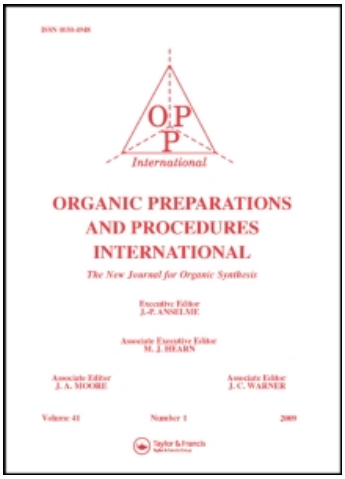

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SYNTHESIS OF 4-(4'-HYDROXYPIPERIDINO)-4-PHENYLCYCLOHEXANOL, A DIHYDROXY PHENCYCLIDINE METABOLITE

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SYNTHESIS OF 4-(4'-HYDROXYPIPERIDINO)-4-PHENYLCYCLOHEXANOL, A DIHYDROXY PHENCYCLIDINE METABOLITE

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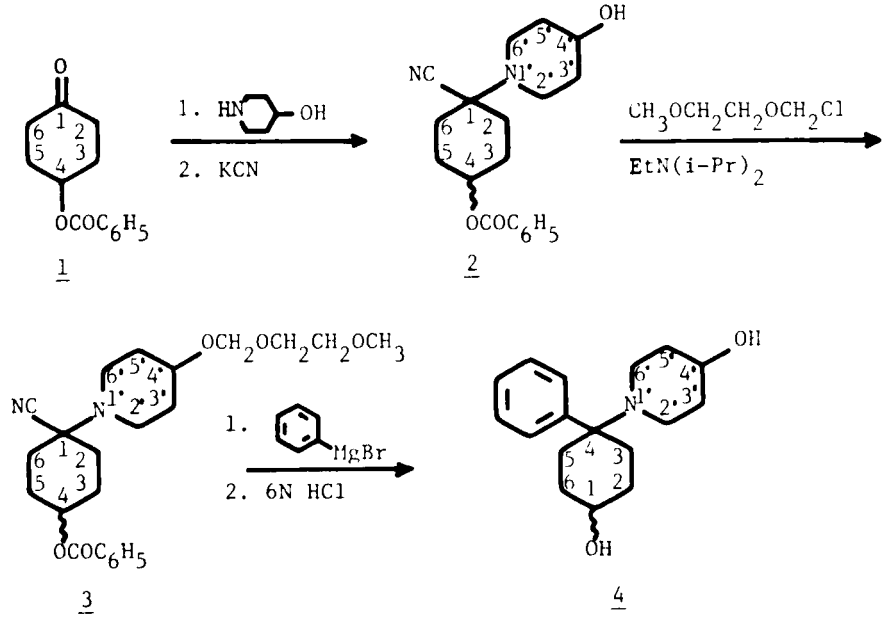
4-(4'-Hydroxypiperidino)-4-phenylcyclohexanol (4), previously postulated as a urinary metabolite of phencyclidine (PCP) in rhesus monkeys and rats,[1-3] has been identified as a PCP metabolite in in vitro rabbit liver homogenates by gas chromatographic/mass spectral comparison to an authentic sample prepared in our laboratory.[4] As no synthesis of this metabolite has been described heretofore, we wish to report our preparation of 4-(4'-hydroxypiperidino)-4-phenylcyclohexanol (4).



1 2 3 4

Sequential treatment of 4-hydroxypiperidine hydrochloride with 4-benzoyloxycyclohexanone (1)[5] and potassium cyanide provided 1-(4'-hydroxypiperidino)-4-benzoyloxycyclohexanecarbonitrile (2). Conversion of compound 2 to 1-(4'-methoxyethoxymethoxypiperidino)-4-benzoyloxycyclohexanecarbonitrile (3) was achieved using 2-methoxyethoxymethyl (MEM) chloride in the presence of diisopropylethylamine.[6] Subsequent treatment of the diprotected carbonitrile 3 with phenylmagnesium bromide (Bruylants reaction[7]) afforded 4-(4'-methoxyethoxymethoxypiperidino)-4-phenylcyclohexanol contaminated with a small amount of the desired product 4. Cleavage of the MEM group was accomplished with hydrochloric acid. The overall yield of 4-(4'-hydroxypiperidino)-4-phenylcyclohexanol (4) from 4-benzoyloxycyclohexanone (1) was 23%.

