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Four New Illicit Cocaine Impurities from the Oxidation of Crude Cocaine Base: Formation and Characterization of the Diastereomeric 2,3-Dihydroxy-3-Phenylpropionylecgonine Methyl Esters from *cis*- and *trans*-Cinnamoylcocaine

ABSTRACT: Four new impurities have recently been detected in the gas chromatographic signature profiles of many illicit cocaine hydrochloride exhibits. These impurities are only seen in exhibits that have been oxidized and are most prominent in samples that have been highly oxidized. Exhibits containing these compounds were subjected to gas and liquid chromatographic–mass spectrometric analyses to determine the identity of the impurities. These impurities were subsequently synthesized to verify their structures. Four diastereomeric diols formed from the oxidation of *cis*- and *trans*-cinnamoylcocaine were characterized by nuclear magnetic resonance spectrometry, mass spectrometry, and synthesis. Oxidation of *cis*-cinnamoylcocaine in neutral conditions yielded (2*R*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester and (2*S*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester, while *trans*-cinnamoylcocaine produced (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester and (2*S*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester. The recent appearance of these new impurities suggests that some illicit cocaine processors have modified their oxidation procedures of crude cocaine base for transformation into illicit refined cocaine hydrochloride.

KEYWORDS: forensic science, cocaine, chromatographic signature analysis, oxidation, mass spectrometry, nuclear magnetic resonance, illicit cocaine impurities

The Drug Enforcement Administration's Special Testing and Research Laboratory (STRL) routinely examines over 3000 illicit cocaine exhibits each year as part of its Cocaine Signature Program (CSP). The CSP performs in-depth signature analyses on exhibits obtained from bulk seizures throughout both the United States and from around the world. Analytical methodologies (1–7) utilized by the STRL give evidence of how and where coca leaf was processed to cocaine base (geographical origin), and how and where cocaine base was converted to cocaine hydrochloride (processing origin). Correlated data from the seizures are reported to the counter-drug intelligence community on a quarterly basis. Intelligence information derived from this program assists the law enforcement community in determining cocaine distribution and trafficking routes throughout the world, and in determining where cocaine base is specifically produced in the Andean Ridge. In addition to reporting trends in geographical and processing origin, analyses are performed to determine the extent of oxidation for illicit samples for strategic intelligence purposes.

After cocaine is extracted from coca leaf, the crude product is usually refined to remove two major impurities, *cis*- and *trans*-cinnamoylcocaine, thus eliminating coloration to give a whiter product. The purification has traditionally been accomplished by adding potassium permanganate to an acidic solution of the crude cocaine (8). This is referred to as an oxidation step, as the olefin

moiety of the cinnamoylcocaine is oxidized and cleaved, generating water soluble by-products (9) that do not carry over to the refined illicit product. The CSP monitors the presence and relative abundance of the cinnamoylcocaines in seized samples to determine the extent of oxidation. Based on our experience from first-hand observations of the illicit production of cocaine in South America, samples containing less than 2% total cinnamoylcocaines, relative to cocaine, are considered to be highly oxidized. Samples containing 2–6% cinnamoylcocaines are considered to be moderately oxidized, while samples containing over 6% cinnamoylcocaines are deemed to be minimally or not oxidized. Beginning in 2003, the CSP began observing an increase in the percentage of samples that were highly oxidized. In 2005, the relative use of oxidizers for cocaine purification reached unprecedented high levels with over 60% of the exhibits being highly oxidized. During one recent quarterly reporting period, 63% of the exhibits were highly oxidized, 36% moderately oxidized, and 1% were minimally or not oxidized. Data depicting the extent of oxidation for a 9-year period is presented in Table 1.

Four new impurities have recently been detected in the gas chromatographic signature profiles of many illicit cocaine hydrochloride exhibits (Fig. 1, peaks 6–9). They appear as three peaks (two of the impurities co-elute as one peak) between *cis*- and *trans*-cinnamoylcocaine. These impurities are only found in exhibits that have been oxidized and are most prominent in samples that have been highly oxidized. They were only detectable when derivatized as bis-trimethylsilyl ethers. Exhibits containing these compounds were subjected to gas and liquid chromatographic–mass spectrometric analyses to determine the identity of the unknowns. The unknowns were subsequently synthesized to verify their structures. Four

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TABLE 1—Data depicting the relative degree of oxidation of illicit cocaine exhibits for a 9-year period.

