TECHNICAL NOTE

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Pyrolysis Products of Heroin

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ABSTRACT: Heating of heroin hydrochloride or of heroin at 250°C led to extensive degradation. Major components of the pyrolysate were identified as heroin, 6-acetylmorphine, *N*,6-diacetylnormorphine, and *N*-acetylnorheroin by comparison of mass spectra and ^{13}C- and ^{1}H-nuclear magnetic resonance (NMR) spectra with those of authentic compounds. There was evidence for degradation of the piperidino moiety and the structure 3,4-diacetoxyphenanthrene was proposed for a minor product.

KEYWORDS: toxicology, heroin, pyrolysis

Pyrolysis Products of Heroin

Opium has been smoked for centuries in the Middle and Far East [*1,2*]. Inhalation of pyrolysate smoke is also the common means of administration of heroin in the Far East [*3*]. A U.S. Army survey revealed in 1970 that some use of opium-treated marijuana existed among U.S. troops in Vietnam [*4*]. Recently use of marijuana suffused with heroin has been reported in the United States [*5*] and Canada [*6*]. Inhalation of opium and its pyrolysis products has been connected to bladder cancer [*7*], cancer of the esophagus [*8*], and lung disease [*9*]. Leucoencephalopathy was recently reported after inhalation of heroin pyrolysate and was attributed to the presence of an unidentified toxin [*10*]. Although some researchers have determined the amount of total phenols available for inhalation in "dragon chasing" [*3*] and "ack ack" [*3,11*], the pyrolysis products of heroin have not been previously identified. We therefore conducted an experiment to identify major pyrolysis products of heroin hydrochloride. Since crude heroin is sometimes a mixture of salt and free base [*12*], heroin itself was pyrolyzed and the pyrolysis products compared to those produced from the hydrochloride salt.

Experimental Procedures

Chemicals

Normorphine hydrochloride and 3,6-diacetylmorphine (heroin) hydrochloride were obtained from the National Institute on Drug Abuse. The latter compound was converted to free heroin by mixing the salt (102 mg) with butyl chloride (1 mL) and shaking it with 0.1*N* sodium

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hydroxide (2.5 mL) at 4°C. The butyl chloride extract was then washed with water (2 by 3 mL), dried over magnesium sulfate and evaporated to dryness in vacuo; 63 mg of heroin (pure by high performance liquid chromatography [HPLC]) was recovered. Solvents for chromatography were obtained from Burdick and Jackson (Muskegon, MI). Other chemicals were standard reagent grade.

Analytical Procedures

HPLC was carried out with a Waters (Milford, MA) model 6000 system on columns (25 by 0.46 cm) of Partisil-10/PAC and Partisil-10/ODS-2 (Whatman, Inc., Clifton, NJ). Solvent systems for the former column consisted of various ratios of hexane and ethanol. For the latter column the solvents were mixtures of a buffer solution (0.01*M* ammonium acetate adjusted to pH 4.0 with acetic acid) and acetonitrile. Flow rate was 2.0 mL/min.

Ultraviolet (UV) spectra were obtained in ethanol solution in a Cary model 14 UV-visible spectrophotometer. Direct probe low and high resolution mass spectral analyses were carried out in an AEI MS-902 instrument at 150 to 180°C probe temperature and 70 eV. Hydrogen-1-nuclear magnetic resonance (NMR) spectra were obtained in deuterochloroform in a Bruker 250 MHz spectrometer. Carbon-13-NMR spectra were obtained in dimethyl sulfoxide-d_6 solution in a modified JEOL JNM-PX-100 FT NMR interfaced with a Nicolet 1085 Fourier transform computer system.

Pyrolysis Procedures

The drug (20 to 41 mg) was placed in a quartz boat in a quartz furnace tube through which air was passed at 30 mL/min. The quartz tube was connected to a dry trap and two bubbler traps (containing 100 mL of absolute ethanol each), all kept at −70°C. A tube furnace was preheated to the desired temperature and placed quickly around the quartz tube. At the end of the pyrolysis the furnace was removed and pyrolysis products were rinsed from the apparatus with ethanol, acetonitrile, and butyl chloride.