Our initial attempts to prepare compound 4 by treatment of the monoprotected carbonitrile 2 with phenylmagnesium bromide were thwarted by the formation of insoluble complexes during the Grignard reaction. These were attributed to the initial cleavage of the benzoyl protecting group and the formation of organometallic complexes at both hydroxyl groups. Use of the diprotected carbonitrile 3 enabled us to overcome this problem since the MEM[6] protecting group was stable to the Grignard conditions. We also obtained compound 4 in approximately 10% overall yield using the less stable t-butyldimethylsilyl[8] group as the second protecting group.

The synthetic metabolite was obtained as a mixture of cis and trans isomers as evidenced by TLC and ^{13}C-NMR analysis. Although the attainment of two isomers was consistent with the presence of a 1,4-disubstituted cyclohexane ring, it did represent an exception to the usual stereochemical course of the Bruylants reaction on a cyclohexanecarbonitrile containing an additional substituent on the cyclohexane ring.[9,10] A similar exception was observed in the earlier synthesis of the monohydroxy metabolite 4-phenyl-4-(1-piperidinyl)cyclohexanol.[2,11] The fact that the synthetic metabolite

4 was a mixture of isomers did not interfere with its use as a reference compound for the identification of the biological sample.[4]

EXPERIMENTAL SECTION

Melting points were taken in capillary tubes using either a Thomas Hoover or a Büchi model 510 apparatus. IR spectra were recorded on a Perkin-Elmer model 467 grating spectrometer, and ^{1}H-NMR spectra were obtained on a Bruker WM-250 high resolution spectrometer. ^{13}C-NMR spectra were run at 22.49 MHz on a JEOL FX-90Q spectrometer using the deuterium resonance of the solvent as an internal lock. All NMR chemical shifts are reported in ppm downfield from TMS. The patterns obtained for the ^{13}C-NMR resonances from single frequency off-resonance decoupling (SFORD) experiments are denoted by the letters s (singlet), d (doublet), t (triplet), and q (quartet). ^{13}C-NMR resonances which are twice as intense as other similar resonances are designated as 2x. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. TLC analyses were routinely carried out using commercially available silica gel plates (E. Merck). The following solvent systems were used: system A - $CHCl_3$:$(CH_3)_2CO$ (9:1); system B - $CHCl_3$:MeOH:conc. NH_4OH (90:10:4 drops/100 ml); system C - $CHCl_3$:MeOH:conc. NH_4OH (80:18:2). Spots were visualized with I_2 or with phosphomolybdic acid spray followed by $Ce(SO_4)_2$ spray.

4-Benzoyloxycyclohexanone (1).- The title compound was prepared in 31% overall yield from commercially available cyclohexane-1,4-diol using the literature[5] procedure.

1-(4'-Hydroxypiperidino)-4-benzoyloxycyclohexanecarbonitrile (2).- Prior to use, the commercial sample of 4-hydroxypiperidine was subjected to bulb-to-bulb distillation, and the KCN was vacuum dried overnight at 57°C. 4-Hydroxypiperidine (11.45 g, 0.113 moles) was added to crushed ice (30.6 g) followed by concentrated HCl (9.2 ml). The pH was adjusted to 3 (pH paper) using concentrated HCl and concentrated NH_4OH. To the resultant clear solution was added dropwise over 40 min a solution of 4-benzoyloxycyclohexanone[5] (24.70 g, 0.113 moles) in absolute EtOH (45 ml). The reaction mixture became heterogeneous almost immediately. A solution of KCN (7.37 g, 0.113 moles) in H_2O (24 ml) was added dropwise over 10 min wherein the reaction mixture changed consistency but remained heterogeneous. Two hrs after the KCN addition, the thickened mixture was diluted (EtOH, 40 ml; H_2O, 60 ml), and the resultant mixture was stirred overnight. Afterwards, the very thick mixture was filtered and the filter cake washed with H_2O.