Reporting quarter	% Highly oxidized*	% Moderately oxidized†	% Minimally or not oxidized‡
March 1997	30	57	13
June 1997	19	55	26
September 1997	24	62	14
December 1997	12	68	20
March 1998	18	62	20
June 1998	18	54	28
September 1998	20	65	15
December 1998	24	50	26
April 1999	22	65	13
July 1999	18	62	20
October 1999	19	69	12
January 2000	28	57	15
April 2000	12	50	38
July 2000	10	35	55
October 2000	8	32	60
January 2001	10	23	67
April 2001	7	22	71
July 2001	10	23	67
October 2001	14	20	66
January 2002	19	22	59
April 2002	10	22	68
July 2002	11	31	58
October 2002	19	29	56
April 2003	19	44	37
July 2003	33	50	17
October 2003	37	55	10
January 2004	34	55	11
April 2004	40	55	5
July 2004	45	49	6
October 2004	49	46	5
January 2005	54	40	6
April 2005	55	40	5
July 2005	49	47	4
October 2006	51	47	2
January 2006	63	36	1
April 2006	60	38	2

*Containing <2% total cinnamoylcocaines relative to cocaine.

†Containing 2–6% total cinnamoylcocaines relative to cocaine.

‡Containing >6% total cinnamoylcocaines relative to cocaine.

diastereomeric diols, illustrated in Fig. 2, were characterized by diastereoselective synthesis, nuclear magnetic resonance (NMR), and mass spectral analysis. The diols are produced from oxidation of the cinnamoylcocaines in neutral or basic conditions. The recent appearance of these new impurities suggests that some illicit cocaine processors have modified their oxidation procedures (i.e., using neutral instead of acidic conditions) of crude cocaine base for transformation into illicit refined cocaine hydrochloride.

Experimental

Solvents, Chemicals, and Materials

All solvents were distilled-in-glass products of Burdick and Jackson Laboratories (Muskegon, MI). *N*-Methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) was obtained from Pierce Chemical (Rockford, IL). The chiral ligand adducts, AD mix- α and AD mix- β , were products of Sigma-Aldrich Chemical (Milwaukee, WI). All other chemicals were of reagent-grade quality and products of Sigma-Aldrich Chemical. *trans*-cinnamoylcocaine was part of the authentic reference collection of this laboratory, and *cis*-cinnamoylcocaine was isolated from illicit crude cocaine as previously reported (10).

Gas Chromatography–Flame Ionization Detection

Gas Chromatography–Flame Ionization Detection (GC–FID) analyses were performed with an Agilent (Palo Alto, CA) Model 6890 gas chromatograph. Sample preparation and chromatographic conditions were identical to those reported by Casale and Waggoner (1), except that MSTFA was utilized as the derivatizing reagent.

Gas Chromatography/Mass Spectrometry

Gas Chromatography/Mass Spectrometry (GC/MS) analyses were performed using an Agilent (Palo Alto, CA) Model 5973 quadrupole mass-selective detector (MSD) interfaced with an Agilent (Palo Alto, CA) Model 6890 gas chromatograph. The MSD was operated in the electron ionization mode with an ionization potential of 70 eV, a scan range of 34–700 mass units, at 1.34 scans/sec. The GC system was fitted with a 30 m \times 0.25 mm i.d. fused-silica capillary column coated with DB-1 (0.25 μ m) (J & W Scientific, Rancho Cordova, CA). The oven temperature was programmed as follows: initial temperature, 100°C; initial hold, 0.0 min; program rate, 6°C/min; final temperature, 300°C; final hold, 5.67 min. The injector was operated in the split mode (21.5:1) and at a temperature of 280°C. The auxiliary transfer line to the MSD was operated at 280°C.

Liquid Chromatography/Mass Spectrometry

Chromatography was performed using a Waters (Milford, MA) 2525 HPLC pump fitted with a Waters 150 \times 4.60 mm C-18 X-Terra column. The flow was optimized at 1.0 mL/min, using the following reversed-phase gradient: (A) water containing 0.1% formic acid; and (B) acetonitrile. The linear gradient solvent started at 90% A, held 0 min, and changed to 50% A and 50% B in 20 min, held 0 min, and finally returned to 90% A and 10% B in 1 min. The HPLC eluent was introduced into a Waters Micromass ZQ single quadrupole mass spectrometer using Electrospray Ionization with positive ion detection. The detector operated in the scan range of 140–400 mass units, a scan time of 0.5 sec, and an inter-scan delay of 0.1 sec.

