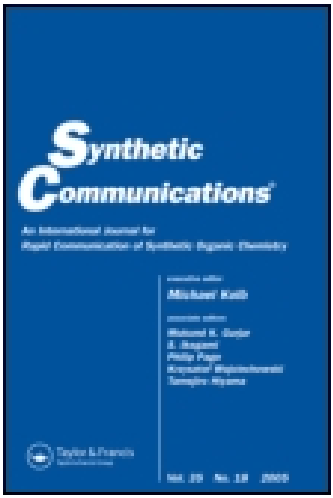

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A CONVENIENT SYNTHESIS OF 2'- OR 4'-HYDROXYCOCAINE

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ABSTRACT

A short, convenient and efficient synthesis of 2'- or 4'-hydroxycocaine is described. The key step involved selective hydrolysis/transesterification of the acetoxy group of 2'- or 4'-acetoxycocaine in methanol saturated with dry HCl gas.

Hydroxycocaines have been reported as cocaine metabolites in bile and urine samples from emergency cocaine overdose patients.[1-3] It was shown that 3'-hydroxycocaine contributed to cocaine's peripheral vasoconstrictive effects[4] and 4'-hydroxycocaine was equipotent to cocaine in locomotor stimulation and convulsant actions.[5] 2'-Hydroxycocaine has not yet been detected as a cocaine metabolite. Nevertheless, 2'-hydroxycocaine is an interesting compound because unlike 3'- and 4'-hydroxycocaines it can form an intramolecular hydrogen

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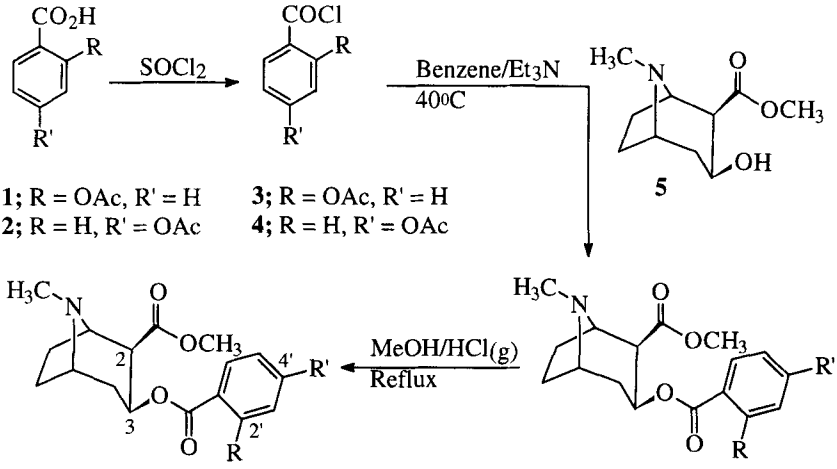
bonding. As a result, 3β-benzoyl ester functionality in 2'-hydroxycocaine will be more stable to hydrolysis due to reduced electrophilicity and also the phenyl ring will be locked in the same plane as that of the carbonyl function. Therefore, synthesis of these hydroxycocaines is exceedingly important in exploring their pharmacological activities.

Several procedures for the synthesis of 2'- and 4'-hydroxycocaines have been reported.[3,6,7] In these approaches ecgonine methyl ester (**5**) was coupled with either 2- or 4-hydroxybenzoic acid in the presence of thionyl chloride[3] or DCC[6], or 2- or 4-acetoxybenzoic acid in the presence of thionyl chloride followed by basic hydrolysis.[7] These methodologies for the preparation of hydroxycocaines are of rather limited use because they gave a mixture of products in typically less than milligram quantities. Recent synthesis of 3'-hydroxycocaine has utilized 3-benzyloxybenzaldehyde, which after oxidation and halodehydroxylation was coupled with ecgonine methyl ester. The advantage of this synthesis was that the benzyloxy group of 3'-benzyloxycocaine could be selectively hydrogenolyzed without affecting any of the other ester functions.[8] The synthesis of 2'- or 4'-hydroxycocaine which we report in this publication is short, efficient, and highly convenient.

As outlined in Scheme 1, commercially available 2- or 4-acetoxybenzoic acid (**1** or **2**) was refluxed in excess of thionyl chloride to afford 2- or 4-acetoxybenzoylchloride (**3** or **4**) in 80-85% yield which without further purification was reacted with ecgonine methyl ester (**5**) in benzene containing triethylamine at 40^0C to gave 2'- or 4'-acetoxycocaine in high yield (80%).

