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# SYNTHESIS OF HYDROXYTRIPELENNAMINE VIA O-DEMETHYLATION OF PYRILAMINE

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O-Demethylation of pyrilamine with 1-propanethiol and potassium tert-butoxide gave hydroxytripelennamine, Compound 2, one of the major metabolites of tripelennamine. The reaction of pyrilamine with other demethylating agents such as 48% of HBr, $BBr_3$, and $(CH_3)_3SiI$ has been explored, and the products thus formed have been isolated and characterized. (AW)

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## PREFACE

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CONTENTS

# SYNTHESIS OF HYDROXYTRIPELENNAMINE VIA O-DEMETHYLATION OF PYRILAMINE

## 1. INTRODUCTION

Tripelennamine (Compound 1, "Blues") has been an important antihistamine drug for a long time. Recently, the abuse of pentazocine (Talwin/"Ts") in combination with Compound 1 ("Ts and Blues") by intravenous narcotic users has been observed in the United States. Although such abuse of pentazocine has now been largely eliminated by the introduction of Talwin NX, the apparent potentiation by Compound 1 of the "high" from pentazocine reported by narcotic abusers has raised questions concerning this effect. Jasinski and his co-workers[1,2] report that Compound 1 induced euphoria and is identified as an opiate in humans. The combination of Compound 1 and pentazocine produced greater subject liking and euphoria than that seen for either drug administration alone. It was also reported that pentazocine and morphine antinociception was potentiated by Compound 1 in mice[3-5] and a rat.[6] Several investigations of this potentiation have been undertaken, including the design of experiments to quantify the metabolites of Compound 1.

N-Demethylation and/or aromatic hydroxylation, followed by conjugation with glucuronic acid, are the primary metabolic pathways of Compound 1. O-Glucuronides of hydroxytripelennamine (Compound 2) and desmethylhydroxytripelennamine, quaternary ammonium N-glucuronide of Compound 1 and tripelennamine N-oxide have been isolated from human urine after oral administration.[7] Hydroxytripelennamine and desmethylhydroxytripelennamine have been characterized by gas chromatography-mass spectrometry (GC-MS) as major metabolites in the urine of the rat after hydrolysis with glusulase.[8] Unfortunately, quantitative measurement of these metabolites has not been possible because authentic samples of these metabolites were not available. We now report the synthesis of one such metabolite, hydroxytripelennamine (Compound 2), and the course of the reactions employed in an unsuccessful attempt of synthesis of Compound 2.

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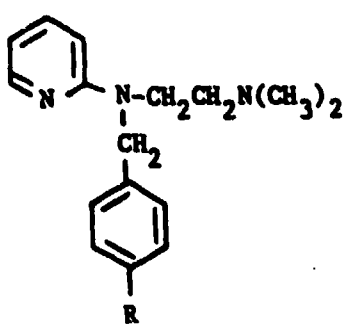



1, R = H

2, R = OH

3, R = $OCH_3$

## 2. CHEMISTRY

The chemical O-demethylation of phenol methyl ethers has been extensively studied using a variety of reagents.[9] Acid reagents such as mineral acids or boron and aluminum halides are the most commonly used reagents.[10] Under basic conditions, powerful nucleophiles such as alkyl mercaptan have also been used for O-demethylation in certain cases.[11] Recently, trimethylsilyl iodide was introduced as a mild reagent for ether cleavage and ester hydrolysis under essentially neutral conditions.[12,13,14]