Nuclear Magnetic Resonance Spectroscopy

Proton (^1H), carbon (^{13}C), and two-dimensional NMR spectra were obtained on a Varian Inova 600 MHz NMR using a 5 mm Varian Nalorac Z-Spec broadband, variable temperature, pulse field gradient (PFG) probe (Palo Alto, CA). All compounds were dissolved in deuteriochloroform (CDCl_3) containing 0.03% v/v tetramethylsilane (TMS) used as the 0 ppm reference compound (Aldrich Chemical, Milwaukee, WI). The temperature of the sample was maintained at 25°C. Standard Varian pulse sequences were used to acquire proton, proton-decoupled carbon, and PFG versions of DEPT, COSY, NOESY, HSQC, and HMBC. The carbon spectrum was acquired with a 1 sec delay, 45° pulse, 1.3 sec acquisition time, and gated-decoupling (decoupling only during acquisition of the free induction decay signal) to obtain a semi-quantitative spectrum. Applied Chemistry Development Inc. (Toronto, Canada) software (i.e., SpecManager, HNMR Predictor, CNMR predictor, and Structure Elucidator) was used to compare experimental to predicted spectra. The diastereomeric ratio (*dr*) of the reaction products was determined for the synthesized diols via integration of the proton spectra.

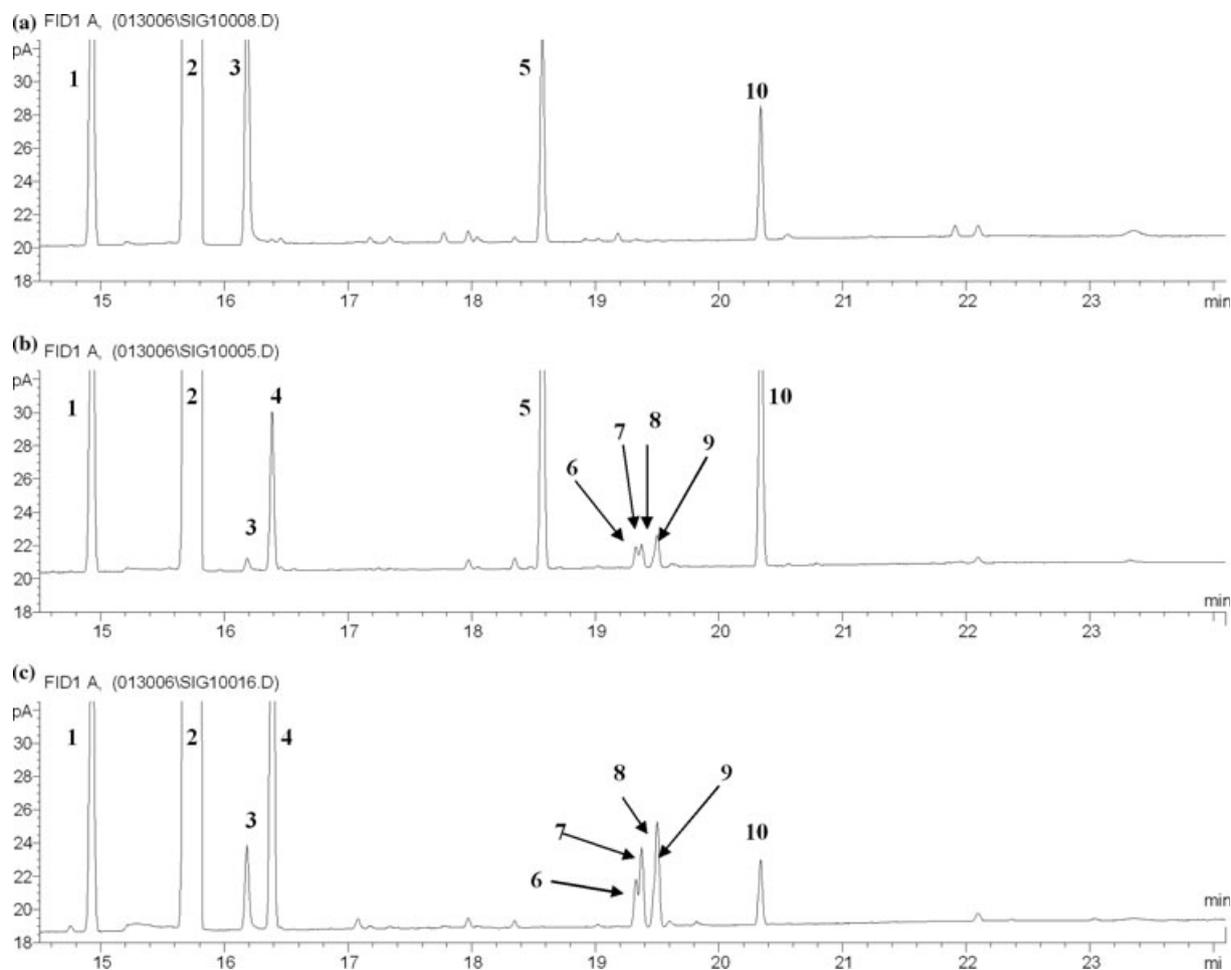


FIG. 1—Capillary gas chromatographic profiles of (a) highly oxidized cocaine HCl exhibit containing no diol derivatives of the cinnamoylcocaines, (b) moderately oxidized cocaine HCl exhibit containing trace levels of the diol derivatives of the cinnamoylcocaines relative to cocaine, and (c) highly oxidized cocaine HCl exhibit containing ~1% sum total of the diol derivatives of the cinnamoylcocaines relative to cocaine. Peak identification: 1 = *para*-fluorococaine (ISTD), 2 = cocaine, 3 = benzoylecgonine-TMS, 4 = norcocaine-TMS, 5 = *cis*-cinnamoylcocaine, 6 = (2*R*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester-di-TMS, 7 = (2*S*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester-di-TMS, 8 = (2*S*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester-di-TMS, 9 = (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester-di-TMS, 10 = *trans*-cinnamoylcocaine.

Synthesis

