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Novel Chlorinated Tropanes Derived from the Treatment of Cocaine with Sodium Hypochlorite

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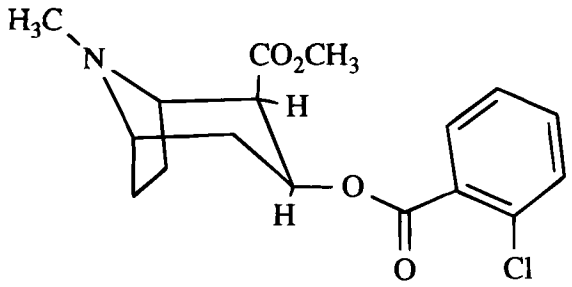
ABSTRACT: Several novel chlorinated tropanes were produced when cocaine was treated with aqueous sodium hypochlorite. Two of these, 2′- and 3′-chlorobenzoyloxy-2-carbomethoxypseudotropine (that is, *ortho-* and *meta*-chlorococaine), were characterized by synthesis and gas chromatography/mass spectrometry. Four other new chlorinated tropanes (*endo*-6- and 7-chlorococaine, *exo*-6- or 7-chlorococaine and N-chlorobenzoylnorecgonine methyl ester) were also tentatively identified via their gas chromatography retention data and mass spectra. The results are of potential use in cocaine signature and comparative analysis.

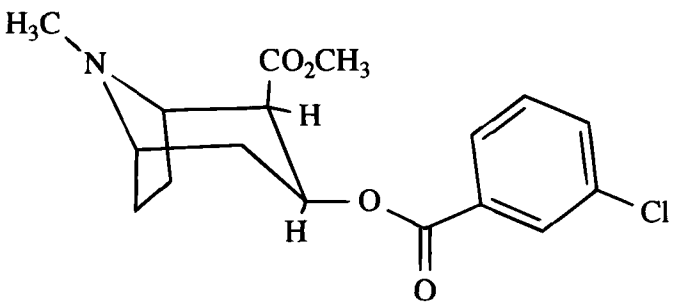
KEYWORDS: criminalistics, cocaine, coca alkaloids, chlorococaine, gas chromatography, mass spectrometry

Historically, drug users/dealers have used various methods to destroy drug evidence upon the imminent threat of arrest and/or evidence seizure. Such methods have included adding strong acid (sulfuric or hydrochloric acid) or household lye (sodium hydroxide), flushing down drains, ingesting orally, and even attempted burning. More recently, cocaine users/dealers have been known to use bleach (that is, aqueous sodium hypochlorite (NaOCl)) in an attempt to destroy cocaine [*1*]. Previous studies have shown that the use of NaOCl or potassium permanganate ($KMnO_4$), both strong oxidizing agents, result in degradation of cocaine [*1,2*].

This study was initiated to determine whether the use of NaOCl would provide unique compounds (vs. $KMnO_4$) for cocaine signature and comparative analysis purposes [*3*]. Previously identified products resulting from the oxidation of cocaine by both NaOCl (Carpenter and Laing [*1*]) and $KMnO_4$ (Brewer and Allen [*2*]) include: N-norcocaine, N-formylnorcocaine, ecgonine methyl ester, benzoylecgonine, ecgonine, ecgonine methyl ester and N-benzoylnorecgonine methyl ester. In this study, more in-depth analysis of the hypochlorite oxidation products indicated, in addition to these, several new compounds, including *ortho-* and *meta*-chlorococaine. The structural formulae of these latter two compounds are illustrated in Fig. 1 their detection and characterization were accomplished using capillary gas chromatography-flame ionization detection (GC-FID) and capillary gas chromatography-mass spectrometric detection (GC-MSD). Structural confirmation of each compound was accomplished by comparison of their retention times and mass spectra with those of synthesized standards. Several other new chlorinated tropanes were also presumptively identified from their mass spectra; proposed structural assignments for these latter compounds are presented in Fig. 2.



ortho-Chlorococaine



meta-Chlorococaine

FIG. 1—*Structures of ortho- and meta-chlorococaine.*

Experimental

Capillary Gas Chromatography-Flame Ionization Detection

A Hewlett-Packard Model 5890 Series II Gas Chromatograph (GC) was used to generate all chromatograms. The GC was fitted with a 30 m × 0.25 mm i.d. fused-silica capillary column coated with 0.25 μm DB-1701 (J & W Scientific). A pressure-programmed constant linear velocity of 36.8 cm/s hydrogen (99.999%,

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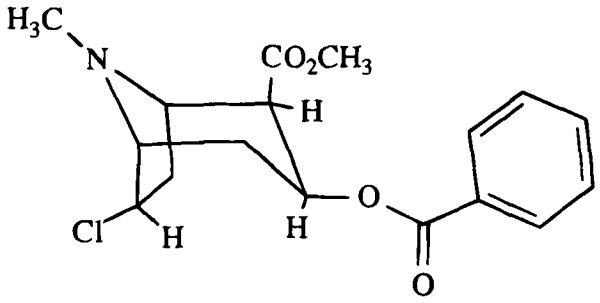
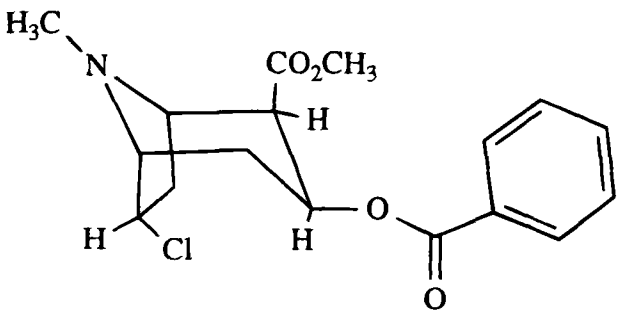


