Illicit Heroin Manufacturing Byproducts: Capillary Gas Chromatographic Determination and Structural Elucidation of Narcotine- and Norlaudanosine-Related Compounds

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Capillary gas chromatographic methodology is described for the detection of trace quantities of narcotine- and norlaudanosine-related manufacturing impurities in illicit heroin. *N*-Acetylnornarcotine (2), *N*-acetylanhydronornarceine (3a,b), 1-acetoxy-*N*-acetylanhydro-1,9-dihydronornarceine (4a,b), and (*E*)-3-[2-(2-(*N*-methylacetamido)ethyl)-4,5-(methylenedioxy)-6-methoxyphenyl]acrylic acid (5) result from the reaction of narcotine (1) with acetic anhydride. The treatment of norlaudanosine (11a) with acetic anhydride yields *N*-acetylnorlaudanosine (9). After isolation from the bulk heroin matrix, these impurities, along with morphine, codeine, and thebaine byproducts, are detected by using both fused silica and glass capillary columns in the split mode with flame ionization detection. The syntheses and spectral characterization of these impurities are described.

The application of high-resolution capillary gas chromatography for the examination of illicit heroin samples is a main focus in current forensic drug research (*1–8*). The unparalleled separation efficiency and sensitivity in this chromatographic technique, and its direct coupling to the mass spectrometer, have led to its increased use in the study of complex matrices of manufacturing impurities in illicit heroin. These investigations have resulted in the development of profiling methods that have been used successfully in our laboratories for heroin comparison analyses and court testimony (*1*).

In earlier studies, we reported on the analyses of heroin manufacturing impurities due to morphine, codeine, and thebaine (*3*, *9*, *10*). We now describe the capillary chromatographic and structural characterization of heroin byproducts related to narcotine and norlaudanosine, both alkaloids present in *Papaver somniferum*. When these alkaloids are subjected to acetylation conditions associated with heroin manufacture, detectable quantities of the byproducts **2**, **3a,b**, **4a,b**, **5**, and **9** are formed. These and other heroin impurities, due to their neutral or acidic character, are easily isolated from the bulk heroin matrix in a one-step extraction and detected by using capillary gas chromatography flame ionization detection. Structural characterization of these impurities was accomplished, after high-performance liquid chromatographic purification, by low- and high-resolution mass spectrometry, nuclear magnetic resonance, ultraviolet, and infrared spectroscopies.

EXPERIMENTAL SECTION

Instrumentation. Two gas chromatographs were used in this study. Instrument 1: Chromatograms were generated in the split mode (60/1) on a Hewlett-Packard 5710A gas chromatograph fitted with a 25 m × 0.25 mm i.d. fused silica capillary column coated with DB-1 (J and W Scientific, Inc., Rancho Cordova, CA) at a film thickness of 0.25 μm. The GC was equipped with a flame ionization detector and interfaced with a Hewlett-Packard 3380A data processor. Injector and detector temperatures were maintained at 300 °C. The oven temperature was programmed as follows: initial temperature, 200 °C; initial hold, none; temperature program rate, 4 °C/min; final temperature, 330 °C; final hold, 4 min. Hydrogen (ultra-high purity) was used as the carrier gas at a flow rate of 50 cm/s. Nitrogen was used as the makeup gas at a flow rate of 30 mL/min. All chromatograms were recorded at an attenuation of 8 and at a chart speed of 1.0 cm/min. Instrument 2: Chromatograms were generated in the split mode (60/1) on a Varian Vista 6000 gas chromatograph fitted with a 25 m × 0.27 mm i.d. glass capillary column coated with SE-54. The GC was equipped with a flame ionization detector. Injector and detector temperatures were maintained at 270 and 300 °C, respectively. The oven was multilevel programmed as follows: (level 1) initial temperature, 150 °C; initial hold, none; temperature program rate, 6 °C/min; final temperature 280 °C; intermediate hold, 1 min; (level 2) temperature program rate, 15 °C/min; final temperature, 300 °C; final hold, 11 min. Hydrogen was used as the carrier gas at a flow rate of 65 cm/s measured at an oven temperature of 200 °C. Argon was used as the makeup gas at a flow rate of 18 mL/min. All chromatograms were recorded at an attenuation of 64 and a chart speed of 1.0 cm/min.

Nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Nicolet (Fremont, CA) 200-MHz spectrometer interfaced with an 1180 data system and 293A pulser. Deuteriochloroform was used as the solvent and tetramethylsilane as the internal standard.

Mass spectra were acquired on a Finnigan 4600 quadrupole mass spectrometer (Sunnyvale, CA) and a Varian MAT 312 double-focusing mass spectrometer (Bremen, F.R. Ger.). Electron impact (EI) mass spectra were collected at an ionizing potential of 70 eV. Chemical ionization (CI) mass spectra were obtained by using methane, isobutane, or ammonia as the reagent gas. Low-resolution and high-resolution mass spectra were acquired by using capillary column and solids probe introduction, respectively.

Infrared (IR) spectra were recorded in KBr on a Beckman 4240 spectrometer (Irvine, CA).