Dihydroxylation of *trans*-Cinnamoylcocaine with Potassium Permanganate: *trans*-cinnamoylcocaine (314 mg, 0.95 mmol) was dissolved into 50 mL of acetone within a 500-mL Erlenmeyer flask, followed by addition of 0.25 mL of 1% aqueous sodium hydroxide and stirred for several minutes. Saturated aqueous potassium permanganate (4 mL) was then added dropwise over 4.5 h while stirring at room temperature. The reaction was filtered and evaporated *in vacuo* to a light yellow oil (170 mg crude material). The crude material was purified on a glass chromatographic column (25 × 1.0 cm i.d.) containing 15 g of basic alumina (150 mesh). The column was washed in succession with (i) 10 mL of CHCl₃, (ii) 10 mL of CHCl₃/acetone (1:1), (iii) 10 mL of acetone, (iv) 10 mL of acetone/MeOH (1:1), and (v) 10 mL of MeOH. The alumina was then removed from the column, dried, and extracted with 40 mL of 0.36 N H₂SO₄ to recover the diols. The extract was adjusted to pH 9 with concentrated NH₄OH and extracted with CHCl₃ (2 × 40 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, evaporated *in vacuo*, and analyzed by NMR. The crude product contained (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl

ester and (2*S*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester as a white semi-crystalline mass (50 mg, 14% yield, *dr* = 50:50).

Dihydroxylation of *cis*-Cinnamoylcocaine with Osmium Tetroxide: *cis*-cinnamoylcocaine (60 mg, 0.18 mmol) was dissolved into 2.5 mL of acetone within a 15-mL centrifuge tube, followed by 2.5 mL of water, 4-methylmorpholine-*N*-oxide (23 mg, 0.20 mmol), and 0.5 mL of 5% aqueous osmium tetroxide. The tube was capped and allowed to react overnight. Sodium metabisulfite (50 mg) was added, and the reaction was extracted with CHCl₃ (1 × 10 mL). The extract was dried over anhydrous Na₂SO₄, filtered, evaporated to dryness, and analyzed via NMR for diastereomeric content; the crude product was (2*R*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester and (2*S*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester (17 mg, 25% yield, *dr* = 50:50).

Sharpless Asymmetric Dihydroxylation of *cis*- and *trans*-Cinnamoylcocaine Using Osmium Tetroxide and Chiral Ligands: The procedure of Spivey et al. (11) was modified slightly. Osmium tetroxide is formed *in situ* from AD mix- α and