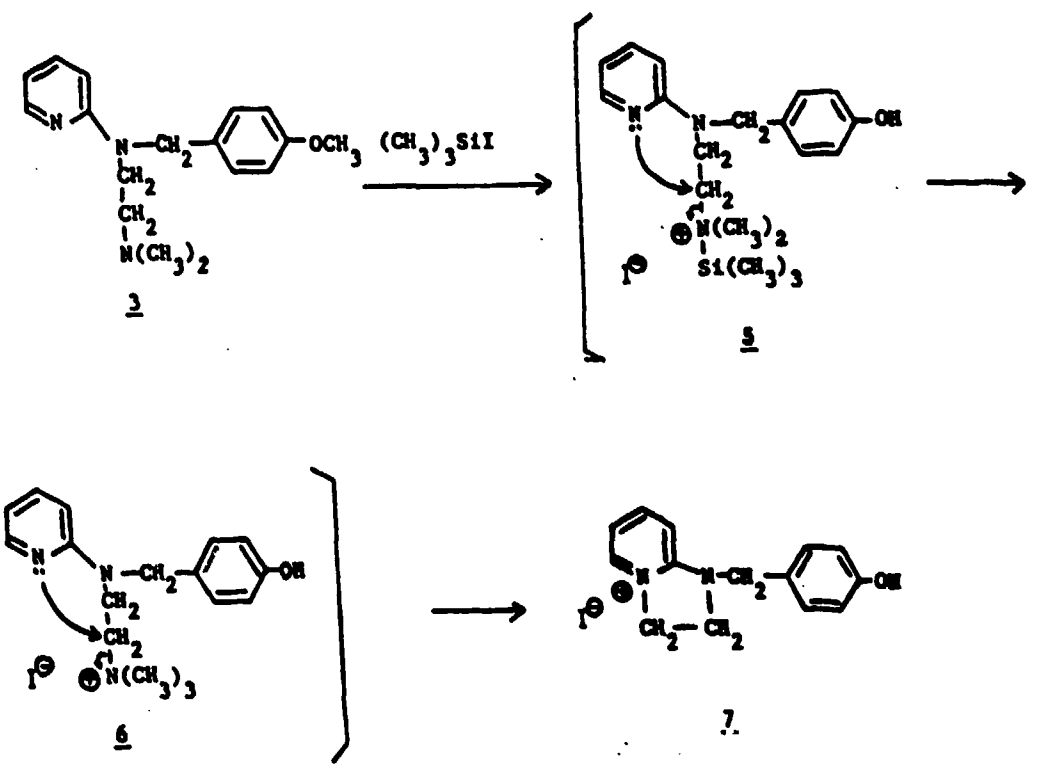
Treating pyrilamine (Compound 3) with 48% HBr at a reflux temperature yielded 2-(2-dimethylaminoethyl)aminopyridine (Compound 4).* The formation of Compound 4 could result from initial cleavage of Compound 3 to Compound 2 followed by loss of the 4-hydroxybenzyl substituent as a quinone methide. The reaction of Compound 3 and $BBr_3$[15] in $CH_2Cl_2$ at room temperature was not satisfactory and afforded a complex mixture of products containing some Compound 2 by thin-layer chromatography (TLC) analysis. The reaction of Compound 3 and trimethylsilyl iodide in toluene, either at room temperature or at 105 °C, yielded a compound soluble in water. The $^1H$- and $^{13}C$ NMR of this material indicated the absence of N,N-dimethylamino group. The proton signal of one of the two connecting methylene groups was dramatically shifted down field, suggesting that changes in the electronic environment of the molecule had occurred. The interaction of amino groups with trimethylsilyl iodide has not been fully understood. However, it has been suggested that the tertiary nitrogen might form a quaternary salt, such as Compound 5, with the trimethylsilyl group.[16] This action is followed by the migration of the methyl group to form the corresponding quaternary salt, such as Compound 6, and the concomitant elimination of the silyl group. The reaction of Compound 3 with trimethylsilyl iodide might proceed via the intermediates, such as Compounds 5 and 6, followed by an intramolecular nucleophilic displacement to yield the 2,3-dihydroimidazopyridinium salt, Compound 7 (Scheme 1). The $^1H$- and $^{13}C$ NMR spectra completely agree with the structure assigned. It did not show the molecular ion, but mass spectra gave a fragment with a base peak at 121 corresponding to the p-hydroxybenzyl group. The elemental analysis of Compound 7 agrees with the proposed structure.

The O-demethylation of Compound 3 was successfully accomplished under basic conditions using 1-propanethiol as the nucleophile. This reaction has been previously used to convert codeine to morphine.[11] The reaction of Compound 3 with 1-propanethiol and potassium tert-butoxide in DMF at 125 °C yielded the desired product, Compound 2. Interestingly, in one

*Yeh, S.Y., N-Debenzylation of Pyrilamine and Tripelennamine in the Rat: A New Metabolic Pathway, unpublished data.