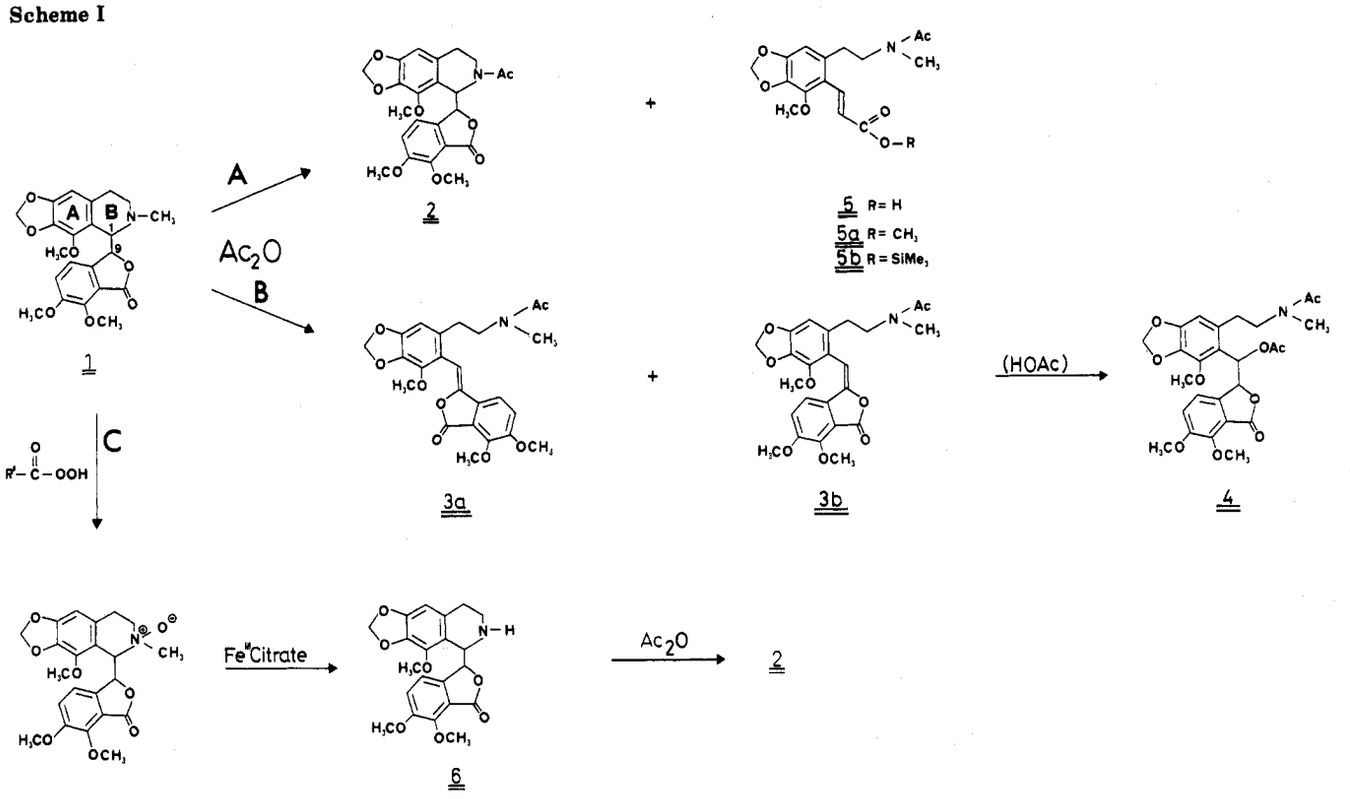
Purification of standard materials was accomplished by high-performance liquid chromatography using either a Waters 6000A or a Varian 5060 liquid chromatograph. Chromatograms were generated on a 15 cm × 4.6 mm i.d. Perkin-Elmer HS-5 C_{18} column using a mobile phase of 13.4% methanol/25.2% acetonitrile/61.4% phosphate buffer (pH 2.2) and UV detection at 254 nm (*11*). Melting points were determined on a Tottoli Fa. Büchi or a Thomas-Hoover apparatus (capillary method) and are uncorrected.

Solvents and Reagents. All solvents were "Distilled in Glass" products of Burdick and Jackson (Muskegon, MI). The derivatization reagent, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA), supplied in 1-mL sealed ampules, was obtained from Pierce Chemical Co. (Rockford, IL).

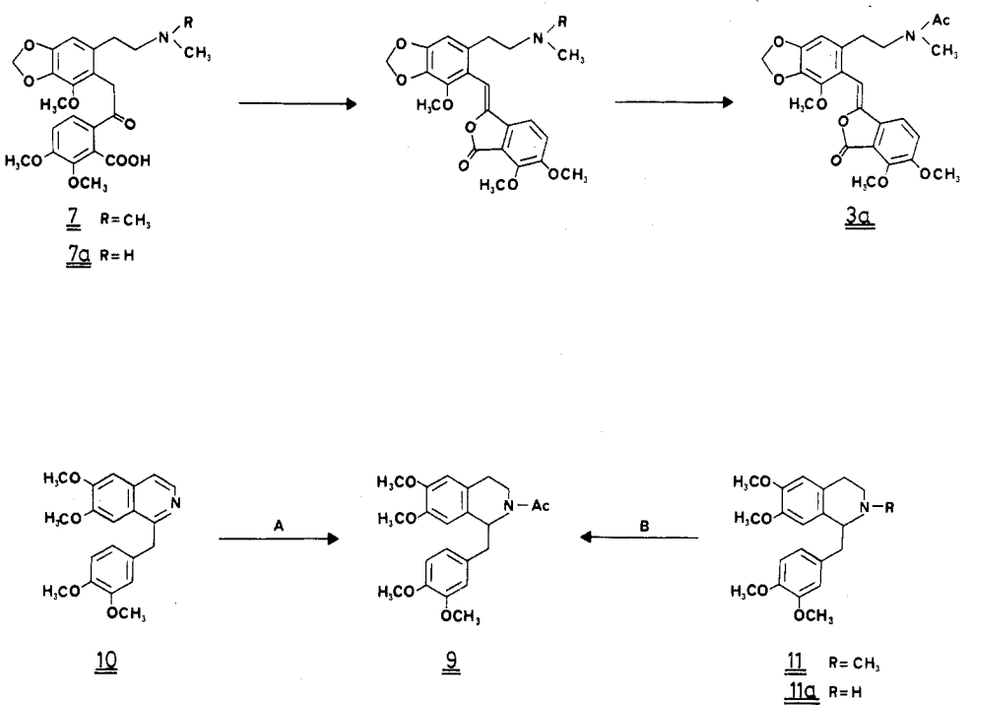
Standards. All standards were prepared as described below. Synthetic pathways and structures are illustrated in Schemes I, II, and III. Purification of standard materials was accomplished by preparative HPLC under conditions described previously.

0003-2700/84/0356-2940$01.50/0

Scheme I



Scheme II



Standard purities were further determined by GC, HPLC, and melting points. Low-resolution EI mass spectra of the standards are given in Figure 3.

Sample Analysis. An amount of sample equivalent to 15 mg of heroin was placed in a 15-mL glass-stoppered centrifuge tube. To the tube was added 5.0 mL of 0.5 N H_2SO_4 to dissolve the sample and then 5.0 mL of toluene. The tube was shaken vigorously for 5–10 s and then centrifuged. About 4 mL of the toluene layer was evaporated to dryness in a conical centrifuge tube. To the residue was added 75 μL of chloroform or toluene (containing 0.30 mg/mL of *n*-dotetracontane internal standard) and 25 μL of MSTFA. This solution was heated at 75 °C for 3 min. About 3 μL was injected into the GC under conditions described previously. The chromatograms of samples of Southeast Asian, Southwest Asian, and Mexican origin are illustrated in Figures 1 and 2.

Syntheses and Spectral Characterization of 2, 3a,b, 4a,b, 5, and 9. Synthetic pathways and low-resolution mass spectra for the title compounds are given in Schemes I and II and Figure 3, respectively.

