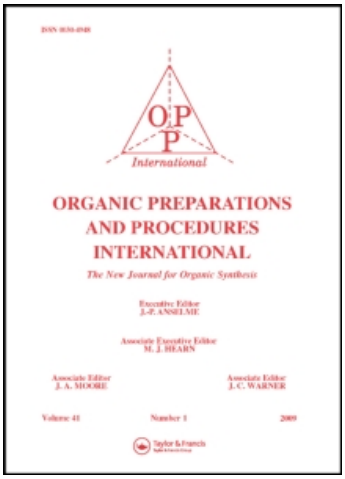

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AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF ANHYDROECGONINE METHYL ESTER

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AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF ANHYDROECGONINE METHYL ESTER

Submitted by (10/02/96)

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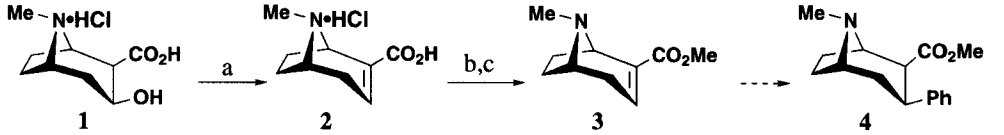
3β-phenyl-2β-carbomethoxytropane (**4**) and its analogs are widely used as probes for the cocaine receptor sites[1] and radiolabeled analogs are being evaluated as medical imaging agents.[2] (-)-Anhydroecgonine methyl ester (**3**), the key intermediate in the synthesis of compound **4**, has typically been prepared by phosphorus oxychloride dehydration of ecgonine hydrochloride (**1**) followed by methanolysis.[3] However, this method is not consistently reliable and uses phosphorus oxychloride as the solvent, posing handling and disposal problems with larger scale preparations. Analytical amounts of **3** have also been prepared *via* the synthesis and esterification of anhydroecgonine hydrochloride (**2**);[4] however, this approach has not found widespread use.



1 2 3 4

(a) 12 M HCl, 110°, 14–15 hrs; (b) acetyl chloride, MeOH, 0–65°; (c) sat. NH_4OH, 0°

As part of our ongoing studies of the structure-activity relationship between analogs of **4** and

the cocaine receptor as well as our commitment to provide 3β-aryl-2β-carbomethoxytropanes to the National Institute on Drug Abuse (NIDA), we require a reliable, efficient method for the preparation of large amounts of **3**. Herein, we describe an improved, upscaled synthesis of anhydroecgonine methyl ester, based on the work of de Jong.[5] This method involves hydrochloric acid catalyzed dehydration of ecgonine hydrochloride (**1**) followed by esterification in methanolic hydrogen chloride.

A number of methods for the conversion of ecgonine hydrochloride (**1**) to anhydroecgonine hydrochloride (**2**) have been reported.[6] Dehydration in refluxing conc. hydrochloric acid[5] employs only volatile, inexpensive and readily disposable reagents while giving good yields of **2**.

Ecgonine hydrochloride is readily dehydrated to anhydroecgonine hydrochloride upon heating at 110–114° in conc. hydrochloric acid for 14–15 hrs. It is important that the temperature be maintained well above 100° to ensure complete dehydration. The reaction is most readily followed by removal of aliquots and examination by ^{1}H NMR for the disappearance of the carbinol hydrogen resonance (δ 4.35 in CD_3OD) of ecgonine hydrochloride. When dehydration is complete, the crude anhydroecgonine hydrochloride (**2**) is recrystallized from water/acetone to remove traces of unreacted ecgonine hydrochloride and dried overnight under high vacuum. Typical yields of **2** range from 75–84%. Esterification of anhydroecgonine hydrochloride had been performed employing sulfuric acid in methanol[4a,4c] or saturated methanolic hydrogen chloride.[4b] We obtained superior results by using 2.0M methanolic hydrogen chloride, generated *in situ* by treatment of methanol with acetyl chloride. Complete and near quantitative esterification of **2** was observed upon heating in 2.0M methanolic hydrogen chloride for 5 hrs. After removal of the solvent and neutralization of the hydrochloride salt, very pure anhydroecgonine methyl ester was obtained as a colorless oil which required no chromatography or distillation. We have obtained consistently higher yields of 3β-aryl-2β-carbomethoxytropanes using anhydroecgonine methyl ester prepared as described here in comparison with material prepared by previously reported methods.[3,7] Furthermore, although **3** slowly decomposes on storage in the dark at -25°, anhydroecgonine hydrochloride (**2**) can be stored at room temperature indefinitely, then converted to anhydroecgonine methyl ester in sufficient quantity as needed.

In summary, we have adapted the work of de Jong into a mild, efficient and reproducible method for the preparation of millimolar to molar amounts of highly pure anhydroecgonine methyl ester. This procedure avoids the use of noxious and difficult to dispose of reagents.