For isolation of pyrolysis products, 30% of the combined quartz boat fractions from 5 individual pyrolyses (of 41 mg of heroin hydrochloride at 250°C for 10 min) was chromatographed on a Partisil-10/PAC column in 23 aliquots. The solvent system for initial isolation of pyrolysis Products *A*, *B*, *C*, *D*, and *E* consisted of a linear gradient of hexane/ethanol from 10% ethanol to 70% ethanol in 30 min. Column effluent from like fractions was combined and examined by HPLC analysis on a Partisil-10/ODS-2 column. Based on UV absorbance, Fractions *A* and *D* were estimated to be 93 and 95% pure, respectively, by HPLC in a solvent system of 60% ammonium acetate buffer solution/40% acetonitrile. Fraction *C* was purified further (65% ammonium acetate/35% acetonitrile) to yield material >98% pure. Fraction *E* was also rechromatographed (60% ammonium acetate/40% acetonitrile) to yield material >90% pure.

For isolation of pure pyrolysate Product *G*, pyrolysate from the quartz boat was chromatographed on a Partisil/10-PAC column with a linear gradient of hexane/ethanol from 10 to 70% ethanol in 25 min (Fig. 1). Fractions containing the desired product were combined and evaporated. The residue was rechromatographed on Partisil/10-ODS-2 with an elution solvent of 60% ammonium acetate buffer solution and 40% acetonitrile. Ammonium acetate and acetic acid were removed from the desired product by passing the fractions through a C_{18} Sep-Pak (Waters) cartridge. After the cartridge was washed with water, the desired compound was eluted sequentially with methanol and with acetonitrile. The resultant product was greater than 98% pure by HPLC.

Derivatization Reactions (Table 1)

Normorphine was obtained from its hydrochloride salt by partition between ammonium hydroxide solution and methylene chloride. The normorphine from 0.1 g of the hydrochloride

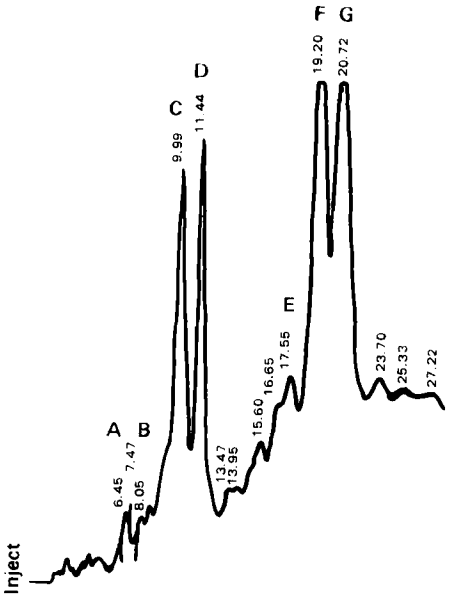

FIG. 1—*HPLC of 250°C pyrolysate of heroin hydrochloride on Partisil 10/PAC eluted with a linear gradient of 10% ethanol to 70% ethanol in hexane over 25 min at 2 mL/min. Detector wavelength was set at 225 nm. For peak identification see Fig. 2.*

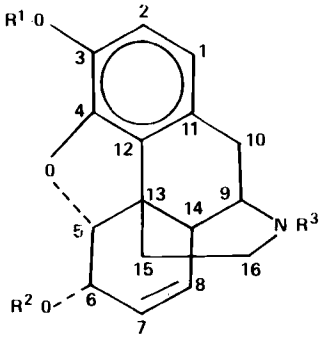

FIG. 2—*Structures of some heroin hydrochloride pyrolysis products:*

C: $R^1 = R^2 = R^3 = CH_3CO$-,
D: $R^1 = H$, $R^2 = R^3 = CH_3CO$-,
F: $R^1 = R^2 = CH_3CO$-, $R^3 = CH_3$ *(heroin), and*
G: $R^1 = H$, $R^2 = CH_3CO$-, $R^3 = CH_3$.

was dissolved in pyridine (300 μL) and acetic anhydride (600 μL) and heated at 40°C for 25 h. Addition of water and extraction with methylene chloride, evaporation of the solvent, and recrystallization of the product from acetone/hexane yielded 60 mg of *N*-acetylnorheroin (mp 165.5 to 166.3°C) which was greater than 95% pure by HPLC. Analysis (Atlantic Microlab, Inc., Atlanta, Ga.) calculated for *N*-acetylnorheroin ($C_{22}H_{23}NO_6$): C, 66.49; H, 5.83; N, 3.52. Found: C, 66.53; H, 5.86; N, 3.52.