***N*-Acetylnornarcotine (2).** Narcotine (1) was oxidized with *m*-chloroperbenzoic acid to yield narcotine *N*-oxide (90% yield (*12*)). Narcotine *N*-oxide (2 g) was treated with ferric citrate hydrate (3 g) in 100 mL of water (adjusted to pH 1–2) and heated to 80 °C in a water bath for 2 h (*13*). Cleanup was effected by making the solution basic with sodium carbonate and extracting the secondary amine into chloroform. This was followed by extracting the amine into 1.0 N sulfuric acid, washing with

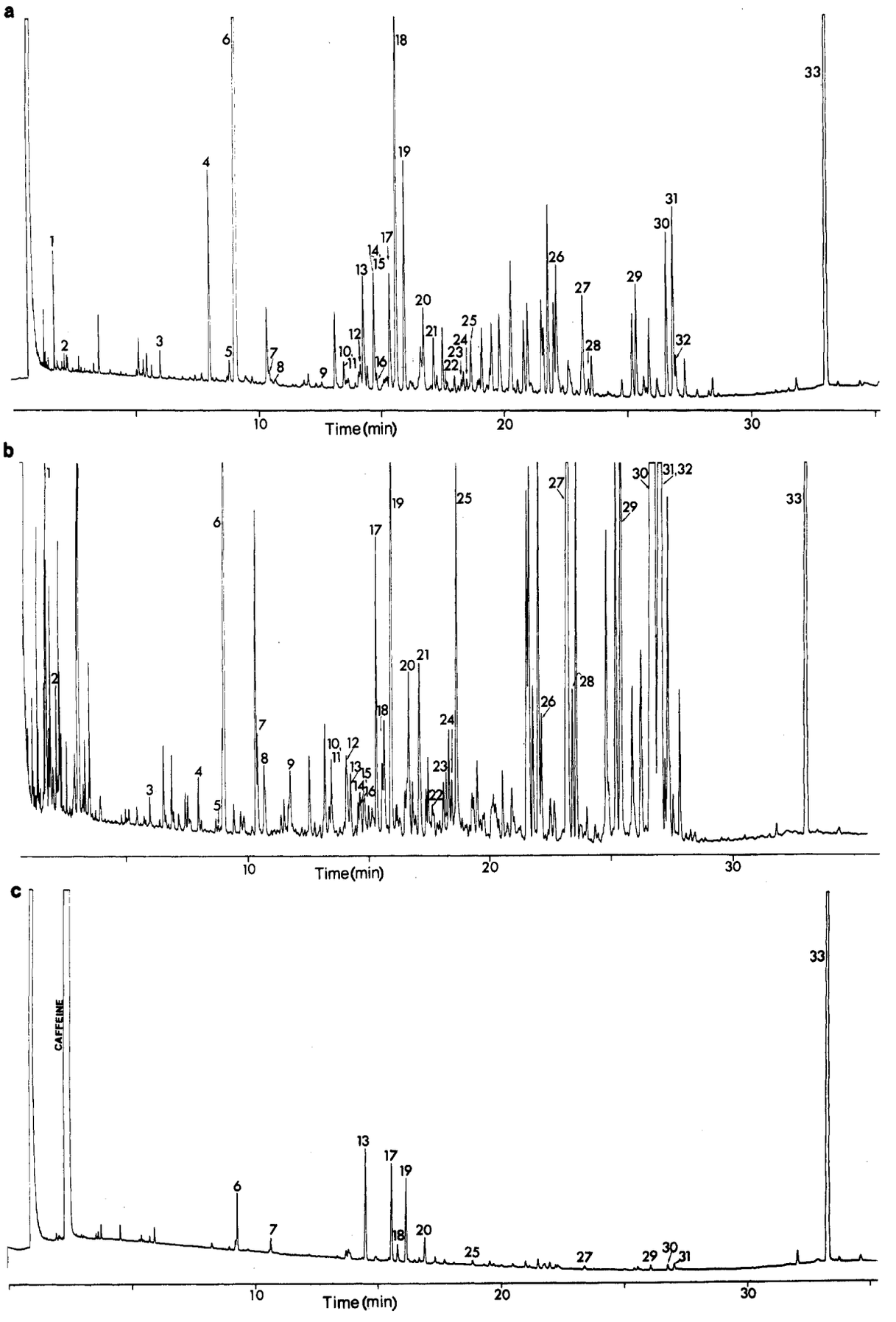
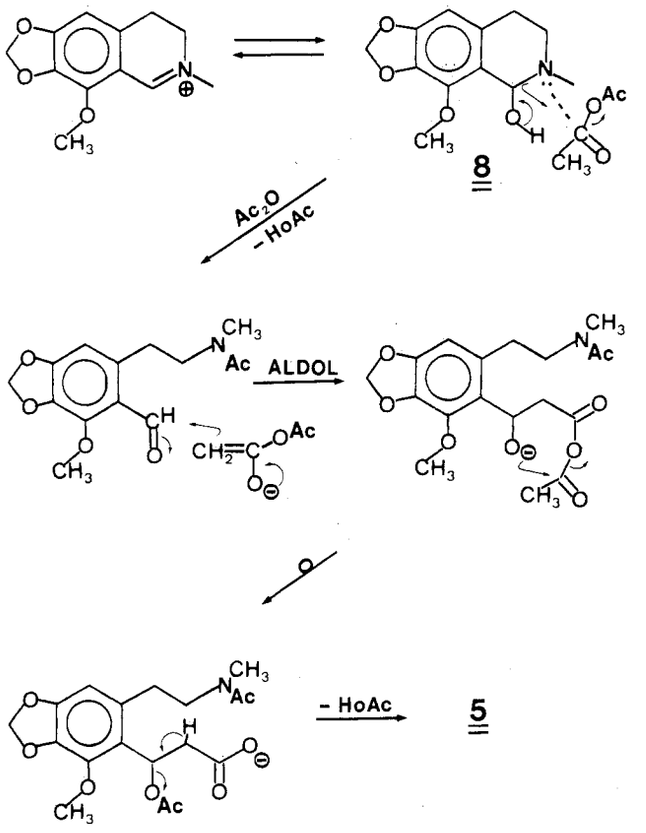


Figure 1. (a) Crudely processed, unadulterated heroin HCl sample from Pakistan. (b) Crudely processed, unadulterated heroin HCl sample from Mexico. (c) Southeast Asian smoking heroin.

