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TECHNICAL NOTE

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Chlorinated Opium Alkaloid Derivatives Produced by the Use of Aqueous Sodium Hypochlorite During the Clandestine Manufacture of Heroin

ABSTRACT: A clandestine chemist was observed producing heroin from crude morphine utilizing a solution of sodium hypochlorite during the process. Numerous chlorinated opium alkaloid derivatives were created when the morphine acetylation reaction was quenched and neutralized with a solution of sodium hypochlorite and ammonium hydroxide. Four of these compounds, 1-chloroheroin, 1-chloroacetylcodeine, 1-chloro-O^6-monoacetylmorphine, and 2′-chloropapaverine, were characterized via preparative isolation, gas chromatography/mass spectrometry, nuclear magnetic resonance spectroscopy, and independent synthesis. These chlorinated derivatives were formed via electrophilic aromatic substitution with free chlorine during the illicit process. Although no illicit heroin exhibits containing these compounds have been observed in seizures to date, mass spectral data are provided for several of these compounds for their identification should they be seen within future seizures of illicit heroin.

KEYWORDS: forensic science, heroin, mass spectrometry, nuclear magnetic resonance, illicit heroin impurities, chloroheroin

One of the ongoing initiatives of the Drug Enforcement Administration's Special Testing and Research Laboratory is the proactive debriefing of clandestine laboratory operators for current trends and methodologies in illicit drug production. Occasionally, this includes observing clandestine operators producing illicit drugs in controlled settings. During a series of cocaine processing debriefings and observations in South America, one of the authors was introduced to a clandestine heroin chemist who stated that he/she was utilizing a new method for the production of heroin. It should be noted that this cooperating individual was unaware of the author's affiliation with narcotics enforcement. The clandestine chemist avowed that the new process utilized bleach after the acetylation of morphine, during the work-up to give a whiter heroin product. As this was an unknown illicit process, the chemist was allowed to carry out the procedure in a controlled setting. Upon completion of the procedure, the product was retained for analysis by our laboratory.

One of our motives for obtaining the sample of this new illicit process was the expectation of new compounds that could provide a signature unique to the sodium hypochlorite procedure. Sodium hypochlorite is known to produce chlorinated derivatives of cocaine through electrophilic aromatic substitution with free chlorine (1). The same mechanism can be expected for heroin and other opium alkaloid derivatives containing an aromatic ring. A chlorinated derivative of heroin has been previously reported as an analytical artifact from using contaminated chloroform (presumably containing phosgene) (2). That chlorinated heroin derivative was not definitively characterized for the position of the chlorine substituent (i.e., 1-chloro- vs. 2-chloro-). Other chloromorphan derivatives, such as 1- and 2-chloromorphine (3) and 1- and 2-chloro-10-alpha-hydroxynaltrexone (4) have been reported, but were not related to illict drugs.

In our work, in-depth analysis allowed for the detection of several chlorinated opium alkaloid derivatives, including the characterization of four new chlorinated opium alkaloid derivatives, 1-chloroheroin, 1-chloroacetylcodeine, 1-chloro-O^6-monoacetylmorphine, and 2′-chloropapaverine. Structural formulae of the characterized compounds (Fig. 1) were elucidated and confirmed through preparative isolation, gas chromatography/mass spectrometry, and nuclear magnetic resonance spectroscopy. Independent synthesis of 1-chloroheroin and 1-chloroacetylcodeine was also completed. Mass spectral data for five other major chlorinated derivatives which could not be isolated and definitively characterized are also presented.

Experimental Procedures

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). All other chemicals were of reagent-grade quality and were products of Aldrich Chemical (Milwaukee, WI). Alumina (basic) was deactivated slightly by adjusting the water content to 4% (w/w). Morphine base (83% purity) was obtained from an illicit source. The morphine also contained approximately 3% codeine and lesser amounts of papaverine, noscapine, and thebaine. Heroin, papaverine, and acetylcodeine were part of the authentic reference collection of this laboratory.