Pyrolysate Product *D* was acetylated by heating at 40°C for 5 h with pyridine/benzene (5:95, v/v, 100 μL) and acetic anhydride (10 μL). For purification the reaction mixture was injected

TABLE 1—*List of standards and derivatives prepared.*

Common Name	Systematic Name	Source (Preparation)
Heroin	7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol diacetate (ester)	hydrochloride salt (NIDA[a]) plus base
Normorphine	7,8-didehydro-4,5α-epoxymorphinan-3,6α-diol	hydrochloride salt (NIDA) plus base
N-acetylnorheroin	7,8-didehydro-4,5α-epoxy-17-acetylmorphinan-3,6α-diol diacetate (ester)	normorphine plus Ac_2O[b] or Product D plus Ac_2O
Codeine acetate	7,8-didehydro-4,5α-epoxy-3-methoxymorphinan-6α-ol acetate (ester)	codeine (NIDA) plus Ac_2O or Product G plus diazomethane
Pseudocodeine acetate	6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-8β-ol acetate (ester)	pseudocodeine plus Ac_2O
Isocodeine acetate	7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-ol acetate (ester)	isocodeine plus Ac_2O
Allopseudocodeine acetate	6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-8α-ol acetate (ester)	β-bromocodide plus acetic acid; then Ac_2O

[a]National Institute on Drug Abuse.
[b]Acetic anhydride.

directly onto a Partisil-10/PAC column and eluted by hexane/ethanol with a linear gradient from 2 to 60% ethanol over a 20-min period. Codeine, pseudocodeine, and isocodeine were acetylated by reaction of 40 to 50 mg of each compound in pyridine (390 μL), benzene (710 μL), and acetic anhydride (400 μL) at 40°C with shaking until reaction was complete (3 to 5 h). Workup as described for *N*-acetylnorheroin gave the desired acetates. Pyrolysate Product *G* (1.6 mg) was methylated by use of diazomethane in ether containing 10% methanol. For preparation of allopseudocodeine acetate, β-bromocodide (0.3 g) was suspended in water (5 mL) and acetic acid was added until the compound dissolved. The solution was refluxed for 4 h, the pH was adjusted to 9 with ammonium hydroxide, and the product was extracted into methylene chloride (2 by 6 mL). The methylene chloride extract was then washed with water and evaporated. Acetylation in a mixture of pyridine (500 μL) and acetic anhydride (475 μL) at 40°C for 4 h was followed by purification on a partisil-10/PAC column. The elution solvent was hexane/ethanol varied linearly from 12 to 80% ethanol over a 20-min period. The fraction containing allopseudocodeine acetate was rechromatographed to give a compound shown to be pure by HPLC.

Results

Pyrolysis of heroin hydrochloride at 250°C resulted in the formation of a large number of compounds as is illustrated by the chromatogram shown in Fig. 1. Although possible differences in chromophores and extinction coefficients require caution in interpreting the intensity of peaks in the chromatogram, it would appear that at least three major products are formed (Peaks *C*, *D*, and *G*) in addition to unchanged heroin (*F*).

At 250°C most of the UV absorbing materials (as evidenced by HPLC with ultraviolet detection) remained in the quartz boat, with small quantities found in the furnace tube and essentially none in the bubbler traps. Increasing the temperature of pyrolysis from 250 to 300, 400 and 600°C resulted in increased decomposition to dark-colored residues. There was some increase in volatilization, with relatively more material found in the furnace tube and dry trap. However the higher temperature did not result in significant increases in the smaller peaks in the chromatogram.

By repeated injections of small amounts of pyrolyzed material it was possible to isolate Peaks

A, *C*, *D*, *E*, *F*, and *G* in purities of 90 to 98% (by HPLC analysis). Purity of the compounds was assessed on both a Partisil 10/PAC column and a reverse phase (Partisil 10/ODS) column as described in the Methods section. Ultraviolet, mass, ^{1}H-NMR, and ^{13}C-NMR spectra obtained from the purified products are presented in Tables 2 through 5.

