Synthesis and Chemistry of *syn*-2-Hydroxyindan 3a,7a-Oxide

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The synthesis, conformation, solvolytic behavior, and reactivity toward lithium thiomethoxide of an indan 3a,7a-oxide (1) are discussed.

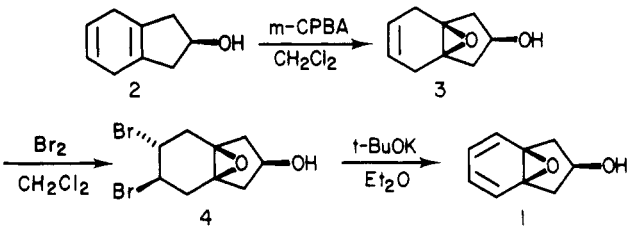
Recently we required a substituted indan 3a,7a-oxide as starting material for an arene oxide to oxepin oxide conversion.[1] Thus, *syn*-2-hydroxyindan 3a,7a-oxide (1, Scheme I) was synthesized and converted to a conformationally locked oxepin oxide; the latter was subjected to an X-ray crystal analysis.[2] Herein we detail the synthesis of 1 and describe its solvolytic behavior and reactivity toward the nucleophile, thiomethoxide (MeS^-).

The preparation of 1 (Scheme I) parallels Vogel's synthesis of indan oxide.[3] Epoxidation of dihydroindanol 2 gives a mixture of the syn epoxide 3 and its anti isomer (81:19 by GLC). Internally hydrogen-bonded 3 is easily separated from the mixture by distillation (72–77% isolated). Bromination (3 → 4, quantitative) and dehydrobromination (4 → 1, 65–71%) yields the desired arene oxide 1.

The ^1H NMR spectrum of 1 shows a large solvent dependence. In the non-hydrogen-bonding solvent $CDCl_3$, the hydroxyl proton is intramolecularly associated with the epoxide (Figure 1, conformation A); $J(H_2/OH) = 11.4$ Hz.[4] The measured vicinal coupling constants, $J(H_{1b}/H_2)$ and $J(H_{1a}/H_2)$, corroborate the assigned conformation (A) in $CDCl_3$: $J(H_{1b}/H_2) \simeq 1$ Hz (torsion angle[5] H_{1b}–C_1–C_2–$H_2 \simeq +100°$); $J(H_{1a}/H_2) = 5.5$ Hz (torsion angle[5] H_{1a}–C_1–C_2–$H_2 \simeq -20°$). In dimethyl-d_6 sulfoxide the hydroxyl group becomes associated with solvent, $J(H_2/OH) = 6.9$ Hz. Somewhat larger vicinal coupling constants, $J(H_{1b}/H_2)$ and $J(H_{1a}/H_2)$, measured in dimethyl-d_6 sulfoxide are compatible with a conformationally mobile molecule showing contributions from the two extremes of geometry (A and B) shown in Figure 1. In dimethyl-d_6 sulfoxide, $J(H_{1b}/H_2) = 2.5$ Hz (average torsion angle[5] H_{1b}–C_1–C_2–$H_2 \simeq 125°$) and $J(H_{1a}/H_2) = 6.3$ Hz (average torsion angle[5] H_{1a}–C_1–C_2–$H_2 \simeq 5°$).

An intramolecular hydrogen bond, such as that seen for 1 in $CDCl_3$, has been noted in the triptolides[4] and in the *syn*-diol epoxides derived from naphthalene and benzo[*a*]pyrene.[6] The pronounced solvent dependence of the rate of nucleophilic addition reported for the *syn*-diol epoxides[6] may be attributed to a conformational effect[6b,d] as seen for 1 (see Figure 1).

