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Synthetic Cocaine Impurities

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ABSTRACT: The compounds 3-aminomethyl-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1.) oct-2-ene (1), 3-benzoyloxy-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene (2), and 3-benzoyloxy-8-methyl-8-azabicyclo(3.2.1)oct-2-ene (3) have been detected in clandestine synthetic cocaine samples. Synthetic rationalization, chromatographic separation (gas liquid chromatography), and spectroscopic information (infrared, ^{1}H nuclear magnetic resonance, ^{13}C nuclear magnetic resonance, and mass spectrometry) of these compounds are provided.

KEYWORDS: toxicology cocaine, chromatographic analysis, spectroscopic analysis

The U.S. Federal drug codes [*1*] are so worded that for cocaine the forensic chemist must not only perform a diastereoisomeric determination but must also perform an enantiomeric determination.

> U.S. Code 1308.12 (4) Coca leaves (9040) and 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 . . .

Implicit in the above is the conclusion that only the levorotary isomer of cocaine is controlled as the coca plant makes only the "levo" stereoisomer. This prompted an earlier publication outlining analytical requirements necessary to unequivocally determine levo-cocaine (1-cocaine) [*2*]. Other workers have also added to the literature analytical schemes capable of assuring the positive recognition of 1-cocaine [*3,4*].

Defense attorneys, in their search for "loopholes," have pressed the analysis issue one step further in inquiring as to the sample's origin, that is, is the sample of "natural" or "synthetic" origin. While this is not a problem under the U.S. Federal codes, it may be under other jurisdictions where the wording "chemically equivalent or identical" is not present in their respective codes. The Canadian Narcotic Control Act is one example in which this omission has necessitated law enforcement or scientific testimony relating to the sample origin.

> Canadian Narcotic Control Act—Chapter, N-1 Coca (Erythroxylon), its preparations, derivatives, alkaloids and salts, including: (1) coca leaves, (2) cocaine, and (3) ecgonine.

In the absence of enforcement collaboration, the origin of cocaine can often be determined analytically through the presence or absence of impurities or byproducts or both. Manske and Holmes [*5*] have enumerated those alkaloids present in erythroxylon coca from which the clan-

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destine "natural" cocaine is derived. Since methods [6–9][2] are available for determination of these cocaine impurities, they may be used to assert the contention of "natural" origin.

In an opposite context, the detection of any of the diastereoisomers of cocaine or its dextro enantiomer mandates synthetic production. Toward this end, methods are available in the literature for identifying these diastereoisomers and enantiomers [2–4]. However, the differentiation of these diastereoisomers requires careful work. In addition, it is conceivable that some sample matrices could make enantiomeric determination difficult. Therefore, it becomes obvious that the ability to detect and identify impurities caused solely by synthetic manufacture would be useful. In previous work on the production of "synthetic" cocaine via the procedures of Findlay [10], we became aware of recurring byproducts (1, 2, and 3, Fig. 1). Furthermore, these same impurities have been detected in actual clandestine "synthetic" cocaine samples. It will be shown that these impurities are also common to most other synthetic routes to cocaine.

During clandestine laboratory investigations the forensic chemist may be asked to illustrate the synthetic route used by the defendant(s). For this reason, the forensic chemist should have a clear understanding of the synthetic routes available to the clandestine chemist. Fortunately, in the case of a cocaine synthesis, we shall see that although there are several synthetic routes possible all except one have common intermediates even though the precursors used vary considerably.

Synthesis

In building the basic structure of cocaine, namely, the 8-methyl-8-azabicyclo(3.2.1) octane ring system, the routes (see Fig. 2) by Willstatter (E [11, 12] and F [13]), Robinson (B [14] and F [15]), Mannich (F [16]), Schoff (B [17], Preobazhenskii (B and D [18]), Keagle (B [19]), Ziegler (B [20]), Zeile (F [21]), Findlay (B, D, F, G, and H [10]), Bazilevskaya (F [22]), Sinnema (H [23]), Kashman (C [24]), and others (A [25] and B [26]) all migrate through a common intermediate, 2-carbo-methoxytropinone (4) (Fig. 2). A more recent stereospecific synthesis by Tufarello [27] involves dramatically different intermediates. However, to date, all seizures of operating clandestine laboratories have utilized those routes migrating through Compound (4). For this reason, Tuparello's synthesis is not discussed in this work.

