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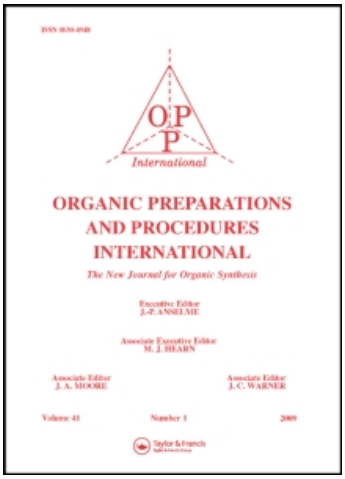

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A FACILE SYNTHESIS OF NATURAL MHPG, A METABOLITE OF NOREPINEPHRINE

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A FACILE SYNTHESIS OF NATURAL MHPG, A METABOLITE OF NOREPINEPHRINE

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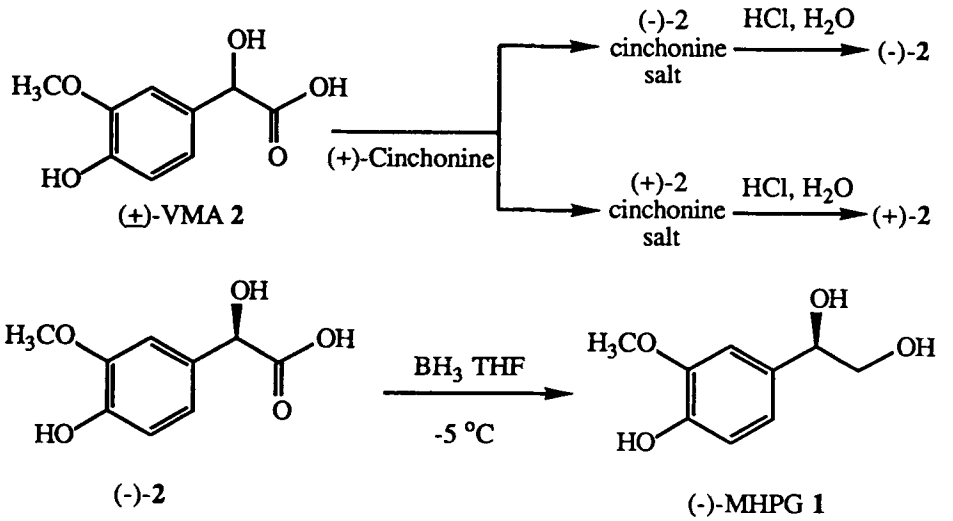
The diol 1 (4-hydroxy-3-methoxyphenyl glycol, MHPG), isolated from urine by Axelrod in 1959, has been suggested to be a metabolite of the neurotransmitter norepinephrine.[1,2] Recent interest in the measurement of urinary MHPG concentration has been prompted by the discovery that variations in concentration could be related to various mental disorders.[3] Some of the analytical methods used to determine MHPG concentration are HPLC,[4] radioimmunoassay[5] and GC/MS.[6] Historically, both research and analytical methods have only used the readily obtainable racemic mixture. Our current studies required enantiomerically pure, natural MHPG. Although several syntheses of racemic 1 have been published,[2,7] no synthesis of the naturally occurring material has been reported. We have achieved the first synthesis of natural MHPG from (-)-VMA as shown in the following scheme.



Racemic VMA was resolved via fractional crystallization of its (+)-cinchonine salt. The diastereomers were treated with acid to give (+)-2 and (-)-2.[8] The production of glycol 1 from VMA was optimized by controlling several reaction parameters. These experiments revealed that critical conditions included temperature and work-up. The reaction temperature must remain below 0° because above +5°, a significant amount of decomposition occurred. Careful control of pH during aqueous workup was necessary to produce consistent yields

(55-60%) of the glycol (±)-1. (-)-VMA was readily reduced under the above optimized conditions to give natural (-)-MHPG ($[\alpha]_D$ = -32.0°; c = 1.0, methanol) in 58% yield while (+)-MHPG ($[\alpha]_D$ = +32.1°; c = 1.0, methanol) was obtained in 61% yield from (+)-2.