Scheme I



Scheme II

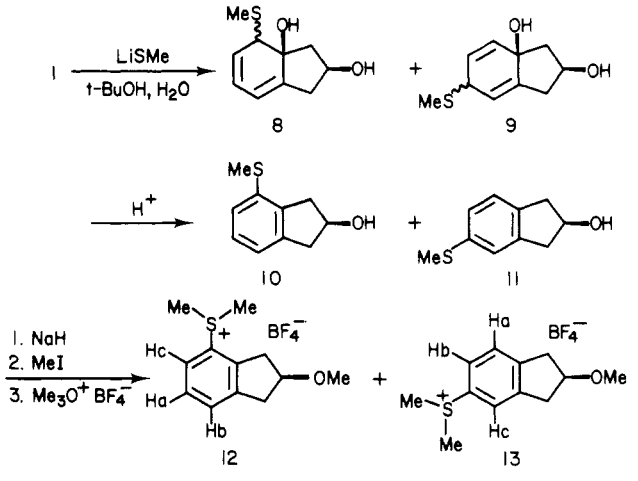
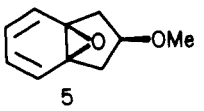


Table I. Aromatic ^1H NMR Absorptions of Sulfonium Salts 12 and 13

	salt 12,[a] δ (Me_4Si)	salt 13,[b] δ (Me_4Si)
H_a	7.53 (t, J = 7.5 Hz)	7.45 (d, J = 8.0 Hz)
H_b	7.61 (d, J = 7.5 Hz)	7.72 (d, J = 8.0 Hz)
H_c	7.93 (d, J = 7.5 Hz)	7.86 (s)

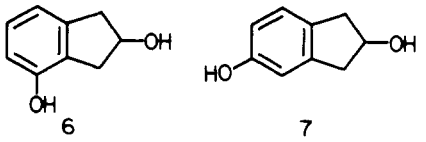
[a] Measured in dimethyl-d_6 sulfoxide solution at 270 MHz. [b] Measured in $CDCl_3$ solution at 270 MHz.

Arene oxide 1 is readily converted to methyl ether 5 (see



Experimental Section). This material will serve as a control standard in future rate studies of nucleophilic additions to hydroxyarene oxide 1.

Aqueous solvolysis of 1 gives phenols 6 and 7. At low



pH, 7 predominates (7:6 ≃ 50:1 by GLC); at high pH, 6

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(2) W. H. Rastetter, T. J. Richard, J. Bordner, and G. L. A. Hennessee, *J. Org. Chem.*, **44**, 999 (1979).
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(6) (a) H. Yagi, O. Hernandez, and D. M. Jerina, *J. Am. Chem. Soc.*, **97**, 6881 (1975); (b) H. Yagi, D. R. Thakker, O. Hernandez, M. Koreeda, and D. M. Jerina, *ibid.*, **99**, 1604 (1977); (c) A. R. Becker, J. M. Janusz, D. Z. Rogers, and T. C. Bruice, *ibid.*, **100**, 3244 (1978); (d) J. M. Janusz, A. R. Becker, and T. C. Bruice, *ibid.*, **100**, 8269 (1978).

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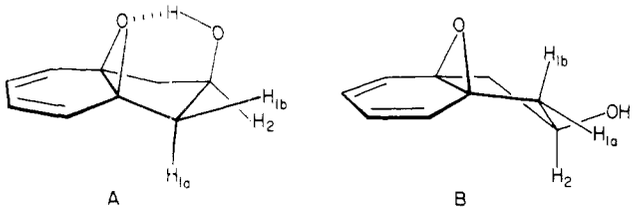
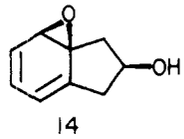


Figure 1. The extremes of conformation available to *syn*-2-hydroxyindan 3a,7a-oxide (1).

predominates (6:7 ≃ 10.8:1 by GLC). The solvolytic chemistry of 1 thus does not deviate markedly from that of indan 3a,7a-oxide.[7]

Reaction of 1 with lithium thiomethoxide in *tert*-butyl alcohol/H_2O leads to dihydro aromatics **8** and **9**. The structures of these materials were elucidated as shown in Scheme II. Aromatization is easily achieved with acid, though separation and characterization of the thioethers **10** and **11** does not provide an unambiguous isomer assignment. Methylation of the alcohol and thioether of the separated isomers **10** and **11** yields sulfonium salts **12** and **13** which are readily distinguished by ^1H NMR (Table I). Thus, isomer **12** shows H_c as a downfield doublet while H_c in isomer **13** appears as a downfield singlet.

