However, two of the target compounds, hexanoyl- (VII) and 2′-furanoylecgonine methyl ester (XI), were found to have lower recoveries of about 82 and 18 percent, respectively. Trans-3-hexenoyl- (VIII) and phenylacetoxyecgonine methyl ester (XX) were not determined in this study because they eluted in the tailing edges of hexanoylecgonine methyl ester (VII) and cocaine, respectively (Fig. 3).

Method Reproducibility

The reproducibility of this method was examined by seven replicate analyses of a selected uniform sample. Results are given in Table 2. All target alkaloids, except XV, had RSD's between ± 1.92 to ± 7.08%. This was surprising, given the low amounts of the target compounds (10^{-3} – 10^{-6} % relative to cocaine), and that absorption column chromatography and recrystallization techniques were employed.

Two chromatograms produced from a single batch of illicit co-

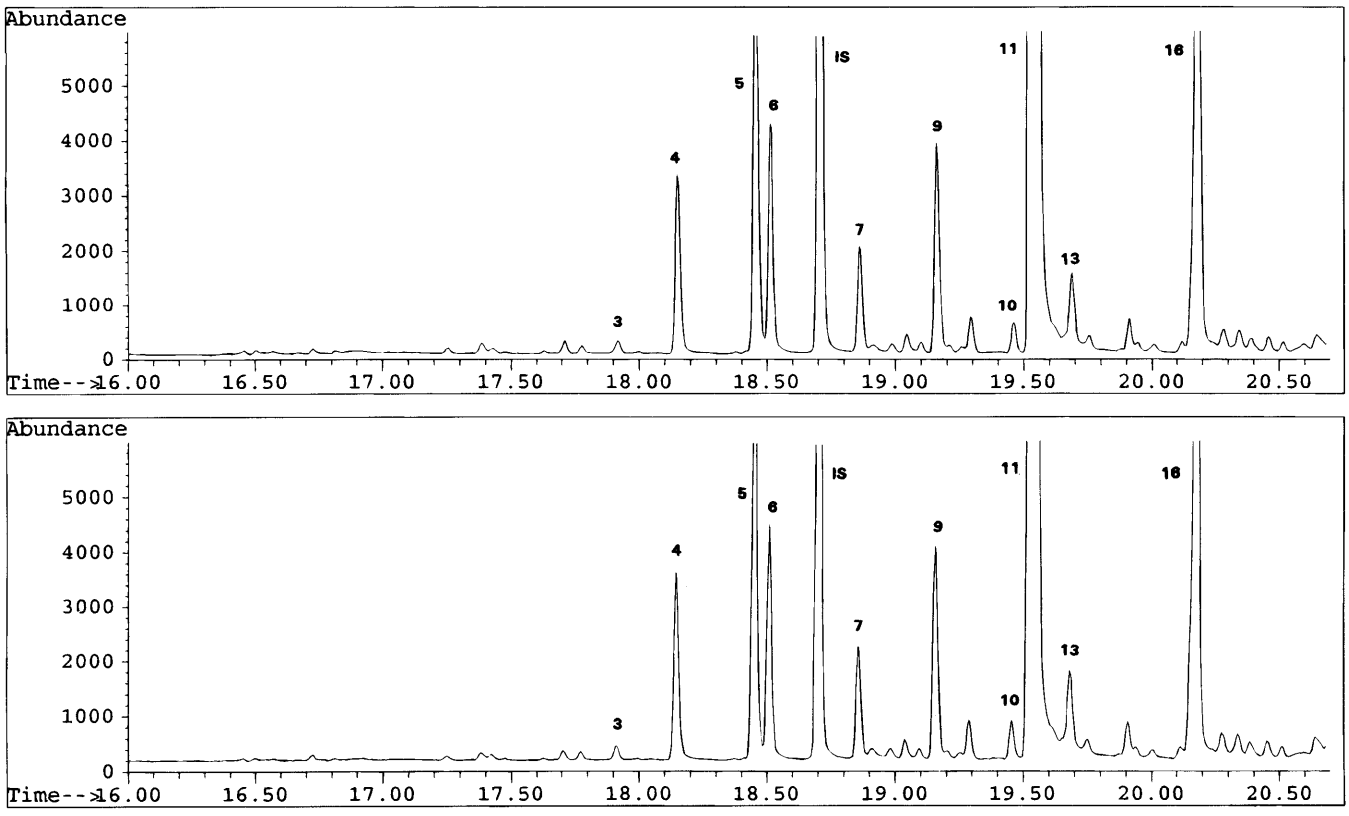

FIG. 4—*Partial reconstructed ion chromatograms (m/z 182) of two samples from a uniform exhibit of illicit refined cocaine HCl.*