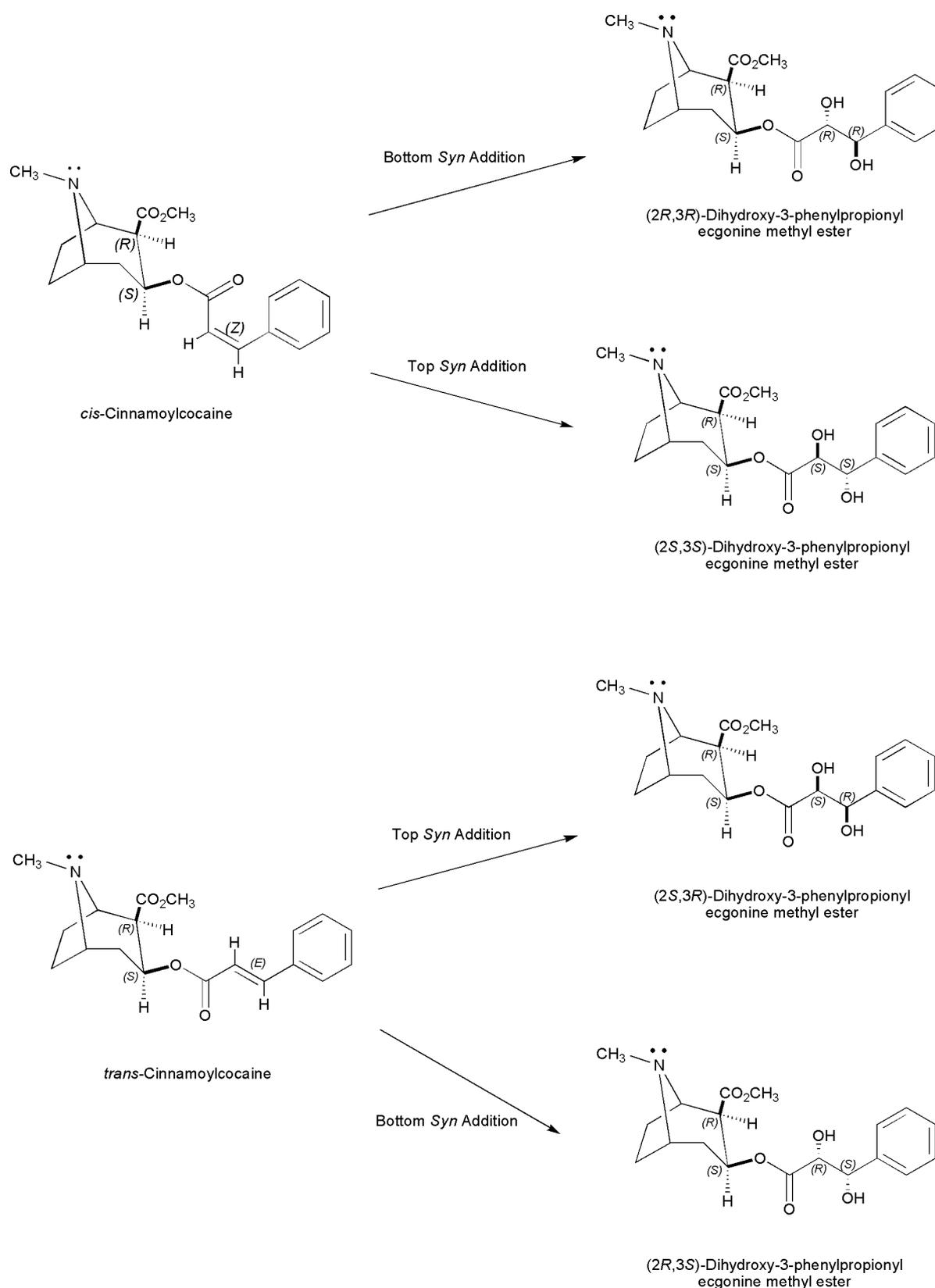


FIG. 2—Production of diol derivatives of cinnamoylcocaines via oxidation of illicit cocaine from organic solvent in neutral/basic conditions.

AD mix- β during the reaction, which is highly toxic and volatile. Extreme care should be taken when handling the reaction materials and during subsequent workup of the reactions.

(2*R*,3*S*)-Dihydroxy-3-Phenylpropionylecgonine Methyl Ester: A 50-mL round-bottom flask, wrapped in foil, was charged with AD mix- α (1.4 g), followed by 5.0 mL of deionized water and 5.0 mL

of *tert*-butanol and stirred. Stirring was continued until all the AD mix had dissolved. Solid *trans*-cinnamoylcocaine (164 mg, 0.50 mmol) was added slowly with stirring over 4 min and then allowed to stir overnight at room temperature. Sodium metabisulfite (0.5 g) was added slowly with stirring, followed by 20 mL of water, and stirred for 30 min. The reaction was extracted with CHCl_3 (2×40 mL). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and evaporated *in vacuo* to a semi-crystalline mass. The crude product was subjected to the column chromatography purification and extraction method as described above to give a white semi-crystalline mass (61 mg, 33% yield, $dr = 92:8$).

(2*S*,3*R*)-Dihydroxy-3-Phenylpropionylecgonine Methyl Ester: The same procedure utilized for synthesis of (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester was incorporated, except that AD mix- β was utilized as the chiral ligand. Workup of the reaction provided a white semi-crystalline mass (57 mg, 31% yield, $dr = 97:3$).

(2*R*,3*R*)-Dihydroxy-3-Phenylpropionylecgonine Methyl Ester: The procedure utilized for synthesis of (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester was employed, except that *cis*-cinnamoylcocaine was used as the starting material. Workup of the reaction provided a white semi-crystalline mass (29 mg, 16% yield, $dr = 64:36$).

(2*S*,3*S*)-Dihydroxy-3-Phenylpropionylecgonine Methyl Ester: The procedure utilized for synthesis of (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester was employed, except that *cis*-cinnamoylcocaine was the starting material and AD mix- β was the chiral ligand. Workup of the reaction provided a white semi-crystalline mass (52 mg, 29% yield, $dr = 56:44$).