We propose the structure 3,4-diacetoxyphenanthrene for the compound of Peak *A*. The large extinction coefficients of this compound at its maxima of 283 and 232 nm (about 28 000 and 68 000, respectively) suggested an extended conjugation (Table 2). High resolution mass

TABLE 2—*Absorption maxima*[a] *of heroin hydrochloride and its pyrolysis products.*

Compound	λ_{max}, nm
A	283
	~232
C	281
	~233
D	287
	~242
G	287
	~240
Heroin hydrochloride	281
	~233

[a]In ethanol solution.

TABLE 3—*Mass spectral analysis of heroin hydrochloride pyrolysis products and related compounds.*

Compound	Molecular Ion[a]	Molecular Formula	Major Fragments, m/z
A	294.0894	$C_{18}H_{14}O_4$	252(M-CH_2CO), 210[B[b], M-2(CH_2CO)]
C	397.1528	$C_{22}H_{23}NO_6$	355(M-CH_2CO), 313[M-2(CH_2CO)], 295(M-CH_2CO-CH_3COOH), 193(B)[c]
D	355.1425	$C_{20}H_{21}NO_5$	313(M-CH_2CO), 297(M-CH_2CO_2), 269, 193(B)
Acetyl derivative of Compound *D*	397.1523	$C_{22}H_{23}NO_6$	355(M-CH_2CO), 313[M-2(CH_2CO)], 295(M-CH_2CO-CH_3COOH), 193(B)
G	327.1473(B)	$C_{19}H_{21}NO_4$	284(M-CH_3CO), 268(B, M-CH_3CO_2), 215
3-0-Methyl derivative of Compound *G*	341.1623(B)	$C_{20}H_{23}NO_4$	299(M-CH_2CO), 298, 282(M-CH_3COO), 229, 225, 204
Heroin·HCl	369	$C_{21}H_{23}NO_5$	327(B, M-CH_2CO), 309(M-CH_3COOH), 268
N-Acetylnor-heroin	397.1523	$C_{22}H_{23}NO_6$	355(M-CH_2CO), 313[M-2(CH_2CO)], 295(M-CH_2CO-CH_3COOH), 193(B)
6-acetylmor-phine	327(B)	$C_{19}H_{21}NO_4$	284(M-CH_3CO), 268(B, M-CH_3COO), 215
Codeine acetate	341.1623(B)	$C_{20}H_{23}NO_4$	299(M-CH_2CO), 298, 282(M-CH_3COO), 229, 225, 204
Pseudocodeine acetate	341.1623(B)	$C_{20}H_{23}NO_4$	282(M-CH_3COO), 224, 209
Isocodeine acetate	341.1623(B)	$C_{20}H_{23}NO_4$	282(M-CH_3COO), 225, 209 (small), 204

[a]By high resolution mass spectrometry measurements.
[b]B = base peak.
[c]Also contained relatively weak impurity peaks at *m/z* 310 and 297. The latter was assigned to trace amounts of Compound *D*.

TABLE 4—*Hydrogen-1-NMR of heroin and pyrolysis products.*[a]

Assignment	Heroin HCL	Heroin (*F*)	6-Acetyl-morphine	Compound *G*	*N*-acetyl norheroin	Compound *C*	Acetyl Derivative of Compound *D*	Compound *D*	Methyl Derivative of Compound *G*	Codeine Acetate	Pseudo-Codeine Acetate	Isocodeine Acetate
8-$OCOCH_3$	...	...	...	...	...	...	...	...	...	...	2.05	...
6-$OCOCH_3$	2.10	2.13	2.15	2.15	2.12	2.14	2.13	2.16	2.15	2.15	...	2.03
3-$OCOCH_3$	2.27	2.27	...	...	2.26	2.28	2.27	...	...	...	...	...
N-$COCH_3$	...	...	...	...	2.12	2.14	2.13	2.13	...	...	...	...
N-CH_3	2.88	2.43	2.44	2.52	...	...	...	...	2.44	2.46	2.45	2.52
C-1-H, C-2-H [b]	6.66,6.84	6.56,6.74	6.60,6.63	6.62,6.66	6.58,6.78	6.59,6.80	6.58,6.79	6.50,6.67	6.52,6.64	6.52,6.64	6.62,6.68	6.56,6.66

[a] Spectra measured in deuterochloroform at 250 MHz. Values in ppm from tetramethylsilane.
[b] The C-1 and C-2 protons always appeared as an AB quartet ($J \simeq 8$ cps).