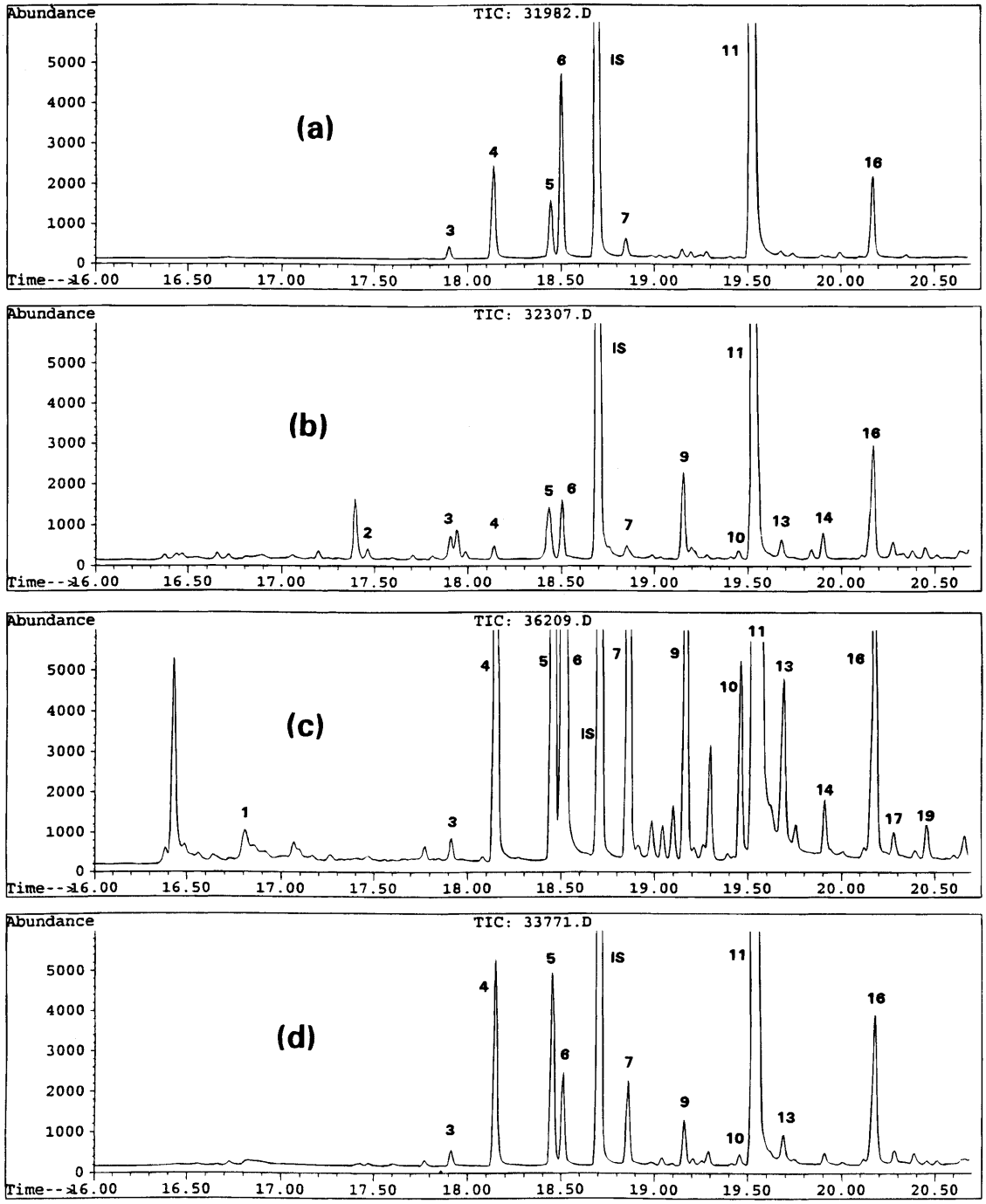

FIG. 5—*Partial reconstructed ion chromatograms (m/z 182) of illicit refined cocaine from: (a) Colombia, (b) Bolivia, (c) Peru, and (d) Ecuador.*

caine are illustrated in Fig. 4. Close inspection of these chromatograms reveals that they are virtually identical; this demonstrates the method's usefulness for comparative work.

Determination of 2-Carbomethoxy-3-Alkyloxy- and Heteroaroyloxy-Substituted Alkaloids in Illicit Cocaine of Known Origins

Thirty cocaine samples of known origin (Colombia = 7, Bolivia = 10, Ecuador = 6, and Peru = 7) were determined in this study. The samples were 5–7 years old. A selected chromatogram from each country is illustrated in Fig. 5. The average concentrations and ranges for the target compounds for each country are given in Table 3. Although this is a limited data set, some preliminary observations are offered. Peruvian exhibits generally had the highest average target alkaloid content. Alkaloids V, VI, and XVII in Peruvian samples had average values of about one order-of-magnitude greater than those from Ecuador, Colombia or Bolivia. Alkaloids IV, X, XIII and XVI in Peruvian samples had average values at least 5× greater than the other countries. Samples from Bolivia had much lower average values for compounds I, II, and IV, compared to the other countries. In fact, IV was not detected