Results and Discussion

The clandestine manufacture of illicit cocaine produces impurities of two types in the refined final product. The first type are alkaloidal impurities (i.e., cinnamoylcocaines and tropacocaine) that are co-extracted from the coca plant. The second type are manufacturing by-products resulting from the chemical manipulations during the isolation, purification, or crystallization processes. These by-products are created by any number of chemical processes which

include: (i) hydrolysis of esters; (ii) *N*-demethylation of the tropane moiety due to solvents containing peroxides; (iii) chemical rearrangements such as transesterifications, epimerizations, and base-assisted benzoyl migration; and (iv) oxidative by-products from the use of potassium permanganate to purify the crude intermediate product (7).

The recent appearance of these four new manufacturing impurities indicates that a change has occurred in the illicit processing procedures for some clandestine cocaine laboratories. These impurities are only found in exhibits that have been oxidized and are most prominent in samples that have been highly oxidized. They chromatograph via GC-FID and GC/MS as three peaks (two co-eluting) between *cis*- and *trans*-cinnamoylcocaine (Fig. 1). As they can only be visualized as their trimethylsilyl derivatives, it was concluded that each possessed highly polar characteristics. GC/MS analysis of exhibits containing the new compounds produced mass spectra which were virtually identical to each other, suggesting they were isomerically related. A mass spectrum representing all four compounds (peaks #6–9 in Fig. 1) as their trimethylsilyl derivatives is illustrated in Fig. 3. Each produced a molecular ion at m/z 507 and a base peak at m/z 182. The presence of ions at m/z 82, 94, 96, and 182 can be attributed to a 2-carbomethoxy-3-oxo substituted tropane (12). The presence of ions at m/z 73 and 147 suggested the presence of two TMS groups. As the 2-carbomethoxy-3-oxo moiety ions were unaffected upon trimethylsilylation with MSTFA, it was concluded that two labile protons resided on the C-3 ester. The mass difference between the molecular ion and two TMS groups, suggested an underivatized molecular weight of 363 Da. Liquid Chromatography/Mass Spectrometry (LC/MS) analysis of the exhibits confirmed a molecular weight of 363 Da, yielding a $[\text{M}+\text{H}]^+$ at m/z 364 for the compounds. Given that the exhibits were highly oxidized and a mass difference of 34 Da from the cinnamoylcocaines (MW = 329 Da) was observed, it was postulated that the compounds were diastereomeric diols produced from oxidation of the cinnamoylcocaines, specifically the (2*R*,3*R*)-, (2*S*,3*S*)-, (2*R*,3*S*)-, and (2*S*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl esters.

Permanganate oxidations of olefins to diols are well known reactions and occur in either neutral or basic conditions. This oxidative hydroxylation of an olefin is not stereoselective and will usually

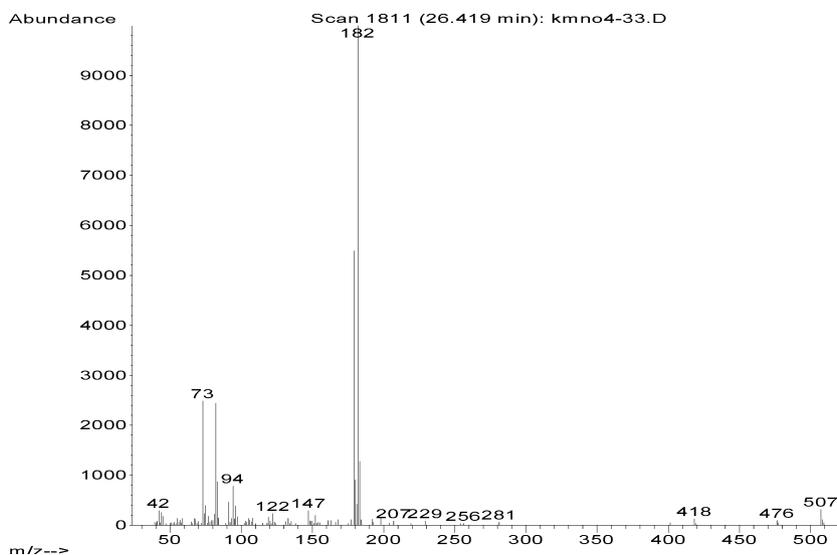


FIG. 3—Electron ionization mass spectrum of the 2,3-dihydroxy-3-phenylpropionylecgonine methyl esters as a di-TMS derivative.

give two products in equivalent amounts. However, as permanganate is a strong oxidizer, the reaction is often difficult to control, leading to over-oxidation as a side reaction. In order to determine which diastereoisomers were derived from which cinnamoylcocaine, we first oxidized *trans*-cinnamoylcocaine with potassium permanganate in weakly basic conditions. Two diastereoisomers were produced in equal amounts ($dr = 50:50$) and chromatographed via GC-FID as their di-TMS derivatives, giving peaks #2 and 4 in Fig. 4. Because the permanganate oxidation of *trans*-cinnamoylcocaine was low yielding, we employed osmium tetroxide as a milder oxidant (13) to produce the diols from *cis*-cinnamoylcocaine. Thus, dihydroxylation of *cis*-cinnamoylcocaine also gave two diastereoisomers in equal amounts ($dr = 50:50$), which chromatographed via GC-FID as their di-TMS derivatives, resulting in peaks #1 and 3 in Fig. 4.