TABLE 5—*Carbon-13-NMR chemical shifts*[a] *for heroin and related compounds.*

Carbon	Morphine[b]	Heroin HCl	Heroin	6-Acetyl-morphine	Com-pound *G*	*N*-Acetyl-norheroin	Compound *C*	Acetylated Compound *D*	Compound *D*	Codeine Acetate	Pseudo-Codeine Acetate	Isocodeine Acetate
1	118.6	119.9	119.1	118.5	119.0	119.8	119.5	119.9	119.4	119.0	119.1	119.2
2	116.4	122.7	121.6	115.9	116.5	122.5	122.2	122.5	116.4	113.7	113.9	113.6
3	138.4	131.7	132.6	138.1	138.9	131.7	131.4	131.7	139.1	141.5	142.7	141.7
4	146.3	149.0	148.9	144.7	145.4	149.3	149.0	149.2	145.4	146.2	143.8	145.1
5	91.5	87.4	88.2	86.8	87.2	88.3	88.0	88.3	86.9	87.6	85.8	90.8
6	66.4	67.0	67.7	67.7	68.0	67.6	67.4	67.6	67.6	67.9	126.3	69.6
7	133.4	129.6	129.9	129.5	130.0	129.2	128.9	129.2	129.6	130.7	132.6	135.9
8	128.5	126.7	128.0	127.6	128.2	129.0	128.7	129.0	128.9	127.1	67.2	126.4
9	58.1	59.2	57.9	58.0	58.3	52.5	52.2	52.5	52.5	58.1	55.1	57.9
10	20.2	20.6	20.3	20.7	20.8	22.1	21.9	22.0	21.9	20.6	20.9	20.9
11	125.5	126.9	131.5	124.6	125.1	130.9	130.6	130.9	123.7	128.1	127.3	127.4
12	131.0	127.0	131.1	130.0	130.5	131.5	131.2	131.5	129.3	129.9	129.0	130.3
13	42.8	39.8	42.1	42.0	42.2	42.8	42.5	42.8	42.5	42.0	40.2	40.4
14	40.6	40.4	39.7	39.9	39.9	39.8	39.8	39.9	39.8	41.2	44.6	43.6
15	35.6	37.0	34.5	34.8	34.8	34.8	34.6	34.8	34.9	34.7	34.6	35.2
16	46.0	46.3	46.0	46.1	46.3	46.9	46.6	47.0	46.9	46.1	46.1	46.3
N-CH_3	43.0	40.4	42.6	42.6	42.7	...	...	...	...	42.6	42.8	42.7
N-$COCH_3$	...	...	...	...	...	29.1	28.8	29.0	28.6	...	...	...
N-$COCH_3$	...	...	...	...	...	168.6	168.3	169.0	168.3	...	...	...
3-$COCH_3$	...	20.3	20.3	...	...	20.6	20.3	20.6	...	...	...	...
3-$COCH_3$	...	168.1	168.1	...	...	168.4	168.1	168.6	...	...	...	...
6-$COCH_3$	...	20.3	20.3	19.9	20.1	20.6	20.3	20.6	20.7	20.0	...	19.8
6-$COCH_3$	...	169.6	169.7	169.3	170.0	170.0	169.8	170.2	169.9	169.8	...	169.8
8-$COCH_3$	...	...	...	...	...	...	...	...	...	...	19.5	...
8-$COCH_3$	...	...	...	...	...	...	...	...	...	...	170.6	...
3-OCH_3	...	...	...	...	...	...	...	...	...	56.2	56.0	56.1

[a]Chemical shifts are in ppm relative to tetramethylsilane in dimethyl sulfoxide-$^2H_6$ solution.
[b]Data from Ref *17*.

spectral analysis (Table 3) showed the molecular formula of the compound to be $C_{18}H_{14}O_4$. Major fragmentations occurred by the loss of 42 and 84 AMU. This is consistent with the loss of one and two molecules of ketene and is indicative of the presence of two aromatic acetate residues. From the molecular formula it is apparent that in addition to the two carbonyls of the acetates there must be an additional ten sites of unsaturation. This is readily accommodated by a phenanthrene structure. We assume that the allylic 6-acetate of heroin would undergo ready elimination and that *O*-alkyl cleavage at C-5 would take precedence over *O*-aryl cleavage at C-3 during pyrolysis. Thus the most reasonable position for the two oxygen atoms would be on the 3- and 4- positions of the phenanthrene ring. This compound was first reported in 1886 when it was obtained by heating the methiodide salt of morphine diacetate with silver acetate and acetic anhydride [*13*]. Reaction with ammonia yielded phenanthrene-3,4-diol [*13*], which was later synthesized from 4-hydroxyphenanthrene-3-aldehyde [*14*].