Dihydro aromatic isomers **8** and **9** may arise via 1,6- and 1,4-addition, respectively, of MeS^- to arene oxide **1**. Another mechanistic possibility is suggested, however, by the chemistry of indan 3a,7a-oxide,[7] which solvolyzes (above pH 7) via an "oxygen-walk" mechanism. The "oxygen-walk" isomer of **1** (**14**) could give rise to dihydro aromatics **8** and **9** by 1,2- and 1,4-addition of MeS^-, respectively. In a control experiment a sample of **1** in buffered (KCl/NaOH, measured "pH" 13) *tert*-butyl-d_9 alcohol-d/D_2O rearranged extensively over the time span required to add MeS^- in *tert*-butyl-d_9 alcohol-d/D_2O (measured "pH" 13) to the arene oxide. The ^1H NMR spectrum of the mixture over a 30-min period shows a decrease in the absorptions due to arene oxide **1** and the appearance of absorptions due to phenol **6** and other, minor components. Phenol **6**, by analogy to the solvolysis of indan 3a,7a-oxide,[7] should arise via "oxygen-walk" isomer **14**. Thus, at least a portion of the observed dihydro



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aromatic products (**8** and **9**) may be derived via isomer **14**.

Experimental Section

General. NMR spectra were obtained on a Varian T-60, Perkin-Elmer Hitachi R-24B, Jeol FX-60 Q, or a Bruker HFX-270; the ^1H spectra were obtained at 60 MHz unless otherwise indicated. Infrared spectra were determined on a Perkin-Elmer 567 grating infrared spectrophotometer and mass spectra on a CEC 110B Mattauch-Herzog (DuPont Instruments) high-resolution mass spectrometer. Melting points are uncorrected and were determined in open capillary tubes.

Synthesis of *syn*-2-Hydroxyindan 3a,7a-Oxide (1). Dihydroindanol **2**[8] (18.0 g, 0.132 mol) in CH_2Cl_2 (100 mL) was maintained between −10 and −5 °C while a solution of 85% *m*-chloroperoxybenzoic acid (*m*-CPBA, 26.82 g, 0.131 mol of active oxygen) in CH_2Cl_2 (280 mL) was added dropwise. After addition, the mixture was stirred at 0 °C for 0.5 h and then warmed to ambient temperature for 1 h. The mixture was recooled on ice and the precipitated *m*-chlorobenzoic acid was removed by filtration with a CH_2Cl_2 wash. The filtrate was washed with 20% aqueous $NaHSO_3$ and saturated aqueous $NaHCO_3$. Drying ($MgSO_4$), evaporation of solvent, and distillation [90–95 °C (3 mmHg)] yielded epoxide **3** (15.43 g, 77%) as a clear liquid. Data for **3**: ^1H NMR ($CDCl_3$) δ (Me_4Si) 1.93 (dd, 2 H, J = 15 and 5 Hz), 2.16 (br d, 2 H, J = 15 Hz), 2.53 (m, 4 H), 2.82 (br m, 1 H, exchangeable), 4.04 (br m, 1 H), 5.49 (m, 2 H); IR (film) 3530 (br), 3040, 2960, 2900, 1425, 1176, 1139, 1067 cm^{-1}; exact mass, calcd for $C_9H_{12}O_2$ 152.08373, found 152.08331.

A similar epoxidation performed in refluxing $CHCl_3$ yielded a mixture of **3** and its anti isomer in a ratio of 81:19 (determined by GLC, 12 ft, 4.1% SE-30 on Chromosorb G). The anti isomer can be isolated (ca. 5%) by silica gel chromatography of the pot residue after vacuum distillation of syn isomer **3**. ^1H NMR data for the anti isomer: ($CDCl_3$) δ (Me_4Si) 1.60 (dd, 2 H, J = 14 and 7.5 Hz), 2.30–2.80 (m, 7 H), 4.13 (quintet, 1 H, J = 7.5 Hz), 5.44 (br s, 2 H).

A solution of epoxide **3** (37.82 g, 0.249 mol) in CH_2Cl_2 (670 mL) was maintained at −78 °C during the dropwise addition of Br_2 (11.5 mL, 0.223 mol) in CH_2Cl_2 (140 mL). The addition was achieved over 4.5 h at a rate such that the color of Br_2 was immediately dissipated throughout the addition. Evaporation of solvent and recrystallization from Et_2O yielded dibromo epoxide **4** (69.40 g, 100% based on Br_2) as white needles. Data for **4**: ^1H NMR ($CDCl_3$) δ (Me_4Si) 1.7–3.2 (complex m, 9 H), 3.8–4.7 (complex m, 3 H); IR (KBr) 3350 (br), 2955, 2925, 1432, 1062 cm^{-1}; exact mass, parent minus C_2H_2O, calcd for $C_7H_{10}OBr_2$, bromine cluster 267.90982, 269.90779, 271.90474; found 267.90855, 269.90477, 271.90169.