In order to determine the absolute stereochemistry for each diastereomer, a series of diastereoselective reactions were conducted. It is well documented that the asymmetric dihydroxylation of ethyl *trans*-cinnamate, using differing chiral amine ligands coordinated to osmium, gives either the (2*R*,3*S*)-ethyl-2,3-

dihydroxy-3-phenylpropionate or (2*S*,3*R*)-ethyl-2,3-dihydroxy-3-phenylpropionate (11). These diastereoselective reactions are based on *syn* addition to either the top or bottom face of the double bond. This procedure was utilized to achieve a diastereomeric enrichment for each of the studied diols. The absolute stereochemistry was assigned based on the literature predicted outcomes using the α - and β -AD mix reagents. The α -AD mix produced the (2*R*,3*S*)- and (2*R*,3*R*)-diols; whereas, the β -AD mix reaction produced the (2*S*,3*R*)- and (2*S*,3*S*)-diols. Using this analogy, the four new impurities were assigned absolute stereochemistry. Thus, peaks #6, 7, 8, and 9 in Fig. 1, corresponding to peaks #1, 2, 3, and 4 in Fig. 4, were determined to be (2*R*,3*R*)-, (2*S*,3*R*)-, (2*S*,3*S*)-, and (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester, respectively.

Finally, direct proton and carbon NMR experiments were performed to acquire accurate chemical shifts for each diastereomer and are illustrated in Table 2. Gated-decoupled carbon experiments were utilized for samples containing both diastereomers. The major constituent carbon signals were differentiated from the minor constituent by peak area integrations. Correlation of carbon to directly bonded hydrogens was accomplished using the heteronuclear,

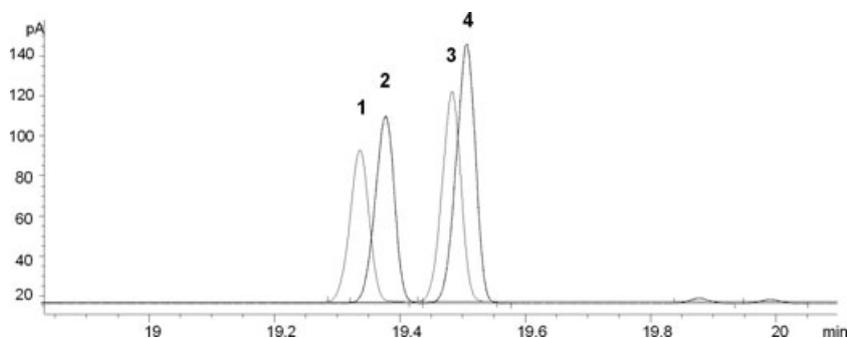


FIG. 4—Capillary gas chromatographic overlays from nonselective dihydroxylation of *cis*- and *trans*-cinnamoylcocaine illustrating the diastereomeric 2,3-dihydroxy-3-phenylpropionylecgonine methyl esters as their di-TMS derivatives. Peak identification: 1 = (2*R*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester, 2 = (2*S*,3*R*)-dihydroxy-3-phenylpropionylecgonine methyl ester, 3 = (2*S*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester, and 4 = (2*R*,3*S*)-dihydroxy-3-phenylpropionylecgonine methyl ester.

TABLE 2—Nuclear magnetic resonance chemical shift (in ppm) data for proton and carbon. All samples dissolved in deuteriochloroform with tetramethylsilane as 0 ppm reference. Proton values are middle of multiplet.