Scheme 1



The key step in the synthesis was to selectively hydrolyze the acetoxy group in **6** or **7** without hydrolyzing the other ester functions. Previous synthesis has utilized water or basic conditions to hydrolyze the acetoxy group of acetoxycocaine.[7] This synthesis has produced a mixture of products, i.e., other ester functions were also hydrolyzed to a certain extent. In our synthesis we used methanol saturated with dry HCl gas to selectively remove the acetyl group. Thus 2'- or 4'-acetoxycocaine (**6** or **7**) was refluxed in MeOH saturated with dry HCl gas for 24-48 h. The trace amount of water present in MeOH (0.02%) hydrolyzed the acetoxy group selectively, and there was no observable hydrolysis of any other ester functions. It was possible that the carbomethoxy group at C-2 might have hydrolyzed to some extent. However, under the reaction conditions it was

reesterified. Another possible mechanism of the HCl gas-catalyzed selective cleavage of the acetoxy group could be the transesterification with MeOH as a nucleophile. The excess of MeOH facilitated the reaction in the forward direction to give **8** or **9** and the trace moisture present in MeOH dissolved enough HCl gas to act as an acid catalyst, but only enough to catalyze the transesterification of the relatively unhindered ester functional groups. Although transesterification of the 2β-carbomethoxy group in **6** or **7** with MeOH would not change the character of this ester function, the 3β-benzoyloxy ester function did not undergo transesterification under the reaction conditions. No work up was required. The excess of methanol was removed and 2'- or 4'-hydroxycocaine hydrochloride salt (**8** or **9**) was precipitated out with ether in quantitative yield.

In summary, a short (2 or 3 steps) and efficient (65-70%) synthesis of 2'- or 4'-hydroxycocaine was developed. This synthesis is more convenient than other syntheses of hydroxycocaines reported thus far, and can also be utilized to prepare 3'-hydroxycocaine. In addition the synthesis could be extended to prepare 2'- or 4'-hydroxybenzoylecgonine, metabolites of cocaine by refluxing the 2'- or 4'-hydroxycocaine free base in water[8] or water/dioxane (1:1).[9] These methods are known to selectively hydrolyze the carbomethoxy ester at C-2.

EXPERIMENTAL

Unless otherwise stated all starting materials were obtained from Aldrich Chemical Company (Milwaukee, WI) and used without further purification. Confiscated crude (-)-cocaine hydrochloride was obtained from the National Institute on Drug Abuse.

^{1}H NMR spectra were recorded on a Varian XL-300 MHz spectrometer. FAB/MS was carried out with VG instruments, ZAB-E spectrometer (Manchester, UK). Melting points were recorded on an Uni-melt Thomas Hoover capillary melting point apparatus in open capillary tubes and were uncorrected. Elemental analysis was performed by Midwest Micro Lab Ltd. (Indianapolis, IN). The purities of the final products (**8,9**) were checked using a Beckman Gold HPLC system equipped with dual Model 110 (A and B) pumps, a Rheodyne loop injector (20 μL loop was used), a 163 variable wavelength uv detector, and an Analog Interface Module 406. A reverse phase column (4.6 x 100 mm; C-18; particle size 3 micron, pore size 100 A^0) (Rainin Instruments Co., Woburn, MA) was used. A solvent system containing methanol/0.05M phosphate buffer (80:20 v/v), pH 7.4 was employed at a flow rate of 1.0 mL/min. The sample was dissolved in methanol (1 mg/mL) and a volume of 5-10 μL was injected.

4-Acetoxybenzoylchloride (4): 4-Acetoxybenzoic acid (**2;** 3.0 g, 16.6 mmol) was dissolved in excess of thionyl chloride (15 mL) and refluxed with stirring for 2.5 h. The excess of thionyl chloride was removed under vacuum to obtain 2.6 g (80%) of **4** as a yellow viscous oil.

