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CONVENIENT SYNTHESIS OF BENZOYLECGONINE ETHYL ESTER, A HOMOLOG OF COCAINE

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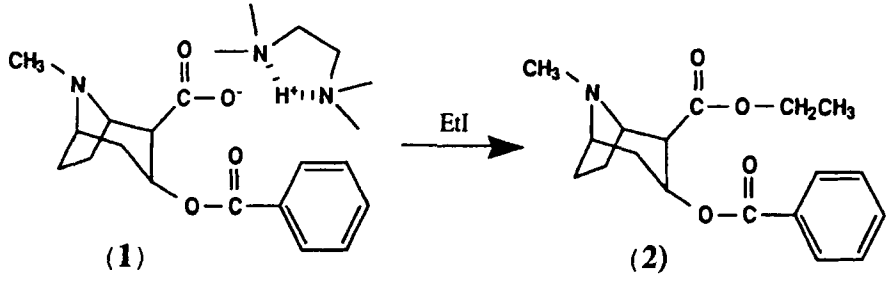
ABSTRACT: Benzoylecgonine reacted with tetramethylethylenediamine to form a lipophilic ion pair, which was alkylated in the absence of water. The ethyl ester was readily recrystallized for pharmacological studies.

Benzoylecgonine ethyl ester (**2**, "cocaethylene"[1-4] or "ethylcocaine"[5,6]) is currently of interest because of its appearance in the urine and blood of individuals co-abusing cocaine and ethanol,[1-4] and in brain tissue obtained at autopsy after deaths associated with concurrent use of these two drugs.[3]



(**1**) (**2**)

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The availability of pure **2** is required in the development of analytical methods[1,6,7] and investigation of its pharmacological properties. Recent reports indicate that **2** stimulates motor activity in rodents to the same degree as cocaine[4,5] and that monkeys will self-administer **2** to the same extent as cocaine.[4] Moreover, at high doses, **2** is substantially more toxic than cocaine.[8] More extensive studies using pure **2** will undoubtedly provide a better understanding of the pathological and behavioral consequences of the all too common co-abuse of ethanol and cocaine.

Preparation of **2** has been carried out by esterification of benzoylecgonine (BE) in the presence of acid[9] or acylating agents,[7,8] by alkylation of salts of BE with ethyl iodide,[1,10] or by benzoylation of ecgonine ethyl ester.[2] We report here a simple procedure that leads to a pure crystalline product without the need for chromatographic purification. As in the extractive alkylation method,[1,11] we used BE in the form of a lipophilic ion pair (**1**). The solubility of **1** in CH_2Cl_2 allowed the alkylation to be carried out in a homogeneous medium, facilitating removal of unchanged BE by washing and isolation of the nearly pure product upon evaporation of the solvent.

Anionic displacement reactions are rarely carried out in nonpolar solvents,[12,13] mainly because of solubility limitations. This approach deserves more attention, because the nucleophilic reactivity of soluble ion pairs is frequently equivalent to that of free ions in the same solvents,[14-16] and the lower dielectric constant of typical aprotic solvents may have only a modest effect on the reaction rates.[15,16]

Hydrolysis of free base cocaine in water gave BE, mp 201-202°C (lit[17] mp 199-201°C), in 53% yield.[17] Conversion of BE to **2** was carried out in a

stirred reaction mixture containing 4-fold excess tetramethylethylenediamine (TEMED), 20-fold excess iodoethane, and CH_2Cl_2 as the solvent. After 3 days at room temperature there was 85% conversion according to HPLC analysis. The reaction mixture was filtered to remove the precipitate of TEMED-HI. The CH_2Cl_2 solution was washed with 5% Na_2CO_3 to prevent isolation of **2** as the iodide salt,[18] which was soluble in CH_2Cl_2. The organic layer was decolorized with dilute $Na_2S_2O_3$ and freed of ions by washing with three portions of water, as determined by conductivity measurements and tests for iodide ion. The CH_2Cl_2 solution was dried with anhydrous Na_2SO_4 and evaporated in vacuo, leaving crude **2**, mp 105-108°C. Recrystallization from a small volume of isopropanol gave pure **2**, mp 108-109°C, in 72% yield from BE. The overall yield from cocaine hydrochloride was 38%.