In Findlay's synthesis [10, 28] of cocaine and variations thereof, 2-carbomethoxytropinone (4) is the key intermediate (Fig. 2). Though different precursors have been used to prepare (4), the byproduct (1) will result from several of these schemes (F, G, and H). Its production is contingent on the presence of excess methyl amine along with (4) in the workup. Methyl amine and (4) result in the production of a Schiff base. The enamine of this Schiff base is (1), a vinylogous amide. This vinylogous amide is extremely stable and as a result is resistant to reduction or benzoylation in the subsequent steps. Although the amide portion of the molecule is neutral in character, the bridge head nitrogen assures that the byproduct (1) will follow cocaine through any extraction sequence.

Compound (4) (2-carbomethoxytropinone) also gives rise to Compound (2), (Fig. 3). This occurs because (4) exists primarily in the enol form (4a) [28] and therefore its dissolved metal reduction is quite slow. As a result, reduction of (4) to Compounds (6) and (7) is invariably incomplete. Thus, in the final step, that is, benzoylation of the alcohols (6) and (7), the ketone (4) is present as a contaminant. Since the ketone (4) is predominately in the enol (4a) form, benzoylation occurs to give (2). The close structural similarity of (2) to cocaine again assures isolation with the clandestine product.

To illustrate the persistent synthetic occurrence of this byproduct (2), note that Willstatter's early work (1923) makes reference to the then unidentified material [13]. Subsequently, Sinnema (1970) identified (2) and attempted, unsuccessfully, to reduce it to cocaine [29].

Because (4) is a critical intermediate to the overall synthesis of cocaine, mastering the ring

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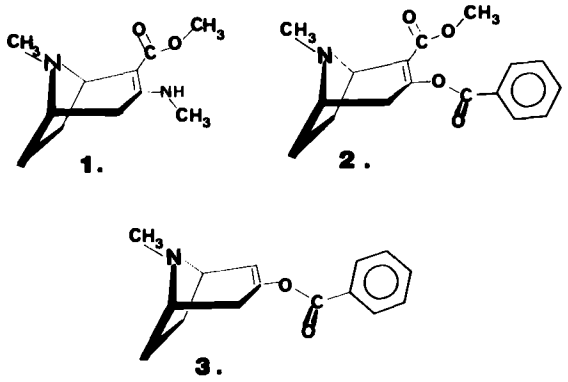

FIG. 1—*Recurring byproducts from production of synthetic cocaine.*

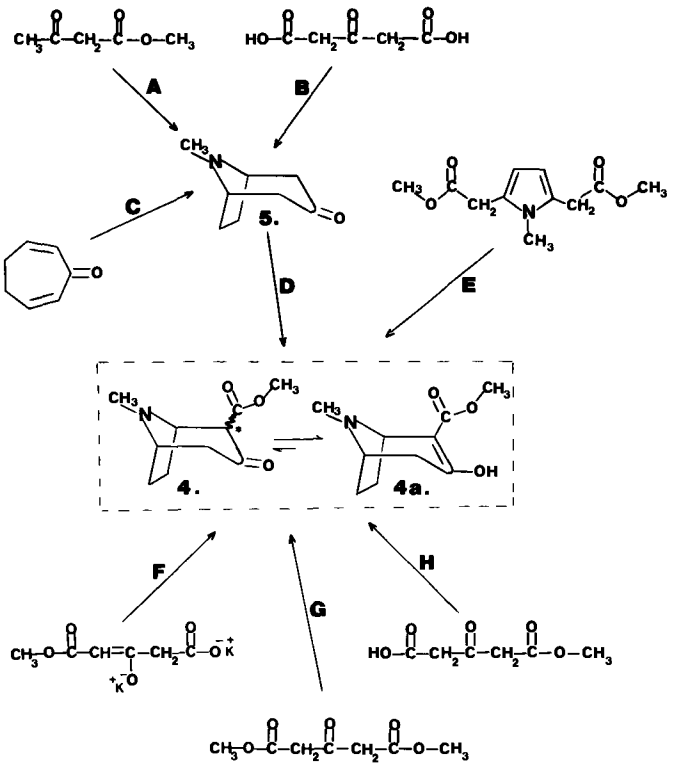

FIG. 2—*Synthetic routes* (A-H) *used for constructing 2-carbomethoxytropinone* (4). *Other precursors for* A, B, F, G, *and* H *are methylamine and succinic dialdehyde;* C, *methylamine;* E, *potassium; and* D, *potassium and dimethylcarbonate.*

