1625 sh, 1595 cm^{-1}; NMR δ ($CDCl_3$) 1.5 [s, 9, $C(CH_3)_3$], 2.08 (s, 3, $COCH_3$), 3.42 (d, 2, CH_2S), 3.65 (s, 2, CH_2Ph), 4.65–5.25 (m, 3, C_6H and CH_2O), 5.85 (q, 1, C_7H), 6.2–6.5 (m, 1, NH), 7.32 (s, 5, aromatic). Anal. ($C_{22}H_{26}N_2O_6S$) C, H, S.

7-(*N*-Morpholinyl)phenylacetamidinocephalosporanic Acid *tert*-Butyl Ester (3f). Phosphorus pentachloride (0.92 g, 4.3 mmol) was dissolved in 10 ml of methylene chloride. Pyridine (0.7 ml, 8.6 mmol) was added and the reaction mixture cooled to −10°. Cephaloram *tert*-butyl ester (0.96 g, 2.15 mmol) was added and stirred at this temperature for 45 min and then at 0° for another 3 hr.

The reaction mixture was poured into 50 ml of 5% $NaHCO_3$ at 0° and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the imino chloride[7] of the cephaloram ester as a dark oil: ir ($CHCl_3$) 1780, 1725, 1670 sh, 1630 cm^{-1}; NMR δ ($CDCl_3$) 1.5 [s, 9, $C(CH_3)_3$], 2.1 (s, 3, $COCH_3$), 3.45 (d, 2, CH_2S), 3.95 (s, 2, CH_2Ph), 4.65–5.6 (m, 4, CH_2O + C_6H and C_7H), 7.3 (s, 5, aromatic).

The resulting iminochloride was dissolved in 6 ml of chloroform and cooled to −30°. Morpholine (0.38 ml, 4.3 mmol) in 2 ml of chloroform was added to the reaction mixture. The temperature was kept at −30° for 30 min and then at 0° for another 3.5 hr. The solvent was evaporated and the resulting dark oil was dissolved in ethyl acetate and filtered to remove the morpholine hydrochloride. The organic layer was washed with aqueous 5% $NaHCO_3$, dried, filtered, and evaporated. The oil was dissolved in ether and precipitated with hexane to yield 0.57 g (53%) amidine ester **3f.**

Electrophoresis. All amidines, trifluoroacetates, and zwitterions were subjected to electrophoresis at pH 6.5 (pyridine–acetate buffer), 60 V/cm for 30 min on Whatman No. 1. They migrated 1.2 cm toward the cathode giving rise to pale spots on blue-purple background after consecutive spraying with 0.05 *N* iodine containing 3.5% sodium azide and 1% starch solution.[8]

Nonaqueous Titrations. The compounds **3f** and **4a–c** in DMF solutions were titrated with 0.1 *N* $HClO_4$ in acetic acid and yielded molecular weights within experimental error.

The zwitterions **4a–c** in methanol solution were also titrated with 0.05 *N* $NaOCH_3$ to give the same results.

Biological Activity Evaluation. The in vitro antimicrobial tests were done using Bacto Antibiotic Medium 1 (Difco) agar plates seeded with *Staphylococcus aureus* Tour, *Escherichia coli* $0111B_4H_{12}$, and *Proteus mirabilis* TH3333 (untitable). A zone of inhibition in agar around filter disks that had been wetted with compounds solutions was used as the indication of activity.

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Synthesis of α-1-Noracetylmethadol. A Facile N-Demethylation of α-1-Acetylmethadol

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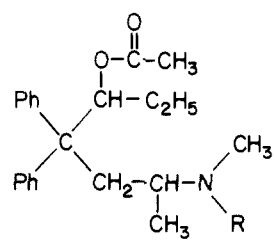
A facile N-demethylation of the narcotic analgesic, α-1-acetylmethadol, was accomplished by allowing it to react with mercuric acetate under reflux in dilute acetic acid. The product, α-1-noracetylmethadol, was isolated as the hydrochloride in 50% yield. Methadone, when allowed to react with mercuric acetate under the same conditions, did not undergo N-demethylation and was recovered unchanged.

The compound α-1-noracetylmethadol (**1a**), a biotransformation product of acetylmethadol (**1b**), has been shown to possess potent antinociceptive activity in the mouse.[2] Studies in laboratory animals[3] and in man[4–6] have suggested that the biotransformation of acetylmethadol (**1b**) is responsible for the time–action characteristics of certain of the pharmacologic effects of this compound. In particular, the relative long duration of suppression of narcotic withdrawal symptoms following administration of **1b** has stimulated both interest in its use in the maintenance treatment of opiate dependence[7,8] and the search for other long-lasting compounds for use in maintenance treatment.

