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AN IMPROVED SYNTHESIS OF OCTOPAMINE

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Recently, we reported an improved synthesis of the naturally occurring hydroxy amides ageline and tembamide using trimethylsilyl cyanide (1). Here, we wish to report the synthesis of amino alcohols (**5**-**7**), useful intermediates in the synthesis of isoquinoline alkaloids (2-4). Amino alcohol **5**, called octopamine, was first isolated from the salivary glands of *Octopus vulgaris* (5). Since then, it has also been detected in other animal (6-8) and plant tissues (9), and it has attracted much attention pharmacologically due to its structural similarity to other adrenalin type compounds (10, 11).

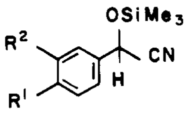
Schwartz and co-workers have elegantly used octopamine in a biosynthetically patterned synthesis of the alkaloid (±) cherylline (3). They obtained the intermediate amino alcohol **8** in 50% yield by lithium aluminium hydride reduction of the cyanohydrin adduct, and we were able to increase the yield of **8** to 75% by BH_3·THF reduction of the trimethylsilyl cyanide adduct (**1**). Adduct **1** was obtained as a crystalline solid in 75% yield by adding trimethylsilyl cyanide dropwise to a mixture of *p*-benzyloxybenzaldehyde and a catalytic amount of zinc iodide in dry Et_2O (12, 13). The reduction of **1** with BH_3·THF gave **8**, and deprotection of **8** with H_2, Pd/C gave octopamine (**5**) in 80% yield.

Using this method, we also synthesized the amino alcohols **6** and **7** in 75 and 80% yield by BH_3·THF reduction of the corresponding trimethylsilyl cyanide adducts. These amino alcohols are useful intermediates in the synthesis of isoquinoline and bisnorargeminine alkaloids (4).

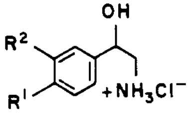
EXPERIMENTAL

Melting points were measured on a hot-stage apparatus and are uncorrected. The ^1H-nmr spectra were measured at 90 MHz on a Varian EM-390 spectrometer, and the ir spectra were determined on a Beckman 137 spectrometer.

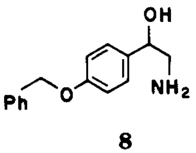
1-(*p*-BENXYLOXYPHENYL)-1-TRIMETHYLSILYLOXYACETONITRILE (**1**).—Trimethylsilyl cyanide (Aldrich) (1.33 ml, 0.01 mole) was added dropwise to *p*-benzyloxybenzaldehyde (2.12 g, 0.01 mole) and zinc iodide (6 mg) in dry Et_2O at 0°. The mixture was stirred for 30 min at room temperature until the aldehyde signal (ir) disappeared. Removal of solvent gave a yellow solid, 2.79 g, (90%), mp 55-60°. ^1H nmr ($CDCl_3$) δ (ppm) 7.3 (m, 7H, ArH), 6.85 (d, 2H, ArH), 5.30 (s, 1H, CHCN), 4.90 (s, 2H, CH_2Ar), 0.20 (s, 9H, $OSi(CH_3)_3$).



1 $R^1=OCH_2Ph$, $R^2=H$
2 $R^1=OCH_2Ph$, $R^2=OMe$
3 $R^1=OMe$, $R^2=OCH_2Ph$
4 $R^1=OMe$, $R^2=OCOCH_3$



5 $R^1=OH$, $R^2=H$
6 $R^1=OCH_2Ph$, $R^2=OMe$
7 $R^1=OMe$, $R^2=OCH_2Ph$



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OCTOPAMINE (**5**).—Compound **1** (2.75 g 0.008 mole) in dry THF (50 ml) was added dropwise to a stirred ice-cold solution of BH_3·THF (15 ml, 1M solution in THF) in dry THF (100 ml). The mixture was allowed to stand at room temperature overnight before careful addition of MeOH. The solvent was removed under reduced prerssure, and the residue was taken up in Et_2O and washed with H_2O (3 × 100 ml). The organic layer was dried over Na_2SO_4; removal of solvent gave *p-O*-benzyloxyoctapamine (**8**) as an amorphous solid in 75% yield, mp 70-72°.

