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The Preparation of *d*-Pseudococaine from *l*-Cocaine

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ABSTRACT: *d*-Pseudococaine, a diastereoisomer of cocaine, is prepared from *l*-cocaine by the action of strong base that epimerizes the carbomethoxy group at C-2 to the equatorial position and transesterifies the ester at C-3. The benzoate ester is regenerated by reaction with benzoyl chloride. The *d*-pseudococaine thus prepared is then subjected to a variety of instrumental and analytical techniques to effect its characterization. The tests done are those commonly used in forensic science laboratories for cocaine analysis. With these data, a laboratory can eliminate or confirm pseudococaine in such an analysis.

KEY WORDS: toxicology, cocaine, chemical analysis, pseudococaine, diastereoisomer, characterization, instrumental techniques

Within the past few years the laws governing the possession and distribution of cocaine have come under increasing attack in the federal and state courts. These challenges have come about because the wording of the applicable statutes is imprecise in that no specific mention is made of cocaine as being a controlled substance. Also, the laws do not cover the diastereoisomers of cocaine (I), namely pseudococaine (II), allococaine (III), and pseudoallococaine (IV) (Fig. 1) [*1-3*].

Federal laws and most state laws control cocaine as "coca leaves, any salt, compound, derivative or preparation of coca leaves, and any salt, compound, derivative or preparation thereof which is chemically equivalent or identical with any of these substances." The forensic chemist must show beyond any reasonable doubt that a suspected cocaine sample is chemically equivalent or identical to the coca leaf derivative, *l*-cocaine. The so-called isomers defense in court attacks the results and conclusions of the cocaine analysis by asserting that the analyst cannot state that the sample analyzed is *not* one of the diastereoisomers that are not covered.

From the standpoint of the forensic science laboratory, the major difficulty is that, although laboratory syntheses of these diastereoisomers are known and have been published, they are mostly quite sophisticated, and as a result none of them except *d*-pseudococaine is presently available commercially. Since these diastereoisomers are so closely related to cocaine, and even though in theory they should differ enough to be differentiated by a combination of techniques, it is difficult to argue in court that such compounds can be ruled out unless one has either known samples of them or at least extensive characterization data.

In this paper, we report the synthesis as well as physical and spectroscopic char-

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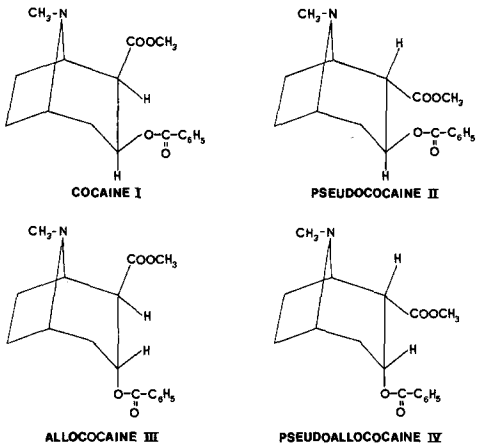

FIG. 1—*Structures of cocaine and three of its diastereoisomers.*

acterizations of *d*-pseudococaine. The preparation involved treating *l*-cocaine free base (I) with a strong base, which results in epimerization of the carbomethoxy group from the axial to the equatorial position as well as transesterification of the benzoate ester to form pseudoecgonine methyl ester (V) (Fig. 2). The ester so formed is treated with benzoyl chloride to regenerate the benzoate ester and form *d*-pseudococaine (II).

Experimental Procedure

Melting points were determined by using a calibrated Thomas-Hoover apparatus. Thin-layer chromatographic analyses were performed on 250-μm silica gel plates using 9:1 chloroform/methanol as eluant. Potassium iodoplatinate was used for visualization. Gas chromatographic separations were achieved on a Perkin-Elmer 900 instrument equipped with a flame ionization detector and a 1.8-m (6-ft) by 2-mm inside diameter stainless steel column containing 3% OV-17 on 100-120 mesh Gas-Chrom Q. The temperature of the inlet was 200°C; of the column, 180°C; and of the manifold, 250°C. Polarimetry results were obtained with a Perkin-Elmer 141 polarimeter using a 10-cm quartz cell and a sodium-D lamp. Infrared spectra were obtained from potassium bromide (KBr) pellets and a Perkin-Elmer 567 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian EM-390 spectrometer in deuterochloroform solution with tetramethylsilane as internal standard. Combination gas chromatography/mass spectroscopy determinations were made on a computer-controlled Finnigan instrument.

