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Isolation, Identification, and Origin of Three Previously Unknown Congeners in Illicit Cocaine

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ABSTRACT: Three previously unknown, overlooked, or perhaps wrongly identified impurities in illicit cocaine seized in the Netherlands Antilles are traced by various combinations of chromatographic and extraction methods. Once isolated using high-performance liquid chromatography, the compounds are identified as norcocaine, *N*-benzoylnorecgnonine methyl ester, and *N*-formyl norcocaine. Their presence in the illicit cocaine samples is explained as a result of the permanganate bleaching procedure that is nowadays routinely performed as part of the illegal production protocol.

KEYWORDS: toxicology, cocaine, impurities, chromatographic analysis, congeners, gas chromatography, mass spectrometry, nuclear magnetic resonance

Illegal cocaine samples usually contain varying amounts of several impurities. These impurities may arise from constituents of the coca leaf, from the manufacturing process, or from adulteration. Besides cocaine, at least 21 different alkaloids have been identified as natural congeners in extracts of coca leaf [*1–6*]. The presence and concentrations of these alkaloids may vary greatly, depending on the species as well as on the growing area. Other alkaloids with an ecgonine-related structure have also been found in extracts of coca leaf, but their real identity is still unknown [*7*].

In illicitly produced cocaine, only the following cocaine congeners have reportedly been detected: *cis*- and *trans*-cinnamoylcocaine, tropacocaine, methylecgonine, benzoylecgonine, anhydromethylecgonine, ecgonine, pseudococaine, ethylcocaine, and the truxillines [*4,6,8,9*]; very recently, norcocaine has also been identified [*10*].

The presence of ecgonine and benzoylecgonine in illicit cocaine is probably due to hydrolysis of the cocaine itself [*2–4,11*], while isomerization to pseudococaine can take place when, during extraction, the cocaine is treated with alkali. Ethylcocaine (benzoylecgonine ethyl ester) may arise when ethanol is used during processing [*4,11,12*], and the presence of anhydromethylecgonine (anhydroecgonine methyl ester) must be seen as an artifact produced by decomposition of cocaine in the heated injection port during gas chromatography analysis [*13*].

In this article, the authors describe the isolation and identification of three congeners, which had been frequently observed in low but varying concentrations in illicit cocaine

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samples, seized in recent years in the Netherlands Antilles. Also, their possible origin is discussed.

Local Situation

The traffic and use of illegal cocaine has grown enormously in the Netherlands Antilles during the past few years. The use of cocaine base has become especially popular, since it is produced by a relatively simple alkaline extraction of coca leaves. Since reliable information about the illicit production of cocaine is often lacking, some general outlines are given here [*9,14*]:

The sun-dried leaves of the genus *Erythroxylum coca* are mixed with an alkaline substance, such as calcium carbonate, and extracted with kerosene (or an equivalent hydrocarbon). Subsequently, the organic layer is filtered and mixed with dilute sulfuric acid. After separation of the immiscible solvents, the acid layer is made basic with ammonia, soda, or another alkaline substance, precipitating the alkaloids. The precipitate is isolated and dried. Depending on the results, the illegal manufacturer sometimes applies oxidation to the crude precipitated cocaine, essentially using the following procedure: The precipitate is redissolved in sulfuric acid and a solution of potassium permanganate is added. When the oxidation is finished, the solution is made basic in the manner mentioned above, precipitating the alkaline substances. The cocaine content of this crude product normally ranges from 70 to 90%.

Substances suspected of containing cocaine and seized in the Netherlands Antilles by the police or by the customs authorities were submitted to our laboratory for analysis, which normally included color reactions, infrared spectrometry, gas chromatography and thin-layer chromatography. In almost all cases the presence of cocaine could be unequivocally established. Cutting or diluting substances were only infrequently encountered. In the more than 5000 illicit cocaine samples analyzed during the past several years, the presence of cocaine salt was established in the minority of these samples, while the majority contained cocaine base.

Along with cocaine, the congeners *cis*- and *trans*-cinnamoylcocaine, tropacocaine, benzoylecgonine, anhydromethylecgonine, and the truxillines were frequently identified in illicit cocaine samples.

Besides these known substances, three additional peaks could be often observed during gas chromatography analysis, and attempts were made to isolate and identify these additional peaks.

Materials and Methods

Reference Substances

Cocaine · hydrochloric acid (HCl) was purchased from Brocacef, Maarsen, The Netherlands. Tropacocaine · HCl was obtained from Aldrich Chemie, Brussels, Belgium, while *trans*-cinnamoylcocaine and benzoylecgonine were donated by the U.S. Drug Enforcement Administration, Special Testing and Research Laboratory, McLean, Virginia. Anhydromethylecgonine was prepared according to the method of Lukazewsky and Jeffery [*13*] and its identity was confirmed by gas chromatography/mass spectrometry (GC/MS) (Forensic Science Laboratory, Rijswijk, The Netherlands).

Solvents

The solvents used were of Baker "analyzed-reagent" quality (methanol, ethanol, chloroform, toluene, cyclohexane) (J. T. Baker Chemical Co., Phillipsburg, New Jersey),

with the exception of diethylamine (Sigma, St. Louis, Missouri). Methylene chloride and methanol, used for high-performance liquid chromatography (HPLC) analysis were "Baker-analyzed" HPLC reagents.

Thin-Layer Chromatography

Thin-layer chromatography (TLC) was performed using 20 by 20-cm silica gel 60 F-254 precoated TLC plates (Merck, Darmstadt, Germany). Development of the plates took place in saturated chambers. Saturation was achieved by double paper lining in 1 h of saturation time. The environmental temperature during the experiments was between 21 and 25°C, and the relative humidity was 75 to 95%. For the spotting of the samples, 5-μL capillaries were used (Drummond Scientific Co., Broomall, Pennsylvania). The development distance was normally 15 cm. Two different types of development solutions were used: Solution A was a mixture of chloroform/methanol (90:10 v/v), and Solution B was a mixture of cyclohexane/toluene/diethylamine (75:15:10 v/v). The spots were detected using ultraviolet (UV) light of 254 nm, followed by spraying with Dragendorff reagent. The latter was prepared by mixing, immediately before use, equal volumes of Dragendorff Solutions A and B, which were purchased from Brinkman Instruments Inc., Westbury, New York. Dragendorff Solution A consisted of 0.94% bismuth subnitrate in 30.6% acetic acid and Dragendorff Solution B was an 11.21% solution of potassium iodide in water.

Gas Chromatography

Gas chromatography (GC) analyses were performed using a Philips PU 4500 chromatograph (Philips/Pye Unicam, Cambridge, England) fitted with dual-flame ionization detectors. The results were processed with a Beckman 427 integrator (Beckman Instruments Inc., San Ramon, California). A 5-ft (1.5-m) glass column 2.0 mm in inside diameter (ID) was used, packed with 3% OV-1 on Chromosorb WHP (100/120 mesh) (Chrompack, Middelburg, The Netherlands). The nitrogen carrier gas flow rate was 30 mL/min. The flow rates for hydrogen and air were 30 and 300 mL/min, respectively. The injector and detector temperatures were maintained at 200 and 350°C, respectively. The oven temperature was held at 100°C for 2 min, then raised by 12°C/min to 320°C and held for 5 min.

High-Performance Liquid Chromatography

During HPLC analyses, a DuPont chromatographic pump, connected to a DuPont Instruments 860 UV-VIS detector was used with the operating detection wavelength at 254 nm (DuPont Instruments, Wilmington, Delaware). Separations were performed on a Chromspher silicon column (10 cm by 3.0 mm ID) with a particle size of 5 μm (Chrompack, Middelburg, The Netherlands) using a mixture of methylene chloride/methanol (98:2), and registration of the chromatograms was done using a Kipp BD-40 recorder (Kipp, Delft, The Netherlands).

Infrared Spectrometry

Infrared (IR) spectra of samples in potassium bromide (KBr) windows (wavelength range, 2.5 to 25 μm) were taken on a Philips 9514 IR spectrometer, using the medium resolution mode.

Mass Spectrometry

Exact masses were determined by direct probe at 70 eV, using an AEI-MS-902 mass spectrometer (Associated Electrical Industries LTD, Urmston, Manchester, England).