After air drying for several hours, the white solid was taken up in hot absolute EtOH and the solution filtered through a cotton plug to remove a small amount of insoluble material. The clear solution was allowed to cool slowly, whereupon the product crystallized as white needles. After collection and vacuum drying, the white needles weighed 18.22 g, mp. 172-174°; IR (CH_2Cl_2) 3615, 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.75 (1H, m, $W_{\frac{1}{2}}$ 20.0 Hz, 4'-H), 5.08 (1H, m, $W_{\frac{1}{2}}$ 15.0 Hz, 4-H), 7.46 (2H, m, ArH), 7.58 (1H, m, ArH), 8.05 ppm (2H, m, ArH); ^{13}C-NMR ($CDCl_3$), δ 26.11 (t, 2x, C-3,5), 30.66 (t, 2x, C-2,6), 34.31 (t, 2x, C-3',5'), 44.52 (t, 2x, C-2',6'), 59.54 (s, C-1), 67.02 (d, C-4'), 70.01 (d, C-4), 118.65 (s, CN), 128.14 (d, 2x, meta), 129.32 (d, 2x, ortho), 130.03 (s, aromatic C-X), 132.83 (d, para), 165.67 ppm (s, CO). The chemical shifts of the aromatic carbons were in excellent agreement with values reported[12] for the benzoyl group of benzoyloxycyclohexane.

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53.
Found: C, 69.44; H, 7.57; N, 8.38.

Three additional crops of white needles were eventually obtained by repeated concentration of the mother liquors. After combination and vacuum drying, these totaled 6.00 g; mp. 171-173.5°. TLC analysis (system B; R_f 0.86) indicated this material to be identical to the first crop material. The combined yield was 24.22 g (65%).

1-(4'-Methoxyethoxymethoxypiperidino)-4-benzoyloxycyclohexanecarbonitrile (3).- The $CHCl_3$ used in this experiment was passed through a silica gel column to remove EtOH. To a stirred solution of methoxyethoxymethyl chloride (8.64 g, 0.069 moles) and diisopropylethylamine (8.95 g, 0.069 moles) in $CHCl_3$ (100 ml) was added a suspension of 1-(4'-hydroxypiperidino)-4-benzoyloxycyclohexanecarbonitrile (15.00 g, 0.046 moles) in $CHCl_3$ (150 ml). The solution was refluxed 22 hrs under nitrogen. Afterwards, the mixture was cooled and washed with H_2O (3 x 500 ml). The $CHCl_3$ layer

was dried (Na_2SO_4) and evaporated to give an off-white solid (20.06 g). Recrystallization from EtOH/hexanes afforded 15.07 g (79%) of (3) as white needles, mp. 124-126°; TLC (system A) single spot, R_f 0.40; IR (CH_2Cl_2) 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.40 (3H, s, OCH_3), 3.57 and 3.72 (each 2H, each m, OCH_2CH_2O), 3.68 (1H, m, 4'-H, partially obscured), 4.80 (2H, s, OCH_2O), 5.09 (1H, m, $W_{½}$ 15.0 Hz, 4-H), 7.46 (2H, m, ArH), 7.58 (1H, m, ArH), 8.05 ppm (2H, m, ArH); ^{13}C-NMR ($CDCl_3$) δ 26.24 (t, 2x, C-3,5), 30.73 (t, 2x, C-2,6), 31.77 (t, 2x, C-3',5'), 44.58 (t, 2x, C-2',6'), 58.82 (q, OCH_3), 59.60 (s, C-1), 66.69 (t, OCH_2C), 70.01 (d, C-4), 71.57 (t, OCH_2C), 71.89 (d, C-4'), 93.48 (t, OCH_2O), 118.65 (s, CN), 128.21 (d, 2x, meta), 129.32 (d, 2x, ortho), 130.16 (s, aromatic C-X), 132.83 (d, para), 165.60 ppm (CO).