Scheme III



chloroform, and then making the aqueous solution basic with sodium carbonate and extracting the amine into chloroform. Evaporation of the solvent gave nornarcotine (**6**) (0.5 g, 26%). Nornarcotine (1 g), prepared as above, was refluxed with acetic anhydride (50 mL) and *p*-(dimethylamino)pyridine (0.5 g) for 1 h. Evaporation of the excess acetic anhydride at reduced pressure gave a gummy residue. Dissolution in methylene chloride followed by extracting with 0.5 N sulfuric acid, 1 M sodium carbonate, and 0.5 N sulfuric acid isolated the amide in the organic phase. Removal of the solvent gave *N*-acetylnornarcotine (**2**) (90%), based on nornarcotine. mp 151.6–153.3 °C. IR (cm^{-1}): 1760, 1635, 1490, 1400, 1265, 1070, and 1020. ^1H NMR (two forms, A + B (ratio 2:1), through hindered rotation due to the amide): δ 7.26–7.17 (2, m, C-2′, C-3′, form A), 7.00 (1, d, J = 8.3 Hz C-3′, form B), 6.38 (1, s, C-5, form B), 6.34 (1, s, C-5, form A), 6.26 (1, d, J = 2.4 Hz C-9, form A), 6.19 (1, d, J = 8.3 Hz, C-2′, form B), 5.98% (2, m, CH_2, form B), 5.92 (1, d, J = 4.9 Hz C-9, form B), 5.81 (2, m, CH_2, form A), 5.77 (1, d, J = 2.4 Hz, C-1, form A), 5.52 (1, d, J = 4.9 Hz, C-1, form B), 4.39–3.17 (2, m, CH_2, forms A and B), 4.14 (3, s, OCH_3, form B), 4.09 (3, s, OCH_3, form B), 3.98 (3, s, OCH_3, form A), 3.90 (3, s, OCH_3 form A), 3.87 (3, s, OCH_3, form B), 3.54 (3, s, OCH_3, form A), 2.77–1.77 (2, m, CH_2, forms A and B), 2.25 (3, s, $NCOCH_3$, form B), 2.20 (3, s, $NCOCH_3$, form A). MS (PCI, solids probe, NH_3): m/z 459 (60, MNH_4^+), 442 (100, MH^+), 248 (12), 206 (7). HRMS (CIMS, isobutane): $C_{23}H_{23}NO_8H^+$ calcd., 442.1502; found, 442.1522.

(*Z*)-*N*-Acetylanhydronornarceine (3a). Narcotine (**1**) was refluxed with acetic anhydride for 24 h. Excess acetic anhydride was removed under vacuum (0.1 mm) at 100 °C. The dark brown residue was dissolved in CH_2Cl_2/Et_2O (40:60) and extracted with 1 N NaOH (note: the basic solution contained compound **5**). The organic layer was extracted with 1 N H_2SO_4 to remove unreacted narcotine and then extracted with aqueous 1 M Na_2CO_3. Removal of the organic solvent gave a dark brown residue which was triturated with ethyl ether to remove meconin. After the ethyl ether layer was decanted, the residue was subjected to preparative HPLC for isolation of **3a**. Mp 118–120 °C (lit.[14] for unspecified isomer mp 120 °C). IR (cm^{-1}): 1770, 1625, 1500, 1470, 1275, 1075, 1040, and 1020. ^1H NMR (two forms, A + B (ratio 1:1), through hindered rotation due to the amide): δ 7.57 (1, d, J = 8.3 Hz, C-3′ form A), 7.45 (1, d, J = 8.3 Hz, C-3′, form B), 7.37 (1, d, J = 8.3 Hz, C-2′, form A), 7.32 (1, d, J = 8.3 Hz, C-2′ form B), 6.50 (1, s, C-5, form A), 6.44 (1, s, C-5, form B), 6.43 (1, s, C-1, form A), 6.25 (1, s, C-1, form B), 5.95 (2, s, C-6, 7-CH_2, form A), 5.94 (2, s, C-6, 7-CH_2, form B), 4.15 (3, s, C-5, form A), 4.14 (3, s, C-5, form B), 4.03 (3, s, C-8, form A), 4.01 (3, s, C-8, form B), 3.96 (3, s, C-4′, form A), 3.95 (3, s, C-4′, form B), 3.44 (2, m, CH_2, forms A and B), 3.53–3.76, 2.86 (3, s, NCH_3, form A), 2.82 (3, s, NCH_3, form B), 2.78 (2, M, CH_2, forms A and B), 1.10 (3, s, $NCOCH_3$, form A), 1.85 (3, s, $NCOCH_3$, form B). HRMS (EI): $C_{24}H_{25}NO_8$ calcd., 455.1580; found, 455.1577.

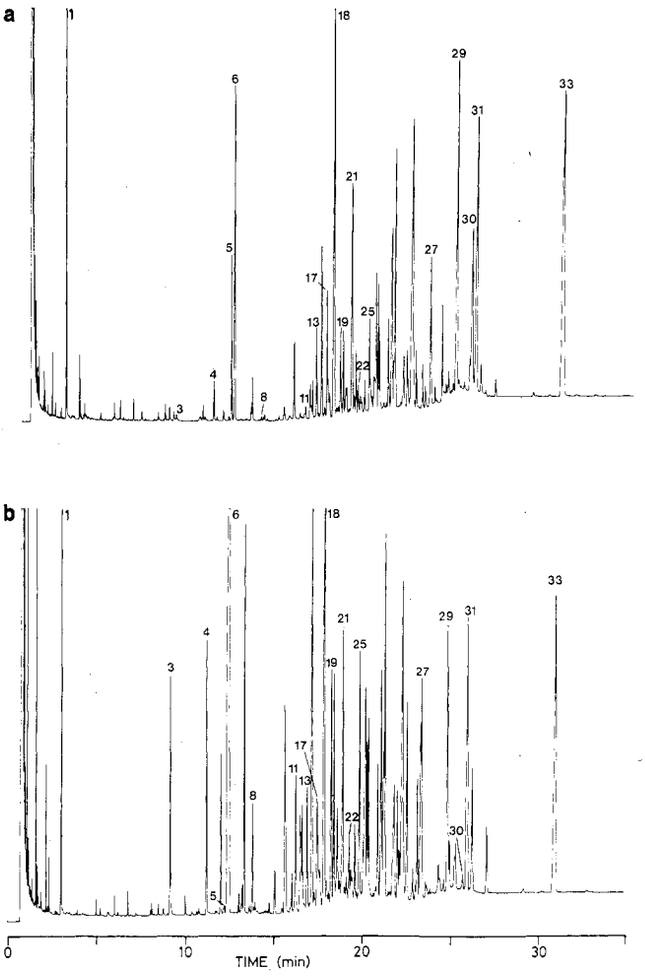


Figure 2. (a) Crudely processed, unadulterated heroin HCl sample from Turkey. (b) Crudely processed, unadulterated heroin base sample from Pakistan.

(*E*)-*N*-Acetylanhydronornarceine (3b). Compound **3b** was prepared and isolated as described for **3a** above. mp 57–61 °C. IR (cm^{-1}): 1775, 1640, 1495, 1475, 1270, 1065, and 1020. ^1H NMR (two forms, A + B (ratio 60:40), through hindered rotation due to amide): 7.06 (1, d, C-3′, J = 8.3 Hz, forms A and B), 6.65 (1, d, J = 8.3 Hz, C-2′, form B), 6.60 (1, s, C-5, form A), 6.49 (1, s, C-5, form B), 6.43 (1, s, C-1, form A), 6.40 (1, s, C-1, form B), 6.00 (2, s, CH_2, form A), 5.99 (2, s, CH_2, form B), 4.12 (3, br, s, OCH_3, forms A and B), 3.89–3.87 (6, br, s, $2XOCH_3$, forms A and B), 3.33 (2, p, CH_2, forms A and B), 2.83 (3, s, NCH_3, form B), 2.82 (3, s, NCH_3, form A), 2.71 (2, m, CH_2, forms A and B), 1.10 (3, s, $NCOCH_3$, form A), 1.88 (3, s, $NCOCH_3$, form B). HRMS (EI): $C_{24}H_{25}NO_8$ calcd, 455.1580; found, 455.1599.