Clandestine Synthesis

Amounts and yields are omitted because of the sensitive nature of the subject matter. Crude illicit morphine base was heated with

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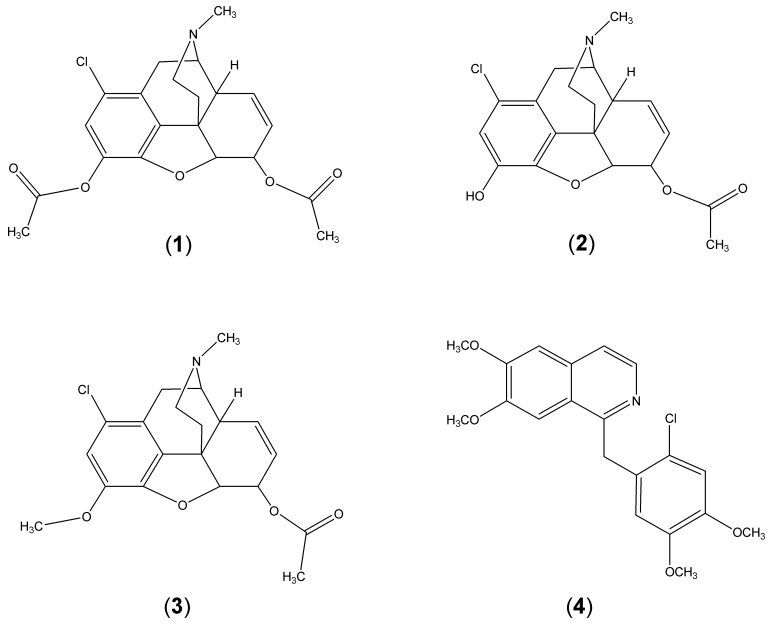

FIG. 1—*Structural formulae for chlorinated opium derivatives.*

acetic anhydride at reflux for approximately 3 h. The reaction was cooled, diluted with water, and treated with aqueous sodium hypochlorite and ammonium hydroxide. The resulting precipitate was collected and dried. The bulk material was immediately destroyed after a representative sample of the material was obtained by the Drug Enforcement Administration.

Gas Chromatography/Mass Spectrometry (GC/MS)

Gas chromatography/mass spectrometry analyses were performed using an Agilent (Palo Alto, CA) Model 5973 quadrupole mass-selective detector (MSD) interfaced with an Agilent Model 6890 gas chromatograph. The GC system was fitted with a 30 m × 0.25 mm ID fused-silica capillary column coated with DB-1 (0.25 μm) (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 MSD was operated in the electron ionization mode with an ionization potential of 70 eV, a scan range of 34–700 mass units, and at 1.34 scans/sec. The auxiliary transfer line to the MSD and the source were maintained at 280°C and 230°C, respectively.

Preparative Isolation via Alumina Column Chromatography

Approximately 7 g of crude illicit product was dissolved in a minimal amount of chloroform and loaded onto a glass chromatographic column (2 × 22 cm) containing 75 g of basic alumina (150 mesh). The column was eluted with 50 mL each of the following series of solvents: (i) $CHCl_3$/hexane (3:1), (ii) $CHCl_3$, (iii) $CHCl_3$/acetone (4:1), (iv) $CHCl_3$/acetone (1:1), (v) acetone, (vi) acetone/MeOH (1:1), and (vii) MeOH. Ten milliliter fractions were collected and examined by GC/MS, both underivatized and following derivatization with MSTFA. Appropriate fractions were combined and evaporated to dryness for further preparative liquid chromatography/mass spectrometry (LC/MS) isolation, as described below.

Preparative Liquid Chromatography/Mass Spectrometry

Preparative isolation was performed using a Waters (Milford, MA) 2525 HPLC pump fitted with a Phenomenex-Synergi, MAX-RP, 150 mm × 21.2 mm, 10 μm, C-18 column. The sample was diluted to a concentration of approximately 200 mg/mL, and the injection volume was 0.5 mL per run. The flow was optimized at 20.0 mL/min, using the following reversed-phase gradient solvents: (A) water containing 0.01% trifluoroacetic acid, and (B) acetonitrile. The linear gradient started at 95% A and 5% B, held 0 min, and changed to 70% A and 30% B in 15 min, held 15 min, and finally returned to 95% A and 5% B in 1 min. The HPLC eluent was split (10,000:1) and 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 110–600 mass units, a scan time of 0.5 s, and an inter-scan delay of 0.1 s. Peaks were collected via a Waters 2767 Sample Manager. Collected target peaks were lyophilized (freeze dried) prior to NMR analysis.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Proton (^1H), carbon (^{13}C), and 2-dimensional NMR spectra were obtained on a Varian (Palo Alto, CA) Inova 600 MHz NMR using a 5 mm Varian Nalorac Z-Spec broadband, variable temperature, pulse field gradient (PFG) probe. All compounds were dissolved in acetonitrile-d_3. Reference chemical shifts were based on acetonitrile: 1.94 ppm proton and 1.39 ppm carbon. 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 s delay, 45 degree pulse, 1.3 s acquisition time, and gated-decoupling (decoupling only during acquisition of the free induction decay signal) to obtain a semi-quantitative spectrum. Applied Chemistry Developments Inc. (Toronto, ON, Canada) software (i.e., SpecManager, HNMR Predictor, CNMR predictor, and Structure Elucidator) was used to compare experimental to predicted spectra.