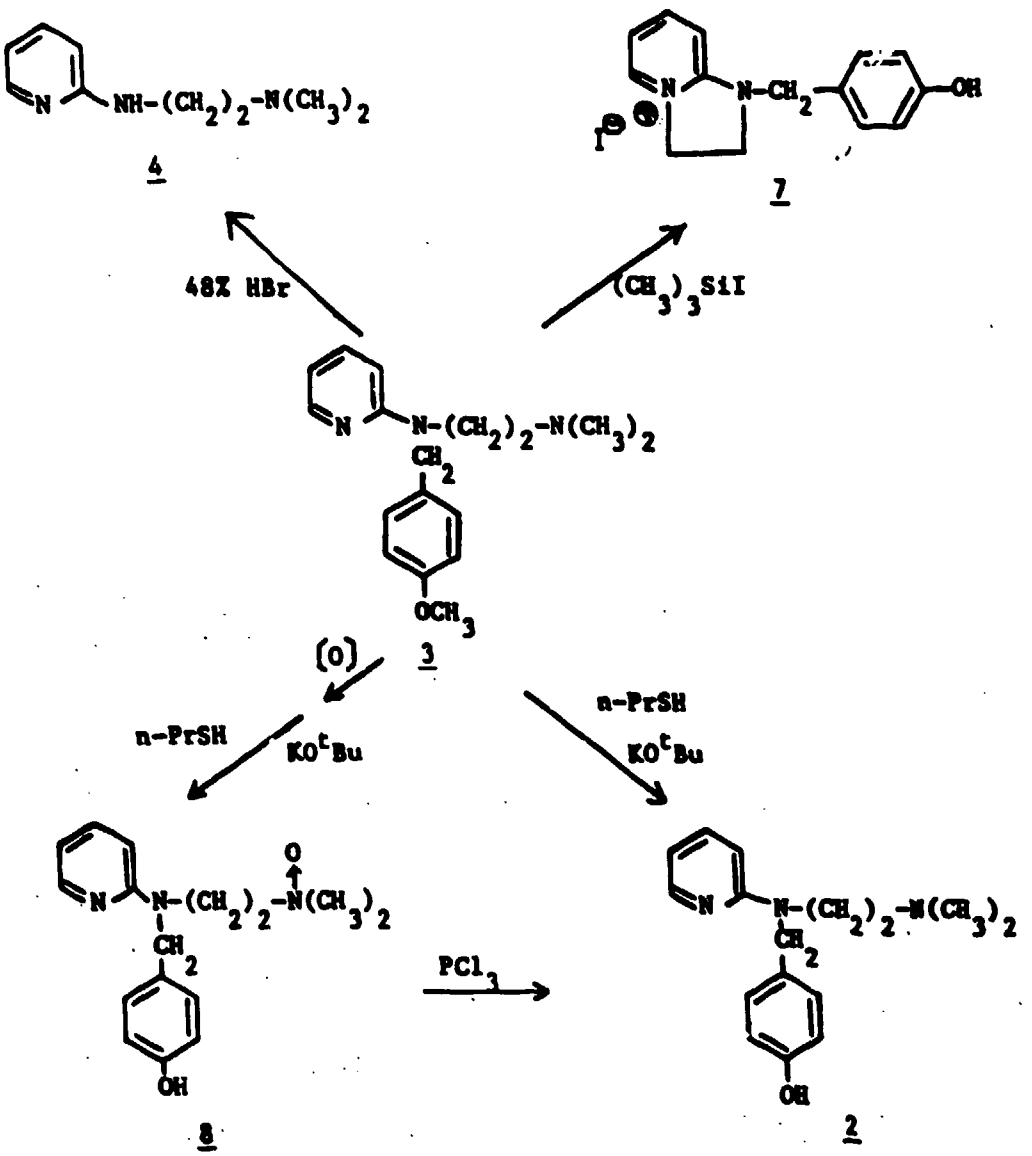
experiment, pyrilamine maleate was converted into the free base that was extracted into the ether layer. The free base Compound 3 was then employed using 1-propanethiol and potassium tert-butoxide as the dealkylating agent under the same conditions. During the course of the transformation, a compound was isolated and characterized as hydroxytripelennamine N-oxide (Compound 8).* The chemical shift (DMSO-$d_6$) of the dimethyl group of Compound 8 is at δ 3.12 (s, 6H), and the methylene group adjacent to the charged nitrogen is at 3.95 (t, 2H, J = 6.0 Hz). The elemental analysis of Compound 8 also agrees with the proposed structure. The N-oxide Compound 8 was then reduced to Compound 2 using phosphorus trichloride as the deoxygenating agent.[17] Scheme 2 summarizes the sequences of reactions of Compound 3.