6-exo-Chlorococaine



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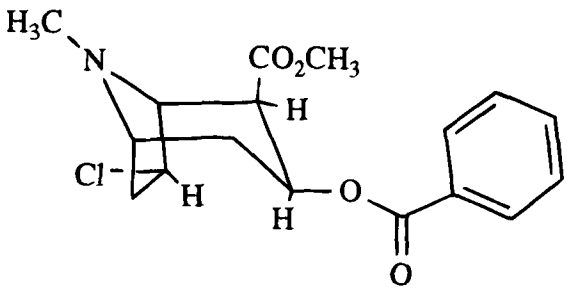
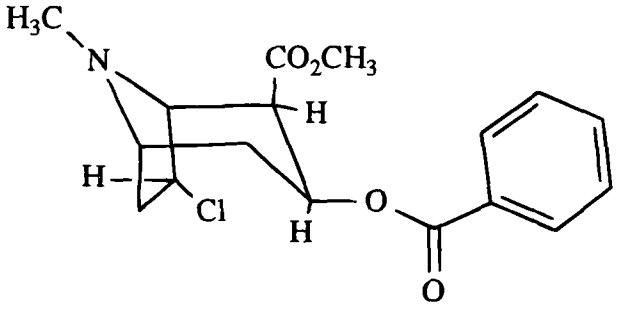
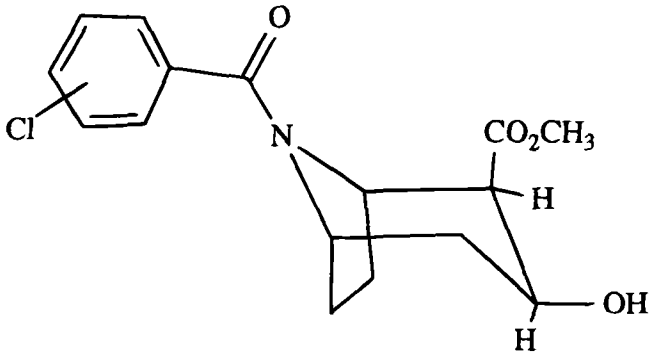


7-exo-Chlorococaine



7-endo-Chlorococaine



N-(chlorobenzoyl)norecgonine methyl ester

FIG. 2—*Proposed structures of compounds containing other chlorine substitutions.*

UHP) was used. The injection port (20:1 split) and flame ionization detector (FID) were maintained at 230° C and 300° C, respectively. Samples were injected using a Hewlett-Packard Model 7673A Auto Injector (2 μL injection). The oven temperature was programmed as follows: initial temperature, 140° C; initial hold, 1.0 min; program rate, 2.0° C/min; final temperature, 275° C; final hold, 18.2 min.

Mass Spectrometry

Mass spectra for all compounds were obtained on a Hewlett-Packard Model 5972 Mass Selective Detector (MSD) interfaced with a Hewlett-Packard 5890 Series II Gas Chromatograph. Operating parameters for the MSD and GC were as follows: The MSD operated under electron ionization (EI) conditions at 70 eV

and in full scan mode. The injection port (20:1 split) and source were maintained at 250° C and 180° C, respectively. A 30 m × 0.25 mm i.d. fused-silica capillary column coated with 0.25 μm DB-1 (J & W Scientific) was employed with a pressure-programmed constant linear velocity of 36.1 cm/s. The oven temperature was programmed as follows: initial temperature, 90° C; initial hold, 1.0 min; program rate, 6.0° C/min; final temperature, 300° C; final hold, 4.0 min.

Reagents and Standards

All solvents were distilled-in-glass products of Burdick and Jackson, while all other reagents were reagent-grade quality (Aldrich). Pharmaceutical-grade cocaine hydrochloride (Merck) and crude illicit cocaine base were obtained from the Reference Standards Collection of this laboratory. Ecgonine methyl ester, N-norcocaine, N-benzoylnorcocaine and N-benzoylnorecgonine methyl ester were synthesized as previously described [*4,5*]. The preparations of the *ortho*-, *meta*- and *para*-chlorococaines were accomplished by acylation of ecgonine methyl ester with the respective chlorobenzoyl chlorides.

Experiment #1—One gram of crude illicit cocaine base was dissolved into 20 mL of dilute sulfuric acid. The pH was adjusted to 2 via addition of additional concentrated sulfuric acid. Sodium hypochlorite solution (containing 5% available chlorine) was added dropwise with stirring until cocaine base precipitation was observed (15 minutes). Dilute sodium hydroxide was then added until the pH exceeded 10. The reaction was extracted with methylene chloride (3 × 20 mL); the combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to a white crystalline mass. The residue was reconstituted in chloroform for cGC-FID and cGC-MSD analyses.

