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The Application of Capillary Gas Chromatography-Electron Capture Detection in the Comparative Analyses of Illicit Cocaine Samples

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ABSTRACT: The gas chromatographic detection of manufacturing impurities in illicit cocaine can be enhanced by chemical derivatization and the use of an electron-capture detector. After derivatization of illicit cocaine hydrochloride samples with heptafluorobutyric anhydride, the isolated heptafluorobutyryl derivatives of the cocaine impurities were subjected to capillary gas chromatography-electron capture detection analysis. The on-column detection of cocaine impurities at low picogram levels was possible for compounds such as N-norcocaine and other N-demethylated impurities, amidic by-products, including N-benzoylnorecgonine methyl ester and tertiary amines possessing hydroxy functions. The latter compounds include the so-called hydroxycocaine impurities, believed to be new coca leaf alkaloids. This methodology is especially suited for sample comparison analyses.

KEYWORDS: forensic science, chemical analysis, cocaine, gas chromatography, electron capture detection, illicit drugs

The significance of the detection and characterization of manufacturing impurities and byproducts in illicit drugs has become increasingly well-recognized in forensic drug chemistry. Perhaps the two most important reasons for the development of so-called impurity signature profiles are to determine geographical origin of the drug, where applicable, and to be able to compare different drug seizures for common source determinations. Such studies have been reported for cocaine [*1–30*], heroin [*31–63*] and amphetamine-type compounds [*64–73*]. There is no question that chromatography, namely, capillary gas chromatography (cGC) and high-performance liquid chromatography (HPLC), have become the techniques of choice in such investigations. Although HPLC has proven successful in generating impurity signature profiles [*10,15,20,21,25,54,59,73*], an inherent advantage in using cGC is found in its far-greater resolving facility. Furthermore, the on-column minimum detectable quantity levels using GC detectors has been shown to be significantly lower than that for conventional HPLC detectors [*74*]. The flame ionization detector (FID) and nitrogen-phosphorous detector, as well as the mass spec-

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trometer (MS), have been the detectors most frequently associated with the cGC analysis of illicit drug manufacturing impurities/byproducts.

In the present study we describe the use of the more sensitive electron-capture detector (ECD) for use with cGC-ECD. This detector has demonstrated its usefulness in impurity signature profile studies for both cocaine [*14,18,74*] and heroin [*34,35,50,51,60,74*]. Although the ECD has been used widely in drug toxicological analyses, it has been used quite sparingly in most forensic laboratories for the indepth analysis of manufacturing impurities and byproducts in solid-dosage illicit drugs. Whereas the use of cGC-ECD is really not warranted for most routine forensic drug analyses, we believe that this technique adds another dimension in the analysis of drug processing impurities, because it allows for the detection of compounds at trace levels that cannot be achieved using more commonly detectors. The on-column minimum detectable quantity levels for certain electrophilic derivatives of illicit drug impurities are common at low picogram (pg) and sometimes high femtogram (ftg) levels when using cGC-ECD [*74*]. When the ECD is interfaced with a capillary GC column and when used with an appropriate pre-column derivatization step, the chemist has a powerful analytical tool.

Our laboratory has been interested in the characterization of illicit cocaine manufacturing impurities and byproducts since the early 1970s, when we first reported the presence of the *coca* alkaloids *cis*- and *trans*-cinnamoylcocaine in illicit cocaine hydrochloride samples [*1*]. In the first report of its kind, Clark used the cinnamoylcocaine manufacturing impurities in the development of cocaine comparison parameters using GC-FID [*4*]. The analysis of the cinnamoylcocaines has also been accomplished using HPLC [*8,10,12,15,20,25*]. In the mid-to-late 1970s GC-FID methodology was presented for the analysis of the cinnamoylcocaines along with cocaine hydrolysis products, namely benzoylecgonine, *10*, ecgonine methyl ester, *2*, and ecgonine, *11* [*2,3*]. These procedures utilized a pre-column trimethylsilylation derivatization step which enhanced the gas chromatographic behavior of the cocaine hydrolysis products. Recently, Casale and Waggoner [*26*] improved upon that methodology, substituting a capillary GC column in place of a packed GC column. Their cGC-FID method not only afforded a marked improvement in resolution but also in sensitivity, which allowed the detection of theretofore unreported cocaine manufacturing impurities. These authors also provided a good rationale for the presence of certain alkaloidal cocaine impurities as well as manufacturing byproducts in illicit cocaine samples.

In 1987 Moore described the cGC-ECD detection of the 11 isomeric truxilline coca alkaloids in illicit cocaine samples and coca leaves [*14*]. This method was also suitable for the detection of truxillic and truxinic acids, the secondary hydrolysis products of the truxillines. This is believed to be the first reported use of cGC-ECD in the analysis of cocaine manufacturing impurities. Subsequently, methyl esterification and the incorporation of a structurally-related internal standard into this methodology allowed for the relative quantitative determination of total truxillines [*18*]. Because of the bulky structural character of the truxillines, their direct analysis using cGC-FID is difficult, due mostly to their thermal degradation in the GC. Lurie circumvented truxilline GC degradation by chromatographing the intact truxillines via HPLC [*15,21*]. When using these procedures it was possible to detect 7 of the 11 truxillines. This methodology was also suitable for the detection of truxilline hydrolysis products as well as other unrelated cocaine manufacturing impurities/byproducts. Recently, Ensing and de Zeeuw [*27*] reported the detection of five truxillines by means of thin-layer chromatography and mass spectrometry.

Since about 1980 there has been a marked increase in the number of laboratories that have made valuable contributions to our understanding of cocaine manufacturing impurities/byproducts and their utilization in sample comparison analyses. Most notable among these are studies by Casale [*22*], Casale and Waggoner [*26*], Ensing and others [*27,28,30*], LeBelle and co-workers [*17,20,25*] and Brewer and Allen [*24*]. Among the

new cocaine manufacturing byproducts reported were N-norcocaine, N-benzoylnorecgonine methyl ester and N-formylnorcocaine. These authors developed comparative and other analytical methodology that included cGC-FID, cGC-MS, HPLC-UV and TLC and resulted in the compilation of cocaine comparison data bases. Although most cocaine studies have been reported for illicit cocaine derived from South American coca, other investigations have focused upon the analysis of synthetic cocaine byproducts [*13,16*] and the diastereomers of cocaine [*7,9,23*].