EXPERIMENTAL SECTION

Mps were determined on a Thomas Hoover capillary apparatus. Optical rotations were determined at the sodium D line using a Rudolf Research Autopol III polarimeter (1 dm cell). NMR spectra were recorded on a Brucker AM 250 spectrometer using tetramethylsilane as an internal standard. TLC analysis was performed on Whatman SiO_2 plates eluting with chloroform/methanol/concentrated ammonium hydroxide 80:18:2. Ecgonine hydrochloride was prepared from cocaine as previously described.[8] Concentrated hydrochloric acid and methanol were purchased from Fisher Scientific and used without purification. Acetyl chloride was purchased from Aldrich Chemical Company and used without purification. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

Anhydroecgonine Hydrochloride (2).- A 3L 3-necked flask equipped with a thermometer, water cooled condenser and a stir bar was charged with ecgonine hydrochloride (221.5 g, 1.0 mol) and 1000 mL of concentrated hydrochloric acid. The resulting solution was heated to ~110° and allowed to reflux for 14 hrs. The reaction was allowed to cool to room temperature and the hydrochloric acid removed under vacuum to give a white solid residue. This residue was azeotroped with toluene (2 × 250 mL) and dried overnight under high vacuum. Recrystallization from water/acetone gave 169.09 g (83%) of anhydroecgonine hydrochloride as a white crystalline solid. [α]= -64.5° (c = 2.03, H_2O) lit.[4a] [α] =-50.76° (c = 2.03, H_2O) mp. 239–241° (lit.[4a] mp. 239–243°);

Anal. Calcd for $C_9H_{13}NO_2$•HCl: C, 53.07; H, 6.93; N, 6.88; Cl, 17.41.
Found: C, 53.00; H, 6.91; N, 6.82; Cl, 17.46.

Note: The ^1H NMR of **1** is complex due the formation of isomeric salts about the bridgehead nitrogen.

Anhydroecgonine Methyl Ester (3).- Methanol (1.2 L) was added to a 5 L 3-neck flask equipped with a 500 mL addition funnel, stir bar, and a water cooled condenser with nitrogen inlet. The addition funnel was charged with acetyl chloride (175 mL, 2.44 mol). The flask was cooled in an ice/water bath and the acetyl chloride was added dropwise over 15 minutes. After addition of acetyl chloride was complete the resulting solution was stirred for 5 minutes, then treated with a solution of anhydroecgonine hydrochloride (**2**, 248.4 g, 1.22 mol) in 1,100 mL of methanol dropwise *via* the addition funnel. When addition of **2** was complete, the ice bath was replaced with a heating mantle and the solution brought to a gentle reflux for 5 hrs, whereupon TLC showed complete consumption of the starting material. The reaction was allowed to cool to room temperature and concentrated under vacuum. The residue was taken up in water (300 mL) and basified to pH 10–11 by careful addition of 200 mL of concentrated ammonium hydroxide. After extraction with methylene chloride (3 x 600 mL), the organic layers were combined, dried over sodium sulfate, filtered and concentrated under vacuum to give 212.5 g (96%) of **3** as a colorless oil. R_f = 0.8 on SiO_2 plates (Whatman) eluting with chloroform/methanol/concentrated ammonium hydroxide 80:18:2. ; [α] = -35.1° (c 1.22, chloroform), ^1H NMR (250 MHz, $CDCl_3$) δ 6.81 (t, 1 H, *J* = 3.3 Hz), 3.79 (d, 1 H, *J* = 3.4 Hz), 3.74 (s, 3 H), 3.26–3.22 (m, 1 H), 2.65–2.58 (m, 1 H), 2.35 (s, 3 H), 2.22–2.12 (m, 2 H), 1.89–1.78 (m, 2 H), 1.54–1.48 (m, 1 H).

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SYNTHESIS OF UNSYMMETRICAL α-(N-ARYLCARBONYL)AMINO DIORGANYL SELENIDES *via* BENZOTRIAZOLE INTERMEDIATES PROMOTED BY SmI_2

Submitted by (06/21/96)

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Various selenium-containing compounds are widely used as reagents and intermediates in organic synthesis.[1] Benzotriazole has taken its place as one of the most useful synthetic auxiliary groups available in the last decade.[2] Because the benzotriazole anion is a good leaving group, it may be used in place of a halogen in many reactions. The benzotriazolyl group has the advantage, however, that the derivatives are frequently much more stable than their chloro or bromo anologues. For example, α-benzotriazolylalkyl amines are stable, easily prepared compounds, whereas the corresponding α-chloroalkyl analogues are highly reactive. Many types of compounds have been synthesized *via* benzotriazole auxiliary, they include amines,[3] enamines,[4] esters,[5] ethers,[6] sulfides,[7] sulfones[8] and phosphorus-containing compounds.[9] To the best of our knowledge, no selenium-containing