TABLE 3—*Average and (range) of alkaloid content for illicit cocaine exhibits of known origin.*|†*

Alkaloid	Average (Range) Peru	Ecuador	Colombia	Bolivia
Acetoxy-(XVI)	2.0 (ND-7.2)	0.4 (ND-1.3)	0.3 (ND-0.3)	0.3 (ND-0.7)
Propionoyl-(XVII)	ND	0.1 (ND-0.3)	ND	ND
Isobutyroyl-(XVIII)	6.2 (ND-22.5)	0.6 (ND-3.3)	ND	0.1 (ND-0.5)
Butyroyl-(I)	33.7 (6.4–109)	16.2 (1.0–52.3)	11.3 (4.1–22.0)	1.3 (ND-2.7)
2-Methylbutyroyl-(II)	69.4 (6.5–282)	46.2 (0.9–241)	16.9 (4.3–54.6)	3.1 (1.0–7.2)
Isovaleroyl-(III)	238 (20.2–968)	72.6 (ND-341)	17.6 (8.2–26.4)	8.1 (2.7–13.7)
Valeroyl-(XIX)	24.8 (2.8–76.3)	4.4 (0.7–12.5)	5.9 (1.6–22.5)	1.1 (0.7–1.4)
Senecioyl-(IV)	1.7 (ND-5.7)	0.3 (ND-1.5)	0.2 (ND-0.4)	ND
Tigloyl-(V)	41.6 (1.1–100)	1.0‡ (0.6–3.2)	1.3 (ND-6.2)	4.1 (0.6–9.1)
trans-4-Hexenoyl-(VI)	6.1 (0.8–12.5)	0.4 (ND-1.0)	0.3 (ND-1.6)	0.6 (ND-1.1)
Hexanoyl-(VII)	1400 (214–3490)	254 (92.4–432)	451 (210–1060)	133 (85.0–234)
3′-Furanoyl-(IX)	7.9 (1.0–14.1)	2.8 (ND-12.8)	0.8 (ND-3.6)	0.9 (ND-1.6)
trans-2-Hexenoyl-(X)	5.9 (0.3–14.5)	0.7 (ND-2.9)	0.3 (ND-1.6)	1.4 (ND-2.7)
2′-Furanoyl-(XI)	0.3 (ND-1.6)	0.2 (ND-0.4)	0.2 (ND-1.1)	<0.1 (ND-0.2)
trans-3-Heptenoyl-(XII)	48.4 (11.5–84.7)	9.0 (0.9–19.7)	16.8 (6.8–47.5)	11.1 (6.3–18.7)
cis-, trans-Hexadienoyl-(XIII)	2.3 (ND-4.9)	0.4 (ND-1.1)	0.4 (ND-2.6)	0.5 (ND-1.2)
trans-, cis-Hexadienoyl-(XIV)	0.7 (ND-2.0)	0.4 (ND-2.6)	0.3 (ND-1.2)	0.2 (ND-0.6)
trans-, trans-Hexadienoyl-(XV)	0.7 (ND-1.6)	0.2 (ND-1.0)	0.6 (ND-2.9)	0.2 (ND-0.5)