Dehydrobromination of **4** (20.55 g, 65.9 mmol) was achieved by the action of potassium *tert*-butoxide (27.0 g, 241 mmol). The dibromo epoxide (**4**) in Et_2O (680 mL) was maintained between −15 and −10 °C during the addition of the solid alkoxide over 1 h 45 min. The mixture was stirred for an additional hour between −15 and −10 °C and then allowed to warm to ambient temperature over approximately 40 min. The resulting Et_2O suspension was washed with 2 N KOH (aqueous), dried ($MgSO_4$), and evaporated. Recrystallization from a minimum amount of Et_2O yielded **7** (7.02 g, 71%) as pale beige needles (mp 76–83 °C dec). Data for **1**: ^1H NMR (also see text for coupling constants) (CD_3SOCD_3, 270 MHz) δ (Me_4Si) 2.15 (dd, H_{1a} and H_{3a}), 2.33 (dd, H_{1b} and H_{3b}), 4.18 (d, OH), 4.26 (m, H_2), 6.32 ($^1/_2$AA′BB′), 6.54 ($^1/_2$AA′BB′); ^1H NMR ($CDCl_3$) δ (Me_4Si) 2.10 (dd, H_{1a} and H_{3a}), 2.53 (dd, H_{1b} and H_{3b}), 2.63 (d, OH), 4.17 (m, H_2), 6.47 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ (Me_4Si) 127.6, 127.0, 71.1, 68.5, 39.9; IR (KBr) 3350 (br), 2950, 2920, 1424, 1064 cm^{-1}; exact mass calcd for $C_9H_{10}O_2$ 150.06808, found 150.06988. Anal. Calcd: C, 71.98; H, 6.71. Found: C, 71.70; H, 6.91.

Methylation of 1. Synthesis of *syn*-2-Methoxyindan 3a,7a-Oxide (5). To *syn*-2-hydroxyindan 3a,7a-oxide (1; 3.601 g, 23.98 mmol) slurried in Et_2O and cooled with an ice bath was added solid NaH (0.710 g, 29.6 mmol) and dimethylformamide (DMF) (7.3 mL). After stirring 1 h at 0 °C, $(CH_3)_2SO_4$ (3.10 g, 25.3 mmol) was added in one portion. The mixture was stirred for an additional 1 h at 0 °C and then diluted with 2 N KOH (aqueous) (20 mL). Extractive workup and Kugelrohr distillation [80 °C (0.1 mmHg)] afforded yellow crystals of *syn*-2-methoxyindan 3a,7a-oxide (**5**; 3.049 g, 77%), mp 34–37 °C. Data for **5**: ^1H NMR ($CDCl_3$) δ (Me_4Si) 2.20 (dd, J ~7 and 15 Hz, 2 H), 2.60 (dd, J ~ 2 and 15 Hz, 2 H), 3.25 (s, 3 H), 4.00 (tt, J ~ 2 and 7 Hz, 1 H), 6.35 (m, 4 H); IR (film) 3040, 2925, 2820, 1441, 1426, 1095 cm^{-1}; exact mass, calcd for $C_{10}H_{12}O_2$ 164.08373, found 164.08392.

Aqueous Solvolysis of 1. Solvolyses were performed at pH 2.1 (0.16 M KCl/0.04 M HCl) and at pH 10.8 (0.05 M Na_2HPO_4/0.01 M NaOH). Product isolation was achieved by extraction (EtOAc), drying ($MgSO_4$), and evaporation of solvent. Product ratios (**6**:**7**) were determined by GLC (12 ft, 4.1% SE-30 on Chromosorb G) after phenol silylation (bis(trimethylsilyl)-acetamide in benzene, 1 h, ambient temperature).