Synthesis

1-Chloroheroin——Heroin base (500 mg, 1.35 mmol), dissolved in 5 mL of 10% H_2SO_4, was treated dropwise with commercial aqueous NaOCl (containing 5% available chlorine) while stirring until no further precipitation was observed. The reaction was rendered alkaline (pH = 10) with aqueous Na_2CO_3, and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to a crystalline mass. The product was recrystallized from Et_2O to provide an off-white powder (112 mg, 20% yield).

1-Chloroacetylcodeine——Acetylcodeine HCl (368 mg, 0.975 mmol), dissolved in 8 mL of water, was treated dropwise with commercial aqueous NaOCl (containing 5% available chlorine) while stirring until no further precipitation was observed. The reaction was rendered alkaline (pH = 10) with NH_4OH and extracted with $CHCl_3$ (2 × 8 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to a crystalline mass which was purified via alumina chromatography (see experimental above for conditions) to provide an off-white powder (186 mg, 51% yield).

Results and Discussion

Sodium hypochlorite is a relatively mild oxidizer, and its aqueous solutions will produce free chlorine in the presence of an acid. In this respect, any generated chlorenium ion would be an electrophilic reagent available for aromatic substitution (halogenation of an aromatic ring). Electrophilic aromatic substitution is a well-known reaction involving not only the benzene ring, but other aromatic, benzenoid, and nonbenzenoid systems (5). The morphan-ring system has two available sites on the A-ring for chlorination through this mechanism; the C-1 and C-2 positions. The C-4 ether oxygen is the strongest activating group on the A-ring and would be *ortho*, *para* directing. As the *para* site (C-1) is the only available location for chlorination, it would reason to be the most likely candidate for electrophilic aromatic substitution. In contrast, the isoquinoline-ring system of papaverine has numerous sites available for chlorination because of its extensive aromatic conjugation.

Characterization of Chlorinated Opium Alkaloid Derivatives

The use of sodium hypochlorite is not typical in heroin processing and was certainly used in excessive amounts by this clandestine chemist, resulting in nearly complete loss of heroin. GC/MSD analysis of the illicit product indicated numerous chlorinated compounds. Examination of the reconstructed total ion chromatogram (Fig. 2) revealed that only traces of heroin (peak no. 1) remained and the remaining peaks all contained complex spectra with isotope abundance ratios consistent with mono-, di-, and tri-chloro substitutions. Only four of these compounds (peaks nos 2, 3, 4, and 7) were readily isolated and purified via column chromatography and LC/MS procedures. The remaining compounds either degraded or could not be isolated in high purity during the preparative work-up.

Peak no. 4 was the most abundant compound and represented approximately 25% of the total ion current. Its mass spectrum (Fig. 3) produced an apparent molecular ion at *m/z* 403 with an isotope abundance ratio consistent with mono-chloro substitution (*m/z* 403/405 = 3:1). It did not form a TMS derivative, indicating no labile protons within the molecule. The spectrum was markedly similar to heroin, with fragment ion shifts of +34 mass units for five of the most abundant heroin ions (*m/z* 215 → *m/z* 249, *m/z* 268 → *m/z* 302, *m/z* 310 → *m/z* 344, *m/z* 327 → *m/z* 361, and *m/z* 369 → *m/z* 403). Fragment ions at *m/z* 361 and *m/z* 344 are consistent with O^3 acetyl and O^6 acetoxy fragmentations, respectively (6). The presence of fragment ion *m/z* 302 is attributed to loss of both the O^3 and O^6 groups. The fragment ion found at *m/z* 204 remains in the same relative abundance to that of heroin, thus supporting chlorine substitution outside the C and D rings (7); fragment ions present at *m/z* 146 and *m/z* 162 (having the same relative intensity to heroin) also support this observation of nonsubstituted B, C, and D rings (8,9). Finally, the ion present at *m/z* 249 is consistent with a chlorine substitution within the fragment ion *m/z* 215 (found in heroin), in which the A ring is intact (9,10).