*Concentration reported as $\times 10^{-5}$ % w/w relative to cocaine. ND = not detected.
†Peru (N = 6 base, 1 HCl), Ecuador (N = 1 base, 5 HCl), Colombia (N = 1 base, 6 HCl) and Bolivia (N = 10 HCl).
‡A sample with a value of 1270 was an outlier and not included. Values = 213 and (0.6–1270) if outlier included.

in any of the Bolivian samples (N = 10). Overall, Bolivian samples had lower values compared to Peru. Data for Ecuador and Colombia were similar and mostly fell between the values for Peru and Bolivia.

It should be noted that the higher values for Peru could be attributed to the number of cocaine base samples examined compared with cocaine hydrochloride; only one hydrochloride sample was available. It could be argued, therefore, that most of these alkaloids would be reduced in the conversion of refined cocaine base to cocaine hydrochloride. However, the relative concentrations of the other minor alkaloids determined in these same exhibits by our four other profiling methods (2, 3, 5 and 6) indicated that this may not be the case.

The analytical results demonstrate that this methodology is well suited for sample-to-sample comparisons. Previous comparative analyses for cocaine have determined alkaloids and impurities in the range of 10^{1} to 10^{-3} % w/w relative to cocaine. This methodology provides the capability to determine a new class of ultra-trace alkaloids at levels to 10^{-6} % (10 ppb).

Structural Characterization of New Alkaloids

Five new alkaloids were detected and characterized during the development of this method. These new alkaloids, represented by peaks 1–3, 7 and 21 in Fig. 3, gave mass spectra with fragment ions m/z 82, 94, 96, 182 and 198 as seen in Fig. 6. All of these ions are indicative of intact 2-carbomethoxy-3-oxo-substituted tropane alkaloids. The relative abundances of ions at 82/83 and 152/155 Daltons were consistent with 3β- and 2α- substituent orientations, respectively (12). Since the major spectral difference between the five new alkaloids and cocaine (Peak 20) was the molecule ion, it was apparent that they differed from cocaine only in the composition of the C-3 substituent. These compounds were subsequently characterized as acetoxy- (XVI), propionoyl- (XVII), isobutyroyl- (XVIII), valeroyl- (XIX) and phenylacetoxy- (XX) ecgonine methyl esters by comparison of their mass spectra and GC retention times with synthesized standards.

Future Studies

At this time, determination of origin using this methodology is uncertain, mainly due to the limited database. We have previously shown that many exhibits from Colombia/Ecuador can be differentiated from Peru/Bolivia based on their truxilline content (4). We have also seen a similar relationship in the trimethoxy-substituted alkaloids found in illicit cocaine from these same regions (2). Although the methodology described herein shows promise, origin