Experiment #2—Approximately 120 mg of crude illicit cocaine base was added "all at once" to 10 mL of aqueous NaOCl and allowed to stand for 1 hour. The reaction solution was worked up as described in Experiment #1.

Experiment #3—Approximately 120 mg of pharmaceutical-grade cocaine hydrochloride was added "all at once" to 10 mL of aqueous NaOCl and allowed to stand for 1 hour. The reaction was worked up as Experiment #1.

Results and Discussion

Oxidation of crude illicit cocaine base with aqueous NaOCl in dilute acid (Experiment #1) resulted in an overall loss of cocaine and produced an abundance of by-products. A chromatographic profile of the resulting product is illustrated in Fig. 3. Increased levels of N-norcocaine, N-benzoylnorecgonine methyl ester, N-formylnorcocaine, and N-benzoylnorcocaine [5], (as compared to $KMnO_4$ [2]) were all observed; interestingly, however, ecgonine methyl ester was detected at only trace levels. In addition, over a dozen new chloro-substituted tropanoid compounds were detected.

Characterization of Cocaine with Chlorine on the Aromatic Ring

GC-MSD analysis of the sodium hypochlorite oxidation products from Experiment #1 indicated two new compounds (peaks #5 and #6, Fig. 3), which possessed a chloro substituent on the aromatic ring. Both compounds yielded virtually identical mass spectra, suggesting positional isomers. A spectrum depicting either isomer is illustrated in Fig. 4. The suspected molecule ion was observed at m/z 337 with an isotope abundance ratio consistent with mono-chloro substitution. Ions supporting the presence of a single chlorine (dual ions with the typical 3:1 isotopic abundance ratio) are seen at m/z 111/113, 139/141, and 306/308. No chloro-substituted fragment ions could be attributed to the tropane moiety. Abundant ions at m/z 82, 94, 96, 122, and 182 compared favorably with the mass spectrum of cocaine, confirming that the 2-carbomethoxytropane moiety was intact. The fragment ions at m/z 306/308 are due to loss of the methoxy moiety at C-2. The remaining ions which exhibited the chlorine isotopic pattern, that is, m/z 111 (phenyl + 35-1) and 139 (benzoyl + 35-1), correspond to the m/z 77 and 105 ions in the spectrum of cocaine. Thus, the m/z 111 and 139 ions mandate a single chlorine substituent on the aryl ring. The mass spectra and retention times of peaks #5 and #6 were virtually identical to synthesized standards of *meta*- and *ortho*-chlorococaine, respectively (Fig. 1). Surprisingly, *para*-chlorococaine was not detected in the sample.

The formation of both *meta*- and *ortho*-chlorococaine most probably occurs via electrophillic aromatic substitution with protonated hypochlorous acid (H_2O^+-Cl), an *in situ* source of chlorenium ion (Cl^+). *A priori*, the *meta*-substituted compound would be expected to predominate, since the carboxyl group is strongly electron withdrawing; thus, the excess presence of *ortho*-chlorococaine and the absence of *para*-chlorococaine are anomalous results.

Compounds Containing Other Chlorine Substituents

Peaks #4a, #4b and #7 (Fig. 3) each yielded a mass spectrum also exhibiting apparent molecule ions at m/z 337; however, the fragmentation patterns for these compounds were markedly dissimilar to those of *ortho*- and *meta*-chlorococaine (Fig. 4). Each exhibited an m/z 94 ion as the base peak. Peaks #4*a* and #4*b* gave virtually identical spectra, again suggesting positional isomers; a representative spectrum for these compounds is illustrated in Fig. 5. The spectrum of peak #7, seen in Fig. 6, differed primarily from #4*a* and #4*b* only in the relative abundances of m/z 116 and m/z 120. The absence of fragment ions m/z 82 and m/z 182, along with the presence of ions m/z 105 and m/z 232, indicated that chlorine substitution had occurred on the tropane ring in all three compounds.

To ascertain the chlorination sites for compounds 4*a*, 4*b* and 7, we re-examined the mass spectra of 1-hydroxytropacocaine [*6*] and 6-*exo*-hydroxytropacocaine[2] to provide insight as to the fragment ions derived from substitution on the N-methylpyrrolidine ring of the tropane moiety. We observed that 6-*exo*-hydroxytropacocaine gives an m/z 94 ion as the base peak. The proposed structure for this fragment is the 1-methylpiperidinium ion, originating from the six-membered ring of the tropane moiety. Coupled with the observation that 1-hydroxytropacocaine (note: 1- and 5-hydroxytropacocaine are equivalent) does not produce an ion at m/z 94, it can be deduced with some certainty that the chlorination occurred at either C-6 or C-7. Another fragment ion of diagnostic value is m/z 116, which corresponds to a 1-methyl-3-chloropyrrolidinium ion and is consistent with 6- or 7-chloro-substituted tropanes. Other logical losses provided additional confirmation for the presence of chlorine within the tropane moiety, but absent at C-2, C-3 or C-4; these included CH_3O (m/z 306/308), Cl (m/z 302), CH_3COO (m/z 278), C_6H_5CO (m/z 232/234), C_6H_5COO (m/z 216/218), C_6H_5CO and CH_3OH (m/z 200/202), and C_6H_5COO and HCl (m/z 180).

[2]Casale, J. F. and Moore, J. M., unpublished data, 1994.