(1*R*,9*S*)-1-Acetoxy-*N*-acetyl-1,9-dihydroanhydronornarceine (4a). Compound **4a** was prepared and isolated as described for **3a** above. mp 81–82 °C. IR (cm^{-1}): 1765, 1640, 1495, 1270, 1230, and 1030. ^1H NMR (Me_2SO at 85 °C, two forms, A + B, were coalesced by using elevated temperatures): δ 7.18 (1, s, J = 8.4 Hz, C-3′), 6.54 (1, s, C-5), 6.08 (1, d, J = 8.8 Hz, C-1 or C-9), 6.04 (1, d, J = 8.4 Hz, C-2′), 6.01 (2, s, CH_2), 5.96 (1, d, J = 8.8 Hz, C-1 or C-9), 3.86 (6, s, $2XCH_3$), 3.74 (3, s, CH_3), 3.00 (3, s, NCH_3), 2.84–2.51 (4, m, CH_2CH_2), 2.04 (3, s, $OCOCH_3$), 1.83 (3, br, s, $NCOCH_3$).

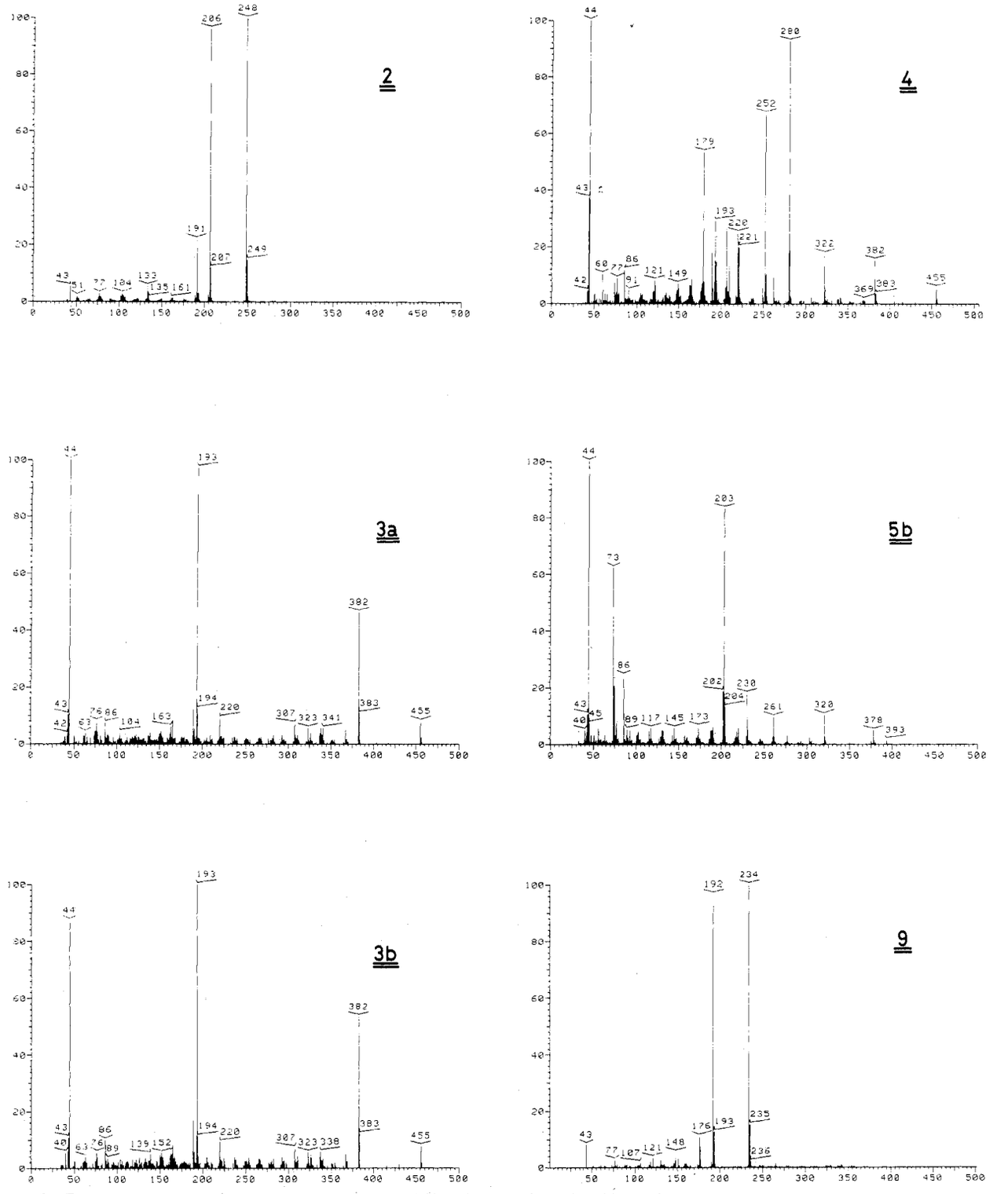


Figure 3. Electron impact mass spectra of narcotine- and *N*-norlaudanosine-related byproducts.

(1*R*,9*R*)-1-Acetoxy-*N*-acetyl-1,9-dihydroanhydronornarceine (4b). Compound **4b** was prepared and isolated as described for **3a** above. mp 81–82 °C. IR (cm^{-1}): 1770, 1635, 1490, 1475, 1270, 1220, 1050, and 1020. ^1H NMR (two forms, A + B (ratio 60:40), through hindered rotation due to amide): δ 7.28 (2, s, C-2′ and C-3′, form B), 2.24 (2, s, C-2′ and C-3′, form A), 6.48 (1, s, C-5, form A), 6.34 (1, s, C-5, form B), 5.96–5.93 (2, s, C-1 and C-9, forms A and B), 5.96–5.93 (2, m, CH_{20}, forms A and B), 4.08 (3, s, OCH_3, form A), 4.08 (3, s, OCH_3, form B), 4.02 (3, s, OCH_3, form B), 4.00 (3, s, OCH_3, form A), 3.93 (3, br, s, OCH_3, forms A and B), 3.76–2.98 (4, m, CH_2CH_2, forms A and B), 2.93 (3, s, NCH_3, form A), 2.91 (3, s, NCH_3, form B), 2.16 (3, br, s, $OCOCH_3$, forms A and B), 2.02 (3, s, $NCOCH_3$, form A), 1.94 (3, s, $NCOCH_3$, form B). MS (**4a+b**; PCI, solids probe, isobutane, NH_3): m/z 516 (45, MH^+), 456 (100, MH^+–AcOH). Reduction of **4** with $LiAlH_4$ and silylation by BSA gave product with the following mass spectrum. MS (PCI, desorption probe, isobutane): m/z 680 (25, MH^+), 608 (100), 590 (20), 518 (20). HRMS (PCI, solids probe, isobutane): $C_{26}H_{29}NO_{10}H^+$ calcd., 516.1870; found, 516.1877.