Gas Chromatography/Mass Spectrometry

GC/MS analyses were performed on a Finnigan MAT 212 mass spectrometer (Finnigan MAT, Bremen, Germany), connected to a Varian 3700 gas chromatograph (Varian, Palo Alto, California). Helium was used as a carrier gas with a flow rate of 1.5 mL/min. A 25-m fused silica CP-Sil 5 CB capillary column with a 0.32-mm ID was employed (Chrompack, Middelburg, The Netherlands). The injection temperature was set at 250°C. After injection the oven temperature was kept at 100°C for 2 min, then programed at a rate of 20°C/min to a final temperature of 280°C. The ion source and interface temperatures were 200°C. In the electron impact (EI) mode, the ionization energy was 70 eV. In the chemical ionization (CI) mode, ammonia was used as a reactant gas, and the ionization energy was 180 eV.

Nuclear Magnetic Resonance Spectroscopy

Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz (Varian, Palo Alto, California). The chemical shifts are reported in δ units (in parts per million). The ^{1}H-NMR shifts were determined in relation to the solvent and converted to the tetramethylsilane (TMS) scale using δ chloroform ($CHCl_3$) = 7.26 ppm. Carbon-13 (^{13}C) nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on the same apparatus at 75.43 MHz. Carbon-13 chemical shifts were determined in relation to the solvent and converted to the TMS scale using $\delta(CDCl_3)$ = 76.91 ppm. The splitting patterns were designated as follows: s (singlet), d (doublet), dd (double doublet), ddd (doubled double doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

Results and Discussion

Gas chromatography analysis of unadulterated illicit cocaine base samples usually showed the dominating presence of cocaine, frequently accompanied by very small, but variable, amounts of congeners, as exemplified in Fig. 1.

By using reference substances, the presence of cocaine, tropacocaine, anhydromethylecgonine, and *trans*-cinnamoylcocaine could be easily established. The mass spectrum of the compound with a retention time (Rt) of 14.70 min (Peak 6) indicated that it was *cis*-cinnamoylcocaine. *Cis*-cinnamoylcocaine has been described as eluting faster than *trans*-cinnamoylcocaine in a similar chromatographic system [*4*].

Three unknown substances, coded as A, B, and C, with retention times of 13.04, 13.85, and 15.39 min, respectively, can be clearly seen in the chromatogram. In an effort to isolate and identify these compounds, 100 μL of a 5% chloroform solution of this cocaine sample was spotted as a streak of approximately 15 cm on a TLC plate, followed by elution in TLC System B, until the solvent front had reached a distance of 15 cm from the start. After the solvent was evaporated, the plate was viewed under UV light of 254 nm, and the quenching zones were marked. Next, the center of the plate was almost completely covered with filter paper, revealing only two small eluted zones at both ends, and these small zones were sprayed with Dragendorff solution, which showed the alkaloids as orange-colored spots against a yellow background. The covering filter paper was

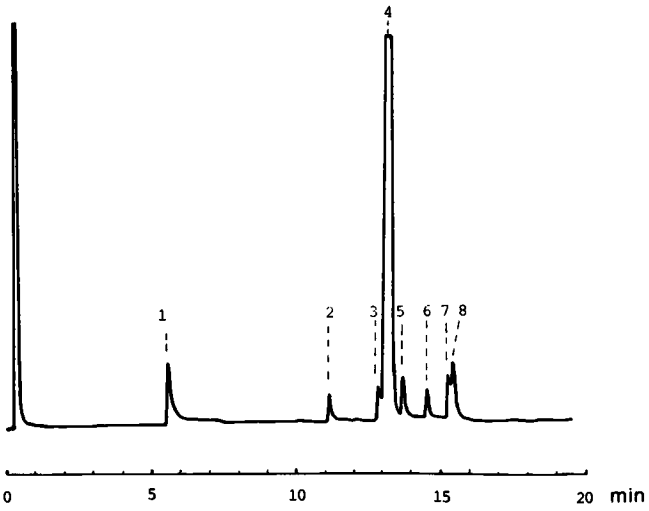

FIG. 1—*Gas chromatogram of an illicit cocaine base sample: (1) anhydromethylecgonine; (2) tropacocaine; (3) Unknown A; (4) cocaine; (5) Unknown B; (6)* cis-*cinnamoylcocaine; (7) Unknown C; (8)* trans-*cinnamoylcocaine.*

removed immediately, and the unsprayed part of the plate was subsequently divided into 30 zones of 0.5 cm, each starting at the solvent front and ending at the spotting zone. The material of each zone was scraped off separately, ground in a mortar, transferred to a disposable pipette closed with a cotton plug at the narrow end, and extracted with 3 mL of a 1:1 mixture of chloroform and methanol. The organic solvent was removed at 60°C under a stream of nitrogen gas. After each residue had been reconstituted in 100 μL of chloroform, gas chromatography (GC) analysis of all the individual zones was carried out. The presence of cocaine was established in Zones 16, 17, 18, and 19, of the cinnamoylcocaines in Zones 19 and 20, of tropacocaine in zone 21, and of anhydromethylecgonine (breakdown product of the truxillines) in Zones 22 and 23. Yet Zone 30 surprisingly revealed the combined presence of all three unknown peaks, A, B, and C (III in Fig. 2).

Based on the observation that the putative substances A, B, and C showed extremely low Rf values in the basic TLC system, and because they appeared to give an (almost unnoticeable) weak visualization reaction with Dragendorff reagent, it was assumed that their basicity is different from that of cocaine and its other congeners.

Therefore, a more efficient separation of Compounds A, B, and C from cocaine and its accompanying alkaloids was attempted, using an acidic extraction of the chloroform solution of an illicit cocaine sample: 10 mL of a 5% chloroform solution was extracted once with 30 mL of aqueous 0.5*N* HCl. Thereafter, the content of the remaining organic phase was analyzed by GC (Fig. 3).

A strong reduction in peak intensity was observed for the compounds tropacocaine, cocaine, and *cis-* and *trans*-cinnamoylcocaine in comparison with that in Fig.1, proving their efficient extraction into the aqueous acid layer. Compounds A, B, and C were still present in the chloroform solution, which indicating that they were not, or were only partially, extracted by aqueous HCl. A second extraction of the chloroform solution with 0.5*N* HCl showed a further removal of the typical basic components, while, after a third extraction, the three unknown substances were almost completely free from the others (Fig. 4)

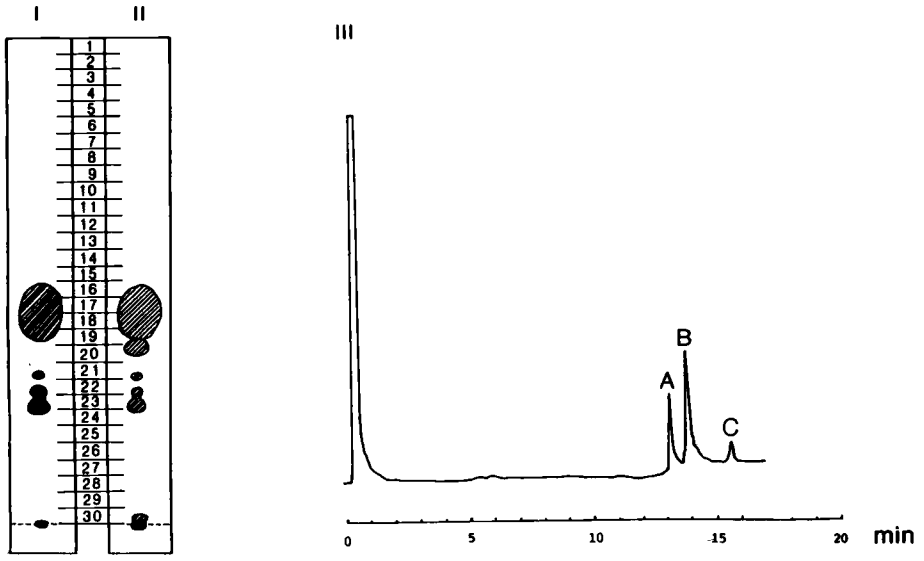

FIG. 2—*Thin-layer chromatogram of an illicit cocaine base developed in TLC System B and the resulting gas chromatogram of TLC Zone 30 (III): (TLC I) alkaloid visualization after spraying with Dragendorff solution; (TLC II) observed quenching areas using 254-nm UV light.*

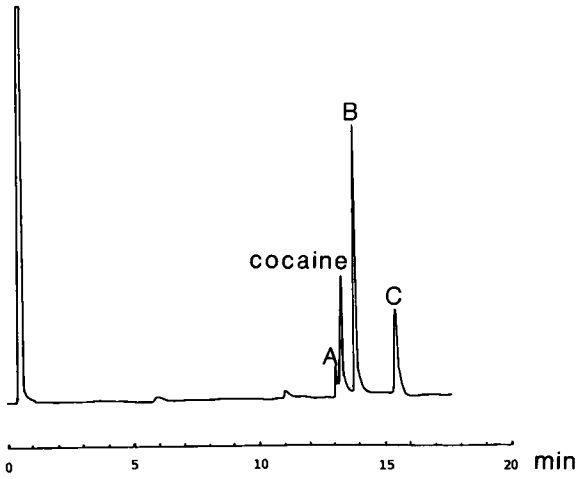

FIG. 3—*Gas chromatogram of a chloroform solution of illicit cocaine base, after a single extraction with 0.5*N *HCl. The unknown substances, A, B, and C, are marked in the chromatogram, together with cocaine.*

The resulting chloroform solution, containing the three unknown substances, was carefully concentrated to a volume of approximately 100 μL, which was subsequently spotted in a streak of about 10 cm on a TLC plate. This plate was developed using a mixture of chloroform/methanol (90:10) until the solvent front had reached a distance of 15 cm from the start. After it had been dried at 105°C for 10 min, the plate was viewed under UV light of 254 nm, and the quenching zones were marked (Fig. 5).