Scheme 1




*Compound 8 was recrystallized from EtOH-$Et_2O$: mp 170-172 °C; NMR (DMSO-$d_6$): δ 3.10 (s, 6H, $2CH_3$) 3.40 (t, 2H, $CH_2$, J = 7.2 Hz), 3.95 (t, 2H, $CH_2$, J = 7.2 Hz), 4.54 (s, 2H, $CH_2$, 6.55 (d, 1H, pyridine-H, J = 8.9 Hz), 6.61 (d, 2H, ArH, J = 8.5 Hz), 6.70 (d, 1H, pyridine-H, J = 8.9 Hz), 6.88 (d, 2H, ArH, J = 8.5 Hz), 7.44 (dt, 1H, pyridine-H, J = 8.9, 2.0 Hz), 8.06 (dd, 1H, Pyridine-H, J = 4.3, 2.0 Hz), 9.96 (br s, 1H, OH); MS (CI/$NH_3$): m/e 272 ($MH^+$ - 16) (10%), 227 ($M^+$ - $Me_2NO$) (50%). Analyses Calculated for: $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.37; N, 14.62. Found: C, 66.50; H, 7.22; N, 14.40.

Scheme 2


NH-(CH2)2-N(CH3)2
4
7
48% HBr
(CH3)3SiI
N-(CH2)2-N(CH3)2
CH2
OCH3
3
(O)
n-PrSH
KO^tBu
n-PrSH
KO^tBu
O
N-(CH2)2-N(CH3)2
CH2
OH
8
PCl3
N-(CH2)2-N(CH3)2
CH2
OH
2

## 3. EXPERIMENTATION

Melting points, determined in open glass capillaries using a Thomas-Hoover Uni-melt apparatus, are correct. NMR spectra were recorded with a Varian XL-200 instrument using $ME_4Si$ as the internal standard. IR spectra were recorded with a Perkin-Elmer 1420 instrument. Mass spectra were recorded on a Finnigan 1015D Spectrometer. Elemental analyses were performed by the Research Directorate, U.S. Army Chemical Research, Development and Engineering Center (Aberdeen Proving Ground, MD). The composition of the reaction mixtures from various runs was monitored by TLC on silica gel 60 GF plates (Analtech, Incorporated, Newark, DE.)

### 3.1 Reaction of Pyrilamine (Compound 3) and Iodotrimethylsilane.

Pyrilamine maleate (4.0 g, 10 mmol) dissolved in 10 mL of $H_2O$ was adjusted to pH 9-10 with 10N of NaOH and extracted with ether. The extract was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was then dissolved in 10 mL of toluene and transferred to a three-neck flask. Through a septum, $Me_3SiI$ (5 g, 25 mmol) was added to this solution. The mixture was stirred at room temperature under $N_2$ (or heated at 105 °C) for 15 hr. TLC (EtOAc:$NH_4OH$ = 17:1) indicated that Compound 3 had completely disappeared. The low boiling solvents were evaporated. The brown colored mass was dissolved in 20 mL of $H_2O$, and the resulting acidic solution was brought to pH 13 with 10N of NaOH. The solution was then extracted with benzene to give a trace amount of Compound 3. The basic aqueous solution was then rendered to pH 9 to yield the yellow precipitate. The yellow solid was filtered and recrystallized from EtOH to yield Compound 7 (2.8 g, 79%): mp 198 to 199 °C; IR (nujol) 3200 $cm^{-1}$: $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.93 (t, 2H, $CH_2CH_2$, J = 9.0 Hz), 4.64 (s, 2H, $CH_2$, 4.66 (t, 2H, $CH_2CH_2$, J = 9.0 Hz), 6.92 (d, 2H, ArH, J = 8.5 Hz), 6.97 (d, 1H, pyridine-H, J = 7.5 Hz), 7.30 (d, 2H, ArH, J = 8.5 Hz), 7.45 (d, 1H, pyridine-H, J = 7.5 Hz), 8.09 (dt, 1H, pyridine-H, J = 8.5, 2.0 Hz), 8.30 (d, 1H, pyridine-H, J = 7.5 Hz), 9.54 (s, 1H, OH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 47.0, 48.2, 49.8, 107.7, 112.7, 115.4, 124.5, 129.4, 138.0, 144.6, 153.9, 157.2; MS (CI/$NH_3$) m/e 121 ($M-I^- - CH_2C_6H_4OH$), 107 ($CH_2C_6H_4OH^+$). Analyses Calculated for: $C_{14}H_{15}IN_2O$: C, 47.47; H, 4.27; N, 7.91; I, 35.83. Found: C, 47.25; H, 4.26; N, 7.83; I, 36.22.

