A PRACTICAL TOTAL SYNTHESIS OF COCAINE'S ENANTIOMERS

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SUMMARY

A simplified total synthesis of the single enantiomers of cocaine and racemic cocaine is outlined. The synthesis employs common laboratory glassware, reagents, and methods which can be performed in most forensic laboratories. The procedure for the isolation and purification of the dextrorotatory enantiomer of cocaine is presented.

INTRODUCTION

In many jurisdictions cocaine is listed as a controlled substance under statutes covering coca leaves and their extracts. Therefore only the levorotatory isomer of cocaine would be controlled. These laws do not include optical isomers and diastereoisomers. The question of enantiomeric composition has recently become popular with defense attorneys. (-)-Cocaine is the naturally occurring alkaloid extracted from coca leaves. Racemic and (+)-cocaine can only be obtained through a chemical synthesis.

The molecular structure of cocaine was first described by Willstätter and Muller[1] in 1898. It was not until the early 1950's that the, principles and methodologies of stereochemistry were applied to cocaine's tropane ring skeleton. Findlay[2], Fodor[3,4], and others established the stereochemistry of the tropane alcohols and their esters. Once this groundwork was laid, the three-dimensional structures of cocaine and its diastereoisomers (pseudococaine, allococaine, and allopseudococaine) were elucidated by Findlay[5-7] and Hardegger *et. al.*[8] Findlay's three-dimensional structures were confirmed in 1968 by Sinnema *et. al.*[9]using NMR spectral analysis. Electron impact fragmentation patterns of the tropane alkaloids were later established by Blossey *et. al.*[10] These workers identified the major mass spectral fragmentation patterns by deuterium and substituent labelling. Fragmentation patterns for various tropinone analogs have also been determined by Kashman and Cherokee[11].

Methods for detection of cocaine diastereoisomers have been established by Allen *et. al.*[12], Olieman *et. al.*[13], Sinnema *et. al.*[9], and Lewin *et. al.*[14] These methods incorporate IR, GC, GC-MS, NMR, and HPLC. Identification of the different enantiomeric mixtures can be done as illustrated by Eskes[15] and Allen *et. al.*[12] One report has been published concerning the detection of cocaine co-synthetics. This work by Cooper and Allen[16] lists and identifies the three most reoccurring substances.

The first total synthesis of cocaine was accomplished by Willstätter *et. al.*[17] Cocaine is prepared following a 3-5-step synthesis which includes one separation of epimers. This route is usually (±)-2-carbomethoxytropinone (2-CMT) → (±)-ecgonine methylester (EME) → (±)-cocaine. The reduction of 2-CMT with sodium amalgam yields a mixture of (±)-EME and (±)-pseudoecgonine methylester (PEME). If this epimeric mixture is not separated prior to benzoylation, a mixture of (±)-cocaine and (±)-pseudococaine results. Any unreacted tropinone or 2-CMT will become benzoylated to yield two co-synthetics identified by Cooper.

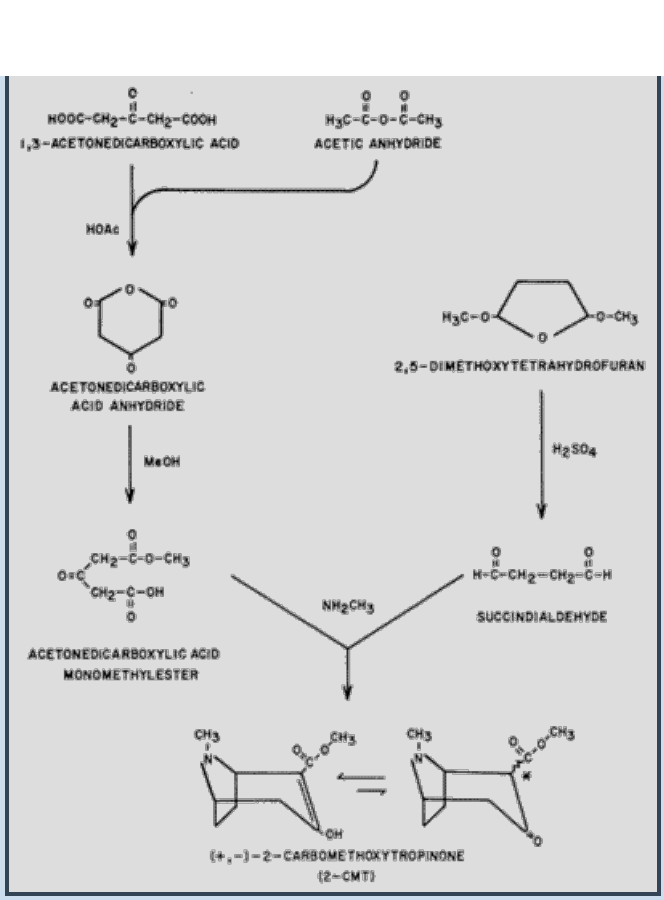
Fig. 1.
Synthetic route to 2-CMT.