The compound isolated from Peak *C* was identified as *N*-acetylnorheroin. It exhibited an UV spectrum almost identical with that of heroin hydrochloride. From its high resolution mass spectrum a molecular formula of $C_{22}H_{23}NO_6$ was obtained, which indicates the net addition of one carbon and one oxygen to heroin. The ^{1}H-NMR spectrum (Table 4) of the compound showed the absence of the *N*-methyl group observed at 2.4 ppm in heroin and a downfield shift of the C-9 hydrogen. A 6-proton singlet at 2.13 ppm and a 3-proton singlet at 2.28 ppm suggested the presence of three acetyl methyl groups. The positions and splitting patterns of the aromatic and vinyl protons suggested that no alteration had occurred in these portions of the molecule.

A ^{13}C-NMR spectrum (Table 5) of the compound also showed the presence of three carbonyl carbon atoms and the absence of an *N*-methyl carbon. The aromatic carbons and vinyl carbon atoms of *C* were essentially unchanged from those of heroin. Taken together the data indicated that the methyl group of heroin had been replaced by an acetyl group to give *N*-acetylnorheroin. This compound was synthesized from normorphine by acetylation and fully characterized. The synthetic material and the pyrolysis product exhibited essentially identical ^{1}H and ^{13}C-NMR spectra and very similar mass spectra.

The compound from Peak *D* was found to be *N*,6-diacetylnormorphine. Its UV chromophore was similar to that of heroin but the λ_{max} had undergone a bathochromic shift (from 281 to 287 nm and 233 to 242 nm). The molecular formula (high resolution mass spectrometry) was $C_{20}H_{21}NO_5$. The ^{1}H-NMR spectrum showed the absence of *N*-methyl protons and the presence of two 3-proton singlets attributed to methyl groups of acetyl moieties. However, the resonance of 2.27 ppm assigned the 3-acetate of heroin was absent. The 6-acetate resonance at 2.16 ppm was still present but was accompanied by a second resonance peak at about 2.13 ppm. The splitting pattern of the aromatic protons remained the same as in heroin but their positions were slightly shifted (see Table 4).

In the ^{13}C-NMR spectrum a shift in resonance of the 3-, 4- and 11-carbons to positions close to those in 6-acetylmorphine confirmed loss of the acetyl group at C-3. Little change was observed in the positions of the vinyl Carbons 7 and 8. The absence of an *N*-methyl group was confirmed as was the presence of a new acetyl carbonyl at the same position as in *N*-acetylnorheroin. Taken together the data indicate that the compound in Peak *D* is *N*,6-diacetylnormorphine. This was confirmed by acetylation of the compound to yield *N*-acetylnorheroin, the identity of which was confirmed by comparison of ^{13}C-NMR, ^{1}H-NMR, and mass spectra with the synthetic compound described above.

High resolution mass spectrometry defined the molecular formula of Compound *G* as $C_{19}H_{21}NO_4$, equivalent to that of 6-acetylmorphine. This assignment of structure was confirmed by comparison of mass spectra, ^{13}C-NMR spectra and ^{1}H-NMR spectra with those of the authentic compound.

Peaks *E* and *B* appeared to arise from other N-C cleavage reactions. Peak *E* had a molecular formula of $C_{22}H_{25}NO_5$ (by high resolution mass spectrometry)—equivalent to formal addition

of CH_2 to heroin. The ^{1}H-NMR was relatively weak but indicated the presence of N-CH_3 and olefinic C-H. The mass spectrum is consistent with formation of an *N,N*-dimethyl function with cleavage of the N-C16 or N-C9 bond and formation of a double bond at the 9(10)-, 9(14)-, or 15(16)-positions. The UV spectrum resembled that of heroin, thereby ruling out a 9(10)-double bond. There were insufficient data to define the structure more completely. Cleavage of the piperidine ring was also indicated by a molecular ion at m/z 411 in the mass spectrum from Peak *B*, consistent with the formation of -N(CH_3)$COCH_3$.