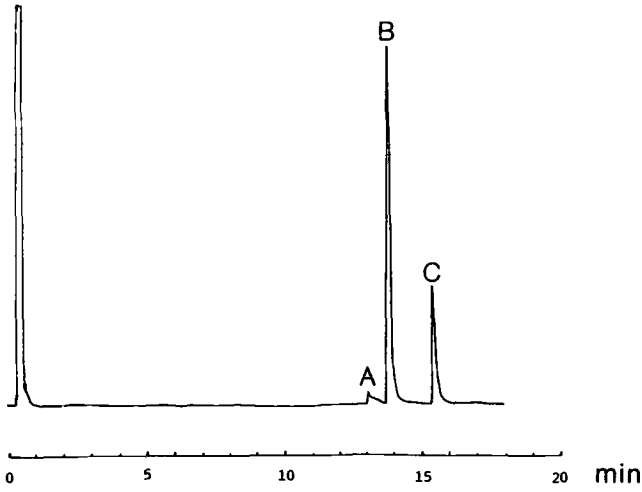

FIG. 4—*Gas chromatogram of a chloroform solution of illicit cocaine base after three repeated extractions with 0.5N HCl, as described in the text. The unknown substances, A, B, and C, are marked in the chromatogram.*

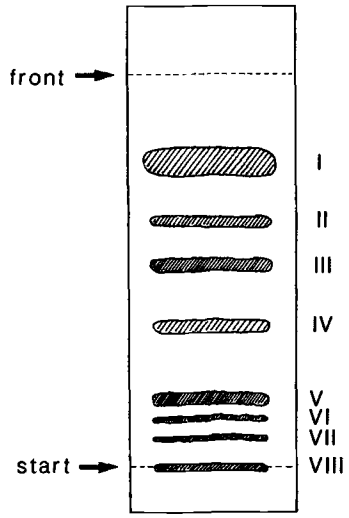

FIG. 5—*TLC chromatogram of a chloroform solution of illicit cocaine base after threefold extraction with 0.5N HCl to remove cocaine and similar basic congeners. Development was done with chloroform/methanol (90:10) and detection was under UV light of 254 nm. The eight observed quenching zones are marked I to VIII.*

The material of the marked zones was scraped off, ground, and extracted in a disposable pipette with a 1:1 mixture of chloroform and methanol, as described before. In each case the organic solvent was removed at 60°C under a stream of nitrogen. After reconstitution of the residues in 0.1 mL of chloroform, GC analysis of each of the solutions showed the presence of Substance A in Zone IV, Substance B in Zone III, and Substance C in Zone II, respectively.

Based on the experiments described, an HPLC separation procedure was developed in order to produce material of sufficient quantity as well as sufficient purity to perform ^{1}H-NMR and ^{13}C-NMR spectroscopy on the three substances, A, B, and C. Hence, 50 g of illicit cocaine base was dissolved in 500 mL of chloroform, and the solution was washed with 1500 mL of 0.5*N* HCl three times. Thereafter, the organic phase was evaporated to dryness and the residue redissolved in 5 mL of a 98:2 mixture of methylene chloride and methanol (the mobile phase for HPLC). Using a flow rate of 1.5 mL/min, separation of the substances was achieved on a straight-phase column. Numerous injections of 50 μL each were necessary to isolate at least about 75 mg of Compound A, 150 mg of Compound B, and 35 mg of Compound C. The thus isolated compounds proved to be at least 90% pure by GC, TLC, and HPLC.

Identification

Compound A

Compound A could be identified as norcocaine, which had already been found as a human metabolite of cocaine [*15*]. Very recently, and toward the end of our investigations, Le Belle et al. [*10*] found presumptive evidence for the occurrence of norcocaine in illicit cocaine and coca leaves by GC/MS. Our identification was based on the following chromatographic and spectrometric observations: the GC elution of Compound A on OV-1, when compared with cocaine, matches the literature description [*16*]. The CI mass spectrum showed a quasimolecular ion of 290, indicating a molecular mass of 289, which equals the mass of cocaine minus 14. The EI mass spectrum, with a base peak at *m/z* 168 and prominent peaks at *m/z* 136, 108, 105, and 77, strongly resembled the mass spectrum of norcocaine described by Lowry *et al.* [*17*].

The IR spectrum of Compound A was essentially identical to that of norcocaine, given by Schmidt and Werner [*18*]. The characteristic feature of norcocaine, that is, that it shows only one C=O frequency at 1720 cm^{-1} for the two ester moieties, was easily recognized. That Compound A was norcocaine was unambiguously proven by its ^{13}C-NMR spectrum. All carbon atoms in the molecule could be easily assigned, although we did not attempt to make a distinction within the pairs C_1/C_5 and C_6/C_7, since this is not essential for proof of the molecular structure. The data, together with the assignments, can be summarized as follows:

Method ^{13}C-NMR (at 25°C)—δ 172.60 (s; $\underline{C}O_2Me$), 165.35 (s; $\underline{C}OPh$), 133.15 (d; Ph), 129.60 (s; Ph), 129.38 (d; Ph), 128.29 (d; Ph), 66.27 (d; $PhCO_2\underline{C}H$), 55.59 (d; $\underline{C}HN$), 53.02 (d; $\underline{C}HN$), 51.83 (q; $\underline{C}H_3O$), 47.43 (d; $\underline{C}HCO_2Me$), 34.29 (t; $\underline{C}H_2CHO_2CPh$), 27.56 (t; $\underline{C}H_2CN$), 26.70 (t; $\underline{C}H_2CN$). These data are in good agreement with those reported for norcocaine · HCl in deuterium oxide (D_2O) [*19*].

Figure 6 shows the IR spectrum, ^{13}C-NMR spectrum, EI mass spectrum, structure, and mass spectral interpretations for Compound A.

Compound B

Compound B was identified as *N*-benzoylnorecgonine methyl ester (Figs. 7*a* and 7*b*), which has the same molecular formula as norcocaine. It has only been reported so far as a synthetic compound. The structure fully agreed with all the spectrometric and chromatographic data:

The CI mass spectrum showed a quasi-molecular mass of 290, indicating a mass of 289. The EI mass spectrum (Fig. 7*b*) showed a base peak at *m/z* 105 and further prominent peaks at *m/z* 77, 136, and 168. The peaks at *m/z* 105 and 77 indicate the presence of a