It has been shown by Findlay[18], Cooper and Allen[16], and myself (unpublished) that direct synthesis of 2-CMT gives greater yields than the carbomethoxylation of tropinone. Preobrashenski[19] and Wallingford[20] synthesized 2-CMT and other beta-keto esters from condensation of alkyl carbonates with ketones. Findlay, Cooper, and myself found that such a route gives poor yields with

resinous by-products. It is noteworthy that Carroll et al.[21] obtained 2-CMT in 80% yield through an alkyl condensation.

Methylamine, acetonedicarboxylic acid, and succindialdehyde are potential starting materials for the synthesis of 2-CMT. 2-CMT is synthesized by first converting acetonedicarboxylic acid into its anhydride (84%) and then preparing the methyl ester from the anhydride (99%). These compounds can be synthesized following the procedures of Adams et al.[22], Kaushall[23] and Findlay[18], respectively. The mono-methyl ester of acetonedicarboxylic acid is reacted with methylamine and succindialdehyde via the Mannich condensation to yield 2-CMT (86%) (Fig. **1**). Thus the overall yield of 2-CMT is 71%.

Data has not been published concerning optimum conditions for 2-CMT synthesis. However an analogy can be drawn from tropinone and 2-CMT to pseudopelletierine optimum synthetic conditions. Pseudopelletierine is a ring homolog of tropinone having an eight-membered ring as opposed to the seven-membered ring of tropinone. Optimum conditions for its synthesis were established by Cope et al.[24]. Those workers found that a buffered solution at pH 3-4 and 25°C gave highest yields. Data by Schoph and Lehmann[25] show highest yields at pH 5-7. Preliminary experiments in our laboratory to synthesize 2-CMT, via the conditions of Cope and Schoph's pseudopelletierine synthesis, indicated the optimum conditions for 2-CMT synthesis were at pH 4-4.5 and 25°C (unpublished). I also found that a buffered reaction is critical for good yields of product. Cope stated that without buffered reactions the pseudopelletierine condensation reaction had a pH rise of 3.5 units. Keagle and Hartung[26] found that tropinone was prepared in highest yield with 0.0225 mol succindialdehyde per liter of solution. My work has shown an 86% yield of 2-CMT from 0.053 mol succindialdehyde per liter of solution. Mastering the ring coupling Mannich reaction is the key step in producing synthetic cocaine.



All practical routes to cocaine have used 2-CMT as the common intermediate. These routes include procedures by Findlay[18], Keagle[26], Kashman[11], Bazilevshaya[27], Sinnema[9], Schopf[25], Robinson[28,29], Mannich[30], Preobazhenskii[19], Zeigler[31], Zeile[32] and Willstätter[17,33,34]. New synthetic methods for entry into the tropane skeleton have been reported by Tufariello[35-37], Hawakawa[38], Noyori[39], Parker[40], Peterson[41], Iida[42] and Kashman[11] but are novel approaches with complicated synthesis.

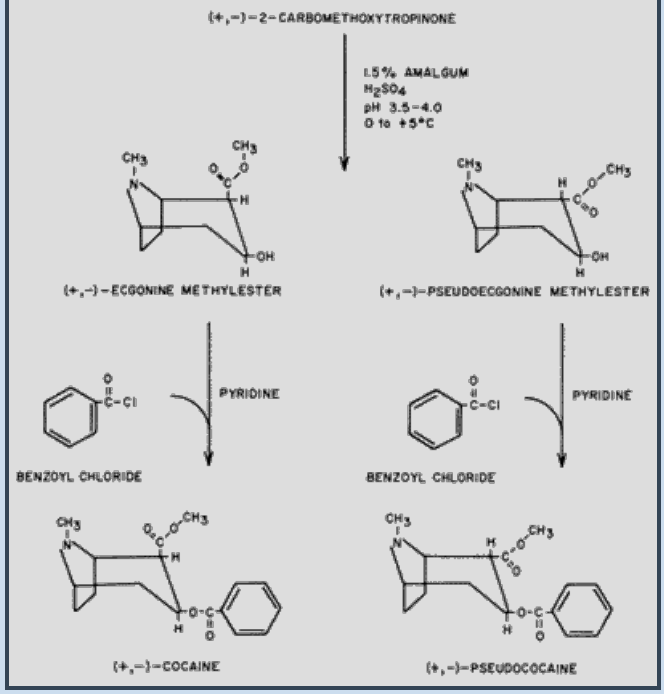
The reported sequence of synthesis (Figs. **1** and **2**) combines several procedures found in the literature. Clean-up procedures are based on the desired intermediate's solubilities in organic solvents.