In this paper we describe the cGC-ECD detection and comparative analyses of secondary ("N-nor") amine, tertiary amine, neutral and suspected hydroxycocaine impurities and byproducts as well as a host of unidentified compounds in illicit cocaine hydrochloride samples. This methodology was a modification of a previously published work that described the detection of manufacturing impurities/byproducts in illicit heroin [*51*]. In the method described herein, unadulterated cocaine hydrochloride samples were derivatized directly in acetonitrile with heptafluorobutyric anhydride (HFBA). After extraction of the heptafluorobutyryl (HFB) derivatives of the manufacturing impurities/byproducts into isooctane, the bulk cocaine matrix was quantitatively removed by back-extraction of the isooctane with a pH 4.0 buffer. This allowed, for the first time, the facile detection at ultratrace levels (< 0.01% w/w relative to cocaine) of at least eight suspected hydroxycocaines in illicit cocaine hydrochloride samples. In addition to the hydroxycocaines, for example, possibly *6* in Fig. 1, this method could also detect hydroxy-containing tertiary amines such as ecgonine methyl ester, *2*, and its C2 epimer, ψ-ecgonine methyl ester; secondary amines including N-norcocaine, *4*, N-norecgonine methyl ester, *6*, N-nortropacocaine, *7*, and N-nor-ψ-tropine *8*, and neutral byproducts, such as N-benzoylnorecgonine methyl ester, *3*, and N-formylnorecgonine methyl ester, *9*. Additionally, present in many cGC-ECD chromatograms were numerous peaks believed to represent illicit cocaine manufacturing impurities/byproducts yet to be identified.

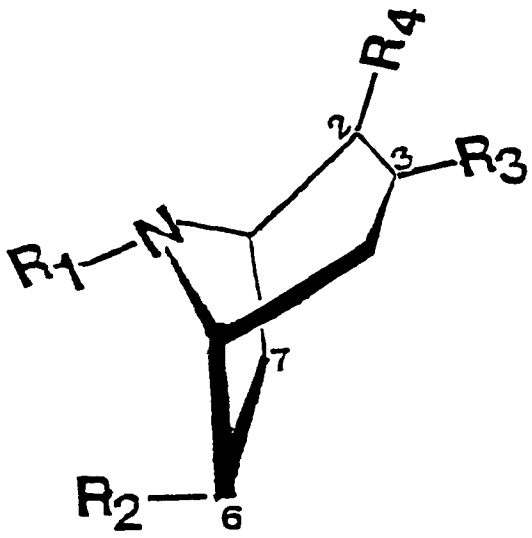
Experimental

Capillary Gas Chromatography-Electron Capture Detection

All cGC-ECD chromatograms were generated in the splitless mode with two Hewlett-Packard gas chromatographs fitted with three 30M × 0.25 mm I.D. fused silica capillary columns coated with DB-1701, DB-5 or DB-1 (J and W Scientific), all at a film thickness of 0.25 μm. The gas chromatographs were equipped with ^{63}Ni electron capture detectors (15 mCi) and interfaced with Hewlett-Packard Level IV data processors. The oven temperatures were multilevel programmed as follows: (level 1) initial temperature, 90°C; initial hold, 5.0 min; temperature program rate, 25°C/min; final temperature, 160°C; final hold, 1.0 min; (level 2) temperature program rate, 4°C/min; final temperature, 275°C; final hold, 15 min. Injector and detector temperatures were maintained at 225–250°C and 300°C, respectively. Hydrogen (Zero Grade) was used as the carrier gas at a velocity of 40–50 cm/s and measured by the injection for isooctane at an oven temperature of 90°C. An argon:methane (95:5) mixture was used as a detector make-up gas at a flow rate of about 35 mL/min. During the splitless injection the solvent was vented after a 1.0 min hold.

Capillary Gas Chromatography-Mass Spectrometry

Low-resolution electron ionization (EI) and chemical ionization mass spectra were acquired on a Finnigan Mat Model 4630 quadrupole mass spectrometer. The samples were introduced into the mass spectrometer via an 11M or 20M × 0.25 mm I.D. fused-



1. R_1=CH_3; R_2=H; R_3=Ph-C(=O)-O; R_4=-C(=O)-OCH_3

2. R_1=CH_3; R_2=H; R_3=OH; R_4=-C(=O)-OCH_3

3. R_1=Ph-C(=O); R_2=H; R_3=OH; R_4=-C(=O)-OCH_3

4. R_1=R_2=H; R_3=Ph-C(=O)-O; R_4=-C(=O)-OCH_3

5. R_1=R_2=H; R_3=OH; R_4=-C(=O)-OCH_3

6. R_1=CH_3; R_2=OH; R_3=Ph-C(=O)-O; R_4=-C(=O)-OCH_3

7. R_1=R_2=H; R_3=Ph-C(=O)-O; R_4=H

8. R_1=R_2=H; R_3=OH; R_4=H

9. R_1=C(=O)-H; R_2=H; R_3=OH; R_4=-C(=O)-OCH_3

10. R_1=CH_3; R_2=H; R_3=Ph-C(=O)-O; R_4=-C(=O)-OH

11. R_1=CH_3; R_2=H; R_3=OH; R_4=C(=O)-OH

FIG. 1—*Structures of some cocaine manufacturing impurities and byproducts subjected to HFBA derivatization and detected using capillary gas chromatography-electron capture detection. NOTE 1 = cocaine, 2 = Ecgonine Methyl Ester, 3 = N-Benzoylnorecgonine methyl ester, 4 = N-Norcocaine, 5 = N-Norecgonine Methyl Ester, 6 = 6-Hydroxycocaine, 7 = N-Nortropacocaine, 8 = N-Nor-ψ-tropine, 9 = N-Formylnorecgonine Methyl Ester, 10 = Benzoylecgonine and 11 = Ecgonine.*

silica capillary column coated with DB-1 at a 0.25μm film thickness. Helium was used as the carrier gas at a velocity of approximately 45 cm/s. Two oven temperature programs were used in conjunction with the capillary columns. Sample injections were accomplished using an on-column injector apparatus (J and W Scientific), whereby sample was introduced into a section of column which was outside of the GC oven. Oven initial temperatures were set to a value approximately 10°C above the boiling point of the injection solvent. Injections were 0.5-1.0 μL and the injection site temperature was estimated to be 50°C. All EI spectra were acquired at an ionization potential of 60 eV and at a source temperature of 150°C. Positive chemical ionization (PCI) spectra were collected at an ionization potential of 100 eV using methane as the reagent gas at a source pressure and temperature of 0.45 torr and 140°C, respectively. Negative electron capture chemical ionization (NCI) data were generated using methane as reagent gas at a source temperature of 120°C, a source pressure of 0.45 torr and at an ionization potential of 100 eV. All source pressures and temperatures were uncorrected.