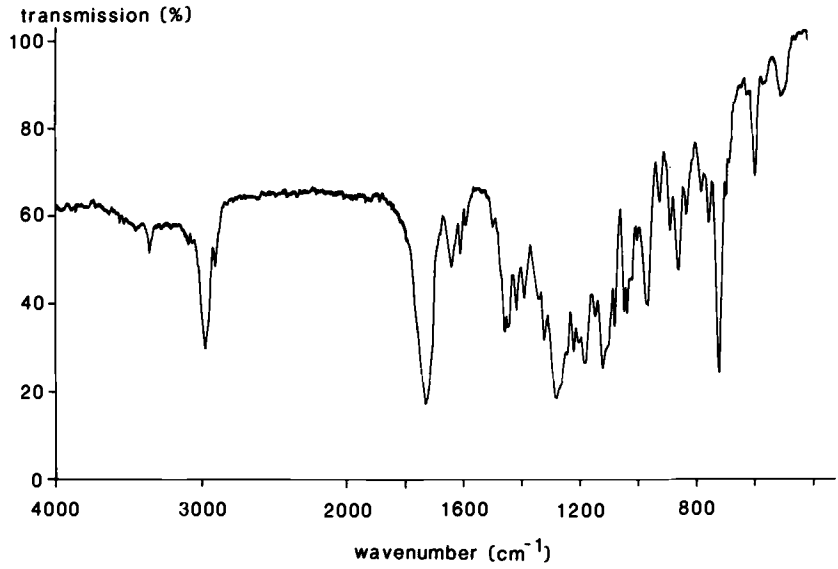

FIG. 6*a*—*IR spectrum of Compound A (norcocaine).*

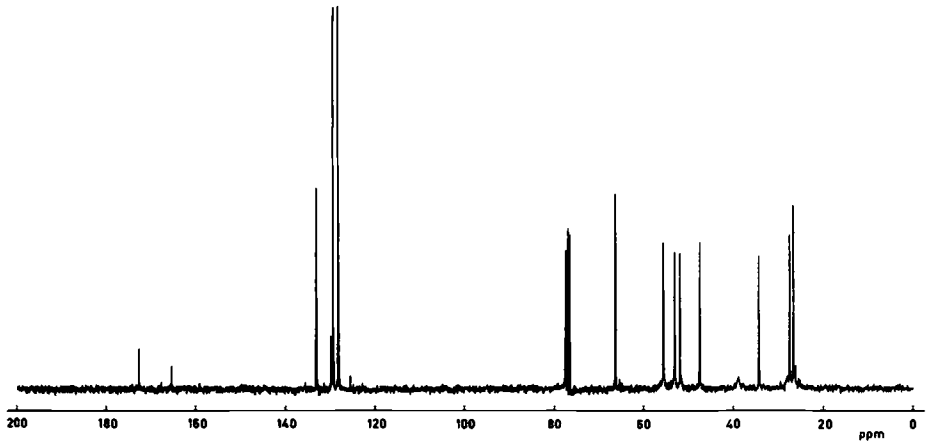

FIG. 6*b*—*Proton decoupled* ^{13}*C-NMR spectrum of Compound A (norcocaine).*

benzoyl moiety. The mass spectral interpretations are also depicted in Fig. 7*b*. The fragment at *m/z* 168 cannot be explained in the EI spectrum of *N*-benzoylnorecgonine methyl ester. It may originate from norcocaine as a result of transformation. The exact mass (289.131) corresponds to the molecular formula $C_{16}H_{19}NO_4$.

The IR spectrum (Fig. 7*a*) indicates the presence of an OH group (3450 cm^{-1}), an aliphatic ester (1740 cm^{-1}), and an amide linkage (1610 cm^{-1}). Werner et al. [*20*] only reported the OH stretching frequency of *N*-benzoylnorecgonine methyl ester at 3500 cm^{-1}. Both the ^{1}H-NMR and the ^{13}C-NMR data for Compound B were somewhat complex because the *N*-benzoyl group is restricted in its freedom of rotation.

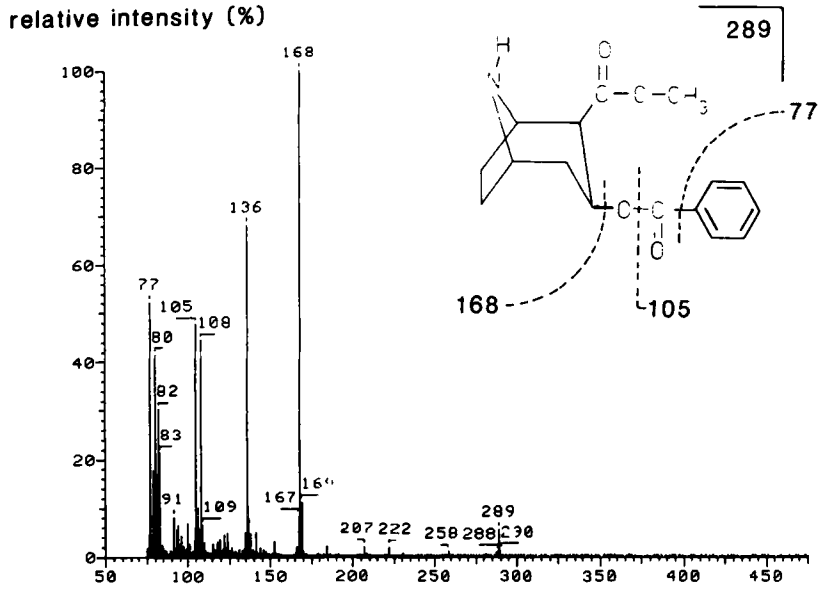

FIG. 6c—*EI mass spectrum, structure, and mass spectral interpretations of Compound A (norcocaine).*

For example, at 21°C, the 300 MHz ^{1}H-NMR spectrum showed very broad resonances at δ 5.2, 3.6, 3.2, 2.9, and 1.9. At 60°C, however, the C—N bond rotation becomes facilitated, allowing the fine structure to be observed. Whereas, in the ^{13}C-NMR spectrum at 21°C, all nortropane skeleton carbon atoms except C_3 showed broadened resonances, at 60°C, only the resonances that stem from C_1 and C_5 (*closest to the amide linkage*) remained broadened. These observations agree nicely with the reported value for the free energy of activation for the C—N bond rotation barrier of *N,N*-dimethyl benzamide in deuterated chloroform ($CDCl_3$), that is, 15.67 kcal/mole [*21*] or 65.3 kJ/mole [*22*].

The chemical shifts of C_3 (in ^{13}C-NMR) as well as of the proton attached to it (in ^{1}H-NMR) are identical in the two conformations of the amide bond because these are the only atoms in the nortropane skeleton that are symmetrically positioned towards these conformations.

The NMR results (at 60°C) and the assignments can be summarized as follows:

Method ^{1}H-NMR—δ 7.38 (m, 5H; PhH), 5.02 (br, 1H; H_1), 4.26 (br, 1H; H_5), 4.06 (m, 1H; H_3), 3.58 (s [broadened], 3H; MeO), 2.92 (br, 2H; H_2 and OH), 2.25 to 1.98 (m, 2H; H_4), 1.96 to 1.83 (m, 2H), 1.76 to 1.59 (m, 2H).

Method ^{13}C-NMR—δ 172.18 (s; $\underline{C}O_2Me$), 167.94 (s; Ph$\underline{C}$O), 135.94 (s; Ph), 129.75 (d, Ph), 128.12 (d, Ph), 126.85 (d, Ph), 63.87 (d, $\underline{C}$OH), 54.49 (d [broad]; $\underline{C}$HN), 54.32 (d [broad]; $\underline{C}$HN), 51.53 (q; $\underline{C}H_3O$), 51.37 (d; $\underline{C}HCO_2Me$), 38.57 (t; $\underline{C}H_2COH$), 27.81 (t; $\underline{C}H_2CN$), 27.03 (t; $\underline{C}H_2CN$).

Compound C

Compound C was identified as *N*-formylnorcocaine, a substance that has never been described in the literature before. The proposal for the molecular structure is based on the following spectrometric observations:

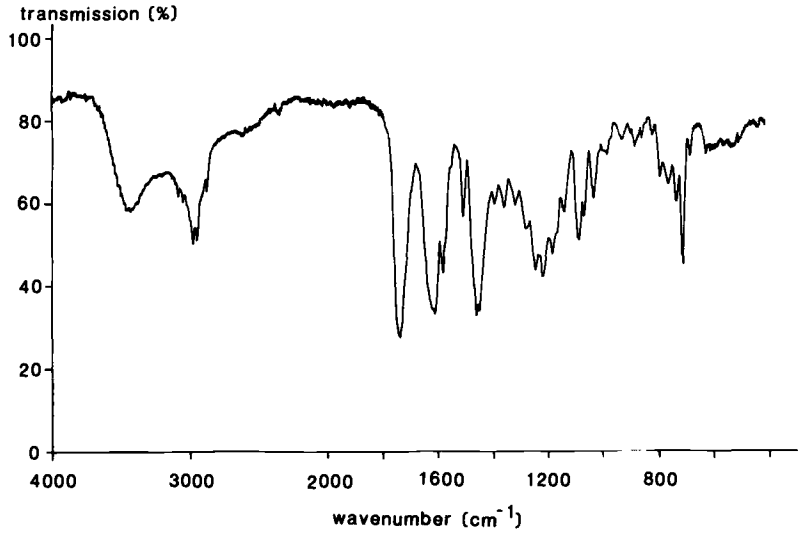

FIG. 7a—*IR spectrum of Compound B (*N*-benzoylnorecgonine methyl ester).*

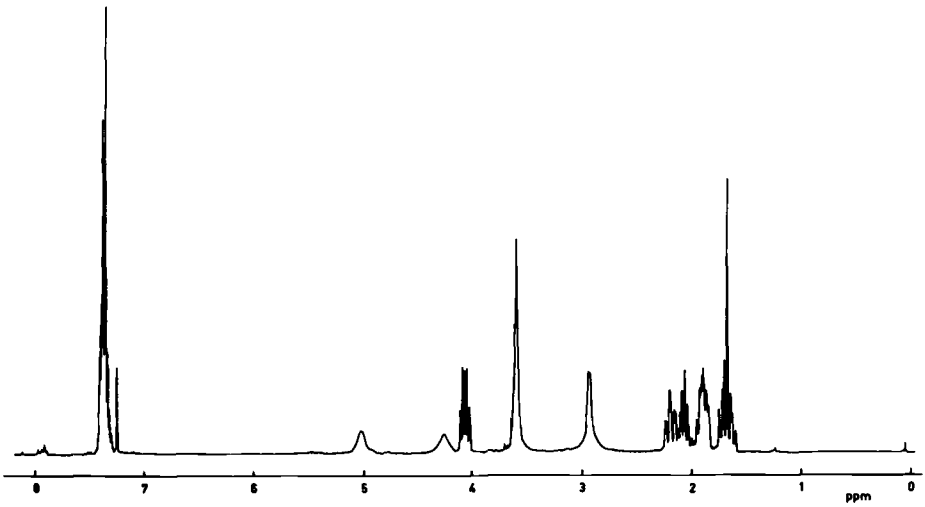

FIG. 7b—^{1}*H-NMR spectrum at 60°C of Compound B (*N*-benzoylnorecgonine methyl ester).*

The CI mass spectrum showed a quasi-molecular ion of 318, indicating a molecular mass of 317. The ion at 335 is due to $(M + NH_4)^+$.

The EI mass spectrum showed a base peak at *m/z* 105, and further major peaks at *m/z* 77, 108, 136, 168, 195, and 289. The peaks at *m/z* 77 and 105 indicate the presence of a benzoyl moiety, as is the case in the mass spectra of norcocaine and *N*-benzoylnorecgonine methyl ester. The M^+ peak at *m/z* 317 was very small, indicating a rapid loss of a fragment with mass 28 (to *m/z* 289). The mass spectrum strongly resembled that of

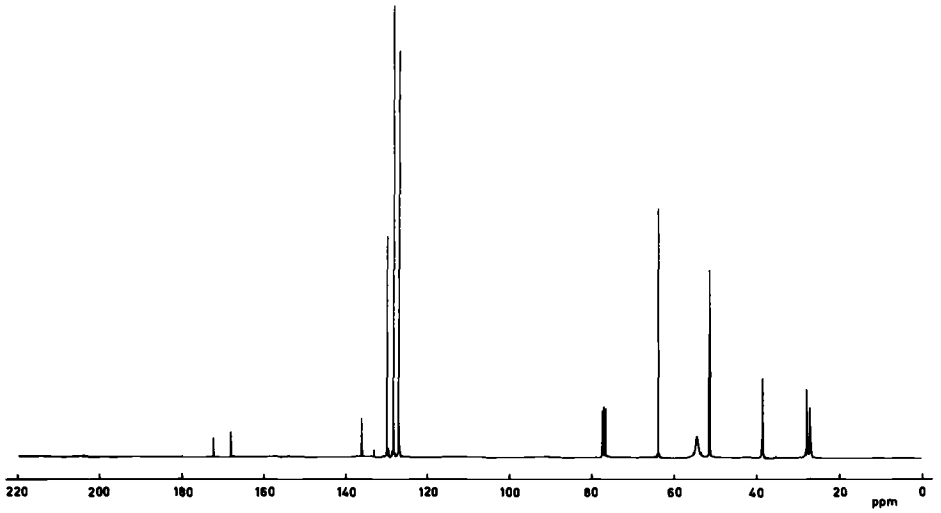

FIG. 7c—*Proton decoupled ^{13}C-NMR spectrum at 60°C of Compound B (N-benzoylnorecgonine methyl ester).*

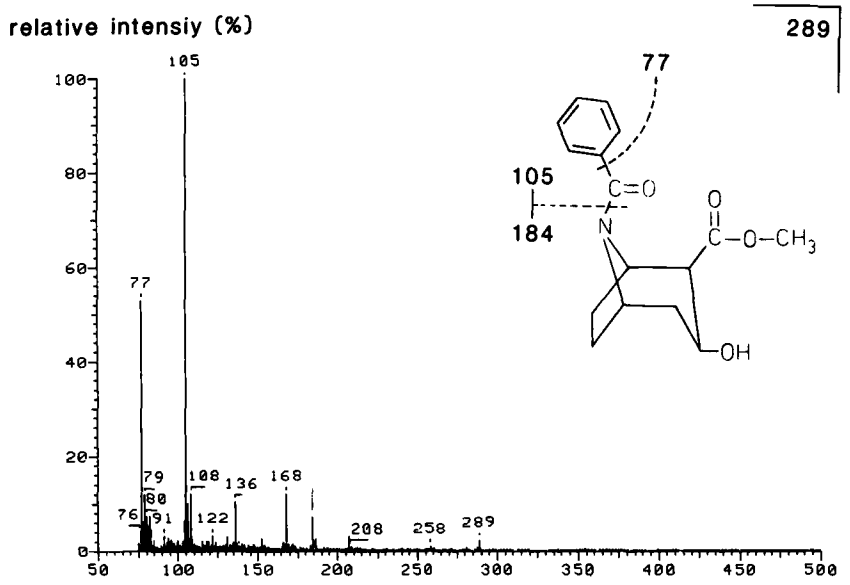

FIG. 7d—*EI mass spectrum, structure, and mass spectral interpretations of Compound B (N-benzoylnorecgonine methyl ester).*

norcocaine up to *m/z* 168. The exact mass of Compound C was 317.126, matching the molecular formula of $C_{17}H_{19}NO_5$ (calculated mass, 317.126), that is, the molecular formula of norcocaine plus a CO fragment, the latter with *m/z* 28, which is rapidly lost upon ionization. See Fig. 8*b* for the mass spectra.

The IR spectrum of Compound C (Fig. 8*a*) showed the formamide bond at 1680 cm^{-1}, while the alkyl and aryl ester carbonyl absorptions were observed at 1750 and 1730 cm;$^{-1}$,

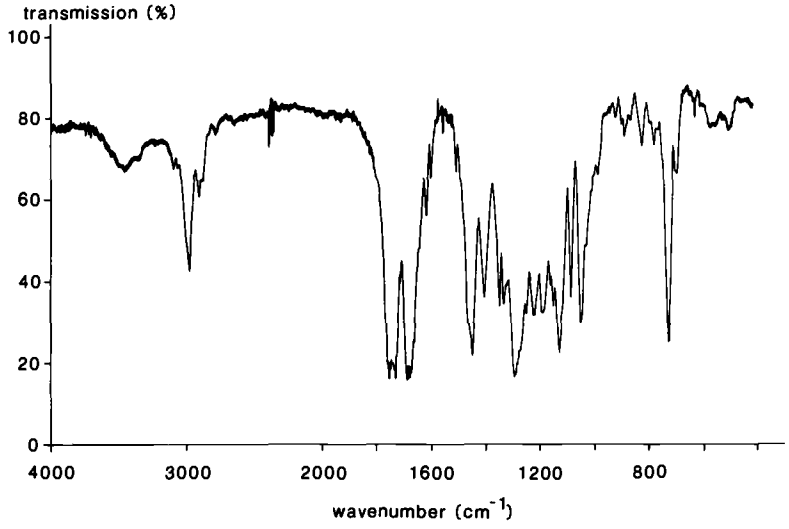

FIG. 8*a*—*IR spectrum of Compound C (*N*-formylnorcocaine).*

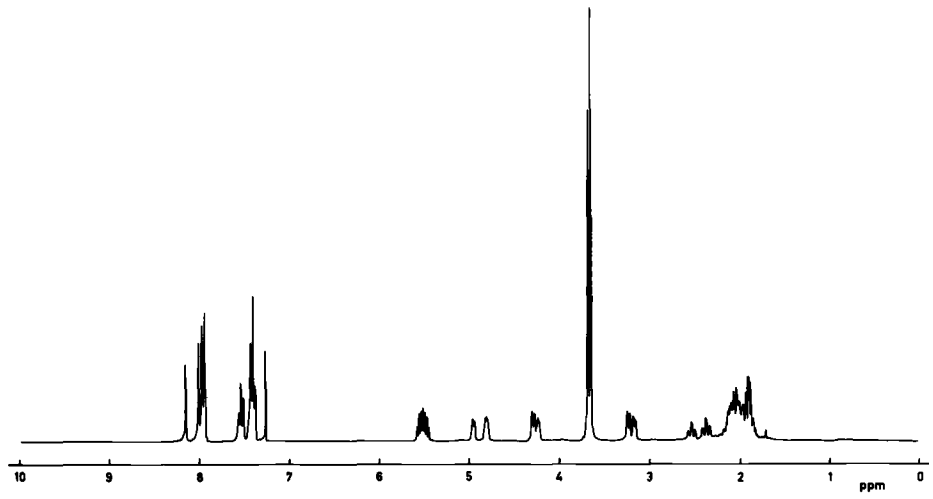

FIG. 8*b*—^{1}*H-NMR spectrum of Compound C (*N*-formylnorcocaine).*

respectively. The monosubstituted phenyl absorption at 720 cm^{-1} was identical to that of norcocaine.