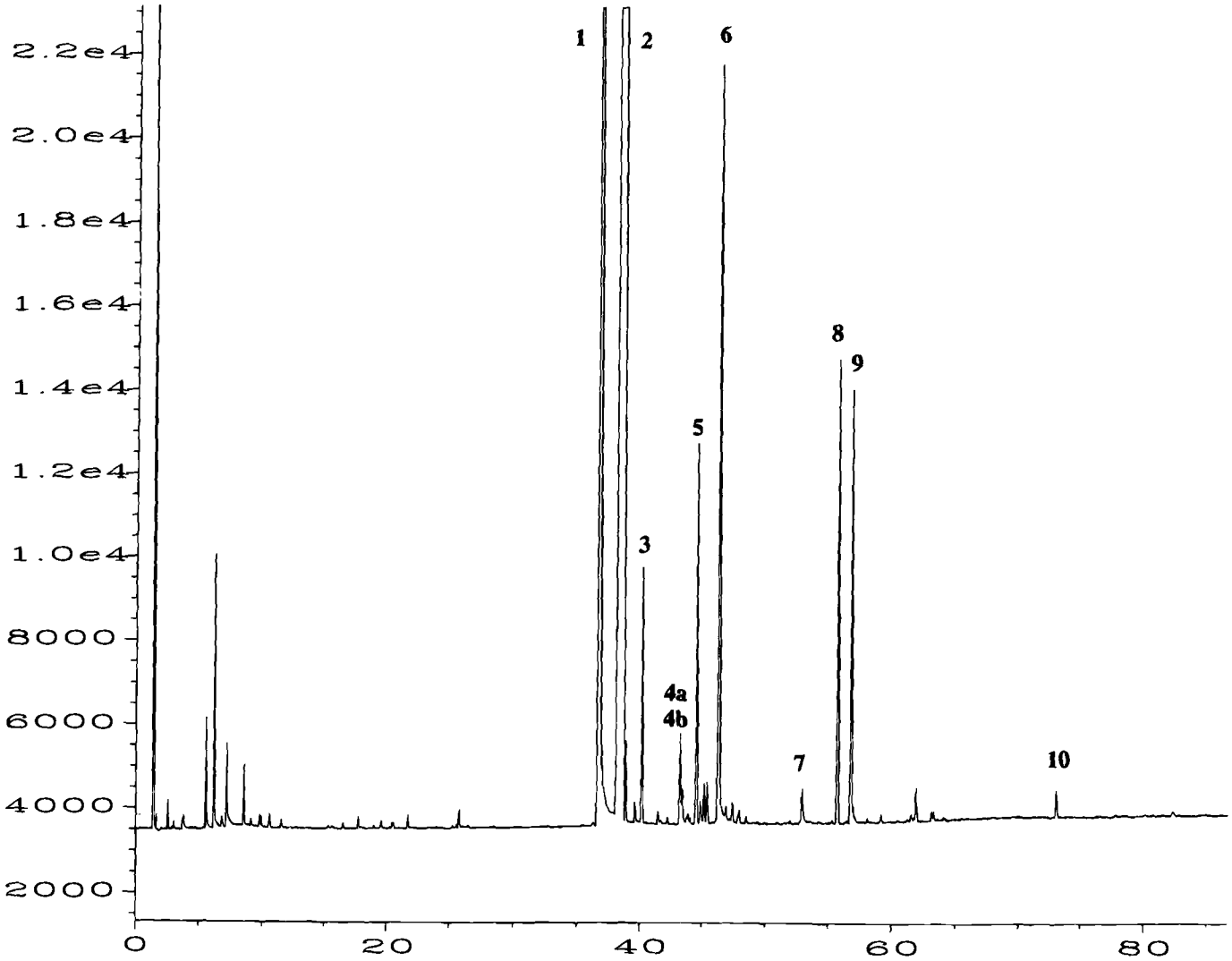


FIG. 3—*Capillary gas chromatogram of an illicit crude cocaine base exhibit after reaction with sodium hypochlorite. Peak identification (min) — 1 = N-norcocaine (36.8 min), 2 = cocaine (38.7 min), 3 = N-benzoylnorecgonine methyl ester (40.2 min), 4a and 4b = 6- and 7-endo-chlorococaines[a] (43.2 min), 5 = meta-chlorococaine (44.5 min), 6 = ortho-chlorococaine (46.4 min), 7 = 6- or 7-exo-chlorococaine[a] (52.9 min), 8 = N-formylnorcocaine (55.7 min), 9 = N-(chlorobenzoyl)norecgonine methyl ester[a] (56.8 min) and 10 = N-benzoylnorcocaine (73.1 min). [a]based on presumptive evidence.*

We have previously observed that the *endo*- configurations of 6- and 7-methoxy-2-carbomethoxytropinones[2] have reduced relative GC retention times vs. the corresponding *exo*- configurations. We have, therefore, equivocally assigned peaks #4*a* and #4*b* as *endo*-configurations of 6- and 7-chlorococaine (Fig. 2). Peak #7 is therefore presumptively assigned as an *exo*-configuration of either 6- and/or 7-chlorococaine (Fig. 2).