Materials

ψ-Ecgonine methyl ester, N-nortropacocaine and N-benzoylnorecgonine methyl ester were synthesized and generously supplied by John F. Casale of the North Carolina State Bureau of Investigation.

All solvents were distilled-in-glass products of Burdick and Jackson and were peroxide- and preservative-free. Heptafluorobutyric anhydride (HFBA), supplied in 1-mL sealed glass ampules, and N,O-bis(trimethylsilyl)acetamide (BSA) were obtained from Pierce.

Derivatization and Chromatography of Illicit Cocaine Hydrochloride Manufacturing Impurities and Byproducts

Into a 15-mL glass-stoppered, conical centrifuge tube, containing 50 μg of heneicosanol internal standard, was weighed 50 to 60 mg of unadulterated illicit cocaine hydrochloride sample. To the tube was added 1.0 mL of acetonitrile and 50 μL of HFBA. After vortexing, the tube was heated at approximately 75°C for 15 min. After cooling, 4 to 8 mL of isooctane (containing aldrin at 25 pg/μL) and 5 mL of a saturated aqueous solution of sodium bicarbonate were added to the tube. Without delay, the tube was shaken vigorously for 5 to 10 s and then centrifuged (ca 2000 rpm) for 5 min. The upper isooctane layer was transferred to another tube and then back-extracted with pH 4.0 acid phthalate buffer to remove the bulk cocaine matrix. After centrifuging as before, the isooctane was transferred to another tube and dried over anhydrous sodium sulfate.

A 1-2 μL aliquot of the dried isooctane extract was injected into the cGC-ECD using the capillary columns and conditions described under Experimental. Figure 2 illustrates two representative cGC-ECD chromatograms of the HFB derivatives of cocaine manufacturing impurities for cocaine samples denoted A and B. If necessary, further dilutions were made with isooctane containing the aldrin internal standard.

Isolation of Suspected Hydroxycocaines from the Bulk Cocaine Matrix

In order to enhance the mass spectral study of the suspected hydroxycocaine impurities (see *6* in Fig. 1) it was necessary to isolate them from the bulk cocaine matrix. This was accomplished using an alumina column (basic, activated, Brockman I, approx. 150 mesh standard grade) and an elutropic series consisting of ethyl ether:methylene chloride (6:4), chloroform, chloroform:acetone (6:4), acetone, and acetone:methanol (1:1). The cocaine sample was introduced to the column as the free base in a minimal volume of

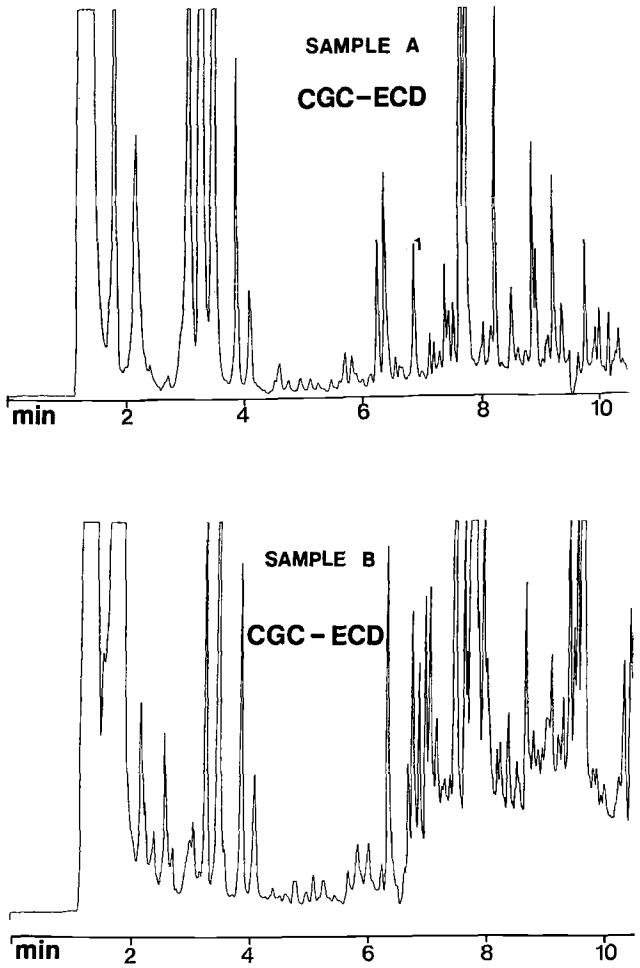


FIG. 2—*Capillary gas chromatographic-electron capture detection chromatograms of heptafluorobutyryl derivatives of some cocaine manufacturing impurities/byproducts in two unrelated and unadulterated illicit cocaine hydrochloride samples. 30 M × 0.25 mm DB-1701 (0.25 μm). Chart Speed = 2.5 cm/min and Attn = 2^7. See Table 1 for Peak Identification.*

ethyl ether:methylene chloride (6:4). The hydroxycocaine impurities were found distributed in the acetone and acetone:methanol (1:1) eluates.

Results and Discussion

For the purposes of this discussion, cocaine manufacturing impurities are considered to be minor coca alkaloids that are extracted from the coca leaf, along with cocaine, during the manufacturing process. Examples include the cinnamoylcocaines and the truxillines. Cocaine manufacturing byproducts are usually the result of hydrolytic and/or oxidative processes upon cocaine and minor coca-leaf alkaloids during manufacture and/or storage. N-norcocaine and benzoylecgonine are two such examples. Both manufacturing impurities and byproducts are found in nearly all illicit cocaine samples at varying levels.