2-CMT exists largely as the enol when hydrated and all three keto-enol isomers are present in solution. The keto nature allows it to be reduced by sodium amalgam to EME and PEME. The reduction is carried out at near the freezing point of water in an acid medium to yield the equatorial 3-hydroxy isomers of EME and PEME. The C-2 axial epimer EME is thermodynamically less stable and is easily irreversibly epimerized under basic conditions to PEME. Clarke et al.[43] attempted to influence the ratio of axial to equatorial C-2 epimers in their initial reactions but were unsuccessful.

EME is a colorless oil which is hydroscopic and any water absorbed causes slow hydrolysis to ecgonine. Aqueous alkaline solutions will also cause slow saponification. The conversion of EME into cocaine was studied at length by DeJong[44,45]. Various solvents and alkaline drying agents were used in his benzoylations. Sinnema et al.[9] also reported benzoylations with high yields.

Resolution of cocaine's enantiomers is accomplished through bitartrate recrystallizations. This resolution can be

Fig. 2.
Reduction and benzoylation of 2-CMT
(Single enantiomers are depicted for simplification, i.e. (-)-EME, (+)-PEME, (-)-cocaine and (+)-pseudococaine).



performed with 2-CMT prior to reduction and benzoylation as demonstrated by Carroll *(pers. comm.)*, Clarke et al.[43], and Lewin et al.[46,47].

Synthesis

Acetonedicarboxylic acid anhydride

To a solution of 30 ml glacial acetic acid and 22 ml of acetic anhydride (*Fisher*) at 10°C was slowly added 20g (0.684 mol) of 1,3-acetonedicarboxylic acid (*Aldrich*). The temperature was not allowed to rise above +12°C until the reaction was complete. For runs where precipitation of product had not occurred within 3 h, it was induced by the addition of benzene. The product was filtered by suction filtration, washed with 100 ml of glacial acetic acid, and next washed with 100 ml of benzene. It was allowed to dry yielding 14.8 g of white powder (84%).

Succindialdehyde

To 400 ml of 0.2 N sulfuric acid was slowly added 44.2 g (0.334 mol) of 2,5-dimethoxytetrahydrofuran (*Aldrich*) and stirred for 15 min. The succindialdehyde was allowed to stand for 4 h without further treatment.

Acetonedicarboxylic acid monomethyl ester

To a flask containing 41.0 g (0.32 mol) of acetonedicarboxylic acid anhydride was added 160 ml of cold dry methanol. The mono-methyl ester solution was allowed to stand for one hour and filtered.

(±)-2-Carbomethoxytropinone

Six liters of 4.4 pH citrate buffer was made by diluting 35.3 g of citric acid and 38.8 g of sodium citrate dihydrate to volume. To the buffer was added 32.0 g (0.48 mol) of methylamine hydrochloride (*Fisher*) and 12.8g (0.32 mol) of sodium hydroxide. The succindialdehyde solution was added dropwise to the buffer over 10 min with stirring at room temperature. The mono-methyl ester solution was next added dropwise over 10 min with stirring. The reaction was stirred 48 h at room temperature. The reaction was extracted in 250-ml portions by making the pH 12 with concentrated ammonium hydroxide and extracted 4 times with 200 ml of chloroform. The extracts were dried over sodium sulfate and evaporated in vacuo. The resulting yellow oil was dissolved in 200 ml of dry diethyl ether and filtered. The filtrate was evaporated in vacuo. The oil was next dissolved into 200 ml of petroleum ether and filtered. The filtrate was evaporated in vacuo and the resulting oil was allowed to hydrate upon standing. The crude hydrate was 95% pure and purified further by sublimation to yield snow white flakes, mp 96-98.5°C. Yield: 58.9 g (86%).