(*E*)-3-[2-(2-(*N*-Methylacetamido)ethyl)-4,5-methylendioxy-6-methoxyphenyl]acrylic acid (5). Compound **5** was prepared in 25% yield as described for **3a** above. Precipitation of **5** from the NaOH solution was effected by the addition of hydrochloric acid. mp 201–202 °C (lit. 15–17 mp 201, 202 °C). IR (cm^{-1}): 1680, 1595, 1470, 1415, 1265, 1205, 1000, and 580. ^1H NMR (two forms, A + B (ratio 60:40), through hindered rotation due to amide: δ 7.88 (1, d, J = 16.1 Hz, C-9, form A), 7.81 (1, d,

J = 16.1 Hz, C-9, form B), 6.73 (1, d, J = 16.1 Hz, C-1, form A), 6.70 (1, d, J = 16.1 Hz, C-1, form B), 6.51 (1, s, C-5, form A), 6.43 (1, s, C-5, form B), 5.99 (2, s, CH_2O, form B), 5.97 (2, s, CH_2O, form A), 4.05 (3, s, CH_3O, form B), 4.03 (3, s, CH_3O, form A), 3.45 (2, m, CH_2, forms A and B), 2.97 (3, s, NCH_3, form A), 2.95 (3, s, NCH_3, form B), 2.93 (2, m, CH_2, forms A and B), 2.09 (3, s, $NCOCH_3$, form A), 2.00 (3, s, $NCOCH_3$, form B). MS (reaction of **5** with dimethylacetal yielded the methyl derivative **5a**, EI): m/z 355 (8, M^+), 262 (25), 203 (50), 44 (100). MS (CI, GC/MS, NH_3): m/z 353 (15, MNH_4^+), 336 (100 MH^+), 321 (75, MH^+–CH_3), 304 (12). Reaction of **5** with BSA yielded the TMS derivative **5b**. HRMS (EI): $C_{19}H_{27}NO_6Si$ calcd, 393.1608; found, 393.1612.

***N*-Acetylnorlaudanosine (9).** Papaverine (**10**) was reduced with tin in concentrated hydrochloric acid, as outlined by Pyman (*18*), to give a mixture of norlaudanosine and pavine. After decomposition of the tin with H_2S, norlaudanosine was isolated by extraction with ethyl ether. Removal of the solvent yielded a residue that was subjected to acetylation as described for **2**. mp 112–114 °C (lit.[19] mp 115 °C). IR (cm^{-1}): 1630, 1505, 1445, 1205, 1105, 1020, and 850. ^1H NMR and MS data were in accordance with literature values (*19*).

RESULTS AND DISCUSSION

Isolation and Capillary Gas Chromatography of 2, 3a,b, 4a,b, 5, 9, and other Heroin Impurities in Illicit Heroin Samples. The neutral character associated with *N*-acetyl and non-nitrogenous byproducts of morphine, codeine, thebaine, narcotine, and *N*-norlaudanosine allowed for their extraction in high yield from the bulk heroin matrix. These impurities in crudely processed heroin can be as high as 0.5% for morphine, codeine, and thebaine byproducts to over 1% for narcotine-related impurities. The selection of an appropriate extraction solvent for these impurities was an important consideration. Whereas toluene was very effective for the isolation of most impurities, it was less so for acidic compounds such as O^6,*N*-diacetylnormorphine and **5**. When ethyl ether/methylene chloride (60:40) was used, the extraction efficiency for these compounds improved significantly while at the same time exhibiting a modest increase in the extraction yields of many other impurities. The main advantage in using toluene was that less heroin and other amines were coextracted with the neutral and acidic impurities when compared to ethyl ether/methylene chloride (60:40). All samples used in study represented crudely processed heroin. This allowed for the use of the split injection technique. For more highly refined heroin samples the use of the splitless or on-column injection technique is recommended.

Figures 1 and 2 illustrate capillary chromatograms of impurities isolated from heroin samples seized in Turkey, Pakistan, Mexico, and Southeast Asia. Most impurities exhibited good chromatography on both fused silica DB-1 (Figure 1) and glass SE-54 (Figure 2) capillary columns. These chromatograms also demonstrated that capillary chromatography was effective for the resolution of complex matrices of heroin impurities. The proper optimization of chromatographic conditions was especially critical for the resolution of the late-eluting narcotine byproducts. Table I lists retention times and mass spectral data for the major heroin impurities using both DB-1 and SE-54 columns.

Inspection of these geographically typical profiles in Figures 1 and 2 illustrates some interesting comparisons. In these chromatograms the impurities arising from morphine (peaks 12, 15, 16, 17, and 19) were easily detected and rather consistent. This is reasonable when one considers that morphine is the major botanical and "processing" alkaloid. Impurities due to thebaine (peaks 3, 4, 6, 8, 14, 18, 20, 23, 24, 26, and 28) dominated the chromatograms in Figures 1a, 2a, and 2b, whereas narcotine byproducts (peaks 1, 2, 9, 25, 27, 29, 30, 31, and 32) were abundant in the chromatogram illustrated in Figure 1b. These results are not entirely the result of agronomic variation but are also coupled to the opium processing, morphine acetylation, and heroin purification.

Table I. Capillary GC Retention Times and Mass Spectral Data for Neutral and Acidic Heroin Manufacturing Impurities

peak	compound	retention times,[a] min DB-1	retention times,[a] min SE-54	mass (base peak)[b]	ref
1	meconin	1.74	2.63	194 (165)	1
2	hydrocotarnine	2.16		221 (178)	27
3	*c*	6.01	8.78	252 (237)	35
4	O^4–tetramethylsilyl-thebaol	7.99	10.98	326 (296)	35
5	*d*	8.78	11.98	390 (149)	
6	O^4-acetylthebaol	9.09	12.27	296 (254)	35
7	heroin	10.40		369 (327)	
8	*e*	10.70	13.62	324 (240)	35
9	**5**[f]	12.58		393 (44)	15
10	papaverine	13.43		339 (338)	
11	*g*	13.45	16.17	383 (100)	36
12	*h*	14.10		441 (100)	37
13	*i*	14.23	16.78	369 (87)	38–40
14	*j*	14.66		369 (254)	
15	*k*	14.66		457 (87)	38–40
16	*l*	14.74		411 (100)	37
17	*m*	15.29	17.38	427 (87)	38–40
18	*n*	15.56	17.77	395 (265)	10
19	*o*	15.89	18.18	397 (87)	41
20	*p*	16.63		423 (44)	35
21	**9**	17.05	18.83	385 (234)	
22	papaveraldine	17.59	19.18	353 (322)	27
23	desthebaine	18.20		353 (353)	10
24	*q*	18.46		423 (44)	42
25	narcotine	18.58	19.80	413 (220)	
26	*r*	22.04		395 (44)	10
27	**2**	23.11	23.30	441 (248)	
28	*s*	23.33		423 (44)	42
29	**3b**	25.28	24.77	455 (193)	
30	**4a**	26.51	25.58	515 (280)	
31	**3a**	26.79	25.87	455 (193)	
32	**4b**	26.87		515 (280)	
33	dotetracontane[t]	32.98	31.82		