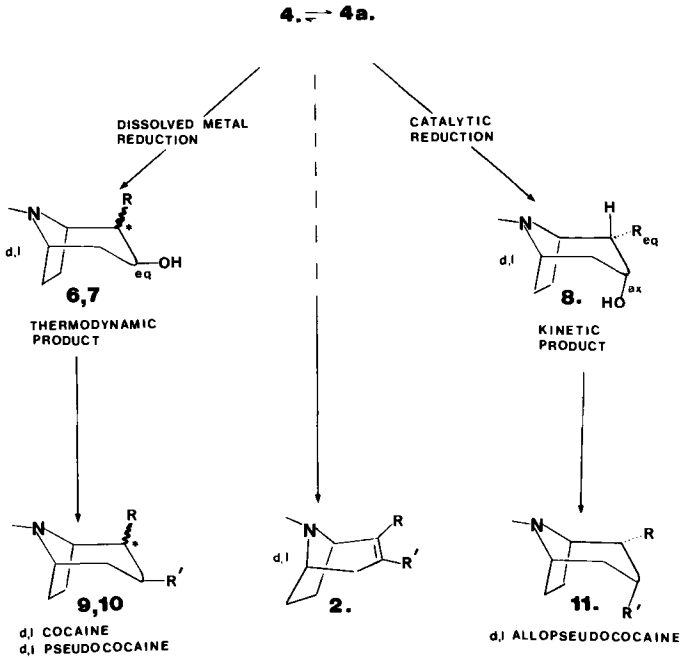

FIG. 3—*Synthetic routes to cocaines* (9, 10, *and* 11) *from 2-carbomethoxytropinone* (4). *The choice of reduction material determines the stereochemical outcome. Contamination of unreduced* (4) *in the final step results in benzoylation of* (4a) *to give* (2).

coupling reaction is essential. This is not an easy task. In following routes F, G, and H, if the pH of the solution is too high, resinous materials are obtained [*10, 24*]. Conversely, if the pH is too low, complete decarboxylation to tropinone (5) occurs. Transformation of tropinone (5) to (4) via route D [*10, 18*] is fraught with difficulties and, in favorable cases, low yields result [*10*]. Any amount of tropinone (5) carried forward as an impurity would yield the alcohol (12) or (13), depending on the choice of reductions. The end result after benzoylation will be the Compounds (14) or (15) (Fig. 4).

Unfortunately, (14) and (15) would be of little diagnostic value in determining origin in that (14) is a natural alkaloid of the plant and (15) is commercially available and not infrequently used as a cutting agent. This is not the case with impurity (3), (Fig. 4) whose presence clearly mandates the synthetic manipulation of tropinone (5). It is the benzoylation of the enol form of tropinone (Fig. 4) that results in the production of (3). This is a situation which is enhanced by the addition of an acid scavenger/acylation catalyst such as pyridine or *p*-dimethylaminopyridine [*30*].

Experimental Procedure

Nuclear magnetic resonance (NMR) spectra were obtained with a Nicolet NT-200WB Fourier transform spectrometer equipped with a model 293A programmable pulser. Spectra were obtained in deuterochloroform and tetramethylsilane was used as the internal standard. Selected NMR experiments were performed as outlined by Hall and Sanders [*31*].

Infrared (IR) spectra were recorded in potassium bromide with a Beckman model 4240 spectrometer.