Ecgonine methyl ester (5): Compound **5** was synthesized from crude (-)-cocaine hydrochloride in two steps. First, cocaine hydrochloride (50 g; 0.147 mol) was dissolved in 1N aqueous HCl acid (500 ml) and heated to reflux. After refluxing for 16 h, the reaction mixture was cooled to room temperature, filtered to get rid of crystallized benzoic acid, and the filtrate was extracted with CH_2Cl_2

(3 x 50 mL) to remove any dissolved benzoic acid. The filtrate was evaporated under reduced pressure to obtain a sticky solid, which was dissolved in methanol, and ecgonine hydrochloride was precipitated out by adding acetone in 86.1% yield (28.1 g), m.p. 240-242^{0}C (lit.[10] 240-244^{0}C). Second, ecgonine hydrochloride (28.1 g; 0.126 mol) was dissolved in 280 mL of dry methanol and dry HCl gas was passed until saturation. The resultant mixture was heated to reflux under dry atmosphere. After refluxing for 30 min, the mixture was cooled and dry HCl gas was again passed through it until saturation. The clear solution was stirred at room temperature for 24 h under anhydrous conditions. The methanol/$HCl_{(g)}$ mixture was removed under vacuum. The last traces of moisture/HCl were removed by azeotropic distillation with benzene. A white solid of ecgonine methyl ester hydrochloride was obtained, which was dissolved in methanol and precipitated out with acetone in 94.4% yield (28.2 g), m.p. 210^{0}C (lit.[11] 210-211^{0}C). ^{1}H NMR (D_2O): δ 4.26 (ddd, $J_{3,4ax}$= 11.1 Hz, $J_{2,3}$= 6.9 Hz, $J_{3,4eq}$= 6.6 Hz, 1H, 3-H), 4.0-3.9 (m, 1H, 1-H), 3.8-3.7 (m, 1H, 5-H), 3.61 (s, 3H, OCH_3), 3.12 (dd, $J_{2,3}$= 7.2 Hz, $J_{1,2}$= 2.4 Hz, 1H, 2-H), 2.64 (s, 3H, NCH_3), 2.2-2.1 (m, 2H, 4-H_2), 2.1-1.8 (m, 4H, 6,7-H_2) ppm.

2'-Acetoxycocaine (6): Ecgonine methyl ester free base (**5;** 0.9 g; 4.5 mmol) was dissolved in dry benzene (15 mL) and triethylamine (1 mL; 10 mmol) was added. To this stirred solution commercially available acetylsalicyloyl chloride (**3;** 1.4 g, 7.0 mmol) was added under dry N_2. The resulting reaction mixture was stirred at 40$\pm$2^{0}C overnight. It was then cooled, and the contents were transferred to a separatory funnel with the help of 5 mL of chloroform. The

combined organic phase was washed with water (5.0 mL), 5% aqueous Na_2CO_3 solution (3 x 5.0 mL), dried over anhydrous $MgSO_4$, and the solvent mixture was removed under vacuum to give an oil. The oily product was dissolved in ether and dry HCl gas passed to obtain hydrochloride salt. Recrystallization from MeOH/ether gave pure **6** (1.24 g, 76%), m.p. 78-80^{0}C. FAB/MS (3-NBA matrix): 362.1 (MH^+; $C_{19}H_{24}NO_6$). ^{1}H NMR (D_2O): δ 7.78 (dd, J= 8.4, 1.2 Hz, 1H, 6'-H), 7.6-7.5 (m, 1H, 4'-H), 7.26 (d, J= 8.7 Hz, 1H, 5'-H), 7.05 (d, J= 8.7 Hz, 1H, 3'-H), 5.4-5.3 (m, 1H, 3-H), 4.1-4.0 (m, 1H, 1-H), 3.9-3.8 (m, 1H, 5-H), 3.5-3.4 (m, 1H, 2-H), 3.45 (s, 3H, OCH_3), 2.69 (s, 3H, NCH_3), 2.18 (s, 3H, 2'-$COCH_3$), 2.3-2.2 (m, 4H, 4,7-H_2), 2.0-1.9 (m, 2H, 6-H_2) ppm. Anal. calcd for $C_{19}H_{23}NO_6$.HCl.1/2H_2O: C 56.12; H 6.14; N 3.44. Found: C 56.01; H 5.89; N 3.68.