To determine the site of chlorination within the A ring, we examined the isolated material via NMR. Previous proton and carbon NMR studies have assigned chemical shifts for various morphine-related compounds (11,12). Clark's work (2) surmised that the chlorine substitution in that heroin impurity was at either the C-1 or C-2 position, and most likely was at C-1. We were able

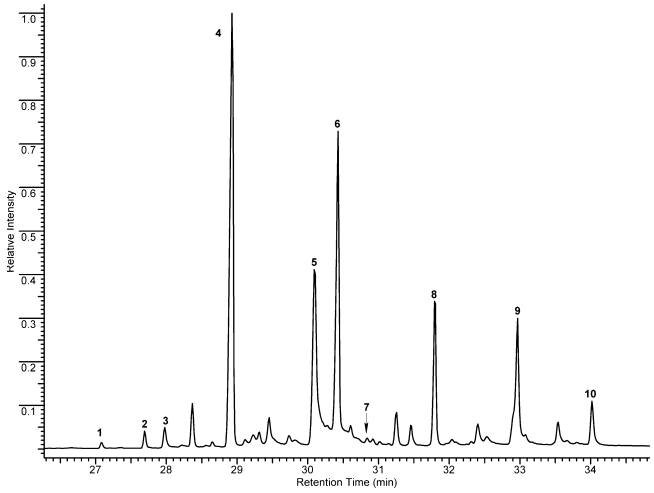

FIG. 2—*Partial reconstructed total ion chromatogram of chlorinated opiates derived from the use of sodium hypochlorite after morphine acetylation. Peak identification: 1 = heroin, 2 = 1-chloroacetylcodeine, 3 = 1-chloro-O⁶-monoacetylmorphine, 4 = 1-chloroheroin, 5 and 6 = uncharacterized chlorinated opium derivatives, 7 = 2′-chloropapaverine, 8–10 = uncharacterized chlorinated opium derivatives.*

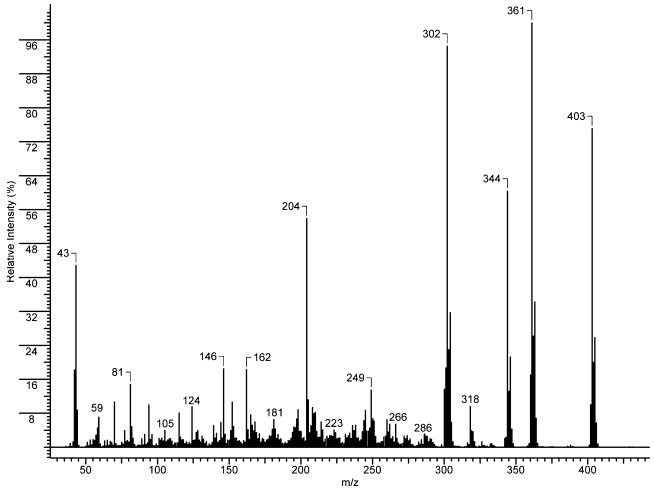

FIG. 3—*Electron ionization mass spectrum of 1-chloroheroin.*

TABLE 1—*Morphan NMR chemical shifts (ppm) for proton (^1H) and carbon (^{13}C) with proton peak appearance.*

	Heroin			1-Chloroheroin			1-Chloro-O^6-Monoacetylmorphine			1-Chloroacetylcodeine		
Position	^1H		^{13}C	^1H		^{13}C	^1H		^{13}C	^1H		^{13}C
1	6.59	bd	119.3	–		124.8	–		121.2	–		125.1
2	6.76	d	121.9	7.00	s	124.5	6.80	s	118.2	6.88	s	115.8
3	–		132.3	–		134.2	–		141.5	–		145
4	–		149.4	–		150.1	–		145.9	–		147.2
5	5.11	dd	88.7	5.24	d	89.4	5.18	m	88.1	5.17	m	88.7
6	5.16	m	68.1	5.16	m	68.1	5.19	m	67.7	5.16	m	68.1
7	5.43	dt	129.5	5.69	bd	131.6	5.73	bd	131.3	5.70	bd	131.6
8	5.62	m	128.5	5.51	bd	127.3	5.52	bd	126.9	5.49	bd	127.4
9	3.37	dd	59.0	4.19	m	60.9	4.19	m	61.0	4.16	m	61.3
10a	2.32	dd	20.7	2.81	dd	22.3	2.78	dd	21.4	2.75	dd	21.8
10b	3.06	d	20.7	3.15	d	22.3	3.11	d	21.4	3.10	d	21.8
11	–		131.8	–		128.7	–		124.5	–		122.7
12	–		131.5	–		133.0	–		131.6	–		131.7
13	–		43.1	–		42.7	–		42.2	–		42.5
14	2.76	bs	40.7	3.29	m	38.8	3.25	m	38.6	3.23	m	38.9
15a	1.89	ddd	35.2	2.02	dd	33.5	2.06	dd	33.2	2.03	m	33.5
15b	2.05	td	35.2	2.32	dt	33.5	2.37	dt	33.2	2.35	dt	33.5
16a	2.37	td	46.5	2.81	dd	48.2	2.87	m	48.2	2.77	dd	48.4
16b	2.60	dd	46.5	3.31	dd	48.2	3.33	dd	48.2	3.29	dd	48.4
$N\text{-}CH_3$	2.44	s	42.8	2.85	s	42.2	2.89	s	41.8	2.85	s	42.1
3-Acetyl	2.27	s	20.7	2.24	s	21.2	–		–	–		–
3-Acetyl	–		168.4	–		169.4	–		–	–		–
6-Acetyl	2.14	s	20.7	2.05	s	21.2	2.11	s	21.0	2.06	s	21.1
6-Acetyl			170.5	–		171.2	–		171.1	–		171.3
3-Methoxy	–		–	–		–	–		–	3.82	s	57.8