Finally, the mass spectrum of peak #9 (Fig. 3) is illustrated in Fig. 7. This compound has an apparent molecule ion at m/z 323. The spectrum is analogous to that of N-benzoylnorecgonine methyl ester (+1 chlorine atom, −1 hydrogen atom). The presence of ion m/z 139 as the base peak is comparable to ion m/z 105 for N-benzoylnorecgonine methyl ester. Loss of the amide moiety gives rise to m/z 184 in the same relative abundance found in N-benzoylnorecgonine methyl ester. Ion m/z 111 (chlorophenyl) also corresponds to the m/z 77 ion found for N-benzoylnorecgonine methyl ester. This compound is therefore tentatively identified as N-chlorobenzoylnorecgonine methyl ester, with the chlorine substitution again on the aromatic ring (Fig. 2).

Several other minor unenumerated peaks in Fig. 3 also appear to be unique products of sodium hypochlorite oxidation. Based on their mass spectra, these compounds are also believed to be chlorinated tropanes; however, their structural elucidation is beyond the scope of this study. It should be stressed that the structural assignments for peaks #4*a*, #4*b*, #7 and #9 are based upon presumptive evidence. Unequivocal characterization of these compounds will require synthesized standards or isolation and comprehensive structural analysis.

Miscellaneous Observations

When crude illicit cocaine base was added directly to a solution of aqueous sodium hypochlorite (Experiment #2), no reaction was observed. The strongly basic nature of aqueous sodium hypochlorite prevented cocaine base from solubilizing for oxidation. However, the addition of cocaine hydrochloride to aqueous sodium hypochlorite (Experiment #3) did produce a variety of products, as illustrated in Fig. 8. Precipitation occurred almost spontaneously after the cocaine was added. Although GC-MSD analysis of this latter product indicated traces of chloro-substituted tropanes, none of the compounds formed from oxidation in dilute acidic media were detected.