Anal. Calcd for $C_{23}H_{32}N_2O_5$: C, 66.32; H, 7.74; N, 6.73.
Found: C, 66.36; H, 7.85; N, 6.66.

4-(4'-Methoxyethoxymethoxypiperidino)-4-phenylcyclohexanol.- A solution of 1-(4'-methoxyethoxymethoxypiperidino)-4-benzoyloxycyclohexanecarbonitrile (14.00 g, 0.034 moles) in THF (200 ml; freshly distilled from $LiAlH_4$) was added dropwise over 15 min to an ethereal solution of phenylmagnesium bromide (0.20 mol). After the addition, the reaction mixture was refluxed 20 hrs. The mixture was cooled to 0°C and treated dropwise with saturated NH_4Cl (200 ml) over 2 hrs. Some additional H_2O was added to dissolve the precipitated solid. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 200 ml). The combined organic layers were extracted with 10% HCl (3 x 200 ml). The combined acid extracts were washed with Et_2O (2 x 200 ml) and made basic (pH 10) with concentrated NH_4OH. The basic aqueous layer was extracted with CH_2Cl_2 (3 x 200 ml). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated to give 7.61 g of 4-(4'-methoxyethoxymethoxypiperidino)-4-phenylcyclohexanol as a clear viscous oil, TLC (system B) major spot, R_f 0.28, and minor spot, R_f 0.04;

IR (CH_2Cl_2) 3605 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.35 and 3.36 (3H total, two s, $O\underline{CH}_3$), 3.49 and 3.62 (each 2H, each m, $OCH_2\underline{CH}_2O$), 4.68 and 4.69 (2H total, each s, OCH_2O), 7.29 ppm (5H, m, Ar$\underline{H}$). The doubling of the $O\underline{CH}_3$ and OCH_2O signals in the spectrum was due to the presence of an isomer mixture. The spectral data clearly indicated that the MEM group had been retained and the benzoyl group lost. The crude product was used with no further purification.

4-(4'-Hydroxypiperidino)-4-phenylcyclohexanol (4).- The crude product (7.61 g, 0.021 moles) from the above reaction was dissolved in 6N HCl (200 ml) and the solution refluxed gently 2 hrs. The cooled reaction mixture was washed with Et_2O (2 x 100 ml), basified with concentrated NH_4OH (pH 10), and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give an off-white solid (5.13 g). The crude solid was recrystallized from absolute EtOH/hexanes to give 4.23 g [46% from (3)] of (4) as a white powdery solid, mp. 174-179° dec.; TLC (system B) single spot, R_f 0.05; TLC (system C) two approximately equal spots, R_f 0.55 and R_f 0.48; IR (CH_2Cl_2) 3609 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.43 (1H, broad s, $W_{\frac{1}{2}}$ 20.0 Hz, 4'-$\underline{H}$), 3.72 and 3.82 (1H total, two overlapping broad s, 1-$\underline{H}$), 7.29 ppm (5H, m, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3/CD_3OD$) major isomer (by integration) δ 29.44 (t, 2x, C-2,6), 30.47 (t, 2x, C-3,5), 34.43 (t, 2x, C-3',5'), 43.42 (t, 2x, C-2',6'), 60.97 (s, C-4), 67.53 (d, C-4'), 68.94 (d, C-1), 139.20 ppm (s, aromatic $\underline{C}$-X); minor isomer δ 29.71 (t, 2x, C-2,6), 30.26 (t, 2x, C-3,5), 34.65 (t, 2x, C-3',5'), 42.93 (t, 2x, C-2',6'), 59.29 (s, C-4), 67.85 (d, C-4'), 68.29 (d, C-1), 137.14 ppm (s, aromatic $\underline{C}$-X). The rest of the aromatic carbon resonances were not well enough resolved to be assigned.

Anal. Calcd $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09.
Found: C, 74.37; H, 9.36; N, 4.91.

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