Samples dissolved in acetonitrile-d_3. Reference chemical shifts are based on acetonitrile: 1.94 ppm proton and 1.39 ppm carbon.

Proton peak appearance abbreviations are: s, singlet; d, doublet; bd, broad doublet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; td, triplet of doublets; m, multiplet; NMR, nuclear magnetic resonance spectroscopy.

to determine the position of the chlorine atom definitively at C-1 (1-chloroheroin) based on a number of NMR experiments comparing the chloroheroin to heroin (Table 1). As was noted in Clark's work (2), an aromatic singlet appears in the chloroheroin indicating that one of the two aromatic protons is missing (having been replaced by chlorine). In the proton spectrum of heroin, the aromatic protons H-1 and H-2 are doublets due to spin-spin 3-bond coupling. However, the height of the H-1 doublet is less than that of H-2, and the peaks of H-1 are broader than that of the H-2 doublet due to coupling other than to H-2. The peak widths at half height of the heroin aromatic peaks were 2.3 Hz for H-1 and 1.2 Hz for H-2. Performing a DQF-COSY experiment (to correlate all the protons coupled to H-1) shows that H-1 is coupled not only to H-2 but also to H-10α and H-10β. This coupling constant (<1 Hz) causes the broadening of the peaks. For chloroheroin, the aromatic proton has a peak width at half height of 0.8 Hz, indicating no proton–proton coupling. DQF-COSY corroborates the lack of proton–proton coupling by the absence of correlation between this proton and the H-10 protons. In addition, a 2D-NOESY experiment showed no spatial proximity to H-10 protons, but showed (very weakly) proximity to the acetyl protons at C-3. Therefore, the chlorine substitution is at C-1 for heroin and assigned structure **1**. Finally, the mass spectrum of peak no. 4 and the NMR spectra of the isolated material were identical to the synthesized standard of 1-chloroheroin.

Peak no. 3 produced a mass spectrum (Fig. 4) with an apparent molecular ion at *m/z* 361 and an isotope abundance ratio consistent with mono-chloro substitution (*m/z* 361/363 = 3:1). It also formed a TMS derivative giving molecular ions at *m/z* 433/435 (3:1), indicating one labile proton within the chlorinated molecule. The underivatized spectrum was similar to O^6-monoacetylmorphine, with fragment ion shifts of +34 mass units for four of the most abundant