Gas chromatography (GC) was performed with a Finnigan 9600 series instrument equipped

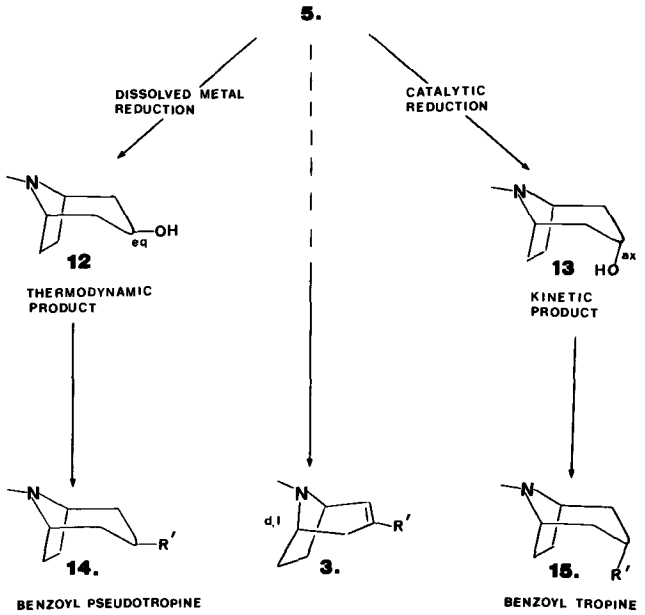

FIG. 4—*Synthetic routes to benzoylated tropeines from tropinone* (5). *The choice of reducing material determines the stereochemical outcome.*

with a Grob type capillary injection system. The capillary column was obtained from Hewlett-Packard and was a fused silica, cross-linked OV-1. Column dimensions were 0.2-mm inside diameter by 12 m and the carrier gas was helium (99.99%) at a head pressure of 83 kPa (12 psi). The injection port temperature was 230°C and sample was injected in the split mode (40/1). The initial column temperature was 150°C and that was ramped at 6°C/min to 250°C. No initial or final hold times were used. The mass spectrometer employed utilized a quadrupole mass analyzer (Finnigan 4600) and was operated under electron impact conditions at 70 eV.

Detection Procedure

The detection/identification of synthetic cocaine impurities is most readily achieved by the combined techniques of gas liquid chromatography and mass spectrometry (GC/MS). Sample analysis involves the simple extraction of sample from sodium bicarbonate solution with chloroform followed by GC/MS analysis. Figure 5 is illustrative of the separation possible for the impurities (1), (2), (3), (14), (15), and cocaine achieved on a fused silica capillary column (OV-1). Figures 6, 7, and 8 present the electron impact mass spectra for compounds (1), (2), and (3).

For those cases where impurities (1), (2), or (3) have become the major component or only product, the IR (Figs. 9 through 11), ^{1}H NMR (Fig. 12), and ^{13}C NMR (Fig. 13) is given.

Conclusion

Detection of any of the diastereoisomers of cocaine or its dextro enantiomer assures "synthetic" production. Methods available in the literature have addressed their identification [*2–4*]. In concert, or aside from the foregoing published methods, the detection of compounds (1), (2), and (3) may serve two functions: (1) add a preponderance of evidence to the case for "syn-

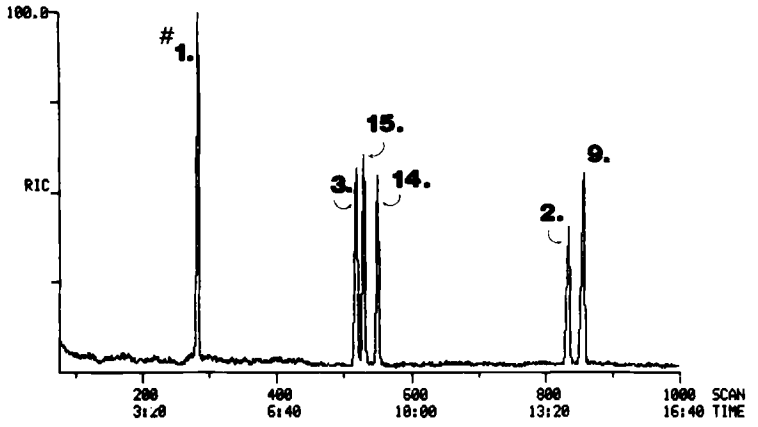

FIG. 5—*Reconstructed ion chromatogram obtained from a mixture of 3-aminomethyl-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (1); *3-benzoyloxy-2-methoxycarbonyl,-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (2); *3-benzoyloxy-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (3); *cocaine* (9); *benzoylpseudotropeine* (14); *and benzoyl-tropeine* (15) *on OV-1 fused silica capillary column.*