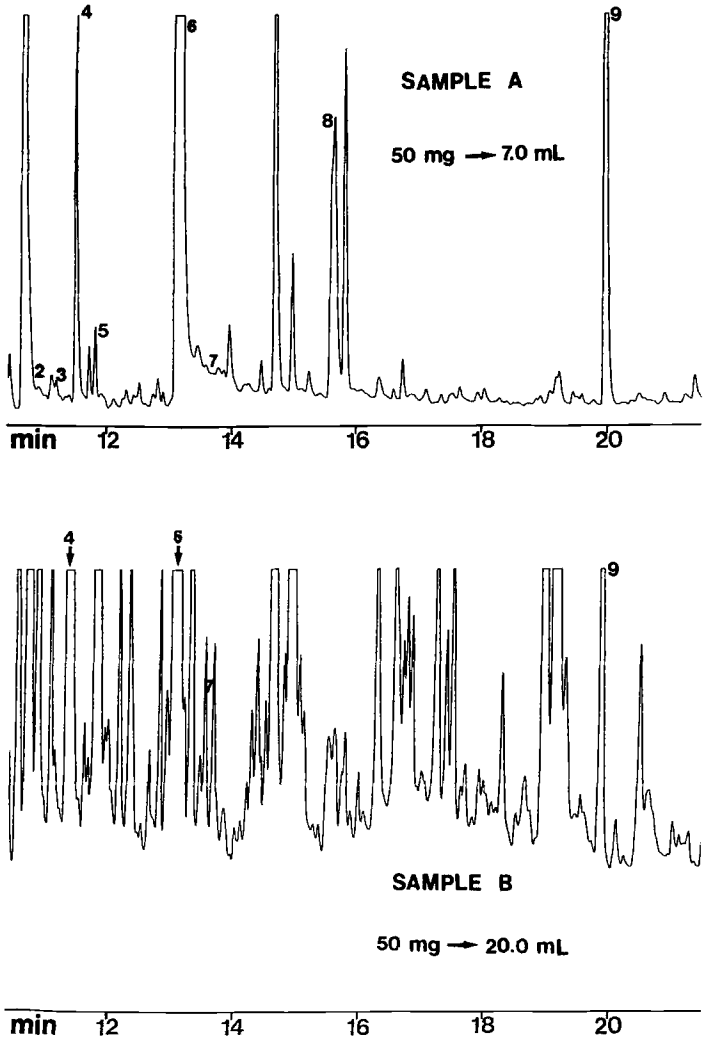


FIG. 2—*Continued.*

Virtually all of the samples studied in this investigation were illicit, unadulterated cocaine hydrochloride seizures from various countries in South America. No drying or other pre-treatment of these samples occurred prior to their analyses.

Derivatization Reaction

As described previously, this derivatization procedure is simple, rapid and requires relatively small sample amounts. Although cocaine itself does not derivatize, the entire sample is solubilized during the first few minutes of the derivatization reaction. In Fig. 1 are illustrated some of the cocaine impurities/byproducts detected in illicit samples using this methodology (excepting benzoylecgonine and ecgonine). Most of these compounds formed heptafluorobutyryl (HFB) derivatives in a facile and essentially quantitative manner when treated with HFBA in acetonitrile. As usual, all derivatization re-

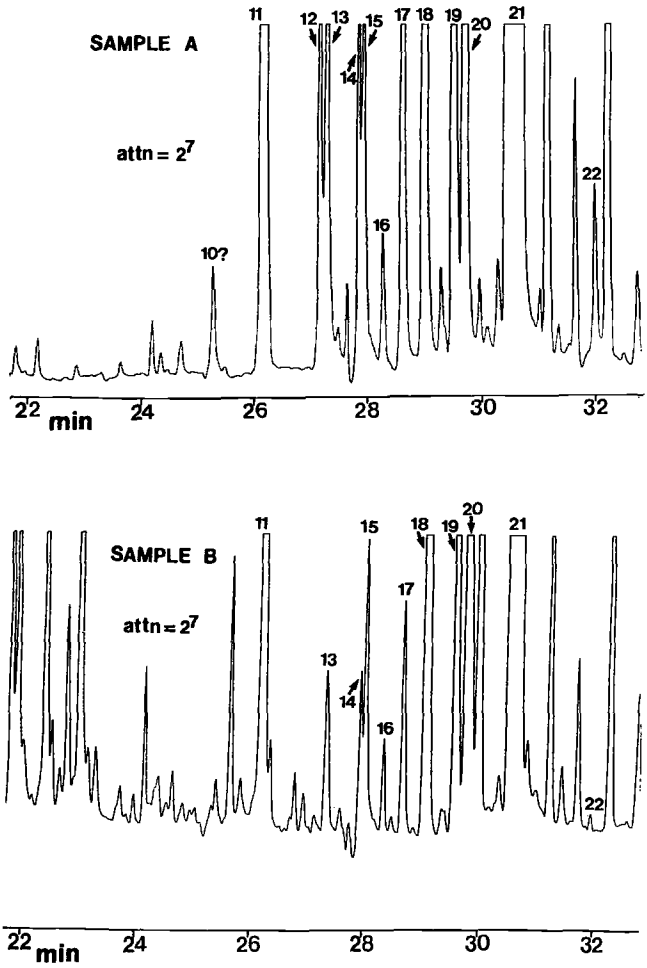


FIG. 2—*Continued.*

actions occurred at either -OH and/or R_1R_2N-H sites in these compounds. Most of the cocaine impurities/byproducts amenable to HFBA derivatization were usually present and detectable in cocaine samples at levels of 10^{-1}–10^{-5} % w/w (relative to cocaine).

It had been determined that most of the compounds in Fig. 1 could form HFB derivatives at room temperature. However, at a derivatization reaction temperature of 75°C additional impurities/byproducts appeared as peaks in the chromatographic profiles. This is illustrated by the unenumerated peaks present in the chromatogram for Sample B in Fig. 2. These compounds are believed associated with the manufacturing process, although their composition remains unknown at this time.