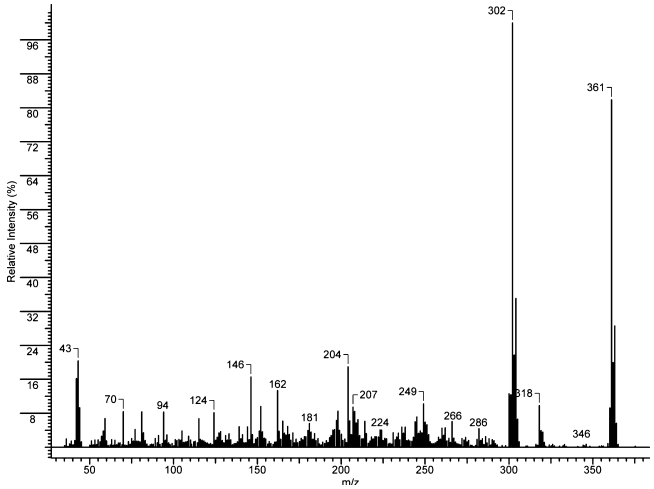

FIG. 4—*Electron ionization mass spectrum of 1-chloro-O^6-monoacetylmorphine.*

ions (*m/z* 215 → *m/z* 249, *m/z* 268 → *m/z* 302, *m/z* 284 → *m/z* 318, and *m/z* 327 → *m/z* 361). Fragment ions at *m/z* 302 and *m/z* 318 are consistent with O^6-acetoxy and acetyl fragmentations, respectively. As in 1-chloroheroin, the fragment ions found at *m/z* 204, *m/z* 162, and *m/z* 146 are present in the same relative abundance, supporting chlorine substitution within the A ring. The ion present at *m/z* 249 is again consistent with a chlorine substitution within the A ring of fragment ion *m/z* 215 (found in O^6-monoacetylmorphine). NMR experiments (Table 1) confirmed the chlorine substitution was at C-1, thus characterizing the compound as 1-chloro-O^6-monoacetylmorphine (**2**).

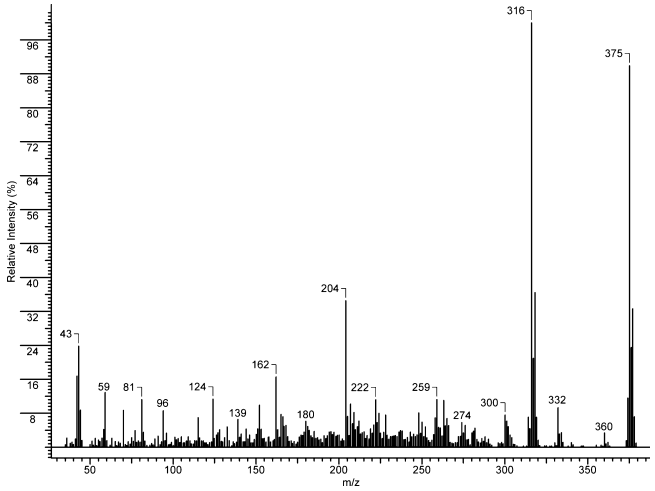

FIG. 5—*Electron ionization mass spectrum of 1-chloroacetylcodeine.*

Peak no. 2 produced a mass spectrum (Fig. 5) with an apparent molecular ion at *m/z* 375 and an isotope abundance ratio consistent with mono-chloro substitution (*m/z* 375/377 = 3:1). It did not form a TMS derivative, indicating no labile protons within the molecule. Its mass spectrum was similar to acetylcodeine, with fragment ion shifts of +34 mass units for four of the most abundant ions (*m/z* 229 → *m/z* 263, *m/z* 282 → *m/z* 316, *m/z* 298 → *m/z* 332, and *m/z* 341 → *m/z* 375). Fragment ions at *m/z* 332 and *m/z* 316 are analogous to O^6 losses found for **2**. The presence of ions at *m/z* 204 and *m/z* 162 again support chlorine substitution within the A ring. Further support for A ring substitution is the shift of ion *m/z* 229 (found in acetylcodeine) to *m/z* 263 (7,9). NMR experiments (Table 1) confirmed the chlorine substitution was at C-1, thus characterizing the compound as 1-chloroacetylcodeine (**3**). In addition, the mass spectrum of peak no. 2 and the NMR spectra of the isolated material were identical to the synthesized standard of 1-chloroacetylcodeine.

Peak no. 7 was a low intensity peak in the reconstructed total ion chromatogram (Fig. 2), but was easily isolated via alumina chromatography because of the weakly basic character and low polarity of the compound (an early eluting compound on alumina). The isolated material produced a mass spectrum (Fig. 6) which

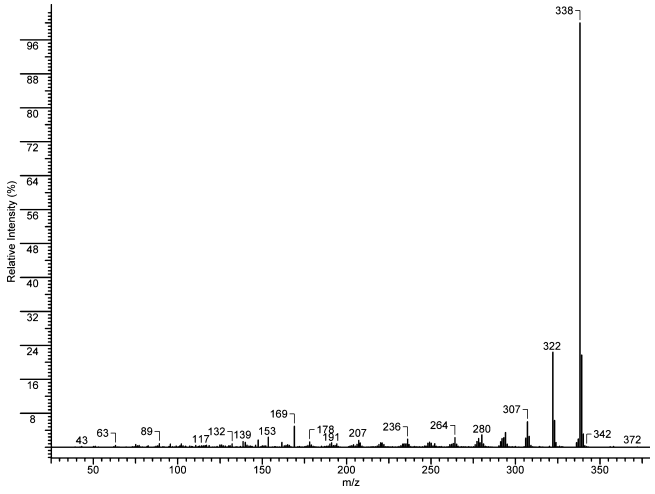

FIG. 6—*Electron ionization mass spectrum of 2′-chloropapaverine.*

TABLE 2—*Isoquinoline NMR chemical shifts (ppm) for proton (^1H) and carbon (^{13}C) with proton peak appearance.*