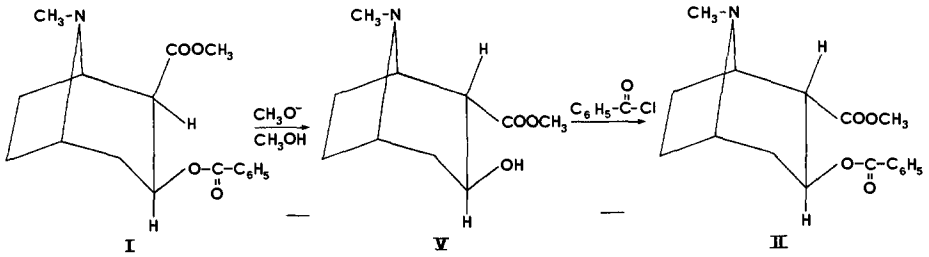

FIG. 2—*Structure of pseudoecgonine methyl ester* (V) *compared with those of cocaine* (I) *and pseudococaine* (II).

l-Cocaine was obtained as the hydrochloride salt from the Mallinkrodt Chemical Works, St. Louis, Mo. This and all other reagents were used without further purification.

Pseudoecgonine Methyl Ester (V)

A 1.00-g (2.94-mmol) portion of *l*-cocaine hydrochloride was dissolved in 10 ml of methylene chloride and washed with 10 ml of 5% aqueous sodium hydroxide [*1*]. After drying with anhydrous sodium sulfate, the solvent was removed in vacuo. The resulting cocaine free base crystals, which formed readily, were dissolved in 10 ml of absolute methanol. A 100-mg (1.85-mmol) portion of sodium methoxide was added and the reaction mixture was refluxed for 8 h. After the mixture cooled to room temperature, 10 ml of methylene chloride and 10 ml of 5% aqueous sodium bicarbonate were added. The aqueous layer was separated and extracted with three 15-ml portions of methylene chloride. The combined organic layers were washed with 10 ml of water, dried with anhydrous sodium sulfate, and evaporated in vacuo to yield a colorless oil that partially solidified. This material had a strong odor of methyl benzoate. Washing with 15 ml of ice-cold petroleum ether (boiling point, 30 to 60°C) gave 0.51 g (87%) of crude pseudoecgonine methyl ester (melting point, 108 to 111°C). The crude product may be recrystallized from petroleum ether to yield needles that melt at 113.5 to 114.5°C (the melting point given in Ref *1* is 114 to 115.5°C).

Pseudococaine (II)

A 5-ml (8 mmol) portion of a solution of 3 ml of benzoyl chloride in 12 ml of dry pyridine was added to crude pseudoecgonine methyl ester [*1*]. The reaction mixture was cooled in ice, and white crystals began separating after 2 min. After the mixture stood at 0°C for 30 min, 10 ml of absolute ether was added, and the resulting voluminous precipitate was collected. Recrystallization from 10 ml of absolute ethanol afforded 0.67 g (67% overall) of pseudococaine hydrochloride as tiny white needles (melting point, 209.5 to 210°C [the melting point given in Ref *4* is 210°C]).

A sample of pseudococaine hydrochloride was neutralized with aqueous base in the same manner as for the cocaine free base above. The pseudococaine free base was obtained as a colorless oil that slowly crystallized after prolonged standing below 0°C. The white prisms thus obtained melted at 41.5 to 42.5°C (the melting point given in Ref *4* is 47°C). Recrystallization from petroleum ether did not improve the melting point.

Results and Discussion

The pseudococaine prepared by the above synthesis was subjected to a variety of instrumental and physical characterizations from which a forensic science laboratory usually chooses its analytical tests on suspected cocaine samples. In most cases, the tests were performed on the hydrochloride form. Where the free base was tested, it will be specified.