Although this study focused on cocaine hydrochloride samples, several seizures of cocaine base were analyzed. Interestingly, their chromatographic profiles were dominated by numerous peaks that were unknown and apparently generated by a single compound. Further investigation revealed this compound to be benzoylecgonine. Under basic reaction conditions benzoylecgonine undergoes degradative heptafluorobutyrylation, resulting in many and varied HFB derivatives that appear as chromatographic peaks. Therefore,

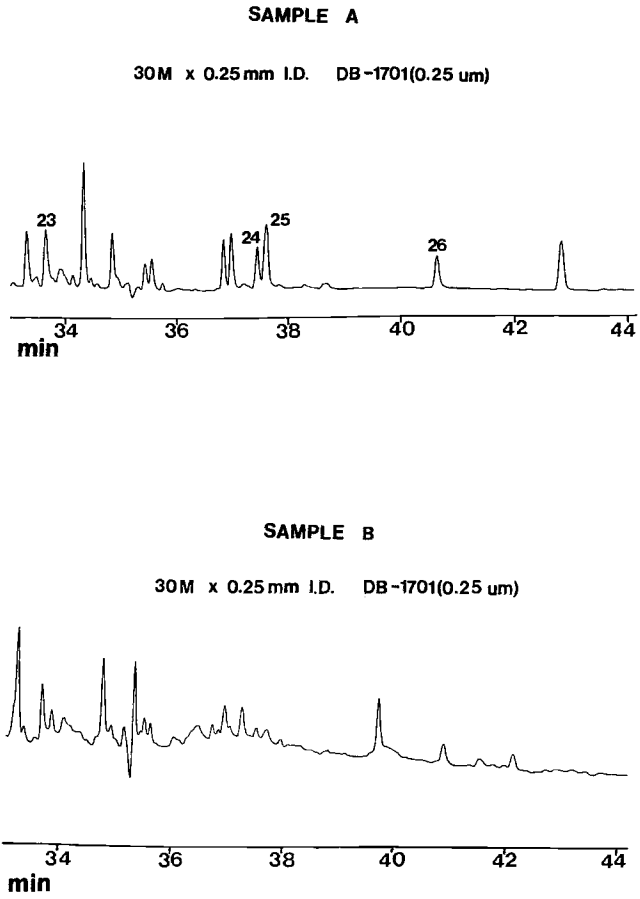


FIG. 2—*Continued.*

prior to the analysis of cocaine base samples, it is recommended that benzoylecgonine be removed via dry-extraction or some other extraction technique. It is cautioned, however, that such procedures may also produce unwanted variations in the chromatographic profiles, for example, the artifactual creation of "N-nor" impurities.

Isolation of HFB Derivatives from Cocaine

After HFBA derivatization of the cocaine sample, the HFB derivatives of the manufacturing impurities/byproducts were effectively extracted into isooctane from a sodium bicarbonate solution in one step. However, also extracted was a significant quantity of cocaine, which caused overloading of the capillary column and resulted in anomolous chromatographic behavior during the cGC-ECD determination. This problem was resolved by back-extracting the isooctane containing the HFB derivatives with a pH 4.0 phthalate buffer. This quantitatively removed cocaine from the isooctane while the N-HFB and O-HFB derivatives were retained in this solvent.

At first it might appear surprising that the O-HFB-derivatized tertiary amines, such as the hydroxycocaine impurities (for example, see *6* in Fig. 1), were not extracted from isooctane, along with cocaine, into the pH 4.0 phthalate buffer, since all are tertiary

amines. Apparently, the O-HFB substituent in hydroxycocaine exhibits a strong electron-withdrawing influence on the nitrogen lone-pair electrons, thereby rendering such derivatives significantly less basic than cocaine itself. Such remarkable behavior has been reported previously for the O-HFB derivatives of tertiary amine manufacturing impurities in illicit heroin [*51,74*]. If the isooctane containing the O-HFB-derivatized cocaine impurities was extracted with a strong acid such as 1N sulfuric acid, in lieu of the pH 4.0 buffer, the bulk of the tertiary amine derivatives were extracted into the acid phase.

Chromatography, Sensitivity and Reproducibility

Figure 2 illustrates cGC-ECD chromatograms of two unrelated, unadulterated, illicit cocaine hydrochloride samples, A and B. The identity of the enumerated peaks, along with their retention times, can be found in Table 1. The chromatography of the HFB derivatives of the cocaine manufacturing impurities/byproducts was studied using three capillary columns. They were 30 M × 0.25 mm fused-silica capillary columns coated with either DB-1701, DB-5 or DB-1, all at a film thickness of 0.25 μm. It was found

TABLE 1—*Capillary gas chromatographic-electron capture detection retention times for the heptafluorobutyrl derivatives of some illicit cocaine manufacturing byproducts/impurities. See Experimental section for chromatographic conditions and Fig. 2 for corresponding CGD-ECD chromatography using DB-1701.*

Peak #[a]	Compound Name[a]	Retention Time (Min)
1	*a*[b]	6.77
2	N-Nor-ψ-tropine[c]	10.90
3	ψ-Ecgonine Methyl Ester[d]	11.24
4	Ecgonine Methyl Ester[d]	11.55
5	*a*[b]	11.87
6	N-Norecgonine Methyl Ester[c]	13.17
7	N-Formylnorecgonine Methyl Ester[d]	13.62
8	*a*[b]	15.67
9	Aldrin Internal Standard	19.92
10	N-Nortropacocaine[e]	25.47
11	Heneicosanol Internal Standard[d]	26.22
12	*b*[f]	27.23
13	*b*[f]	27.35
14	*b*[f]	27.90
15	*b*[f]	27.99
16	*b*[f]	28.32
17	*b*[f]	28.66
18	*b*[f]	29.03
19	N-Benzoylnorecgonine Methyl Ester[d]	29.52
20	*b*[f]	29.72
21	N-Norcocaine[e]	30.54
22	*a*[b]	31.99
23	*a*[b]	33.71
24	*a*[b]	37.45
25	*a*[b]	37.61
26	*a*[b]	40.62

[a]See Figures 1 and 2.
[b]A suspected hydroxy-containing tertiary amine impurity chromatographed as O-HFB derivative.
[c]Chromatographed as N,O-di-HFB derivative.
[d]Chromatographed as O-HFB derivative.
[e]Chromatographed as N-HFB derivative.
[f]A suspected hydroxycocaine, e.g. *6* in Figure 1, chromatographed as O-HFB derivative.

that the DB-1701 column provided superior resolution of the suspected HFB-hydroxycocaine derivatives, these being most of the enumerated peaks found between 11 and 21 min in the chromatograms in Fig. 2. The excellent chromatography of HFB-derivatized compounds is well-illustrated by observing the good peak symmetry for HFB derivatives eluting between 34 and 44 minutes, as shown for Sample A in Fig. 2.