	Papaverine			2′-Chloropapaverine		
Isoquinoline	^1H		^{13}C	^1H		^{13}C
1	–		157.80	–		155.0
3	8.37	d	141.02	8.30	d	132.7
4	7.42	d	118.70	7.93	d	122.5
4a	–		133.44	–		137.5
5	7.04	s	105.28	7.47	s	107.3
6	–		152.42	–		157.5
7	–		149.78	–		155.4
8	7.32	s	104.22	7.56	s	105.6
8a	–		122.94	–		123.6
6-Methoxy	3.99	s	55.87	4.01	s	57.4
7-Methoxy	3.9	s	56.00	3.94	s	57.2
Benzyl group						
CH2	4.53	s	42.24	4.86	s	35.9
1′	–		132.25			126.3*
2′	6.82	d	120.50			125.4*
3′	6.76	d	111.19	7.00	s	114.0
4′	–		147.52			150.1
5′			149.03			149.1
6′	6.82	dd	111.87	6.85	s	114.9
4′-Methoxy	3.77	s	55.80	3.79	s	56.7
5′-Methoxy	3.82	s	55.85	3.65	s	56.8

*Two carbons can be assigned to either the 1′ or 2′-positions.

Samples dissolved in acetonitrile-d_3. Reference chemical shifts are based on acetonitrile: 1.94 ppm proton and 1.39 ppm carbon.

Proton peak appearance abbreviations are: s, singlet; d, doublet; dd, doublet of doublets; NMR, nuclear magnetic resonance spectroscopy.

was quite similar to papaverine. The mass spectrum of papaverine exhibits an ion at *m/z* 338 as the base peak due to $[M\text{-}H]^+$. The isolated material also produced a *m/z* 338 base peak in combination with a cluster of very low intensity ions from *m/z* 372 to *m/z* 376; this was consistent with a chlorinated $[M\text{-}H]^+$ for papaverine (apparent molecule ion of *m/z* 373). The molecular weight for this compound was confirmed via LC/MS, yielding a $[M+H]^+$ at *m/z* 374, consistent with the molecular weight assignment of 373. NMR experiments (Table 2) confirmed that the isoquinoline portion of the papaverine structure was intact, and the chlorine substitution was at the C-2′ position on the C-ring, thus characterizing the compound as 2′-chloropapaverine (**4**). The two remaining protons present on the C-ring (6.85 and 7.00 ppm) were observed as singlets in the ^1H NMR spectrum, confirming a *para*-relationship to each other, eliminating the *ortho* possibility. One-dimensional NOE interactions of the 7.00 ppm proton to the 4′-methoxy protons at 3.79 ppm, and the 6.85 ppm proton to the 5′-methoxy protons at 3.65 ppm, further confirmed the *para*-relationship of the two protons on the C-ring. A two-dimensional gHMBC correlation of the benzylic protons at 4.86 ppm to the carbon at 114.9 ppm, and a gHSQC correlation of the 6.85 ppm proton to the same carbon at 114.9 ppm, secures the assignment of the 6.85 ppm proton to the 6′-position of the C-ring. Therefore, the described *para*-relationship places the 7.00 ppm proton at the 3′-position, and the chlorine atom at the 2′-position.

The remaining major components (Fig. 2, peak nos 5, 6, and 8–10) could not be isolated and characterized. However, the major ions/abundances from their mass spectra are illustrated in Table 3. Peaks nos 5 and 6 appear to be acetylated opium alkaloid derivatives with isotope abundance ratios consistent with tri-chloro substitutions (*m/z* 485/487 and *m/z* 455/457 = 1:1, respectively). Peak nos 8 and 10 appear to be acetylated opium derivatives with isotope abundance ratios consistent with di-chloro substitutions (*m/z* 435/437 and *m/z* 463/465 = 3:2, respectively). Finally, peak no. 9

TABLE 3—*Fragment ion/mass list for uncharacterized chlorinated opium derivatives.*

Peak No.	Chlorine Substituents	RT (min)	m/z (Relative Intensity)
5	3	30.09	485 (12), 451 (8), 379 (99), 337 (100), 302 (67), 43 (88)
6	3	30.42	455 (9), 413 (93), 371 (67), 336 (37), 254 (27), 43 (100)
8	2	31.79	435 (68), 393 (100), 316 (22), 260 (15), 81 (6), 43 (43)
9	1	32.98	443 (12), 431 (28), 389 (31), 243 (57), 87 (100), 43 (45)
10	2	34.02	463 (26), 421 (67), 319 (34), 284 (36), 260 (61), 43 (100)

appears to an acetylated opium alkaloid derivative with an isotope abundance ratio consistent with a mono-chloro substitution (*m/z* 443/445 = 3:1); the base peak at *m/z* 87 suggests that the A–D ring system has been opened.