Resolution of (±)-2-carbomethoxytropinone

To a solution of 26.60 g (0.124 mol) of sublimed racemic 2-CMT in 106 ml of absolute ethanol was added dropwise a solution of 18.57 g (0.124 mol) of (-)-tartaric acid in 133 ml of absolute ethanol. After 48 h the mother liquor was decanted and set aside. The crystals were washed with 50 ml of absolute ethanol and then dissolved into a minimal amount (approx. 200 ml) of hot dry methanol. The solution was filtered while hot into an Erlenmeyer flask and covered. The solution was left undisturbed for 72 h. The solution was decanted off and combined with the first mother liquor. The crystals of anhydrous (-)-2-CMT bitartrate were washed with 100 ml of dry acetone and dried yielding 6.8g (30%), $[\alpha]_D^{24}$ -16.9° (c=2, H_2O). Findlay[18] reported $[\alpha]_D^{20}$ -16.9° (c=2, H_2O). The mother liquors were evaporated to dryness and dissolved into 200 ml of water, made pH 8 with sodium carbonate, and extracted 5 times with 200 ml of methylene chloride. The extracts were dried over sodium sulfate and evaporated in vacuo. The (+)-enriched 2-CMT was hydrated yielding 17.5 g of powder.

To a solution of 17.2 g (0.08 mol) of (+)-enriched 2-CMT in 70 ml of absolute ethanol was added a solution of 12.0 g (0.08 mol) of (+)-tartaric acid in 86 ml of absolute ethanol. Subsequent recrystallizations yielded 6.95 g of anhydrous (+)-2-CMT bitartrate (30%), $[\alpha]_D^{24}$ +16.9° (c=2, H_2O). Freebasing the mother liquors and retreatment with (-)-tartaric acid yielded 6.0 g more anhydrous (-)-2-CMT bitartrate, $[\alpha]_D^{24}$ -17.0° (c=2, H_2O). Thus the overall yield of anhydrous (-)-2-CMT bitartrate was 12.8 g (57%).

(+)-Ecgonine methyl ester

Into a three-neck 500 ml round bottom flask was placed 7.70 g (0.036 mol) of (-)-2-CMT hydrate with 51 ml of ice cold 10% sulfuric acid. Bromophenol blue (approx. 2 mg) indicator was added. With stirring the solution was treated with 1028 g of 1.5% sodium amalgam in small portions over 2.5 h. The temperature was kept under +5°C. The pH was monitored via the indicator and kept between pH 3 and 4 with cold 30% sulfuric acid. Periodic addition of water was necessary to dissolve sodium sulfate salts. The reaction was stirred an additional 45 min after the addition of amalgam was complete. The solution was separated from the mercury, adjusted to pH 12 with sodium hydroxide and extracted three times with 200 ml of chloroform. The extracts were dried over sodium sulfate and evaporated in vacuo to a light green oil containing a 3:1 ratio of EME to PEME. The oil was dissolved into 200 ml of petroleum ether and filtered. The filtrate was evaporated in vacuo. The resulting oil was dissolved into 500 ml of dry diethyl ether and the hydrochloride salts were made with ethereal HCl. The salts were filtered and immediately dissolved into a minimal amount of dry methanol. The methanol was evaporated in vacuo and 120 ml of dry chloroform was added to the crystals. The slurry of crystals was filtered and dried yielding 2.28 g of (+)-ecgonine methyl ester hydrochloride (27%). The product was recrystallized from methanol and diethyl ether to yield 2.2 g of pure product $[\alpha]_D^{24}$ +52.3° c=1, MeOH), mp 213-214°C. Lewin et al.[47] reported mp 213.5-214.5°C, $[\alpha]_D^{24}$ +52.3° (c=1, MeOH).

Racemic and (-)-EME can be synthesized by the same reduction procedure and clean-up using (±)-2-

CMT and (+)-2-CMT respectively.

(+)-Cocaine

In an oven-dried 100-ml round bottom flask was added 1.00g (4.25 mmol) of (+)-ecgonine methyl ester HCl with 7 ml of dry pyridine and stirred in an ice bath. The reaction was protected from moisture with argon. Dropwise over 5 min was added a solution of 0.8 ml (6.85 mmol) of benzoyl chloride in 5 ml of pyridine. After addition was complete the ice bath was removed and the reaction was stirred 24 h under argon. Dry acetone (200 ml) was added and the slurry was filtered by suction filtration. The crude (+)-cocaine hydrochloride was washed with an additional 100 ml of dry acetone. The product was dried yielding 1.28 g (89%). The hydrochloride was dissolved into 20 ml of water, made pH 8 with 5% ammonium hydroxide, and extracted 4 times with 50 ml of methylene chloride. The solvent was dried over sodium sulfate and evaporated in vacuo. The free base was recrystallized from diethyl ether and petroleum ether yielding 1.01 g (78%) of pure (+)-cocaine base, $[\alpha]_D^{24}$ +35.8° (c=1, 50% aqueous EtOH), mp 96.0-97.5°C. The literature[48] lists the (-)-enantiomer at $[\alpha]_D^{24}$ -35° (c=1, 50% aqueous EtOH), mp 98°C.