When comparing cGC-ECD with cGC-FID, the primary advantage the former has over the latter is the 2–4 orders of magnitude enhancement in sensitivity for electrophilic derivatives, especially halogenated compounds. For this reason, cocaine impurities such as the hydroxycocaines are easily detected as HFB derivatives by cGC-ECD, whereas chromatographic profiles using cGC-FID has not allowed for their detection. As O- and N-HFB derivatives, the compounds in this study could be detected on-column at low picogram levels. For impurities/byproducts with two or three HFB substituents, minimum on-column detection quantities of below 5 pg to high-femtogram levels might be expected. Typically, this methodology is capable of the facile detection of HFB-derivatizable compounds in cocaine in the range of 10^{-5}–10^{-2}% w/w (based on 50 mg cocaine).

For sample comparison purposes, especially for court presentation, good method reproducibility is essential. To determine the reproducibility for this methodology, a selected unadulterated cocaine hydrochloride sample was subjected to six repetitive analyses during the same day. Figure 3 illustrates three of these chromatographic profiles, demonstrating excellent reproducibility. Only the retention window of 26 to 38 min is shown in Fig. 3, since this has proven to be the most discriminatory and diagnostic section in the chromatographic run.

Characterization of Cocaine Impurities/Byproducts

In the development of comparison methodology, it is desirable to ascertain the composition of as many peaks in the chromatogram as possible. Of the peaks and compounds listed in Table 1, peak #'s 2, 3, 4, 6, 7, 10, 19 and 21 are all cocaine manufacturing byproducts; that is, they were produced during the manufacturing process. Some of the aforementioned peaks represent compounds that have been reported previously in the literature and are referenced in this paper. Others are oxidative and/or hydrolytic products of known compounds. It should be noted that there is an element of uncertainty regarding the presence of the byproducts represented by peak #'s 2, 3 and 7 in Samples A and B (See Fig. 2 and Table 1). This is due to the diminished magnitudes of their chromatographic responses.

The unenumerated peaks in Figs. 2 and 3 are believed to be bonafide cocaine manufacturing impurities and/or byproducts. Although their structural characterization has not been done, they are believed to be neutral and/or secondary amine compounds.

The compounds in Table 1 that are denoted as *a* and *b* are the most intriguing and are believed to be individual tertiary amines possessing a hydroxy function(s). Of these, the *b* compounds appear to be the most important. Peak #'s 12-18 and 20 represent suspected hydroxycocaine impurities. These compounds are believed to possess the basic cocaine structure but are substituted with a hydroxy group(s) somewhere on the tropane moiety. An example of such a compound is "6-hydroxycocaine," as illustrated by structure *6* in Fig. 1.

It was of some significance to determine if the purported hydroxycocaines were alkaloidal impurities or manufacturing byproducts. Analysis of coca paste samples, the crude intermediate in the cocaine manufacturing process, revealed the presence of the hydroxycocaines. Since the conversion of coca leaves to coca paste is known to be a "gentle" chemical process, it was unlikely that the hydroxycocaines were produced as artifacts. This led to the conclusion that they were coca leaf alkaloids. Indeed, a cursory

