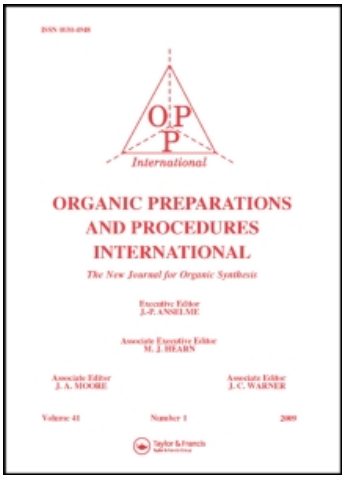

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PREPARATION OF 2(2-HYDROXYMETHYL-6-METHYL)PHENYLETHANOL

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PREPARATION OF 2(2-HYDROXYMETHYL-6-METHYL)PHENYLETHANOL

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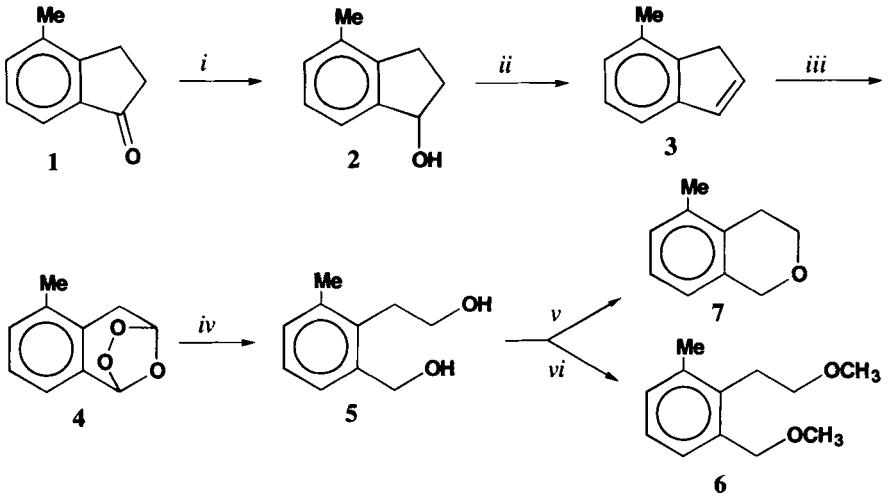
The present report describes an unambiguous synthesis of compound **5**,[1] required as a valuable intermediate for the synthesis of some pterosines and related natural products.[2] o-Methyl hydrocinnamic acid,[3] conveniently prepared by the catalytic reduction of o-methylcinnamic acid,[4] was cyclized by the procedure of Floyd and Allen[5] to give 4-methylindan-1-one (**1**) which was converted to **5** by the sequence shown below. The overall yield was 51%.



i) $NaBH_4$ ii) *p*-TosOH/80° iii) O_3 iv) LAH v) NaH, MeI vi) $ZnCl_2$

It was observed that **5** undergoes facile cyclization to **7** in chloroform (presumably due to acid impurities in the solvent). Compound **5** was converted to its stable derivative **6** for storage and use in other syntheses. Finally **5** was converted to **7** in 75% by treatment with $ZnCl_2$ in CCl_4.

EXPERIMENTAL SECTION

Mps. are uncorrected and were determined on a Thomas Hoover apparatus. Infrared spectra were performed on a Jasco spectrometer neat or as Nujol mulls. The ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker or a Varian FT 80A spectrometer in $CDCl_3$. Chemical shifts are reported in ppm downfield from internal TMS. The mass spectra were determined on a Varian mat Model CH7A spectrometer and elemental microanalyses were performed in our laboratories using a Coleman Analyzer. The reaction steps were monitored by thin layer chromatography (Silica gel GF_{254}, chloroform).

3-(2-Methylphenyl)propanoic acid.- A mixture of o-methylcinnamic acid (9.70 g, 0.06 mole),[4] mp. 170-172°[8] prepared in 75% yield (lit.[4] 70%) and Pd/C (5%) (1.3 g) in glacial acetic acid (200 mL) was hydrogenated (30 psi) in a Parr apparatus during 1.3 hr at room temperature. The solution was filtered and the solvent was removed *in vacuo* to give a solid. Recrystallization from ethanol gave 9.1 g (90%) of 3-(2-methylphenyl)propanoic acid, mp. 102-103°, lit.[3] 102°.