### 3.2 Reaction of Pyrilamine (Compound 3) and n-PrSH/KO$^t$Bu.

Pyrilamine maleate (15 g, 37 mmol) dissolved in 50 mL of $H_2O$ was made basic with 10N of NaOH and extracted with EtOAc. The extract was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was dissolved in 200 mL of dry DMF (distilled from BaO) and degassed under $N_2$ by repeated stirring under vacuum. Following the addition of KO$^t$Bu (11.8 g, 0.1 mol), the degassing process was repeated, and 11.8 mL of n-PrSH was

injected with a syringe. The yellow mixture was stirred at 125 °C under $N_2$ for 4 hr, cooled to room temperature, and quenched with 12 mL of AcOH. The solvents were removed under high vacuum, and the residue was dissolved in 120 mL of 1N HCl. The acidic solution was washed with several portions of ether and decanted. The acidic solution was treated with 18 mL of 20% $NaHSO_3$ and adjusted to pH 8 to 9 with concentrated $NH_4OH$. The solution was extracted with EtOAc, and the phenolic product was then extracted into 1N of NaOH from EtOAc. This basic solution was adjusted to pH 8 with AcOH; the turbid solution was left standing overnight. The resulting crystalline product was filtered, washed with $H_2O$, and dried to give Compound 2 (5.6 g, 56%). Analytically, the pure sample was recrystallized from EtOH; mp 134 to 135 °C; IR (KBr) 3350 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$/$CD_3OD$) δ 2.18 (s, 6H, $2CH_3$), 2.41 (t, 2H, $CH_2$, J = 7.0 Hz), 3.60 (t, 2H, $CH_2$, J = 7.0 Hz), 4.63 (s, 2H, $CH_2$), 6.54 (dd, 2H, pyridine-H, J = 7.0, 2.0 Hz), 6.73 (d, 2H, ArH, J = 8.0 Hz), 7.06 (d, 2H, ArH, J = 8.0 Hz), 7.41 (dt, 1H, pyridine-H, J = 7.0, 2.0 Hz), 8.09 (dd, 1H, pyridine-H, J = 7.0, 2.0 Hz); $^{13}C$ NMR (DMSO-$d_6$/$CD_3OD$ δ 45.4, 45.7, 50.6, 56.2, 105.7, 111.4, 115.2, 128.1, 129.1, 137.2, 147.6, 156.2, 157.2; MS (CI/$NH_3$) m/e 272 ($MH^+$). Analyses Calculated for: $C_{16}H_{21}N_3O \cdot 0.25\ H_2O$: C, 69.67; H, 7.86; N, 15.23. Found: C, 69.84; H, 7.93; N, 15.06.

## 4. CONCLUSION

A variety of reagents are available for O-demethylation of phenol methyl ethers. Based on the reagents used, the reaction can be carried out under acidic, basic, or neutral conditions. Pyrilamine has several functional groups in its structure. Under acidic conditions, N-debenzylation occurred. Under neutral conditions, the reaction of pyrilamine with iodotrimethylsilane yielded 2,3-dihydroimidazopyridine, while the reaction with n-propanethiol and potassium tert-butoxide provided a good yield of hydroxytripelennamine.

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