The foregoing *p-O*-benzyloxyoctopamine (**8**) was dissolved in EtOH and subjected to hydrogenolysis using Pd/C as catalyst. The mixture was filtered through Celite, and the solvent was removed under reduced pressure to give a residue which was taken up in Et_2O and treated with HCl gas to give octopamine hydrochloride as colorless crystals, mp 170-171°, ir (KBr) 3450, 3200, 1600, 1125, 1130 cm^{-1}.

^1H nmr (D_2O) δ (ppm) 7.1 (d, 2H, J=8Hz, ArH), 6.7 (d, 2H, J=8Hz, ArH), 4.70 (dd, 1H, J=6Hz, *C*HOH), 3.10 (d, 2H, J=6Hz, CH_2NH_3). *Anal*: calcd for $C_8H_{12}ClNO_2$: C, 50.66; H, 6.37; N, 7.38. Found: C, 50.61; H, 6.35; N, 7.34.

1-(4′-*O*-BENZYLOXY-3′-METHOXYPHENYL)-1-TRIMETHYLSILYLOXYACETONITRILE (**2**).—Red liquid, 75% yield. Attempted distillation above 100° led to decomposition. ^1H nmr ($CDCl_3$) δ (ppm) 7.8-7.4 (m, 8H, ArH), 5.7 (s, 1H, CHCN), 5.4 (s, 1H, CH_2Ar), 4.15 (s, 3H, OCH_3), 0.6 [s, 9H, $Si(CH_3)_3$].

1-(4′-METHOXY-3′-*O*-BENZYLOXYPHENYL-1-TRIMETHYLSILYLOXYACETONITRILE (**3**).—Red liquid, 76% yield. Attempted distillation above 100° led to decomposition. ^1H nmr ($CDCl_3$) δ (ppm) 7.7-7.3 (m, 8H, ArH), 5.7 (s, 1H, CHCN), 5.5 (s, 2H, CH_2Ar), 4.2 (s, 3H, OCH_3), 0.6 [s, 9H, $Si(CH_3)_3$].

1-(3′-*O*-ACETYL-4′-METHOXYPHENYL-1-TRIMETHYLSILYLOXYACETONITRILE (**4**).—Red liquid, 73% yield. Attempted distillation above 100° led to decomposition. ^1H nmr ($CDCl_3$) δ (ppm) 7.35 (dd, 1H, J=9Hz, 1.5 Hz, ArH), 7.15 (d, 1H, J=9Hz, ArH), 5.65 (s, 1H, CHCN), 4.80 (s, 3H, OCH_3), 2.60 (s, 3H, $COCH_3$), 0.52 [s, 9H, $Si(CH_3)_3$].

α-(AMINOMETHYL)-4-BENZYLOXY-3-METHOXYBENZYL ALCOHOL·HCl (**6**).—Semi-solid, 80% yield. ^1H nmr (D_2O) δ (ppm) 7.4 (m, 8H, ArH), 5.38 (s, 2H, CH_2Ar), 4.12 (s, 3H, OCH_3), 4.68 (br. s, 1H, CHOH), 3.08 (m, 2H, CH_2NH_3).

α-(AMINOMETHYL)-3-BENZYLOXY-4-METHOXYBENZYL ALCOHOL·HCl (**7**).—Semi-solid, 75% yield. ^1H nmr (D_2O) δ (ppm) 7.41 (m, 8H, ArH), 5.36 (s, 1H, $ArCH_2$), 4.1 (s, 3H, OCH_3), 4.66 (br, s, 1H, CHOH), 3.08 (m, 2H, CH_2NH_3).

α-(AMINOMETHYL)-4-HYDROXY-3-METHOXYBENZYL ALCOHOL/HCl.—The above hydro chlorides (**6** and **7**) were subjected to hydrogenolysis under the same conditions as described for the synthesis of octapamine (**8**); mp 190-191° (from MeOH-Et_2O). *Anal*: calcd for $C_9H_{14}ClNO_3$: C, 49.31; H, 6.39. Found: C, 49.12; H, 6.32.

α-(AMINOMETHYL)-3-HYDROXY-4-METHOXYBENZYL ALCOHOL/HCl.—Mp 166-170° (from MeOH-Et_2O). *Anal*: calcd for $C_9H_{14}ClNO_3$: C, 49.31; H, 6.39. Found: C, 48.98; H, 6.11.

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