[a] See Experimental Section for GC conditions. [b] EIMS at 70 eV using Finnigan 4010 and 4630, Kratos MS-30, and Varian Mat 312 mass spectrometers. [c] 3,6-Dimethoxy-4,5-epoxyphenanthrene. [d] Diisooctylphthalate (plasticizer). [e] 4,6-Diacetoxy-3-methoxyphenanthrene. [f] Chromatographed as TMS derivative. [g] O^6,*N*-Diacetyl-α-norcodimethine. [h] O^6,*N*-Diacetyl-O^3-trimethylsilyl-α-normorphimethine. [i] O^6,*N*-Diacetylnorcodeine. [j] Unknown ($M^{+\cdot}$ = 369). [k] O^3,O^6-Di(trimethylsilyl)-*N*-acetylnormorphine. [l] O^3,O^6,*N*-Triacetyl-α-normorphimethine. [m] O^3-Tetramethylsilyl-O^6,*N*-diacetylnormorphine. [n] 4-Acetoxy-3,6-dimethoxy-5-[2-(*N*-methylacetamido)]ethylphenanthrene. [o] O^3,O^6,*N*-Triacetylnormorphine. [p] 4,6-Diacetoxy-3-methoxy-5-[2-(*N*-methylacetamido)]ethylphenanthrene. [q] 4,8-Diacetoxy-3-methoxy-5-[2-(*N*-methylacetamido)]ethylphenanthrene. [r] 4-Acetoxy-3,6-dimethoxy-8-[2-(*N*-methylacetamido)]ethylphenanthrene. [s] 4,6-Diacetoxy-3-methoxy-8-[2-(*N*-methylacetamido]ethylphenanthrene. [t] Internal standard.

Derivatization of Selected Heroin Impurities. After isolation from heroin, the impurities were subjected to trimethylsilylation using MSTFA. Most impurities, including **2**, **3a,b**, **4a,b** and **9**, were not amenable to direct derivatization, and thus their chromatography was unaffected. However, for acidic compounds such as **5** and O^6,*N*-diacetylnormorphine, derivatization was an important prerequisite to provide good chromatographic behavior for these impurities. The introduction of trimethylsilyl groups at hydroxyl, phenolic, and carboxyl sites in these impurities proceeded in high yield, allowing, in many cases, for their facile detection.

Reaction of Narcotine, *N*-Norlaudanosine, and Other Opium Alkaloids with Acetic Anhydride. Illicit morphine used in the heroin conversion process usually contains varying amounts of other opium alkaloids, including narcotine, codeine, thebaine, papaverine, and *N*-norlaudanosine. Narco-

tine, the second most abundant alkaloid in *Papaver somniferum* (*20*), has been reported in heroin samples at levels as high as 23% (*21*). Although heroin is by far the major product resulting from the acetylation of illicit morphine, additional acetylated products of morphine, narcotine, and the other alkaloids can be found in amounts as high as 1%. These N- and O-acetylated compounds include **2**–**5**, **9**, O^6,*N*-diacetylnorcodeine, and O^3,O^6,*N*-triacetylnormorphine (Scheme I, paths A and B, Scheme II, and Table I).

The formation of the *N*-acetyl derivatives can occur via several pathways. The N-demethylation, and subsequent acetylation, to yield **2**, O^6,*N*-diacetylnorcodeine, and O^3,O^6,*N*-triacetylnormorphine is believed to proceed through an *N*-oxide precursor. Thus, the formation of **2** can be attributed to the acetylation of narcotine *N*-oxide. The source of such tertiary amine *N*-oxides can be due to either their presence in illicit morphine or their formation as transient intermediates during the acetylation process. The mechanisms supporting these reactions were first reported by the Polonovskis (22–24) and since studied by others (*25*, *26*).

Although compounds **3**, **4**, and **5** are N-acetylated species, their presence in illicit heroin is not due to a Polonovski-type reaction. The formation of **3** from **1** may be envisioned as a loss of the proton at C-9 with the concomitant formation of a double bond at C-1 to C-9 and cleavage of the C-1 to N bond in a concerted reaction. The electron pair resulting from the C-1 to N cleavage is then available to attack acylium ions in solution.

The presence of compound **4** can be rationalized as the addition of acetic acid to the C-1 to C-9 double bond in **3** (Scheme I, path B). It is interesting to note that **4** can undergo decomposition to small amounts of **3a** and **3b** in the injection port of the GC.

The phenylacrylic acid **5** is the main product resulting from the reaction of narcotine with acetic anhydride (Scheme I, path A). Because it is well-known that narcotine is readily cleaved with dilute acid to yield cotarnine (**8**) and opianic acid (*27*), the formation of **5** from **8** with acetic anhydride can be envisioned as the Perkin reaction of the tautomeric aldehyde form (*28*) of cotarnine (Scheme III).

The presence of *N*-acetylnorlaudanosine (**9**) in illicit heroin is believed to be due to the N-acetylation of *N*-norlaudanosine (**11a**), an alkaloid present in opium (*29*) (Scheme II, path B).

Synthesis of Reference Compounds. Our synthesis of **2** from narcotine via the *N*-oxide and *N*-nornarcotine (**6**) is believed to be the most facile approach to date for this compound (Scheme I, path C). Our preparation of **3a,b** and **4a,b**, as mentioned previously, involved acetylation of **2**, with subsequent isolation by preparative HPLC. The formation of **3a** and **3b** is outlined in Scheme I, path B. Only one rearrangement of this type has been previously addressed (*27*). In this reaction the B ring of narcotine was opened using benzoyl chloride in lieu of acetic anhydride. The Polonovskis (*14*) reacted *N*-nornarceine (**7a**) with acetic anhydride and isolated the unsaturated rearrangement products of **3**. In that study the cis and trans isomeric composition for **3** was not reported. The rearrangement products **3a** and **3b** can also be prepared from narceine (**7**) as illustrated in Scheme II. Compound **5** was first prepared about 100 years ago by reacting cotarnine (**8**) with acetic anhydride (*15*). Other routes of **5** used the precursor materials cotarnineperoxide (*16*) or acetylcotarnine (*17*).