Position	(2 <i>R</i> ,3 <i>R</i>)		(2 <i>S</i> ,3 <i>S</i>)		(2 <i>S</i> ,3 <i>R</i>)		(2 <i>R</i> ,3 <i>S</i>)	
	¹ H	¹³ C						
1	3.55	64.7	3.55	64.7	3.57	64.7	3.55	64.6
2	2.18	41.1	2.18	41.0	2.19	41.0	2.20	41.0
3	4.95	68.7	4.93	68.6	4.96	68.8	5.03	68.6
4a	1.71	35.4	1.71	35.2	1.68	35.2	1.79	35.5
4b	2.21	35.4	2.21	35.2	2.17	35.2	2.33	35.5
5	3.22	61.4	3.22	61.4	3.21	61.4	3.26	61.5
6a	1.61*	25.1 or 25.3	1.61*	25.2	1.60*	25.2	1.63	25.2 or 25.3
6b	2.06	25.1 or 25.3	2.06	25.2	2.05	25.2	2.07	25.2 or 25.3
7a	1.61*	25.1 or 25.3	1.61*	25.2	1.60*	25.2	1.65	25.2 or 25.3
7b	2.11	25.1 or 25.3	2.11	25.2	2.11	25.2	2.13	25.2 or 25.3
NCH ₃	2.86	49.7	2.84*	49.9	2.97	49.9	2.95	49.6
CO ₂ -CH ₃	—	171.1	—	170.8	—	171.0	—	171.1
CO ₂ -CH ₃	3.72	51.7	3.71	51.7	3.72	51.8	3.70	51.7
O ₂ C-CHOH	—	171.8	—	171.5	—	172.2	—	172.3
O ₂ C-CHOH	4.40	74.9	4.44	74.7	4.39	74.7	4.38	74.9
CHOH-Ph	4.83	74.8	4.83	74.6	4.99	74.1	5.05	73.9
Ph quat.	—	139.0	—	138.7	—	139.7	—	140.0
<i>ortho</i>	7.33	128.2	7.33	128.2	7.44	126.2	7.39	126.2
<i>meta</i>	7.35	126.5	7.37	126.8	7.34	128.2	7.33	128.2
<i>para</i>	7.29	128.0	7.29	128.1	7.27	127.8	7.27	127.7

*Denotes position derived from 2D experiments (i.e., COSY, HSQC) due to busy spectrum.

1-bond, ^1H - ^{13}C , two-dimensional HSQC experiment. The two-dimensional homonuclear, 2- to 3-bond, ^1H - ^1H COSY experiment assigned all the tropane protons. The heteronuclear, 2-4 bond, ^1H - ^{13}C correlation HMBC experiment differentiated carbonyl carbons in the molecule (the lower chemical shift carbonyl associated with the methoxy group and the higher chemical shift carbonyl with the cinnamoyl group). The homonuclear ^1H - ^1H two-dimensional NOESY experiment, which correlates protons that are spatially near one another ($<4 \text{ \AA}$ apart), was used to assign positions of the two CHOH groups in the cinnamoyl group. Predicted carbon spectra for the compounds compared well with experimental data.

It is highly unlikely that illicit processors are utilizing mild oxidizers such as osmium due to its extreme toxicity, high cost, slow reaction rates, and the higher expected levels of the diols than are currently seen in illicit samples. Potassium permanganate has been the oxidant of choice for illicit processors for over 40 years, because it is a strong oxidant and the reaction proceeds quite rapidly (ca. 30 min on a kilogram scale of cocaine). The recent emergence of these new impurities strongly suggests that some cocaine processors have modified their illicit oxidation procedures. It is clear from the signature profiles obtained to date that the majority of the cinnamoylcocaines are being oxidized to water-soluble products, not appearing in the refined cocaine HCl. Additionally, increased levels of *N*-norcocaine (Fig. 1, peak #4) confirm that the exhibits are being oxidized with a strong oxidizing agent (1,9). However, reaction conditions currently being utilized by some processors are allowing incomplete oxidation of the olefin moiety to produce the title compounds that are appearing in the final product. The chemistry required for the formation of these compounds requires that neutral, instead of acidic, conditions are being utilized in the oxidation process. Basic conditions would not be possible on the illicit reaction scale due to cocaine's solubility properties (it would be insoluble). This leaves two possible types of reaction conditions: (i) illicit processors are adding aqueous potassium permanganate to cocaine base dissolved in a water miscible solvent, such as an alcohol, acetone, or methyl ethyl ketone; or (ii) illicit processors are performing the oxidation as a bi-phase mixture of a water immiscible organic solvent containing cocaine base and aqueous potassium permanganate (with vigorous stirring).

Conclusions

Four new illicit cocaine manufacturing by-products were identified and characterized via GC-FID, GC/MS, LC/MS, and NMR techniques, coupled with independent synthesis from *cis*- and *trans*-cinnamoylcocaine. Incomplete oxidation of the cinnamoylcocaines (i.e., dihydroxylation of the olefin moiety) directly results in the formation of four diastereomeric 2,3-dihydroxy-3-phenylpropionylecgonine

methyl esters. Illicit refined cocaine exhibits containing these compounds produce unique analytical signature profiles with reduced levels of cinnamoylcocaines, as well as increased levels of norcocaine.

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