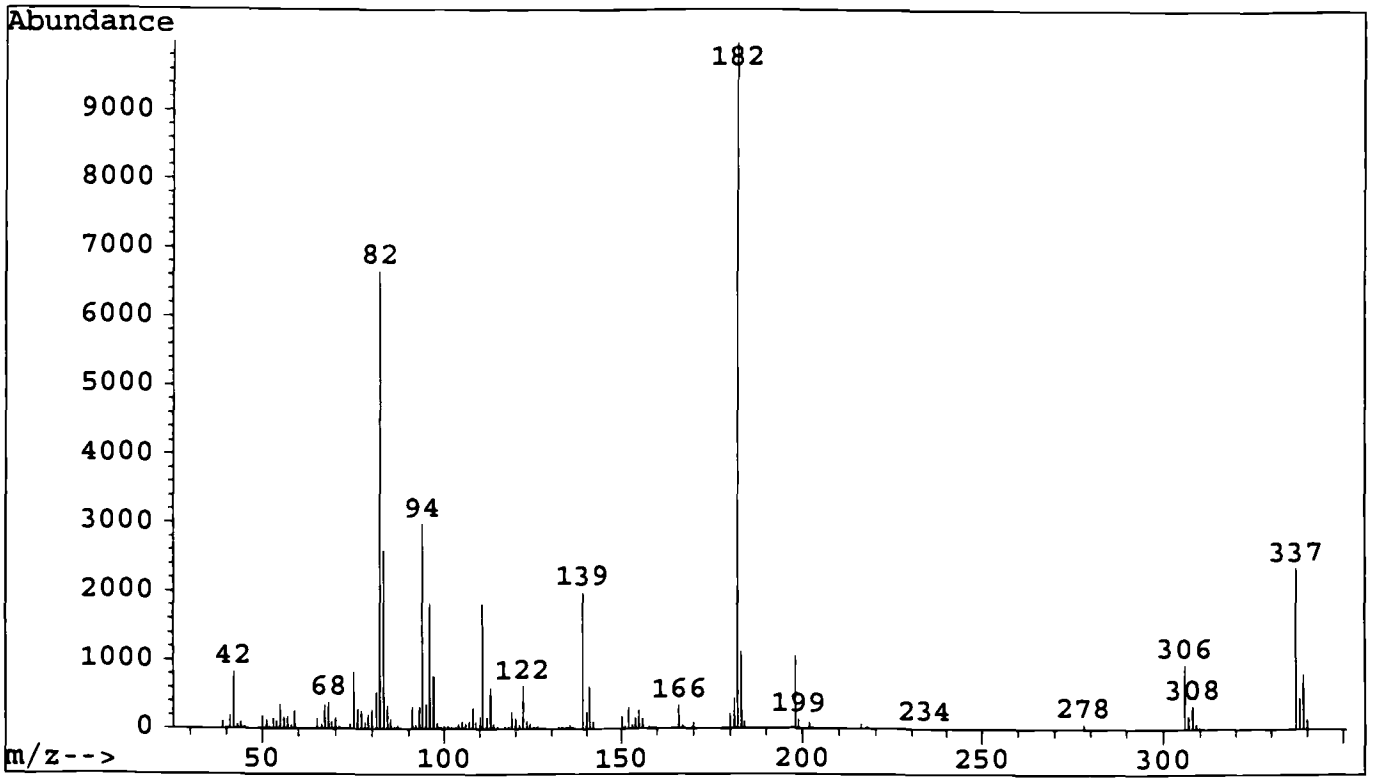


FIG. 4—*Electron ionization mass spectrum of ortho- or meta-chlorococaine.*

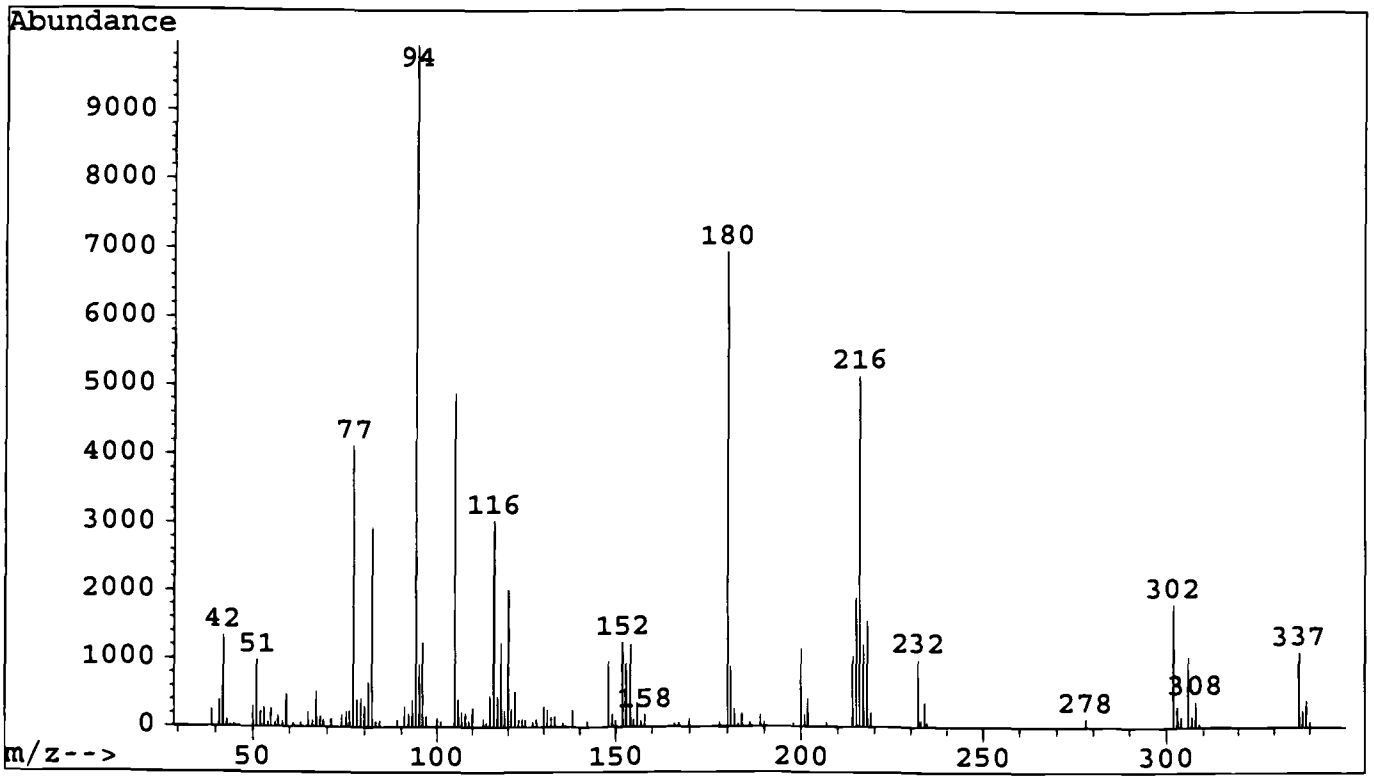


FIG. 5—*Electron ionization mass spectrum of peaks #4a and #4b.*

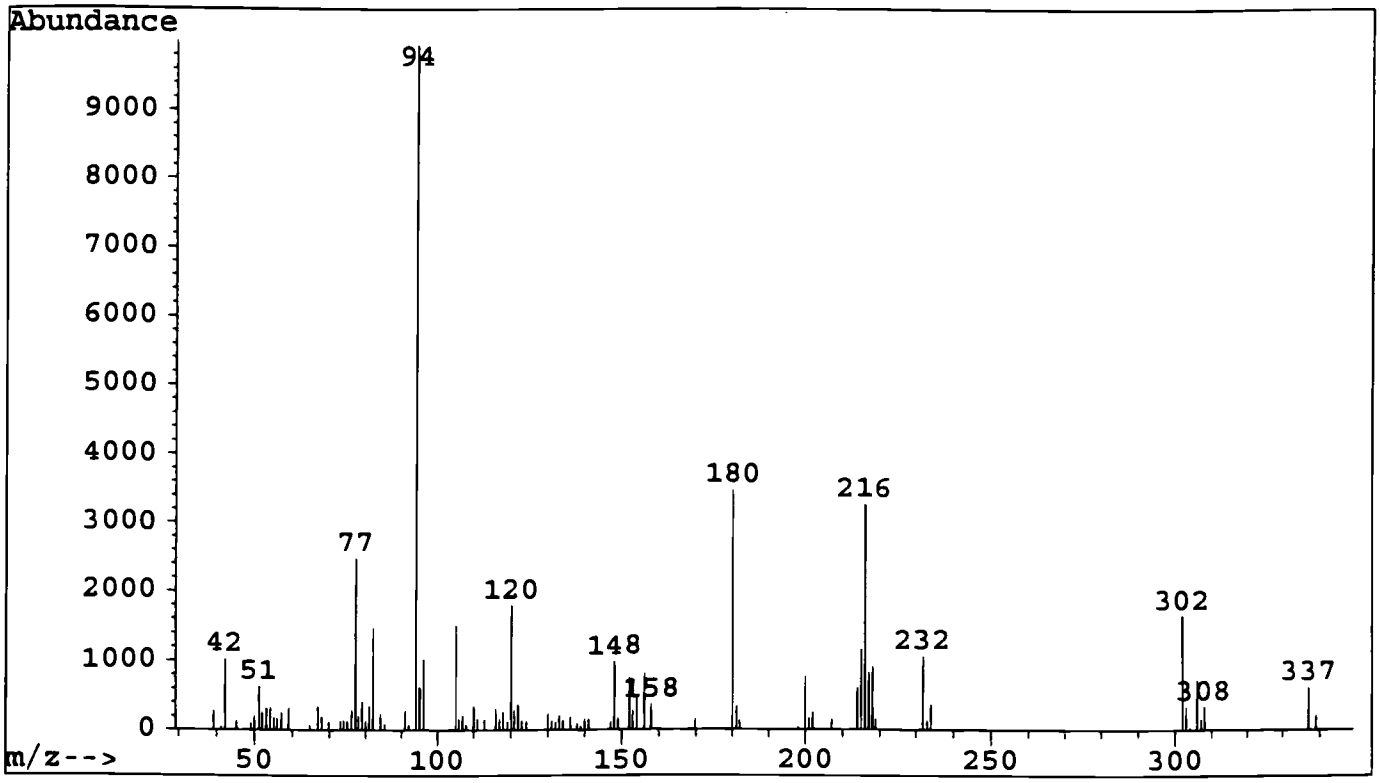


FIG. 6—*Electron ionization mass spectrum of peak #7.*

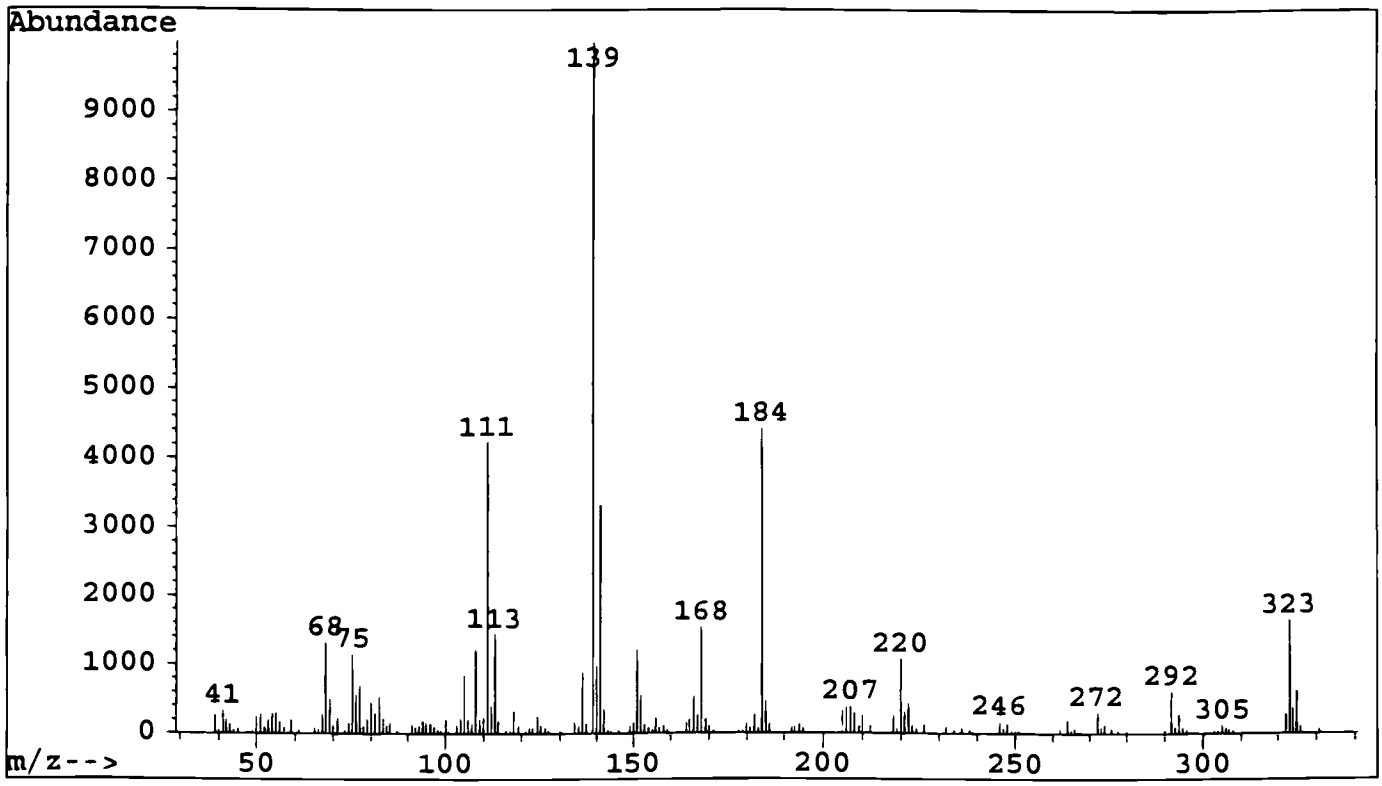


FIG. 7—*Electron ionization mass spectrum of peak #9.*

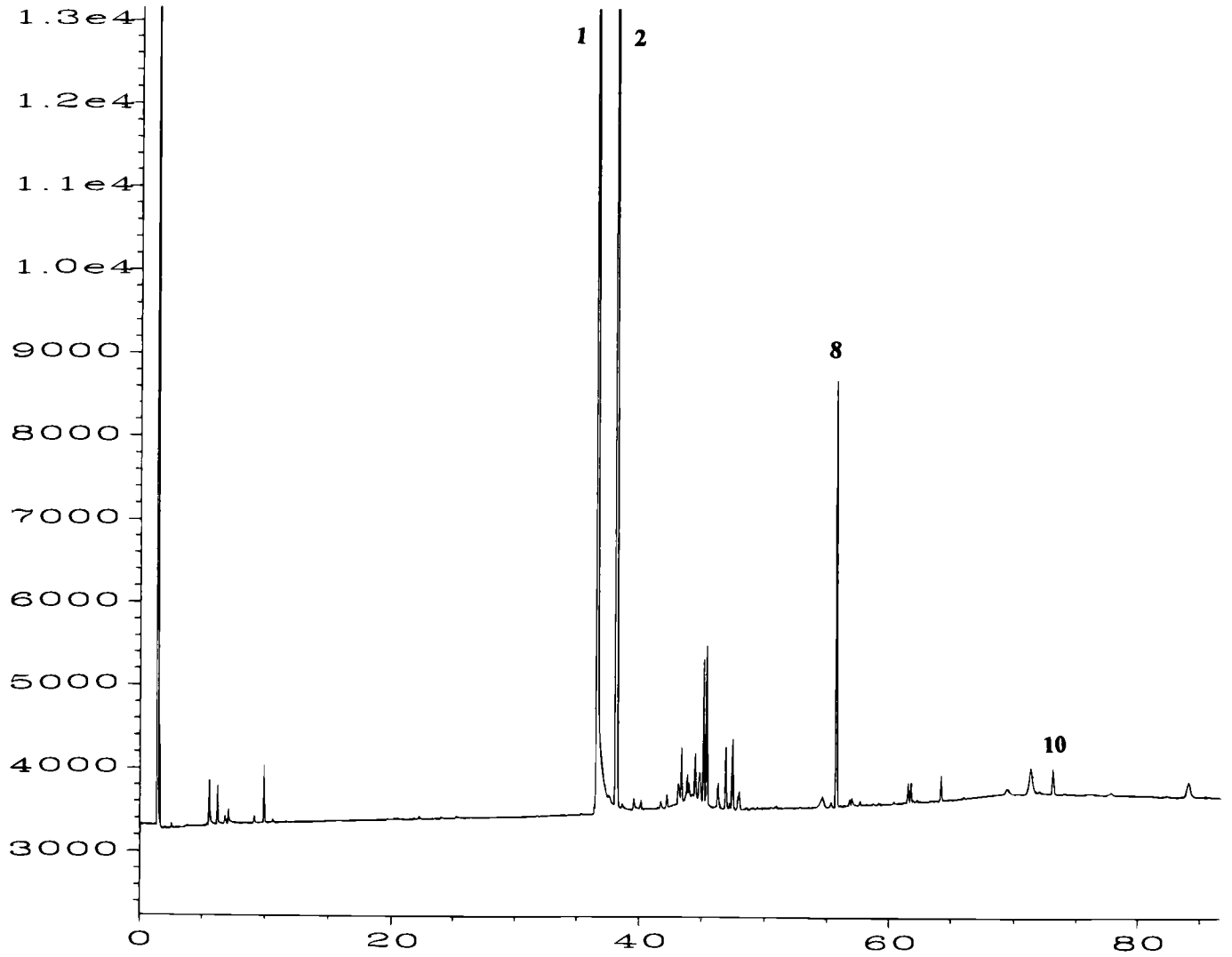


FIG. 8—*Capillary gas chromatogram of a cocaine hydrochloride exhibit produced from Experiment #3. Peak identification (min) – 1= N-norcocaine (36.8 min), 2 = cocaine (38.7 min), 8 = N-formylnorcocaine (55.7 min), and 10 = N-benzoylnorcocaine (73.1 min).*

Conclusions

Oxidation of crude illicit cocaine base with sodium hypochlorite in dilute acid generated a series of chlorinated tropanes. Two new products, *ortho*-chlorococaine and *meta*-chlorococaine, were identified and characterized by comparison of their GC retention data and mass spectra with synthesized standards. Four other new chlorinated tropanes were tentatively identified as *endo*-6- and 7-chlorococaine, *exo*-6- or 7-chlorococaine and N-chlorobenzoylnorecgonine methyl ester. These chloro-substituted tropanes may be useful indicators for signature classification of illicit cocaine exhibits.

Acknowledgments

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