The behavior of Compound C in NMR spectroscopy was typical for an *N,N* disubstituted formamide, that is, two conformers were observed at 25°C as well as at 60°C. Since compounds such as *N,N*-dimethylformamide and *N,N*-diisopropylformamide show an energy of activation for the rotational barrier in the C—N amide bond of 20.6 kcal/mole [*23,24*], a similar value may be expected for *N*-formylnorcocaine. Hence, the coalescence temperature is expected to be well above 100°C.

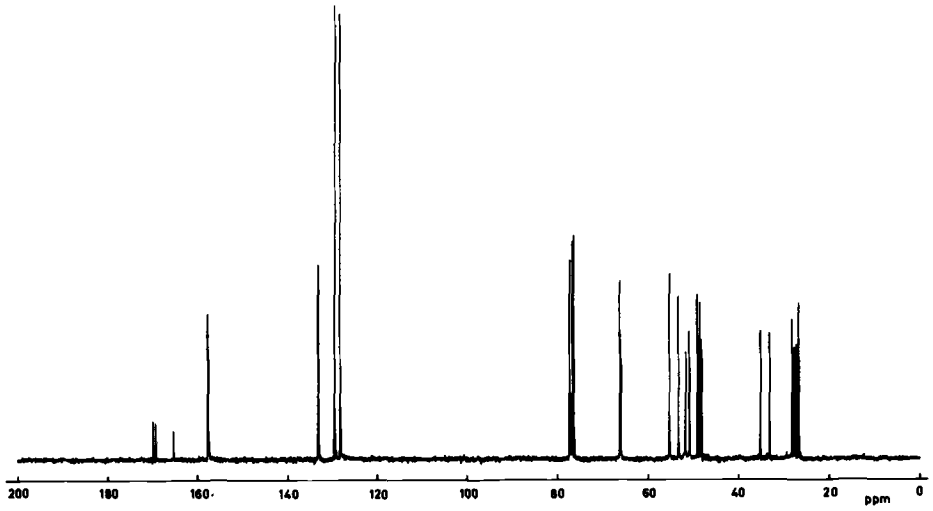

FIG. 8c—^{13}C-NMR *spectrum at 25°C of Compound C (*N*-formylnorcocaine).*

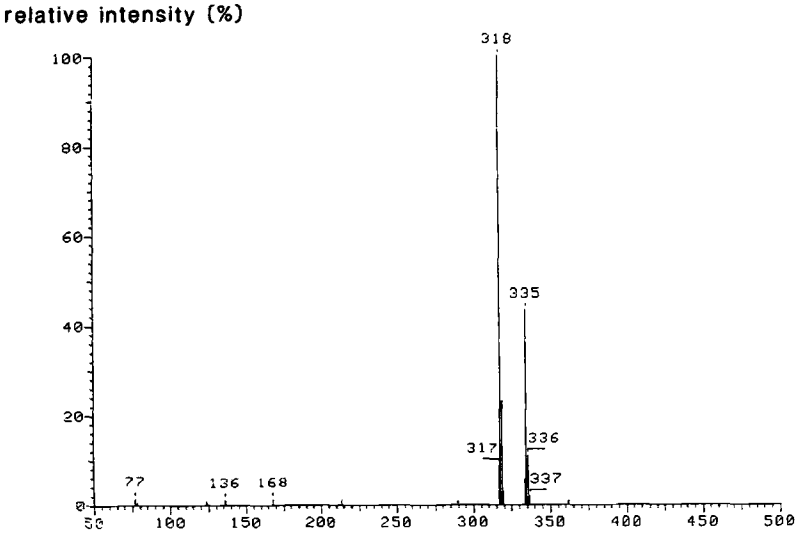

FIG. 8d—*CI mass spectrum of Compound C (*N*-formylnorcocaine).*

At room temperature, the 300 MHz spectrum distinguished the two conformers with a remarkable accuracy: 10 out of 17 carbon atoms (including the ester methyl group) gave rise to dual resonances in the proton-decoupled ^{13}C-NMR spectrum and 5 types of hydrogen atoms showed baseline separated resonances for the two conformers in the ^{1}H-NMR spectrum! Even the symmetrically positioned C_3 carbon atom, which gives only one resonance in *N*-benzoylnorecgonine methyl ester, showed a small (0.085 ppm), but

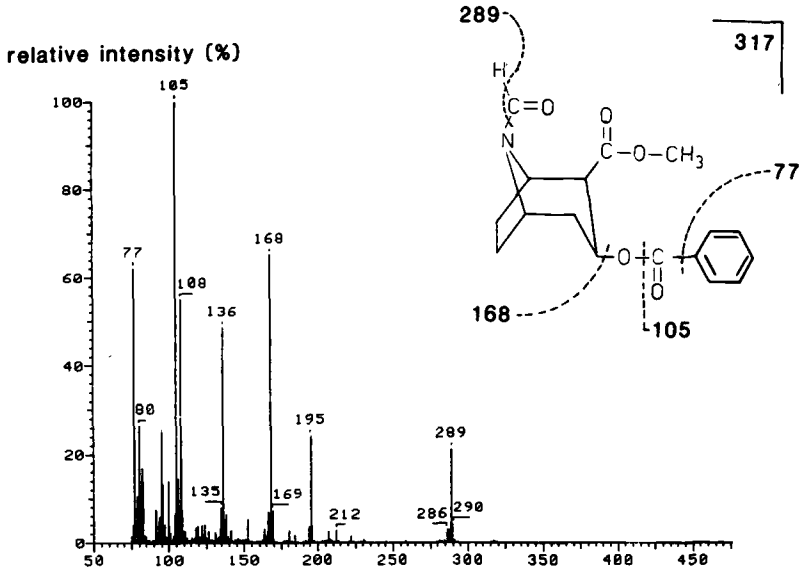

FIG. 8*e*—*EI mass spectrum, structure, and mass spectral interpretations of Compound C (N-formylnorcocaine).*

noticeable, difference in chemical shift. The two NMR spectra of Compound C are shown in Fig. 8*b*. The data, together with the assignments, can be summarized as follows:

Method ^{1}H-NMR (25°C)—δ 8.15 (s, 0.5H; CHO), 8.01 (s, 0.5H; CHO), 7.95 (d with superimposed fine structure, J = 8.4 Hz, 2H; ortho PhH), 7.55 (t with superimposed fine structure, J = 7.5 Hz, 1H; para PhH) 7.42 (dd with superimposed fine structure, $^3J_{m,o}$ = 8.4 Hz, $^3J_{m,p}$ = 7.5 Hz, 2H; meta PhH), 5.50 (seven lines on 6.1 Hz distance; relative intensity, 1:2:2.25:2.66:2.5:2:1; 1H; H_3), 4.94 (m, 0.5H; H_1), 4.80 (m, 0.5H; H_1), 4.29 (m, 0.5H; H_5), 4.26 (m, 0.5H; H_5), 3.67 (s, 1.5H; OCH_3), 3.64 (s, 1.5H; OCH_3), 3.24 (dd, $^3J_{2,1}$ = 2.5 Hz, $^3J_{2,3}$ = 6.5 Hz, 0.5H; H_2), 3.16 (dd, $^3J_{2,1}$ = 2.5 Hz, $^3J_{2,3}$ = 6.5 Hz, 0.5H; H_2) 2.52 (ddd, $^2J_{4e,a} \approx {}^3J_{4a,3}$ = 12.2 Hz, $^3J_{4a,5}$ = 3 Hz, 0.5H; H_4a), 2.36 (ddd, $^2J_{4e,a} \approx {}^3J_{4a,3}$ = 12.2 Hz, $^3J_{4a,5}$ = 3 Hz, 0.5H; H_4a), 2.26 to 1.72 (m, 5H; H_4e, endo and exo H_6, endo and exo H_7).