^{1}H NMR: δ 2.13 (s, 3H, CH_3), 2.70 (m, 2H, 3-CH_2), 2.85 (m, 2H, 2-CH_2), 7.15 (s, 4H, ArH), 10.90 (s, 1H, COOH).

4-Methylindan-1-one (**1**) was prepared in 82% yield by a procedure adapted from that of Floyd and Allen,[5] mp. 94-95° (hexane), lit.[3] 95°. ^{1}H NMR: δ 2.25 (s, 3H, CH_3), 2.50-2.60 (m, 2H, 3-CH_2). 2.80-2.90 (m, 2H, 2-CH_2), 7.10-7.30 (m, 2H, 5, 6-ArH), 7.50-7.60 (dd, 1H, 7-ArH).

4-Methylindan-1-ol (2).- Sodium borohydride (3.0 g, 0.08 mole) was added slowly (45 min) to a stirred solution of **2** (3.5 g, 0.023 mole) in methanol (50 mL). After an additional 90 min. at reflux the solvent was removed *in vacuo*, methylene chloride (70 mL) was added and the solution was washed with water (70 mL). The organic layer was separated and dried over sodium sulfate. The dried solution was filtered and the solvent evaporated in v cue to give a solid which was recrystallized from water:ethanol (9:1) to afford 2.8 g (80%) of white crystals of **2**, mp 57-59°.

IR (neat cm^{-1}): 3250 strong, 1070 strong.

^{1}H NMR: δ 1.75 (m, 2H, 2-CH_2), 2.25 (s, 3H, CH_3), 2.40-2.90 (m, 3H, 3-CH_2 and OH), 5.25 (t, 1H, CH), 7.00-7.20 (m, 3H, ArH).

^{13}C NMR: δ 18.5 (CH_3), 28.4 (C 3), 34.9 (C 2), 76.3 (C 1), 121.3 (C 7), 126.6 (C 6), 128.7 (C 5), 133.8 (C 4), 141.8 (C 8), 144.5 (C 9).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.11. Found: C, 81.09; H, 8.10

4-Methylindene (**3**).- A solution of **2** (2.5 g, 0.017 mole) in anhydrous benzene (250 mL) was treated with *p*-toluenesulfonic acid (25 mg). After an additional 3 hrs at reflux, the solution was transferred to a separatory funnel, washed successively with sodium hydroxide (5%) (2x125 mL), brine (2x125 mL) and water (125 mL). The organic layer was separated and dried over sodium sulfate. The dried solution was filtered, concentrated *in vacuo*, to give 1.75 g (80%) of an oil, bp 64-66°/2.2 mmHg, lit.[7], 88°/13 mmHg.

^{1}H NMR: δ 2.50 (s, 3H, CH_3), 3.40 (t, $J_{1,3}$ 1.35 Hz, $J_{2,3}$ 2.05 Hz, 2H, CH_2), 6.65 (dd, $J_{1,2}$ 5.60 Hz, $J_{2,3}$ 2.05 Hz, 1H, 2CH), 7.00-7.60 (m, 4H, 1 -CH and ArH).

^{13}C NMR: δ 18.4 (CH_3), 37.7 (C 3), 118.5 (C 7), 125.6 (C 6), 126.4 (C 5), 132.6 (C 4), 133.4 (C 2), 142.1 (C 9), 144.3 (C 8).

4-Methylindeneozonide (**4**).- A stream of dried 03/02 (produced by an ozonizer Stage K GC) was bubbled rapidly through a solution of 4-methylindene (**3**) (3.8 g, 0.030 mole) in tetrachloromethane (90 mL) at room temperature, until a saturated solution of KI/starch became blue (4.5 hrs). The solution was diluted with methylene chloride (150 mL) and transferred to a separatory funnel, washed successively with sodium carbonate (5%) (2x100 mL) and water (150 mL). The organic layer was separated and dried over sodium sulfate. The dried solution was filtered, concentrated *in vacuo* at

room temperature to give 4.96 g (95%) of white, solid, amorphous product, similar to paraffin in appearance (**CAUTION**, organic ozonides are highly explosive. In all cases, a shatter proof screen of laminated safety glass should be placed between the operator and the reaction flask). The ozonide was used in the next step without purification.

^{1}H NMR: δ 2.25 (s, 3H, CH_3), 3.05 (br d, 2H, 3-CH_2), 5.60 (m, 1H, 2-CH), 6.35 (s, 1H, 1-CH), 7.00-7.35 (m, 3H, ArH).