4'-Acetoxycocaine (7): To a stirred solution of 4-acetoxybenzoyl chloride (**4**; 1.58 g, 8.0 mmol) in 10 mL of dry benzene, ecgonine methyl ester free base (**5**; 1.0 g; 5.0 mmol) dissolved in 10 mL of dry benzene and triethylamine (2 mL; 20 mmol) were added. The resultant reaction mixture was stirred at 40$\pm$2^{0}C under dry N_2 overnight. The mixture was cooled, added 5 mL of water, and the organic phase was separated. The organic phase was additionally washed with cold aqueous 5% Na_2CO_3 (3 x 5 mL), brine (5 mL), and dried over anhydrous Na_2CO_3. The solvent was stripped of under vacuum to obtain an oil, which was dissolved in 5 mL of ether and dry HCl gas was passed to obtain pure hydrochloride salt of **7** in 80% yield (1.59 g), m.p. 145-148^{0}C . FAB/MS (3-NBA matrix): 362.1 (MH^+;

$C_{19}H_{24}NO_6$). ^{1}H NMR (D_2O): δ 7.84 (d, J= 8.7 Hz, 2H, 2',6'-H), 7.09 (d, J= 8.7 Hz, 2H, 3',5'-H), 5.45 (dd, J= 16.2, 6.9 Hz, 1H, 3-H), 4.1-4.0 (m, 1H, 1-H), 4.0-3.9 (m, 1H, 5-H), 3.5-3.4 (m, 1H, 2-H), 3.45 (s, 3H, OCH_3), 2.71 (s, 3H, NCH_3), 2.4-2.2 (m, 4H, 4,7-H_2), 2.17 (s, 3H, 4'-$COCH_3$), 2.1-2.0 (m, 2H, 6-H_2) ppm. Anal. calcd for $C_{19}H_{23}NO_6$.HCl.2H_2O: C 52.63; H 6.45; N 3.22. Found: C 52.49; H 6.14; N 3.48.

2'-Hydroxycocaine (8): 2'-Acetoxycocaine hydrochloride (**6**; 0.9 g, 2.5 mmol) was dissolved in 40 mL of MeOH and dry HCl gas was passed. The resulting solution was refluxed with stirring for 48 h under dry atmosphere. It was then cooled and the solvent was removed under vacuum to obtain a white solid. Recrystallization of the solid from MeOH/ether afforded pure **8** (0.75 g, 94%), m.p. 104^{0}C. FAB/MS (3-NBA matrix): 320.1 (MH^+; $C_{17}H_{22}NO_5$). ^{1}H NMR (D_2O): δ 7.58 (dd, J= 7.8, 1.5 Hz, 1H, 6'-H), 7.4-7.3 (m, 1H, 4'-H), 6.9-6.8 (m, 2H, 3',5'-H), 5.5-5.4 (m, 1H, 3-H), 4.1-4.0 (m, 1H, 1-H), 4.0-3.9 (m, 1H, 5-H), 3.5-3.4 (m, 1H, 2-H), 3.46 (s, 3H, OCH_3), 2.70 (s, 3H, NCH_3), 2.4-2.2 (m, 4H, 4,7-H_2), 2.1-2.0 (m, 2H, 6-H_2) ppm. Anal. calcd for $C_{17}H_{21}NO_5$.HCl.1/2H_2O: C 56.00; H 6.30; N 3.84. Found: C 56.34; H 6.38; N 3.55. HPLC showed a single peak at a retention time of 3.30 min (for HPLC conditions see experimental).

4'-Hydroxycocaine (9): 4'-Acetoxycocaine hydrochloride (**7**; 1.59 g, 4.0 mmol) was dissolved in 80 mL of methanol and dry HCl gas was passed until saturation. The resultant clear solution was refluxed for 24 h under anhydrous conditions. The mixture was cooled to room temperature and the solvent removed

under reduced pressure to obtain a white solid. Recrystallization of the white solid from methanol/ether furnished pure **9** in 81% yield (1.15 g), m.p. 169-171^{0}C. FAB/MS (3-NBA matrix): 320.1 (MH^+; $C_{17}H_{22}NO_5$). ^{1}H NMR (D_2O): δ 7.68 (d, J= 8.7 Hz, 2H, 2',6'-H), 6.76 (d, J= 9.0 Hz, 2H, 3',5'-H), 5.35 (dd, J= 15.0, 6.9 Hz, 1H, 3-H), 4.1-4.0 (m, 1H, 1-H), 3.9-3.8 (m, 1H, 5-H), 3.5-3.4 (m, 1H, 2-H), 3.43 (s, 3H, OCH_3), 2.67 (s, 3H, NCH_3), 2.3-2.1 (m, 4H, 4,7-H_2), 2.1-2.00 (m, 2H, 6-H_2) ppm. Anal. calcd for $C_{17}H_{21}NO_5$.HCl.H_2O: C 54.65; H 6.42; N 3.74. Found: C 54.28; H 6.28; N 3.97. The retention time of **9** on a C-18 column (as described under experimental) was 2.54 min and a single peak.

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