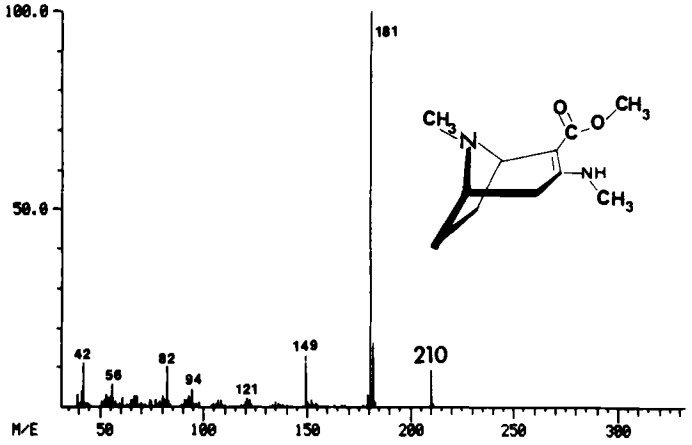

FIG. 6—*Electron impact mass spectrum of 3-aminomethyl-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (1).

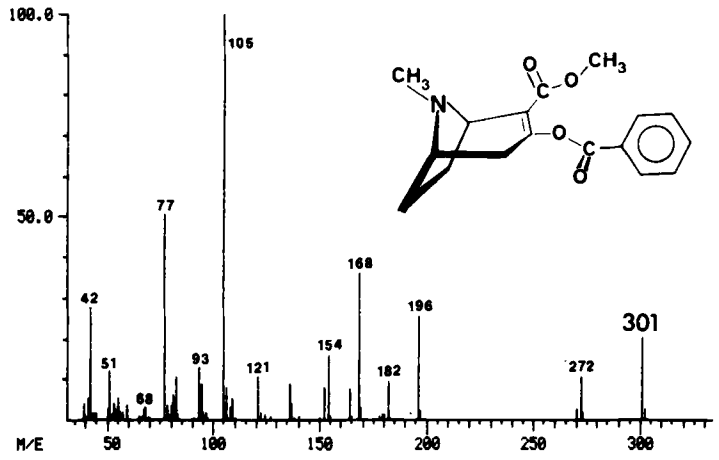

FIG. 7—*Electron impact mass spectrum of 3-benzoyloxy-2-methoxycarbonyl-8-methyl-azabicyclo (3.2.1)oct-2-ene* (2).

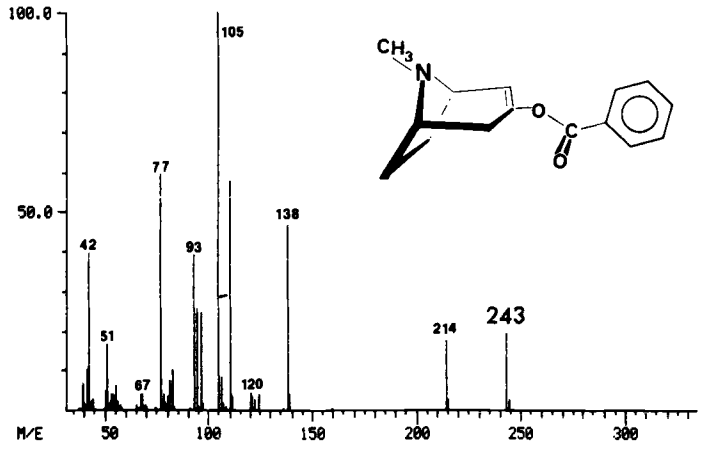

FIG. 8—*Electron impact mass spectrum of 3-benzoyloxy-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (3).