In summary, natural (-) and unnatural (+)-MHPG were synthesized from commercially available, racemic vanillomandelic acid in two steps. The natural isomer of MHPG and derivatives of natural MHPG are currently being used in the development of an immunoassay.

EXPERIMENTAL SECTION

(±)-VMA, (±)-MHPG piperazine salt, (+)-cinchonine and borane THF complex (BH_3·THF) were purchased from Aldrich. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl immediately prior to use. (±)-VMA was resolved as described in the literature to give (-)-VMA ($[\alpha]_D^{22}$ = -131.5°, c = 1.0, H_2O; lit. $[\alpha]_D^{25}$ = -133°; mp. 151-152°, lit. 152° and (+)-VMA ($[\alpha]_D^{22}$ = +128.1°, c = 1.0, H_2O, lit. $[\alpha]_D^{25}$ = +133°; mp. 149-150.5°.[8] ^1H, ^{13}C NMR spectra were obtained on a GE-300 MHz NMR, mass spectra were run on a Nermag 3010 and optical rotations were run on a Perkin-Elmer Model 241 polarimeter. Both (-) and (+)-MHPG had identical ^1H, ^{13}C NMR spectra and molecular ion peaks (DCI) as (±)-MHPG.

(-)-MHPG (1).- BH_3·THF (2.0 mL, 1.0 M, 2.0 mM) was added dropwise to a -15° solution of (-)-VMA (99 mg, 0.50 mM) in 3 mL of the THF under N_2, warmed slowly to -5° and stirred 2 hrs at -5°. The reaction mixture was cooled to -15°, cautiously quenched by dropwise addition of excess methanol(1.5 mL) and stirred 30 min at 25°. The mixture was poured into toluene (5 mL)/water (15 mL, pH = 10), separated and the organic layer was discarded. The aqueous layer was adjusted to pH = 5.8 with 1 M HCl and then extracted with ethyl acetate (5 x 20 mL). After drying the organic extracts over Na_2SO_4, the solvents were removed in vacuo to afford an oil which was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 90:10, v/v) to yield 54 mg (-)-MHPG (58%). $[\alpha]_D^{22}$ -32.0° (c = 1.0, methanol). ^1H NMR ($CDCl_3$): δ 6.93 (d, J = 1.81 Hz, 1H), 6.84 (d, J = 7.99 Hz, 1H), 6.80 (dd, J = 7.99 Hz, J = 1.84 Hz, 1H), 6.51 (s, 1H), 4.75-4.67 (m, 1H), 3.89 (s, 1H), 3.85 (s, 3H), 3.73-3.56 (m, 1H), 3.51-3.42 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 146.90, 145.40, 133.00, 119.03, 114.49, 109.07, 74.49, 68.23, 55.88; MS: m/z $(M + H)^+$ calcd 185.814, obsd 185.0814.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.66; H, 6.56. Found: C, 58.25; H, 6.41

(+)-MHPG.- In a similar manner (+)-MHPG was obtained from (+)-VMA in 61% yield. $[\alpha]_D^{22}$ = +32.1° (c = 1.0, methanol).

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ULTRASOUND-PROMOTED SODIUM BOROHYDRIDE REDUCTION OF PENTACYCLO[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]UNDECANE-8,11-DIONE (PCUD-8,11-DIONE) AND OF 4,4-DIMETHOXY-2,3,5,6-TETRACHLORO-PCUD-8,11-DIONE

Submitted by (08/04/89) Alan P. Marchand* and G. Madhusudhan Reddy

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In connection with a continuing study of the synthesis and chemistry of substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diones (PCUD-8,11-diones),[1] a substantial quantity of PCUD-endo, endo-8,11-diol (2a) was needed. Sodium borohydride reduction of PCUD-8,11-dione (1) has been reported to afford a mixture of 2a and PCUD-exo,endo-8,11-diol (2b).[2,3] This method for reducing 1 has several drawbacks, i.e., it requires (i) the use of a large excess of sodium borohydride, (ii) long reaction times (i. e., 24 hrs), and (iii) tedious separation of 2a from the product mixture.[2] Accordingly, this procedure does not lend itself