Racemic and (-)-cocaine can be synthesized using the same benzoylation procedure and clean-up using (+)-EME and (-)-EME respectively.

Experimental Procedure

Melting points were determined on a Mel-Temp capillary tube apparatus. Optical rotations were recorded at the sodium D line with a Rudolph Autopol III Automatic Polarimeter (1 dm cell). Infrared (IR) spectra were recorded in potassium bromide disks with a Beckman Microlab 600 spectrometer. A Finnigan Model 5100 GC-MS with Supelcos Data System was used for producing the mass spectra. A 30-m fused silica, SE 54 capillary column (i.d. 0.25 mm) (Supelco) was employed with helium (99.99% VHP) as the carrier gas. The injection port temperature was 250°C and the sample was injected in the splitless mode. The initial column temperature was 120°C and was ramped at 10°C/min to 260°C. The quadrupole mass analyzer operated under electron impact conditions at 70 eV.

Figures **3-11** present infrared spectra of the intermediates and final products. Figures **12-17** present mass spectra of the same compounds.

- Fig. 3. Infrared spectrum of (±)-2-CMT hydrate.
- Fig. 4. Infrared spectrum of (±)-2-CMT anhydrous base.
- Fig. 5. Infrared spectrum of (-)-2-CMT hydrate.
- Fig. 6. Infrared spectrum of (±)-EME hydrochloride.
- Fig. 7. Infrared spectrum of (+)-EME hydrochloride.
- Fig. 8. Infrared spectrum of (±)-PEME base.
- Fig. 9. Infrared spectrum of (+)-PEME base.
- Fig. 10. Infrared spectrum of (±)-cocaine base.
- Fig. 11. Infrared spectrum of (+)-cocaine base.
- Fig. 12. Electron impact mass spectrum of tropinone.
- Fig. 13. Electron impact mass spectrum of 2-CMT.
- Fig. 14. Electron impact mass spectrum of EME.
- Fig. 15. Electron impact mase spectrum of PEME.
- Fig. 16. Electron impact mass spectrum of cocaine.
- Fig. 17. Electron impact mass spectrum of pseudococaine.

Discussion

(+)-Cocaine base was obtained overall in 8.6% of theoretical yield. Isolation and purification of intermediates and final product were performed through their solubilities in organic solvents and recrystallizations. Liquid chromatography was not used in this procedure but could be used to increase the yield of EME.

Extracting 2-CMT from the Mannich reaction at pH 12 restricts gummy tar-like substances from co-extracting. The extraction must be performed quickly since the product will undergo self-condensation at this pH. Conversely a very acidic pH will cause decarboxylation to tropinone. Dissolution of 2-CMT in diethyl ether and petroleum ether precipitates any resinous by-products. 2-CMT was found to be more stable as the hydrate. The anhydrous base would turn dark brown within one week if it was not hydrated.

EME hydrochloride is practically insoluble in chloroform. This property allows PEME hydrochloride and other impurity hydrochlorides to be separated. EME will slowly hydrolyze to ecgonine in water. Its extractions from aqueous alkaline solutions must be done promptly to prevent saponification.

Cocaine hydrochloride is insoluble in dry acetone. This allows cocaine to be separated from unreacted benzoyl chloride, EME, and pyridine.

(+)-Cocaine gives an identical microcrystalline precipitate to that of (-)-cocaine in gold chloride-HOAc. When the separate enantiomers are mixed they give racemic crystals in gold chloride-HOAc as described by Allen *et. al.*[12] and identical crystals to a sample of racemic cocaine synthesized from this procedure.

The infrared spectra of levo-, dextro- and racemic cocaine hydrochloride are identical. The infrared spectra of racemic cocaine base and its single enantiomers have definite differences (Figs. **10** and **11**).

It is my hope that this procedure will allow other forensic laboratories to synthesize their own (+)-cocaine and (±)-cocaine without the use of expensive and sophisticated equipment.

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