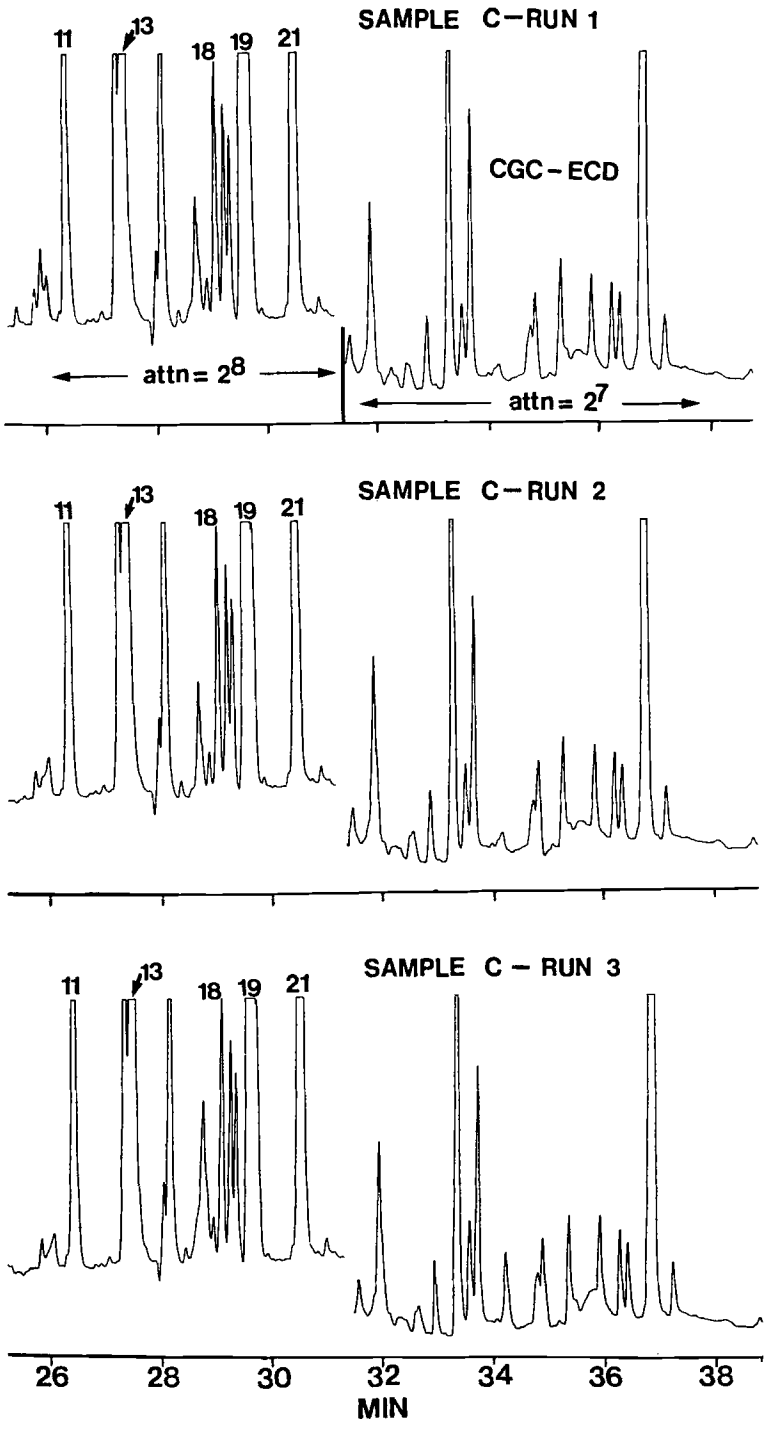


FIG. 3—*The repetitive heptafluorobutyric anhydride derivatization and capillary gas chromatographic-electron capture detection analysis of an illicit, unadulterated cocaine hydrochloride sample. 30 M × 0.25 mm DB-1701 (0.25 μm). See Table 1 for Peak Identification.*

examination of South American coca leaves indicated the presence of the two major hydroxycocaines, represented by peak #'s 18 and 20 in Fig. 2 [*77*].

The mass spectral analyses of some of the hydroxycocaines is described in the following.

Mass Spectrometric Analysis of the Suspected Hydroxycocaines

The illicit cocaine hydrochloride Sample A, illustrated in Fig. 2, was relatively rich in hydroxycocaines and was, therefore, selected for HFBA derivatization and MS analysis. However, instead of extracting the HFB derivatives with isooctane, they were extracted with petroleum ether to facilitate a subsequent evaporation/concentration step. Prior to evaporation the petroleum ether extract was back-extracted with pH 4.0 buffer to remove cocaine, the cinnamoylcocaines and the truxillines.

The petroleum ether extract from above was subjected to cGC-MS analysis using electron ionization (EI). Review of the resultant mass spectral data revealed four late-eluting compounds, each yielding an apparent molecule ion at m/z 515. This was consistent with an HFB(O)- substituent in cocaine. Further evidence was found for the unequivocal assignment of a benzoyl and methoxy substructure within the four compounds. Additionally, the data was consistent with the presence of a HFB(O)- moiety on the tropane ring. However, the substitution sites were equivocal and could not be assigned with certainty. It is considered likely, though, that the HFB(O) substitution does occur in some hydroxycocaines at the C-6 and or C-7 positions (see *6* in Fig. 1).

For a more indepth mass spectral study of the suspected hydroxycocaines, it was first necessary to isolate them from the bulk cocaine matrix. This was done using alumina column chromatography, as described under Experimental. This process significantly enriched the presence of the hydroxycocaines in two fractions from the alumina column. These fractions were divided into two aliquots. One aliquot was subjected to HFBA derivatization followed by mass spectral analysis using negative chemical ionization (NCI). The other aliquot was further divided into two fractions. Both fractions were prepared for cGC/PCI-MS analysis, one by reconstitution in an appropriate solvent without derivatization, and the other by derivatization of the residue in BSA-dimethylformamide at 60°C for 5 min.

A review of the cGC/NCI-MS spectra for the alumina-isolated hydroxycocaines subjected to HFBA derivatization revealed the presence of five compounds that all gave a significant ion that was attributed to what is a typical loss of HF from the molecule ion (M^- = 515 daltons). The underivatized hydroxycocaine fraction gave mass spectra for a number of compounds under PCI conditions which had protonated molecule ions at m/z 320. Both of these data sets were consistent with hydroxycocaines.

The most definitive MS data were acquired using cGC-PCI-MS in the analysis of the two alumina column fractions as trimethylsilyl (TMS) derivatives. Found in the acetone fraction were five suspected hydroxycocaines, including one of two major hydroxycocaines identified as peak #18 in Fig. 2. These compounds yielded similar PCI mass spectra, including a protonated molecule ion found at 392 daltons (MH^+), indicative of a single TMS(O)- group in the molecule. Logical losses from the protonated molecule ion included CH_3 (m/z 377), CH_3O (m/z 361), TMS-OH (m/z 302) and benzoic acid (m/z 270). This data provided strong evidence for the presence of the C-2 carbomethoxy and the C-3 benzoyloxy moieties of the "cocaine" molecule and, in addition, for the presence of a hydroxyl substituent on the tropane ring. The cGC/MS analysis of the acetone:methanol (1:1) fraction from the alumina column indicated the presence of the second major hydroxycocaine, identified as peak #20 in Fig. 2. Unfortunately, the presence of interfering basic compounds precluded an indepth analysis of this fraction. Figure 4 illustrates the reconstructed total ion gas chromatogram of five suspected hydroxyco-

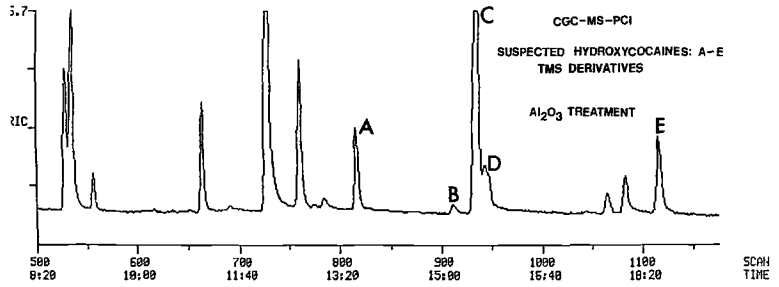


FIG. 4—*Reconstructed total ion capillary gas chromatogram (positive chemical ionization) of the trimethylsilyl derivatives of some suspected hydroxycocaines isolated from illicit cocaine using alumina column chromatography.*

caines (A-E) isolated from a cocaine sample using alumina column chromatography. Peak C in this chromatogram is the same as peak #18 in Fig. 2. Figure 5 provides the mass spectra for the suspected hydroxycocaine peaks A and C.