The crystalline product was characterized by HPLC,[6,19] GC/MS,[6,20] and ^{1}H-NMR.[21] HPLC showed a single peak, confirming the removal of BE during the isolation procedure. GC/MS showed a single gas chromatographic peak which yielded the expected $(M-H)^-$ peak at m/z 317.[22] A commercially available analytical standard[23] displayed identical results on HPLC and GC/MS. The ^{1}H-NMR spectrum of **2** exhibited changes expected for the replacement of methoxy by ethoxy, including a triplet at 1.25 ppm (CH_3) and a 16-line multiplet centered at 4.25 ppm (CH_2).[24] The multiplet is consistent with the presence of non-equivalent methylene protons, apparently due to restricted rotation of the ethyl group.[25] A 5-line multiplet at 5.1 ppm confirmed that **2** has the same stereochemistry as cocaine.[26]

For pharmacological studies, **2** was converted to the hydrochloride salt in a solution of absolute ethanol saturated with dry HCl. Evaporation of the

solvent yielded the salt, mp 147-153°C,[27] and HPLC showed less than 1% hydrolysis of **2**. Treatment of **2** with aqueous HCl (0.01 M), resulted in substantial hydrolysis to BE. The method is useful for the preparation of large quantities of pure **2**-HCl.

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18. An authentic sample of the salt was prepared by extraction of HI from an aqueous solution of NaI and HCl with a CH_2Cl_2 solution of **2**. Evaporation of the dried CH_2Cl_2 solution gave a quantitative yield of **2**-HI, mp 175-182°C, recryst. from isopropanol, mp 188-189°C. ^{1}H-NMR (300 MHz, $CDCl_3$) 7.4-8.0 (m), 5.5-5.6 (5-line m), 4.5-4.7 (m), 4.1-4.3 (m), 3.3 (s), 2.1-3.6 (m), 1.0 (t). The salt appeared identical to **2** in GC/MS and HPLC, exhibiting the same retention times and MS pattern.

19. Reversed-phase chromatographic (RP-HPLC) conditions: column, Beckman Ultrasphere C8 (15 cm x 4.6 mm x 5 μm) maintained at 43°C; mobile phase, 23% acetonitrile in .25 M KH_2PO_4-100 mM pentane-sulfonic acid, pH 2.7; flow rate 1.4 mL/min; detection 235 nm, .01 AUFS. Retention times: BE, 2.11 min.; **2**, 8.19 min.

20. GC/MS: dried extracts of BE and **2** were reconstituted and derivitized with N-methyl-N-(trimethylsilyl) trifluoroacetamide/trimethylchlor-

osilane (100/2). Instrument: Hewlett-Packard 5970B GC/MS equipped with a phenylmethyl-silicone column (Ultra-2, 12 m, .2 mm i.d., .33 μm film); carrier gas, helium at 45 cm/sec and 200°C.

21. Internal standards: TMS ($CDCl_3$), 3-(trimethylsilyl)-propionic-2,2,3,3-d_4 acid (D_2O). Instruments: Varian EM360A NMR spectrometer (60 MHz), GE QE300 NMR spectrometer (300 MHz).

22. m/e calc'd for $C_{18}H_{22}NO_4$: 317.37, found 317.2; 317 (M^+, 31.3), 272 (16.4), 212 (10.4), 196 (76.9), 122 (8.9), 82 (100), 77 (25.4).

23. Ethanol solution containing 1 mg/ml of **2** was obtained from Radian Corporation, Austin, Texas 78720-1088.

24. ^{1}H-NMR (300 MHz, $CDCl_3$) 7.3-8.1 (m), 5.2-5.3 (m), 4.1-4.4 (m, CH_2), 3.0-3.7 (m), 2.2 (s), 1.7-2.5 (m), 1.2 (t, CH_3).

25. Using a spectrum simulation program resident on a GE 300 MHz spectrometer, the ethoxy spectrum was satisfactorily simulated as an ABX_3 spin system: chemical shifts, A(4.26 ppm), B(4.12 ppm), X(1.24 ppm); coupling constants, J(A,B) = 12 Hz, J(A,X) = J(B,X) = 7.1 Hz.

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27. ^{1}H-NMR (300 MHz, 99.8% D_2O) 7.6-8.1 (m), 5.6-5.7 (m), 4.2 (q), 3.7-3.8 (m), 3.0 (s), 2.3-2.7 (m), 1.0 (t).

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