Chlorinated opium alkaloid derivatives may be detected in illicit heroin exhibits because of: (i) the use of sodium hypochlorite during illicit processing, (ii) their formation as analytical artifacts, or (iii) their formation due to attempts by drug traffickers to destroy evidence by dumping heroin into bleach during a raid by law enforcement personnel (13). Detection of the aforementioned compounds in an illicit heroin exhibit should be scrutinized carefully. The transformation of heroin to 1-chloroheroin as an artifact in contaminated chloroform has been well documented (2). Although we have yet to come across any seized heroin exhibits containing these compounds since observing the clandestine chemist utilizing this new process, mass spectral data are provided for several of these compounds for their identification should they be encountered within future seizures of illicit heroin.

Conclusions

Clandestine synthesis of heroin which utilizes aqueous sodium hypochlorite during its manufacture will produce numerous chlorinated byproducts. Four new illicit heroin manufacturing by-products, 1-chloroheroin, 1-chloroacetylcodeine, 1-chloro-O^6-monoacetylmorphine, and 2'-chloropapaverine were identified and characterized via a combination of preparative chromatography, GC/MS, LC/MS, NMR techniques, and independent synthesis. Analytical data is presented for these compounds and five additional uncharacterized chlorinated opium derivatives to assist forensic chemists who may encounter these compounds in seized heroin exhibits.

References

1. Casale JF, Moore JM, Cooper DA. Novel chlorinated tropanes derived from the treatment of cocaine with sodium hypochlorite. J Forensic Sci 1995;40(5):816–22.
2. Clark JD. Identification of a heroin/chloroform-impurity reaction product. Microgram 1994;27(11):385–94.
3. Singh BB, Chauhan RS, Madyastha KM, Bhatnagar SP, Kirk KL, Weiss U. 1- and 2-Cholromorphine. Halogenation of morphine meta to the free phenolic hydroxyl group. Heterocycles 1982;19(5):837–47.
4. Meredith W, Nemeth GA, Boucher R, Carney R, Hass M, Sigvardson K, et al. Isolation and synthesis of 2-chloro-10-α-hydroxynaltrexone, a new naltrexone degradant. Tetrahedron Lett 2003;44:7381–4.
5. Morrison RT, Boyd RN. Organic chemistry. Boston, MA: Allyn and Bacon, Inc., 1972; 341–68.
6. Moore JM, Klein M. Identification of O^3-monoacetylmorphine in illicit heroin using gas chromatography-electron-capture detection and mass spectrometry. J Chrom 1978;154:76–83.
7. Audier H, Fetizon M, Ginsburg D, Mandelbaum A, Rull T. Mass spectrometry of the morphine alkaloids. Tetrahedron Lett 1965;1:13–22.
8. Mandelbaum A, Ginsburg D. Studies in mass spectrometry IV. Steric direction of fragmentation in *cis*- and *trans*-B:C ring-fused morphine derivatives. Tetrahedron Lett 1965;29:2479–89.
9. Wheeler DMS, Kinstle TH, Rinehart KL. Mass spectral studies of alkaloids related to morphine. J Am Chem Soc 1967;89(17):4494–501.
10. Waller GR. Biochemical applications of mass spectroscopy. New York, NY: John Wiley & Sons, Inc., 1972; 693–5.
11. Carroll FI, Moreland CG, Brine GA, Kepler JA. Carbon-13 nuclear magnetic resonance spectra of morphine alkaloids. J Org Chem 1976;41(6):996–1001.
12. Allen AC, Moore JM, Cooper DA. $\Delta^{16,\ 17}$-Dehydroheroinium chloride: synthesis and characterization of a novel impurity detected in illicit heroin. J Org Chem 1983;48(22):3951–4.
13. Carpenter A, Laing RR. Cocaine in bleach: destroying the evidence—identification of degradation products. Microgram 1994;27(8):249–52.

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