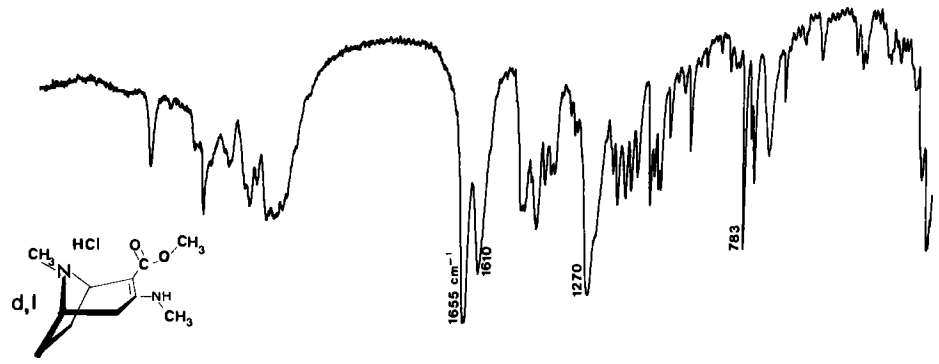

FIG. 9—*IR via KBr dispersion of* d,*1-3-aminomethyl,-2-methoxycarbonyl-8-methyl-8-azabicyclo (3.2.1)oct-2-ene hydrochloride* (1).

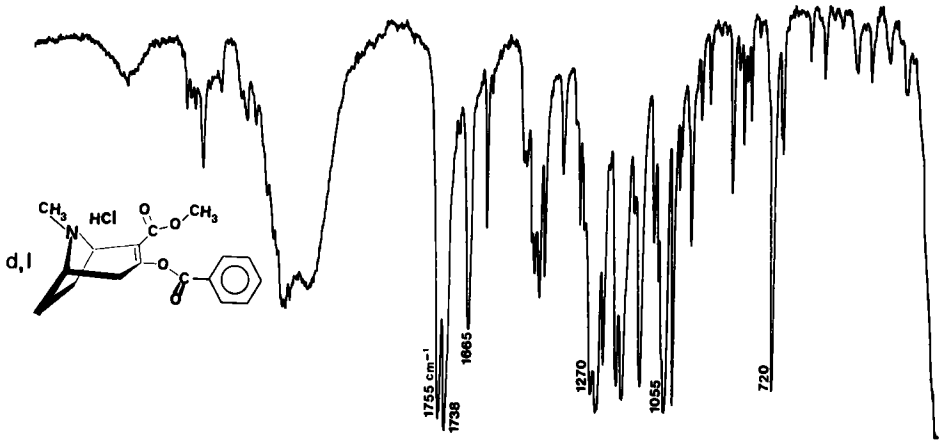

FIG. 10—*IR via KBr dispersion of* d,*1-3-benzoyloxy,-2-methoxycarbonyl-8-methyl-8-azabicyclo (3.2.1)oct-2-ene* (2).

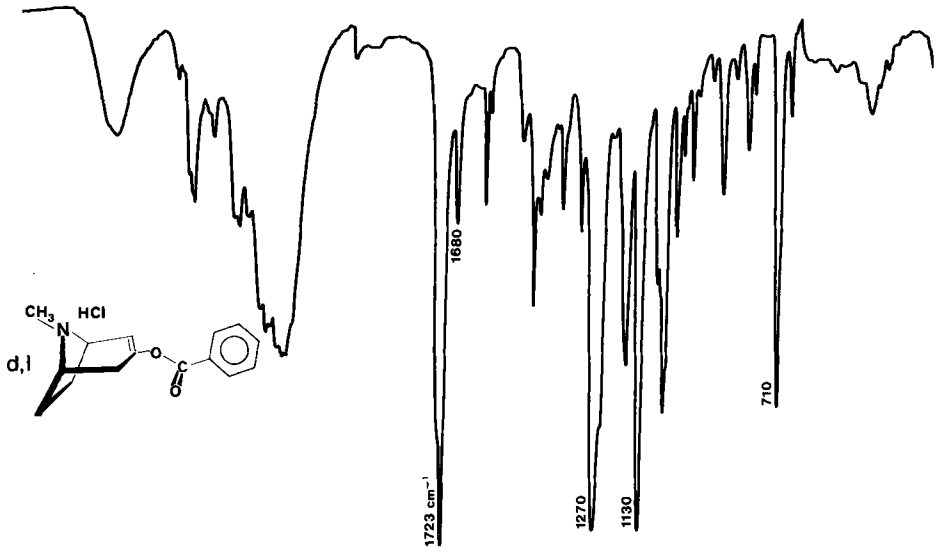

FIG. 11—*IR via KBr dispersion of* d,*l-3-benzoyloxy-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (3).