Method ^{13}C-NMR (25°C)—δ 169.95 (s; $\underline{C}O_2Me$), 169.53 (s; $\underline{C}O_2Me$), 165.60 (s; $\underline{C}OPh$), 157.79 (d, J = 189 Hz; N$\underline{C}$HO), 157.67 (d, J = 189 Hz; N$\underline{C}$HO), 133.18 (d; Ph), 129.54 (d; Ph), 129.46 (s; Ph), 128.31 (d; Ph), 66.23 (d, J = 144 Hz; $\underline{C}HO_2CPh$), 66.14 (d, J = 144 Hz; $\underline{C}HO_2CPh$), 55.32 (d, J = 147 Hz; $\underline{C}$HNCHO), 53.39 (d, J = 147 Hz; $\underline{C}$HNCHO), 51.88 (q, J = 151 Hz; $O\underline{C}H_3$), 51.76 (q, J = 151 Hz; $O\underline{C}H_3$), 50.96 (d, J = 147 Hz; $\underline{C}$HNCHO), 49.24 (d, J = 137 Hz; $\underline{C}HCO_2Me$), 48.57 (d, J = 147 Hz; $\underline{C}$HNCHO), 48.36 (d, J = 137 Hz; $\underline{C}HCO_2Me$), 35.25 (t, J = 130 Hz; $\underline{C}H_2CHO_2CPh$), 33.29 (t, J = 130 Hz; $\underline{C}H_2CHO_2CPh$), 28.27 (t, J = 135 Hz; $\underline{C}H_2CHN$), 27.76 (t, J = 135 Hz; $\underline{C}H_2CHN$), 27.29 (t, J = 135 Hz; $\underline{C}H_2CHN$), 26.79 (t, J = 135 Hz; $\underline{C}H_2CHN$).

With these assignments and those obtained for Compounds A and B, a consistent set of values was obtained wherein analogous substructures of cocaine [*25*], norcocaine, *N*-benzoylnorecgonine methyl ester, and *N*-formylnorcocaine showed essentially the same chemical shifts.

The ^{13}C-NMR assignments reported here appear to be in agreement with those reported by Baker and Borne for cocaine, ecgonine, *O*-benzoylecgonine, norcocaine, *O*-benzoylnorecgonine, norecgonine, and *N*-allylnorcocaine. We have been cautious in using these data for comparison, however, since they were recorded using the corresponding hydrochloride salts in D_2O [*19*].

Origin of Norcocaine, *N*-Benzoylnorecgonine Methyl Ester, and *N*-Formylnorcocaine in Illicit Cocaine

After having established the chemical identity of the three new congeners in illicit cocaine just described, it is of interest to consider the possible origin of these compounds. Are these three substances natural congeners or are they formed during the process of isolation or purification, or both, of (illicit) cocaine? It is possible to exclude a natural origin, in view of the fact that *N*-benzoylnorecgonine methyl ester and *N*-formylnorcocaine are not very well extracted by acid aqueous solutions, so one might not expect all three compounds to be coextracted with cocaine if the cocaine had been obtained from kerosine by extraction with dilute sulfuric acid. Moreover, and for the same reason, even if a fraction of these compounds had been extracted into the aqueous layer, it seems unlikely that these compounds would precipitate together with cocaine upon the subsequent addition of base. Of the three compounds, only norcocaine would be expected to accompany cocaine through the isolation and purification process up to that point. On the other hand, if the compounds were natural constituents of the coca leaf, why did they remain unnoticed for so long? None of the three compounds, however, has been reported in the literature before to be natural congeners of cocaine in the coca leaf, except in a recent publication by Le Belle et al. on norcocaine [*10*]. However, there are also reasons to assume that the three compounds are formed during the illicit preparation of cocaine, to the extent that norcocaine and *N*-formylnorcocaine are formed during the treatment of the crude cocaine with permanganate and during the first part of the subsequent workup procedure, while *N*-benzoylnorecgonine methyl ester can be formed from norcocaine through isomerization.

Norcocaine and N-*Benzoylnorecgonine Methyl Ester*

The oxidative demethylation of tropane alkaloids and derivatives to the corresponding nor compounds using potassium permanganate ($KMnO_4$) has been described a number of times since 1883, when Merling reported the conversion of tropine into nortropine [*26*]. Examples include ecgonine to norecgonine [*27,28*], *O*-benzoylecgonine to *O*-benzoylnorecgonine [*27,28*], and cocaine to norcocaine [*20,29*]. Although the yield of norcocaine from cocaine is clearly affected by the pH of the reaction mixture, it can be obtained from acidic as well as basic permanganate oxidation [*20,29*]. The acidic permanganate oxidation of cocaine, reported by Stenberg et al. [*29*], is apparently a slow reaction since, after a reaction period of more than 20 h at room temperature, still 50% of the starting material was recovered.

N-benzoylnorecgonine methyl ester (Compound B) has been reported as a by-product in both the basic and the acidic permanganate oxidation of cocaine [*20,29*]. It is formed as the result of an O → N benzoyl migration in norcocaine. Such O → N migrations of benzoyl and acetyl groups are reversible [*30–32*]. The equilibrium of the migration reaction is regulated by the pH of the medium; that is, the *N*-benzoyl formation is favored under basic conditions, whereas the *O*-benzoylation is preferred under acidic conditions. Hence, *N*-benzoylnorecgonine methyl ester is formed from norcocaine primarily under basic circumstances. These basic circumstances exist during the illegal cocaine purification protocol: the acidic oxidation reaction mixture after $KMnO_4$ oxidation has to be made

at least slightly basic in order to precipitate the purified cocaine base. Thus, the initial formation of norcocaine may take place during the permanganate oxidation under acidic conditions, whereas the isomerization to *N*-benzoylnorecgonine methyl ester and the relative ratio of these two compounds are dependent on the subsequent alkaline conditions applied in the precipitation of cocaine base.

N-*Formylnorcocaine*

At first sight, the presence of *N*-formylnorcocaine in permanganate-bleached cocaine base seems less obvious, also because the formation of *N*-formyl compounds during oxidation of tropane alkaloids has never been reported. However, a number of cases have been described in which tertiary amines are oxidized by permanganate or manganese dioxide (MnO_2) to yield other than dealkylation products [*33–41*]. *N*-formyl compounds have been obtained in yields up to 80% (from tertiary *N*-methylamines and other tertiary *N*-alkylamines) by Highet and Wildman [*34*] and Henbest and co-workers [*35–37*] using MnO_2 as the oxidant. Using $KMnO_4$ in four different modes, Henbest and Thomas [*35*] obtained *N*-methylformanilide from *N,N*-dimethylaniline in yields ranging from 6 to 24%. Also using $KMnO_4$, the *N*-ethyl group of delpheline could be oxidized to an *N*-acetyl moiety [*40*], and the two nitrogen-bridgeheads-containing polycyclic alkaloids atisine and isoatisine could be oxidized to lactams [*41*]. Especially from the work by Henbest and Thomas, it has become clear that tertiary *N*-methylamines can yield both demethylated amines and *N*-formyl compounds by means of a common intermediate, that is, the carbinolamine. Hence, the demethylation product is the result of formaldehyde elimination from the carbinolamine, whereas the *N*-formyl compound is the result of a (competing) further oxidation of the carbinolamine (see Fig. 9).

The *N*-formyl compounds are relatively stable under the reaction conditions, since amides are far less easily oxidized than amines. The selective oxidation of the *N*-methyl group (to either the corresponding nor compounds or the *N*-formyl compounds) by $KMnO_4$ in the cases of cocaine, ecgonine, and *O*-benzoylecgonine is easily explained assuming that the initial steps in the oxidation reaction are electron abstractions from the nitrogen atom, α-proton abstraction from the resulting radical ion, and further oxidation to an iminium ion, respectively. Both the proton abstraction and the formation of the iminium ion can only occur on the methyl atoms, since the other two α-hydrogen atoms are on the tropane bridgehead positions, and therefore such a reaction would lead to severely strained "anti-Bredt's-rule" structures (Fig. 10).