The following tests were performed: thin-layer chromatography, gas chromatography, melting point determinations, mixed melting point determination with *l*-cocaine, gold chloride microcrystalline test, infrared spectrophotometry, nuclear magnetic resonance spectroscopy, gas chromatography/mass spectroscopy, and polarimetry. In all cases, comparative analysis was performed with *l*-cocaine.

Thin-Layer Chromatography

Cocaine and pseudococaine can easily be separated by thin-layer chromatography employing the plates and conditions described above. The R_f values were 0.81 for cocaine

and 0.37 for pseudococaine. Both spots turned blue brown in the visualizing reagent. Pseudococaine streaked somewhat under these conditions.

Gas Chromatography

Under the aforementioned gas chromatographic conditions, pseudococaine had a retention time of 15 min and 6 s from the chloroform solvent, whereas cocaine had a retention time of 15 min and 48 s. An injection containing both substances resulted in two peaks 40 s apart with about 25% overlap.

Gold Chloride Microcrystalline Test

The gold chloride microcrystalline test was done on a microscope slide with 5% aqueous reagent. The cocaine and pseudococaine were dissolved in 10% hydrochloric acid. The cocaine gave characteristic cross-shaped crystals. The pseudococaine crystals were much more nondescript, resembling rosettes or clumps.

Melting Points

Table 1 is a summary of the melting point data obtained for the hydrochloride salts and free bases of cocaine and pseudococaine. A mixed melting point test was attempted on cocaine free base and pseudococaine free base by mixing equal portions and dissolving them in chloroform. When the chloroform was evaporated, the mixture failed to crystallize even though *l*-cocaine free base sets up easily by itself under the same conditions. Presumably, the failure of crystals to form indicates that the mixed melting point was depressed below ambient temperature. This test can be quite useful in eliminating pseudococaine from consideration if it is routinely performed on suspected cocaine samples.

Infrared Spectrophotometry

The infrared spectra of cocaine hydrochloride and pseudococaine hydrochloride are reproduced in Figs. 3 and 4, respectively. The free base spectra were not obtained owing to the difficulty of forming pseudococaine free base crystals. It will be noted that the infrared spectra differ significantly in several regions.

Nuclear Magnetic Resonance Spectroscopy

The nuclear magnetic resonance (NMR) spectra of cocaine and pseudococaine free bases appear in Figs. 5 and 6, respectively. Examination of these two spectra indicates that these two substances can be easily differentiated by this technique.

Moreover, the stereochemical differences between cocaine and pseudococaine are evidenced in the NMR spectra. The multiplet near $\delta 5.5$ is assigned to the axial proton at C-3. The differences observed for the two multiplets are due to the different values of

TABLE 1—*Summary of melting point data.*

Compound	Melting Point, °C	Melting Points, °C, as Given in References
l-Cocaine base	96 to 96.5	98 [*4*]
l-Cocaine hydrochloride	192 to 192.5	195 [*4*]
d-Pseudococaine base	41.5 to 42.5	47 [*4*]
d-Pseudococaine hydrochloride	209.5 to 210	210 [*4*]