Spectral Characterization of 2, 3a,b, 4a,b, 5, and 9. The title compounds were subjected to spectral analyses using infrared, ^{1}H NMR, and low- and high-resolution mass spectrometry (electron impact and chemical ionization). These data are presented in detail in the Experimental Section. Figure 3 illustrates the low-resolution EIMS of these compounds. All spectral data was consistent with the assigned structures.

As is well-known, narcotine does not yield an observable molecular ion under EIMS conditions due to the facile cleavage of the C1–C9 bond (*30*). Likewise, no molecular ion was observed for **2**, **4**, and **9**. However, accurate mass measurements for the molecular ions of these compounds were possible under CIMS conditions using isobutane. Compounds **2** and **9** were characterized, in part, under EIMS conditions by yielding analogous fragmentation patterns. Both **2** and **9** exhibited fragment ions at m/z 248 and m/z 234, respectively, due to the *N*-acetylisoquinolinium ion. This ion loses ketene to yield ions at m/z 206 and m/z 192 for **2** and **9**, respectively (*19*).

E and Z determinations for compounds **3a** and **3b** were made based on the bathochromic shift exhibited in the ultraviolet spectrum of **3a** (max 358 and 298 nm) relative to **3b** (max 350 and 280 nm). Furthermore, the mass spectra of **3a** and **3b**, viewed in the perspective of the Myerson–Weitkamp hypothesis (*31*), reflected a similar conclusion. In accordance with these observations were the melting point data of **3a** (118–120 °C) and **3b** (57–61 °C).

The determination of erythro and threo isomers for compounds **4a** and **4b** was made based on the considerations of Safe et al. (*32*) involving the ^{1}H NMR chemical shifts of the aromatic H-2′ and H-3′ and the substituent C-8-OCH_3 resonances for narcotine-related compounds (*33*). Similarly, considerations by Snatzke et al. (*34*), concerning the optical rotatory dispersion of phthalideisoquinolines, agree with these conclusions.

Registry No. **1**, 128-62-1; **2**, 92543-13-0; **3a**, 92543-23-2; **3b**, 92543-15-2; **4a**, 92543-24-3; **4b**, 92543-16-3; **5**, 92543-14-1; **5a**, 92543-17-4; **5b**, 92543-18-5; **6**, 92621-03-9; **9**, 860-23-1; **10**, 58-74-2; **11a**, 4747-98-2; meconin, 569-31-3; hydrocotarnine, 550-10-7; thebaol, 481-81-2; O^4-acetylthebaol, 47192-97-2; papaverine, 58-74-2; papaveraldine, 522-57-6; desthebaine, 2579-67-1; 3,6-dimethoxy-4,5-epoxyphenanthrene, 4504-42-1; 4,6-diacetoxy-3-methoxyphenanthrene, 16654-23-2; O^6,*N*-diacetyl-α-norcodimethine, 92575-04-7; O^6,*N*-diacetyl-α-normorphimethine, 92575-05-8; O^6,*N*-diacetylnorcodeine, 89493-70-9; *N*-acetylnormorphine, 92543-19-6; O^3,O^6,*N*-triacetyl-α-normorphimethine, 92543-20-9; O^6,*N*-diacetylnormorphine, 92543-21-0; 4-acetoxy-3,6-dimethoxy-5-[2-(*N*-methylacetamido)]ethylphenanthrene, 89469-84-1; O^3,O^6,*N*-triacetylnormorphine, 65846-34-6; 4,6-diacetoxy-3-methoxy-5-[2-(*N*-methylacetamido)]ethylphenanthrene, 16654-24-3; 4,8-diacetoxy-3-methoxy-5-[2-(*N*-methylacetamido]ethylphenanthrene, 7463-47-0; 4-acetoxy-3,6-dimethoxy-8-[2-(*N*-methylacetamido)]ethylphenanthrene, 91295-74-8; 4,6-diacetoxy-3-methoxy-8-[2-(*N*-methylacetamido)]ethylphenanthrene, 92543-22-1; heroin, 561-27-3.

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Automated Cryogenic Preconcentration and Gas Chromatographic Determination of Volatile Organic Compounds in Air

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The methodology used in reduced temperature preconcentration of volatile organic compounds (VOCs) has been tested by using a specially designed system for automated sampling and analysis. The system design incorporates microprocessor-controlled trap temperature cycling and gas chromatographic valve sequencing. Stabilized trap temperature levels are electronically maintained by either controlled release of vaporized liquid N_2 during sampling or by intermittent resistive heating during thermal desorption. A unique trap design permits rapid cooling and heating. During methodology testing, VOC collection and recovery efficiencies were 100 ± 5% and the integrity of sample components was unaffected by the use of a Nafion tube dryer or by cocollection of ozone and nitrogen dioxide. Two nominally identical automated systems gave nearly identical results during simultaneous monitoring of the same laboratory air samples.

The reduced trapping technique for preconcentration of volatile organic compounds (VOCs) from ambient air has proven to be a viable approach to achieve optimum analytical sensitivity and selectivity for VOC monitoring. In most cases the samples are first collected by some convenient means such as on solid adsorbents, or in specially prepared canisters or polymeric bags, and transported to the appropriate analytical instrumentation. Sample is then pulled through a packed, coiled tubular trap immersed in a cryogenic fluid such as liquid nitrogen or liquid oxygen to "cryofocus" the sample prior to thermal desorption (*1-4*). Some of the most recent applications include the determination of concentrations of 44 organics during on-site monitoring in 10 US cities (*5*), the monitoring of selected trace gas concentrations as indicators of the source of pollution (*6*), and the development of new analysis procedures for trace level organics in ambient air (*7*). In some instances, whole air samples are cryocondensed using liquid nitrogen or liquid helium. The required equipment can be made portable so that large sample volumes can be collected remotely and returned to the laboratory for analysis. This approach has been utilized in numerous tropospheric (*8, 9*) and stratospheric (*10, 11*) sampling programs.

Our application is for direct sampling from a manifold located at the sampling site, e.g., sampling from a stationary mobile van or fixed installation, or for sampling from canisters that have been returned to the fixed installation for analysis. A given sample volume is passed through a reduced temperature trap cooled to typically −150 °C. The trap is warm enough to allow the main components of air to pass completely through yet cold enough to collect trace organics efficiently. This procedure has several limitations which must be considered when designing a sampling and analytical system. A limiting factor of major importance is the trapping of water vapor from the ambient air sample. One liter of air at 50% relative humidity and 25 °C will contain approximately 10 mg of water that appears as ice in the collection trap. The possibility of ice plugging the trap and stopping or altering flow is of concern. Even when the trap is not plugged, carrier flow stoppage can still occur at the head of the capillary

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