Hence, the formation of norcocaine, *N*-benzoylnorecgonine methyl ester, and *N*-formylnorcocaine during the permanganate bleaching of cocaine can be rationalized by the following overall reaction scheme (Fig. 11):

In order to prove that these compounds can be obtained under such conditions, we have oxidized 3 g of pure cocaine with $KMnO_4$ at pH 9.2, according to the method

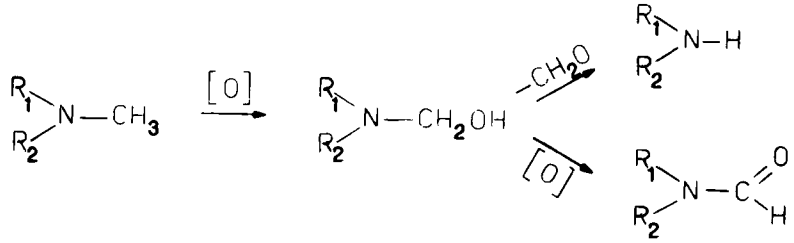

FIG. 9—*Proposed oxidation of tertiary methylamines, leading to* N-*demethylated as well as to* N-*formyl substances.*

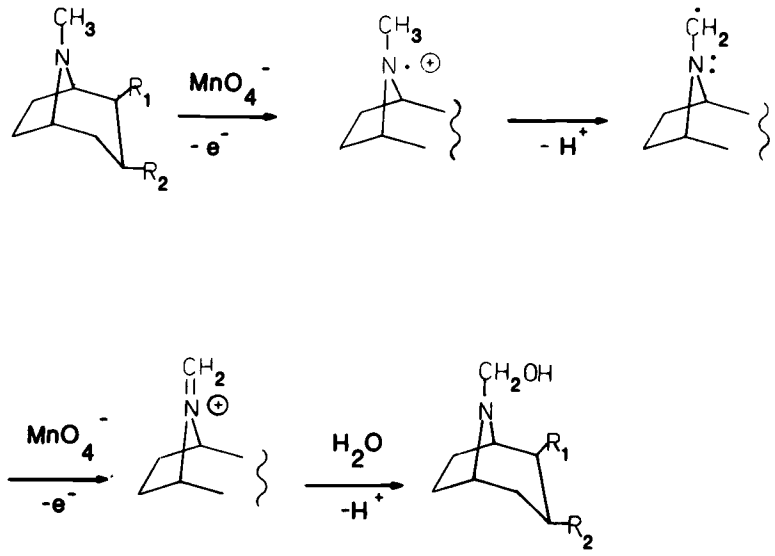

FIG. 10—*Proposed oxidation of tropanes.*

described by Schmidt and Werner [*18*]. After 9 h, the oxidation was stopped by the addition of ethanol, and the reaction mixture was extracted with 1.0 L of chloroform. The chloroform solution was concentrated to 100 mL, and the contents were analyzed by GC. The resulting chromatogram is shown in Fig. 12.

Upon comparison of the chromatogram shown above with that shown in Fig.3, it is clear that most of the starting material has been oxidatively transformed into norcocaine, *N*-benzoylnorecgonine methyl ester, and *N*-formylnorcocaine.

Finally, another observation has to be mentioned. In the routine GC analysis of cocaine samples, it was our impression that when *cis*- and *trans*-cinnamoylcocaine were present in relatively large amounts, none, or only trace amounts of norcocaine or *N*-benzoylnorecgonine methyl ester could be seen, whereas samples showing relatively low amounts of the cinnamoylcocaines appeared to contain higher amounts of norcocaine and *N*-benzoylnorecgonine methyl ester. Under the latter circumstances, *N*-formylnorcocaine could often be observed, as well, although at a lower abundance than norcocaine and *N*-benzoylnorecgonine methyl esther.

Discussion

We have explained the presence of norcocaine, *N*-benzoylnorecgonine methyl ester, and *N*-formylnorcocaine in illicit cocaine as the result of the permanganate bleaching procedure that nowadays seems common practice in the process of illicit cocaine production. The final balance between norcocaine and *N*-benzoylnorecgonine methyl ester appears to be pH dependent. We have neither considered nor investigated the possible further influence of aging on the contents of these compounds in the final cocaine product. However, the influence of (sun)light during or after the production process remains to be seen, because a photochemical reaction, converting cocaine partially to norcocaine has been mentioned by Singh et al. [*42*]. The formation of *N*-formylnorcocaine during such a photooxidative degradation of cocaine might also be possible, since analogous conversions have been described [*43–46*]. Other chemical reagents that can convert

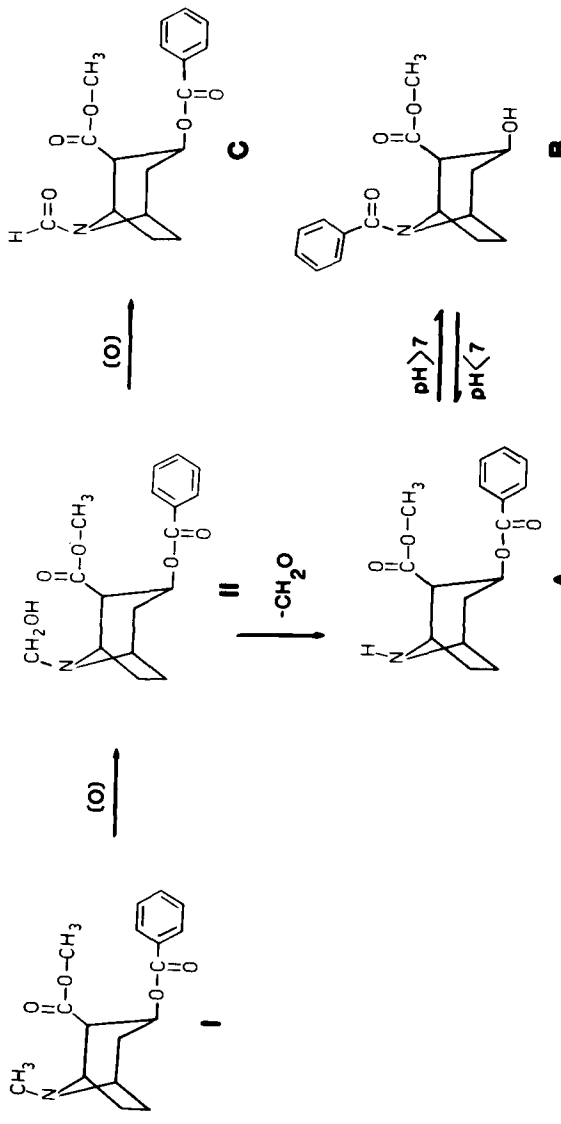

FIG. 11—*Proposed formation of norcocaine (A), N-benzoylnorecgonine methyl ester (B), and N-formylnorcocaine (C) from cocaine (I). Intermediate II has not been isolated so far.*

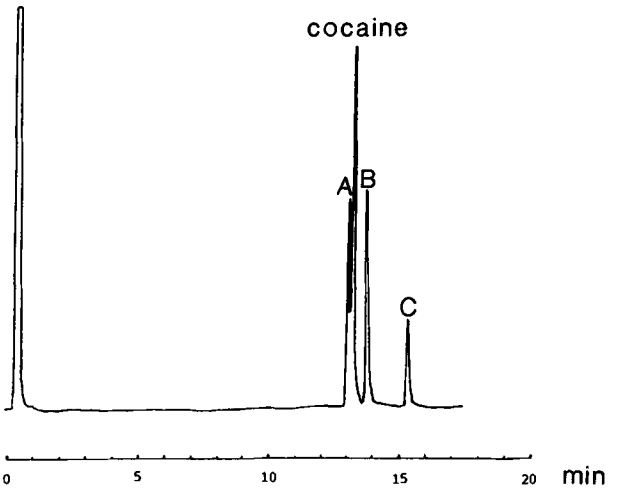

FIG. 12—*Gas chromatogram of the crude product mixture from permanganate oxidation of pure cocaine.*

N-methylamines to the corresponding demethylated amines or to *N*-formylamines are ozone [*36*], mercuric acetate [*47,48*], and chromium trioxide [*49*]. These reagents (and the corresponding proper reaction conditions) are not known to be part of the production process of illicit cocaine. Hence, since permanganate bleaching is the common step during the production process and since a simple permanganate oxidation of pure cocaine yields all of the three compounds, we believe that this is the main cause of their presence in illicit cocaine.

It should be noted that the similarity between the published mass spectrum of benzoylecgonine [*17*] and that of *N*-benzoylnorecgonine methyl ester can easily lead to incorrect interpretations of mass spectrometry results. An accurate consideration of the gas chromatogram may exclude a possible misinterpretation because *N*-benzoylnorecgonine methyl ester with a retention index (RI) of approximately 2200, is eluting closely after cocaine on a column of low polarity like OV-1, whereas benzoylecgonine (RI = 2570) elutes significantly later than cocaine (RI = 2185) [*16*].

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