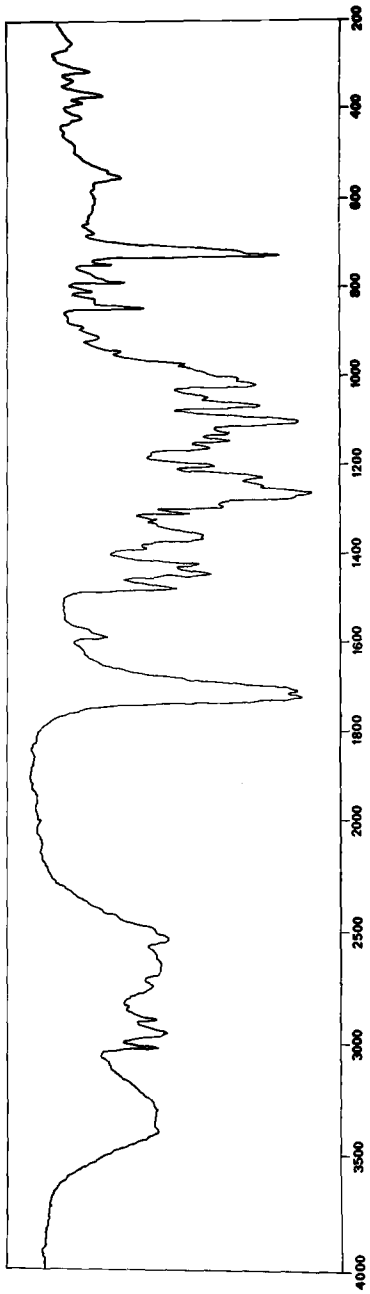

FIG. 3—*Infrared spectrum of cocaine.*

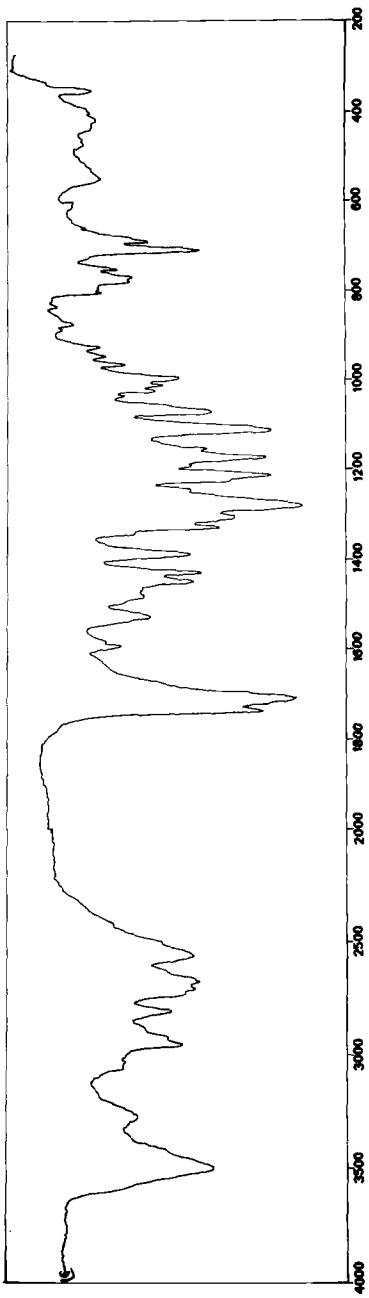

FIG. 4—*Infrared spectrum of pseudococaine.*

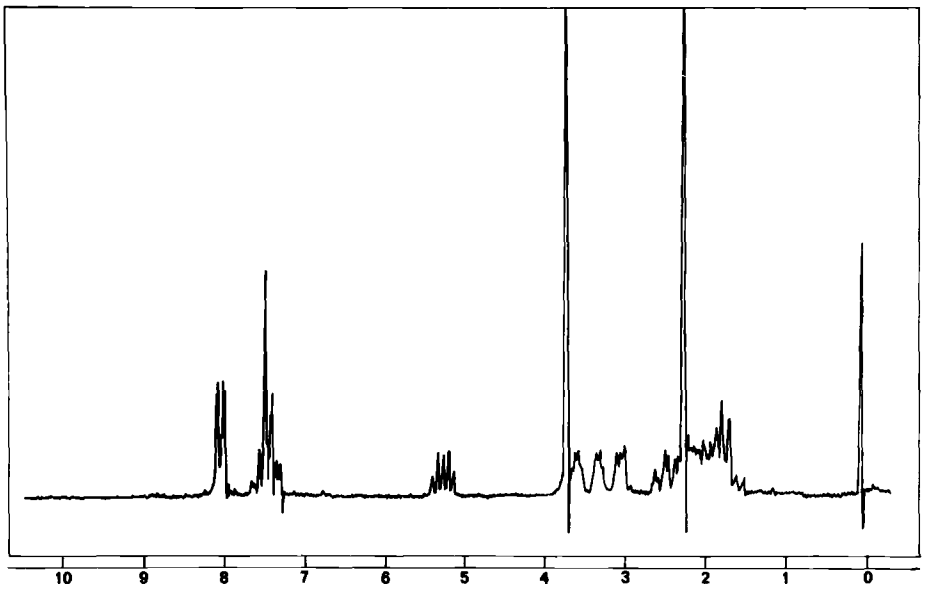

FIG. 5—*Nuclear magnetic resonance spectrum of cocaine.*

the axial-equatorial and axial-axial coupling constants between the protons at C-2 and C-3 of the two diastereoisomers. This same effect of different coupling constants is manifested in the appearance of the multiplet near δ3.1, which is assigned to the proton at C-2. In pseudococaine (Fig. 6), the AB quartet is partially obscured, but it is apparent that the appearance of the multiplet is due to the larger axial-axial coupling constant compared to the axial-equatorial coupling constant [5] in cocaine (Fig. 6). Finally, the