Examination of the ^{1}H-NMR spectrum of Compound *G* before the final purification process showed significant differences between its spectrum and that of 6-acetylmorphine. Further work showed that the ^{1}H-NMR spectrum of this compound is quite sensitive to the presence of traces of water, ammonium acetate, and acetic acid from the HPLC solvent system. To obtain a consistent spectrum it was necessary to remove these substances by isolation of the material on a C-18 silica gel cartridge. After this purification step the ^{1}H-NMR spectrum was identical to that of pure 6-acetylmorphine. However, because of the initial uncertainties we entertained the hypothesis that reactions involving the allylic acetate system might have occurred under the pyrolysis conditions. Compound *G* was therefore methylated (diazomethane) and compared with authentic samples of codeine acetate, pseudocodeine acetate, isocodeine acetate, and allopseudocodeine acetate. Comparison of the various spectra showed that the methylated product from Compound *G* was codeine acetate and not one of the isomeric acetate derivatives. (Again removal of ammonium acetate impurities from the codeine acetate was necessary to achieve reproducible ^{1}H-NMR spectra. Carbon-13-NMR spectra were much less sensitive to the degree of purity.)

When heroin was pyrolyzed as the free base at 250°C, products formed that were similar to those observed from pyrolysis of the hydrochloride. More of the material was found in the furnace tube, where all three of the major products formed in the pyrolysis of heroin hydrochloride were found (Compounds *C*, *D*, and *G*) along with some unchanged heroin. The quartz furnace boat contained only *N*-acetylnormorphine. One strongly UV-absorbing compound intermediate in polarity between heroin and 6-acetylmorphine on reverse phase HPLC was observed in the pyrolysis of the free base of heroin. Attempted isolation by preparative HPLC showed that only a very small weight of the material was present and it could not be identified.

Discussion

The formation of *N*-acetylnormorphine derivatives during pyrolysis of heroin hydrochloride is chemically reasonable. One may visualize a nucleophilic attack by chlorine on the methyl group of heroin hydrochloride to displace the amine which then interacts with a phenolic acetyl group to yield an acetamide derivative. In the case of the free base of heroin, quaternary *N*-acetyl intermediates might be invoked. Methyl chloride formed in the demethylation could quaternize another molecule of heroin and elimination reactions of the Hofmann type would result in cleavage of the piperidine ring as indicated by the data from Peaks *B* and *E*. Further elimination could lead to a phenanthrene skeleton (Peak *A*).

Although the presence of small amounts of heroin isomers cannot be ruled out, since there were several unidentified smaller peaks in the chromatogram of pyrolysis product, it appears that isomerization of the allylic acetate moiety does not play a major role in heroin pyrolysis.

N-acetylnorheroin has been previously reported as a very minor constituent of illicit heroin, detected by gas chromatography in amounts of $<0.4\%$ of the material [*15*]. Our observation that this compound is a major pyrolysis product of heroin suggests that it might also be formed in trace amounts on injection of heroin hydrochloride into a heated chromatograph. The mass spectra of our synthetic and isolated compound are in agreement with that reported by Klein [*15*].

Conclusion

In conclusion we have demonstrated that heating of heroin hydrochloride or heroin at relatively modest temperatures which might be involved in inhalation of heroin by smoking (for example, dragon chasing) leads to extensive degradation of the compound. One breakdown product (6-acetylmorphine) is a narcotic and would thus have an effect similar to that of heroin itself, which is rapidly deacetylated in the body [*16*]. We could find no data on the narcotic activity of the *N*-acetylnormorphine derivatives. Since they do not possess a basic nitrogen atom, which appears to be intimately involved in the receptor affinity for morphine, it seems unlikely that they would have significant narcotic activity unless they undergo rapid metabolic hydrolysis. Whether they have other biological activities is an interesting but open question at this point. A number of other compounds were produced in minor amounts during heating of heroin. The pharmacological and toxicological implications of these compounds remain to be determined.

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