Although all of the data presented thus far provided reasonable presumptive evidence for the presence of the hydroxycocaines in illicit cocaine, unequivocal characterization must await the acquisition of standards, additional mass spectral analyses and, possibly, ^{1}H and ^{13}C nuclear magnetic resonance studies.

Sample Comparison Analyses

Based upon the cGC-ECD analyses of over 100 illicit cocaine hydrochloride samples, it has been concluded that the methodology described herein is highly suitable for the comparison analyses of illicit, unadulterated cocaine hydrochloride samples. When using the cGC-ECD retention time window of highest reproducibility, that is, between 25 and 45 min on DB-1701, we have found excellent discrimination among the cocaine samples examined. The discrimination power and excellent reproducibility of this methodology is apparent in Figs. 2 and 3. For example, the quantitative levels and ratios for the hydroxycocaines in Samples A, B and C differ substantially. Perhaps this is most apparent when comparing the ratio of hydroxycocaine (peak #13) to the other hydroxycocaines in the three samples. Furthermore, the N-benzoylnorecgonine methyl ester (*3*, peak #19) content of Sample C is substantially higher compared to Samples A and B. Conversely, the N-norcocaine content for Sample C is markedly reduced when compared to Samples A and B. We have also observed that the enumerated and unenumerated peaks eluting after N-norcocaine (peak #21) were of significant discriminatory character. It should be emphasized that the foregoing discussion should not preclude the use of the first 26 min of the cGC-ECD chromatograms, as this retention time window can also contribute when evaluating cocaine comparison chromatographic data. Finally, this methodology was a successful and key element, along with other scientific data, in the recent criminal prosecution of a case involving cocaine comparison analyses [*78*].

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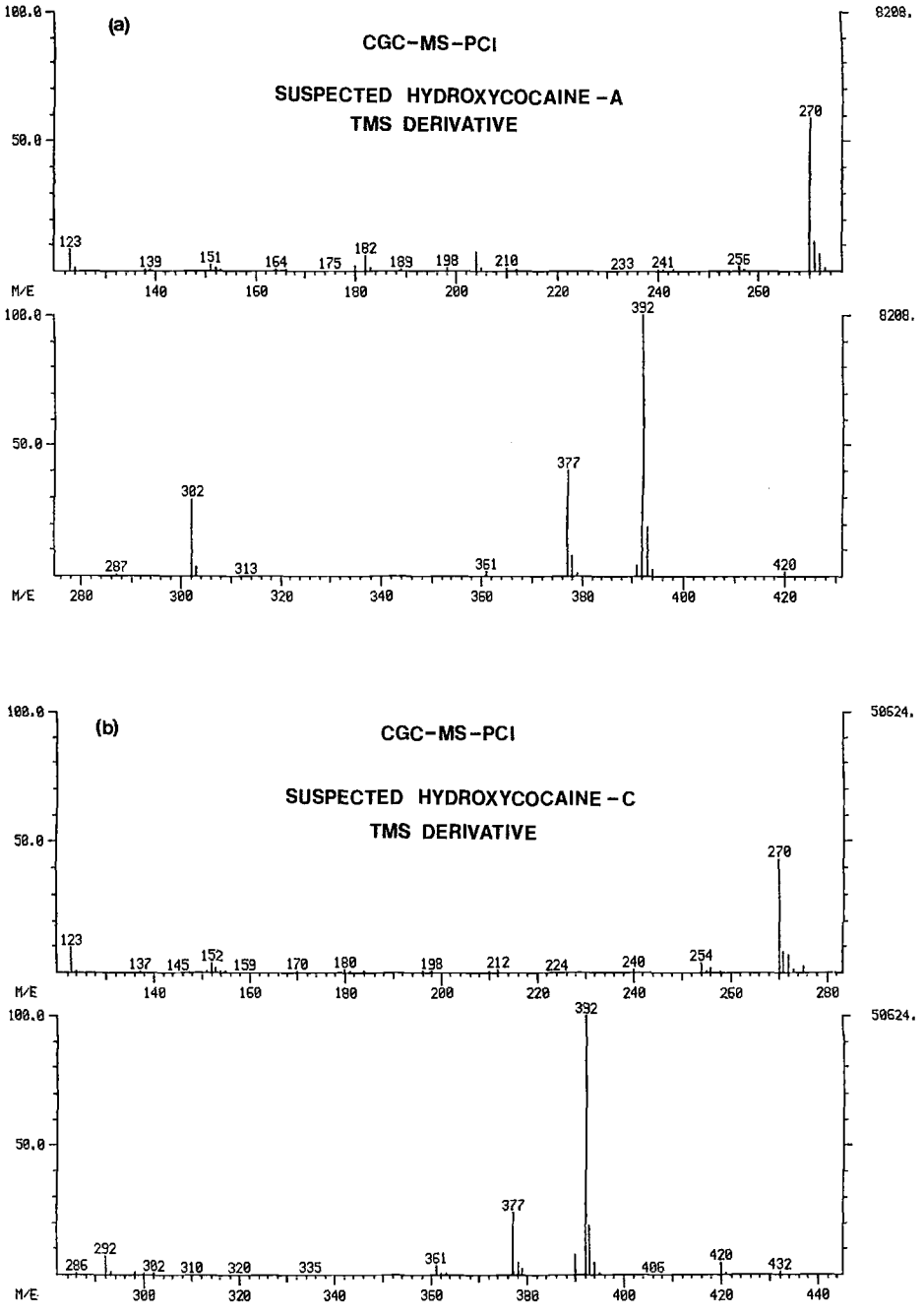

FIG. 5(*a*) and (*b*)—*Positive chemical ionization mass spectra of two suspected hydroxycocaines isolated from illicit cocaine using alumina column chromatography. (See Fig. 4 for reconstructed total ion gas chromatogram.*

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