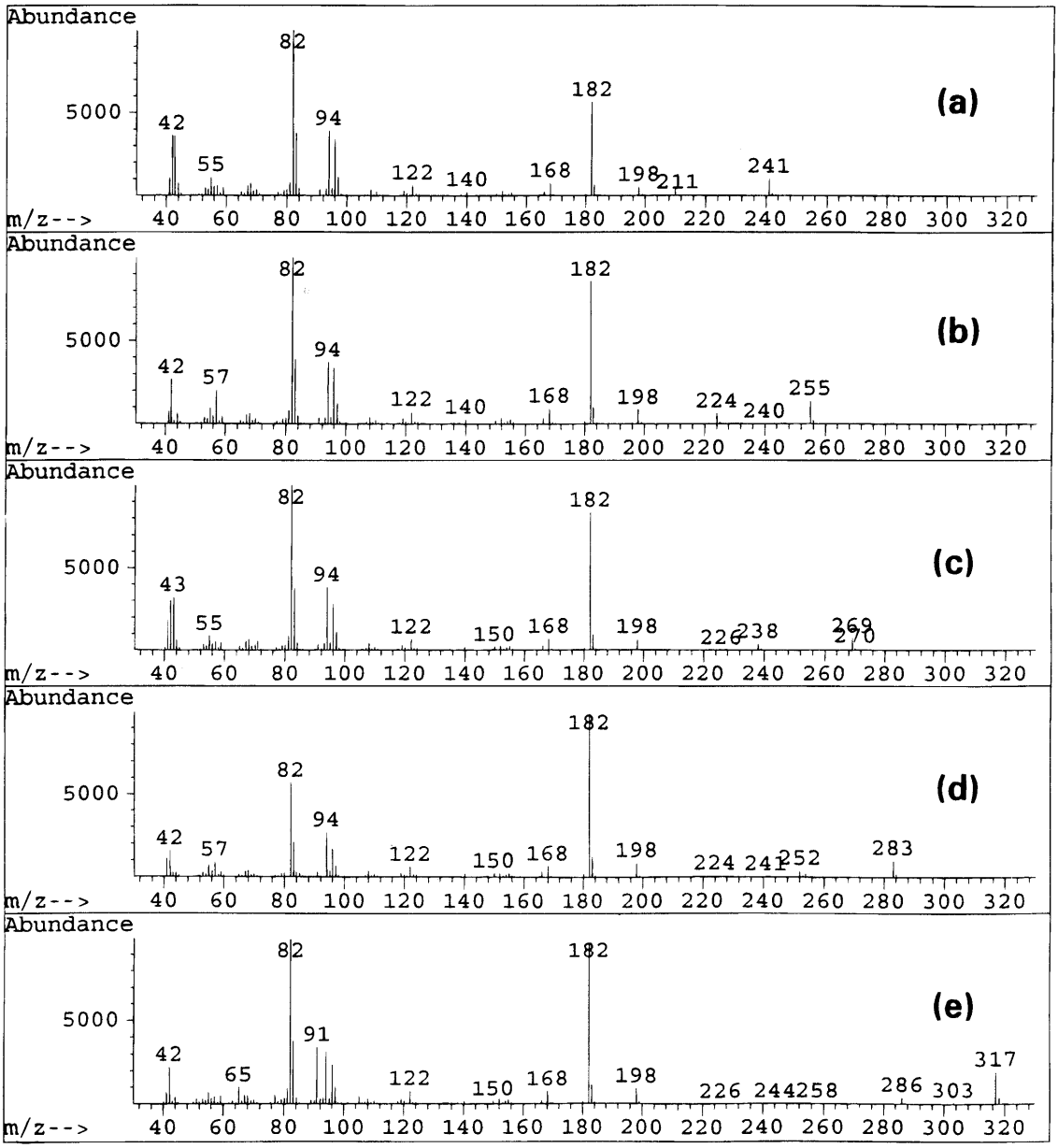

FIG. 6—*Electron ionization mass spectra of (a) acetoxyecgonine methyl ester, (b) propionoylecgonine methyl ester, (c) isobutyroylecgonine methyl ester, (d) valeroylecgonine methyl ester, and (e) phenylacetoxyecgonine methyl ester.*

classification may require a combination of methods determining all classes of coca alkaloids.

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