Our studies on the biotransformation of **1b**[4,5] and interest in chemical N-demethylation procedures[9] prompted us to investigate a facile synthetic procedure to obtain significant quantities of **1a** from the more readily available **1b.** Further, it was of interest to us to obtain **1a** as the α-1 diastereoisomer (3*S*,6*S*) from the parent compound **1b** having the same stereochemistry. Compound **1a** could also serve as a convenient synthon for an alternative and more facile synthesis of the corresponding primary amine, which has also been shown to be an active metabolite.[3b,6]

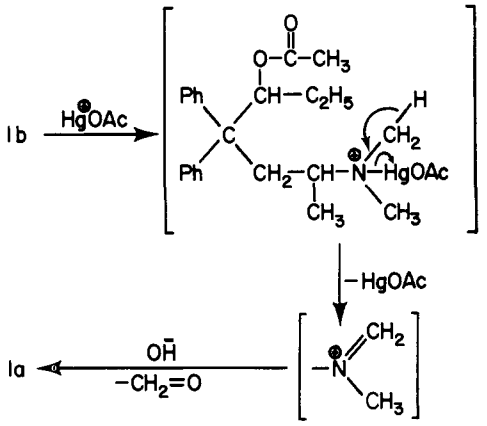


1a, R=H
b, R=CH_3

The synthetic objective has now been partially achieved by us in a reaction wherein **1b** is allowed to react with mer-

curic acetate in dilute acetic acid under reflux. These conditions are similar to those used by Leonard and Morrow in their oxidative N-demethylation of *N*-methylgranatanine.[10] Our reaction, however, gave a smooth conversion of **1b** to **1a** in a yield of 50%. This reaction apart from being a novel one for converting a tertiary acyclic amine to the corresponding secondary amine will further yield **1a** (in one step from **1b**) with no alteration of the crucial sterochemistry[11] at C-3 and C-6 of the skeleton of **1a** (see Scheme I). It

Scheme I



also appears to contrast favorably with the published original synthesis of **1a** by Pohland and others[12,13] and a more recent synthesis of **1a** from **1b**, by Montzka and others.[14] Leonard and Hauck[15] have pointed out that cleavage of the N–carbon bond (in mercuric acetate oxidations of tertiary amines) occurs in the order of ease, as tertiary –CH > secondary –CH > primary –CH. However, this order was established in the case of cyclic tertiary amines. In the present case the primary –CH bond of the methyl groups of **1b** seems to undergo cleavage preferentially to yield the demethylated compound.

Compound **1a** obtained from the reaction (Scheme I) was converted to the hydrochloride which was found to be indistinguishable from a sample of α-1-noracetylmethadol hydrochloride,[16] by a comparison of the ir, mass spectral, and NMR data and chromatographic properties.

Methadone, which was also subjected to the same conditions with mercuric acetate, curiously did not yield any product of demethylation or nitrogen-free product.[9] Only starting material was obtained on work-up of the reaction.

Pharmacology. The antinociceptive activity of **1a** in mice[17] was measured by use of the hot-plate method of Eddy and Leimbach.[18] The antinociceptive ED_{50} (subcutaneous) is 0.3 ± 0.1 (SE), with an onset, peak, and duration of activity of 4.9, 34.2, and 158 min, respectively. Smits has recently reported a similar ED_{50} value for **1a** using the mouse writhing test.[2]

Experimental Section

General procedures were described earlier.[9] α-1-Acetylmethadol hydrochloride[19] was a manufactured compound obtained from Merck and Co., Inc., through the agency of The Controlled Substances Program of the National Institute on Drug Abuse. Microanalyses for elements indicated were within 0.4% of the theoretical values.

Synthesis of 6-Methylamino-4,4-diphenyl-3-heptanol Acetate (1a). Reaction of α-1-Acetylmethadol with Mercuric Acetate. A solution of 940 mg (2.6 mmol) of the free base **1b** in 200 ml of a 3% solution of glacial acetic acid (pH of solution 3–4) was treated with mercuric acetate (11 g, 34.5 mmol) and the reaction mixture was heated on a mantle with stirring under a current of nitrogen for 18 hr (temperature of reflux was 100°). The reaction was monitored by TLC [Analtech silica gel plates in a solvent system of EtOAc–hexane–EtOH–NH_4OH (60:25:14:1); R_f of **1b** 0.52; R_f of **1a** 0.48] until the starting material was consumed. The reaction was worked up after cooling the mixture and filtering the precipitated mercurous acetate. The filtrate was warmed and saturated with H_2S to precipitate mercuric sulfide. This step was followed by a filtration after digesting on a water bath. The aqueous solution was thereafter chilled in ice and made alkaline to a pH of 8–9 and extracted with ether (800 ml). The ether layer was decolorized (charcoal), dried (Na_2SO_4), and evaporated in vacuo. The residual free base was converted to the hydrochloride by dissolving in the minimum of acetone and treating with 6 *N* HCl. A white precipitate of **1a** hydrochloride was isolated by filtration. This material weighed 435 mg (50%), mp 233–235° dec. Recrystallization from $CHCl_3$–hexane gave white crystals: mp 235–237° dec (lit.[20] mp 228.5–230.5°); $[\alpha]^{25}D$ −74.4° (*c* 0.47, H_2O); ir (KBr disk), 3225 (NH), 2725 (NH_2^+), 2460 (NH_2^+), 1730 and 1240 cm^{-1} (ester); ^1H NMR spectrum ($CDCl_3$, TMS), δ 8.80 (br s, 1 H), 7.32 (d, 10 H, aryl), 5.74 (distorted d, 1 H), 2.64 (m, 3 H), 2.42 (s, 3 H, $-NCH_3$), 2.08 (s, 3 H, CH_3CO–), 1.72 (m, 1 H), and 0.88 (m, 7 H); mass spectrum *m/e* 340 ($M^+ + 1$) and 280 ($M^+ + 1 - CH_3COOH$). The compound had an identical retention time with an authentic sample of α-1-noracetylmethadol or its hydrochloride by a gas chromatographic analysis.[4] Anal. ($C_{22}H_{30}NO_2Cl$) C, H, N, Cl.

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