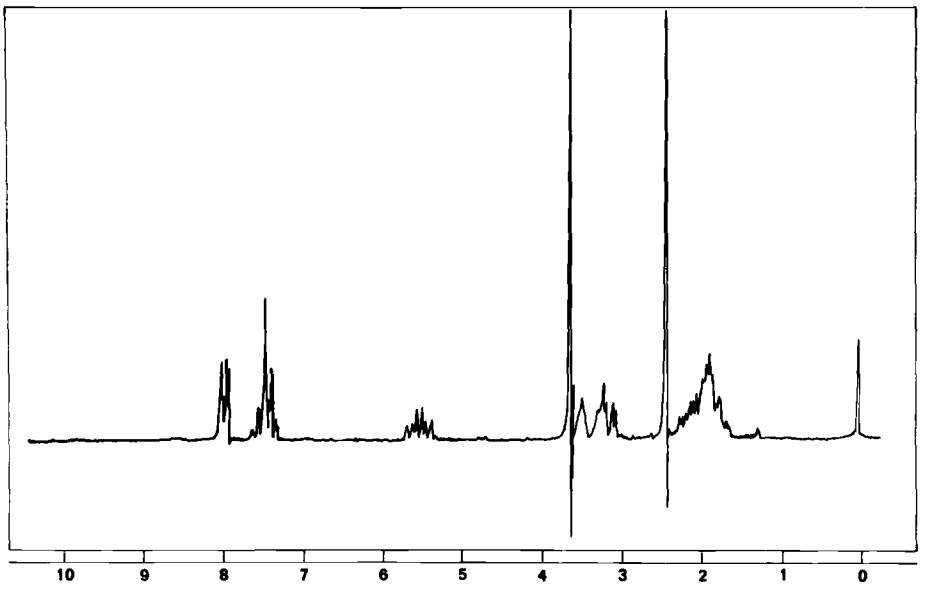

FIG. 6—*Nuclear magnetic resonance spectrum of pseudococaine.*

different multiplets near δ2.0 for the methylene protons are a consequence of the axial versus equatorial orientations of the carbomethoxy substituent in the two isomers.

The NMR spectra generated in this paper compare favorably with those published by Sinnema et al [*2*].

Gas Chromatography/Mass Spectroscopy

Although there are some significant differences in the gas chromatographic/mass spectroscopic spectra of cocaine and pseudococaine, they are not as easily delineated as those of the other techniques used. However, the two diastereoisomers can be distinquished by this method.

Polarimetry

The optical rotation data were obtained from chloroform solutions of cocaine and pseudococaine. The results are summarized in Table 2. It will be noted that these two substances rotate light in opposite directions. Even if absolute rotation cannot be obtained, an instrument that measures direction of rotation can differentiate cocaine from pseudococaine.

TABLE 2—*Summary of polarimetry results.*[a]

Compound	Concentration, g/100 cm^3	$[\alpha]_D^{20}$	$[\alpha]_D^{20}$ from Ref *2*
Cocaine base	4	−16°C	−16°C
Pseudococaine base	5	+41°C	+42°C

[a] Where $[\alpha]_D^{20}$ is specific optical rotation at 20°C for the D (sodium) line.

Conclusions

It is clear from the panel of analytical tests reported here that cocaine and pseudococaine can be easily distinguished in the laboratory. Every forensic science laboratory performs some or all of the tests described and so can eliminate one or the other compound from consideration. If a laboratory has a sample of pseudococaine to test against its suspected cocaine samples, the analyst can confirm or reject a sample unequivocally. In the absence of pseudococaine standard, the analyst would still be able to determine if the sample is or is not pseudococaine by referring to the results of the tests presented here.

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