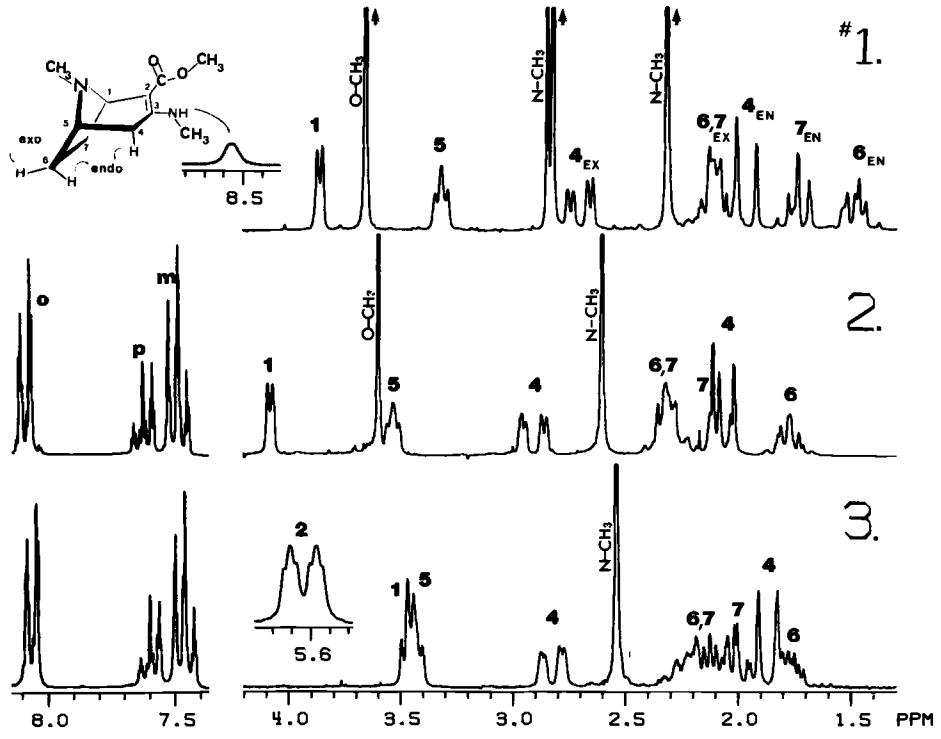

FIG. 12—*Hydrogen-1 NMR at 200 mHz in deuterochloroform of 3-aminomethyl.-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (1); *3-benzoyloxy,-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (2); *and 3-benzoyloxy-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (3).

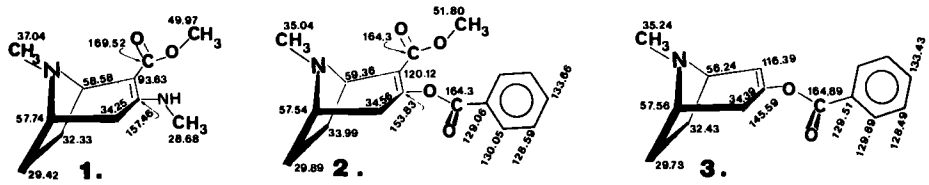

FIG. 13—*Carbon-13 NMR data obtained at 200 mHz in deuterochloroform at a concentration of 100 mg/mL for 3-aminomethyl,-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (1); *3-benzoyloxy,-2-methoxycarbonyl-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (2); *and 3-benzoyloxy,-8-methyl-8-azabicyclo(3.2.1)oct-2-ene* (3).

thetic" origin or (2) provide a less exacting (tedious) method for the determination of "synthetic" cocaine or both.

As an addendum, comment should be made upon the literature references one finds in the clandestine laboratory. Experience has shown that the neophyte chemist usually acquires clandestine laboratory books, such as those sold in "head shops," and these most often contain reprints of the work by Preobazhenskii [*18*]. The next most frequently encountered situation is the apprentice chemist, who through his college textbook is aware of the Willstatter [*11–13*] or Robinson- [*14,15*] Schoff [*17,32*] syntheses. The last and least commonly encountered situation is where the experienced chemist is involved. In this situation, the work by Findlay [*10,28*] generally will be the route of choice.

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