2-(2-Hydroxymethyl-6-methyl)phenylethanol (5).- A solution of ozonide 4 (4.9g, 0.028 mole) in anhydrous tetrahydrofuran (78 mL) was added over a 30 min period to a stirred suspension of $LiAlH_4$ (6.6 g) in anhydrous tetrahydrofuran (50 mL). The mixture was heated at reflux for 30 min and then allowed to come to room temperature. The reaction mixture was treated with water (200 mL), acidified with sulfuric acid (25%) and then extracted with methylene chloride (3x150 mL). The organic extract was dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give a solid. Recrystallization from benzene:hexane (4:1) yielded **5** (3.8 g, 84%) as colorless crystals, mp 86-87°.

IR (neat, cm^{-1}): 3250 strong, 1040 strong.

^{1}H NMR: δ 2.25 (s, 3H, CH_3), 2.90 (t, J 6.25 Hz, 2H, CH_2), 3.70 (t, J 6.25 Hz, 2H, CH_2), 4.10 (br s, 2H, OH), 4.45 (s, 2H, CH_2-Ar), 7.05 (s, 3H, ArH).

^{13}C NMR: δ 19.5 (CH_3), 31.6 (CH_2), 60.7 (CH_2OH), 63.0 (CH_2OH), 126.2, 127.4, 130.2, 135.7, 136.8, 139.3.0

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.30; H, 8.45

2-(2-Methoxymethyl-6-methyl)phenylethyl Methyl Ether (6).- To a solution of alcohol 5 (3.0 g, 0.018 mole), in anhydrous 2-methoxyethyl ether (diglyme) (30 mL), and methyl iodide (3.5 mL) was added in small portions sodium hydride (1.81 g, 0.075 mole). A new portion of methyl iodide (1.8 mL) was added and the solution was then heated to 70° for 2 hrs. The reaction mixture was cooled, diluted with ether (50 mL), filtered and the filtrate was washed with ether (2x25 mL). The organic layer was washed with water (2x50 mL) dried over sodium sulfate and evaporated, giving 3.3 g (99%) of **6**, as an oil. It was purified by preparative thin layer chromatography (Silica gel GF_{254}, methylene chloride).

^{1}H NMR: δ 2.40 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.40 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.55 (m, 2H, CH_2), 4.50 (s, 2H, CH_2-Ar), 7.15 (m, 3H, Ar-H).

^{13}C NMR: δ 18.7 (CH_3), 28.7 (CH_2Ar), 56.9, 57.4 (OCH_3), 71.5 (CH_2O), 72.6 (CH_2) 125.3, 126.5, 129.3, 135.0, 136.1.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.22; H, 9.28. Found: C, 74.20; H, 9.29

5-Methylisochroman (7).- To a solution of diol **5** (170 mg, 1 mmole) in anhydrous carbon tetrachloride (10 mL), was added in small portions zinc chloride (250 mg, 1.8 mmole). The solution was refluxed during 4 hrs. The reaction mixture was cooled, washed with water and extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated giving an oil. Recrystallization from benzene:hexane (4:1) yielded **7** (110 mg, 75%), mp 149-150°.

^{1}H NMR: δ 2.25 (s, 3H, CH_3), 2.70 (br t, J 6.50 Hz, 2H, CH_2), 4.00 (t, J 6.50 Hz, 2H, CH_2), 4.75 (s, 2H, CH_2-Ar), 6.80-7.10 (m, 3H, ArH).

^{13}C NMR: δ 18.7 (CH_3), 26.0 (CH_3-Ar), 65.5 (CH_2), 68.2 (CH_2), 121.9, 125.6, 127.6, 136.4, 137.7.
M.S. (m/e): 148.0 (85.7), 149.0 (10.6, 118.0 (100).
Anal. Calcd for $C_{10}H_{12}$: C, 81.08; H, 8.11. Found: C, 81.05; H, 8.13

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A CONVENIENT SYNTHESIS OF δ-CONICEINE

Submitted by (02/09/95)

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The indolizidine alkaloids have elicited an enormous interest on account of their exotic provenance and appealing biological activity.[1,2] They have been isolated from diverse classes of organisms, including ants, neotropical arrow poison frogs and plants. Many methods have been devised for their synthesis. Indolizidine (or δ-coniceine **4**), although not naturally occurring, has been considered as a typical synthetic target molecule.[3] As a consequence, a whole range of synthetic methodologies have been applied to the synthesis of 1-azabicyclo[4.3.0]nonane (**4**). Most