Phenol **7** (mp 110–114 °C) was purified from the low pH solvolysis mixture by trituration with CH_2Cl_2. Data for **7**: ^1H NMR ($CDCl_3$/CD_3SOCD_3) δ (Me_4Si) 2.7–3.5 (m, 4 H), 4.47 (m, 2 H), 6.80 (m, 3 H), 8.58 (s, 1 H); IR (KBr) 3400 (br), 2940, 1610,

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1455, 1260, 1027 cm^{-1}; exact mass, calcd for $C_9H_{10}O_2$ 150.06808, found 150.06918.

Phenol **6** (mp 118–120 °C) was purified from the high pH solvolysis mixture by column chromatography (silica gel, EtOAc). Data for **6**: ^1H NMR ($CDCl_3/CD_3SOCD_3$) δ (Me_4Si) 2.6–3.4 (m, 4 H), 4.60 (m, 2 H), 6.4–7.2 (m, 3 H), 8.33 (s, 1 H); IR (KBr) 3400 (br), 2950, 1590, 1472, 1285, 1050 cm^{-1}; exact mass calcd for $C_9H_{10}O_2$ 150.06808, found 150.06939.

The structures of phenols **6** and **7** follow unambiguously by comparison of their ^1H NMR spectra with the published[9] spectra of 4-indanol and 5-indanol, respectively.

Addition of LiSMe to Arene Oxide 1. Synthesis and Characterization of Thioethers 10 and 11. To arene oxide **1** (0.456 g, 3.04 mmol) in *tert*-butyl alcohol (5 mL) was added LiSMe (0.56 g, 10.37 mmol) in H_2O (5 mL) and the mixture was stirred 45 min at ambient temperature. Extraction (4 × 25 mL of Et_2O), drying ($MgSO_4$) and removal of solvent gave a mixture (0.58 g, 97%) containing dihydro aromatics **8** and **9**. The NMR spectrum of the mixture is complex but shows (270 MHz, $CD_3SOCD_3/CDCl_3$) olefinic absorptions [δ (Me_4Si) 5.6–6.2] and two clearly discernible singlets attributable to –SMe bound to saturated carbon at δ (Me_4Si) 1.88 and 1.83 in the ratio of 2.5:1, respectively. Upon acidification (CF_3COOH) or upon standing overnight the mixture aromatized to **10** + **11**. The ^1H NMR spectrum (270 MHz, $CD_3SOCD_3/CDCl_3$) of **10** + **11** lacks absorptions in the region δ (Me_4Si) 5.6–6.2 and shows one predominant –SMe peak (singlet) at δ (Me_4Si) 2.38.

Column chromatographic separation of **10** and **11** was achieved on silica gel (35 g) using 3:1 hexanes/EtOAc as eluent. The first eluting compound (110 mg, 20%) was shown (vide infra) to be thioether **10**, mp 56–57 °C. Data for **10**: ^1H NMR ($CDCl_3$) δ (Me_4Si) 2.38 (s, 3 H), 2.93 (m, 5 H), 4.55 (m, 1 H), 6.96 (m, 3 H); IR (KBr) 3300 (br), 2942, 1580, 1455, 1442, 1028 cm^{-1}; exact mass calcd for $C_{10}H_{12}OS$ 180.06089; found 180.06147. Anal. Calcd: C, 66.63; H, 6.71. Found: C, 66.63; H, 6.90. A middle eluting fraction (40 mg) was shown (TLC) to be a mixture of **10** + **11**. The last eluting fraction (124 mg, 23%) was shown (vide infra) to be thioether **11**, mp 67–69 °C. Data for **11**: ^1H NMR ($CDCl_3$) δ (Me_4Si) 2.38 (s, 3 H), 2.93 (m, 5 H), 4.55 (m, 1 H), 6.95 (br s, 3 H); IR (KBr) 3295 (br), 2950, 1595, 1568, 1480, 1422, 1036 cm^{-1}; exact mass calcd for $C_{10}H_{12}OS$ 180.06089, found 180.06305. The combined yield of material eluted from the column was 50%; the remaining material was not accounted for.

Synthesis of Sulfonium Salts 12 and 13. Structure Assignments for Thioethers 10 and 11. Separated thioethers **10** and **11** were converted to **12** and **13**, respectively, by the procedure given below for **10** → **12**.

To thioether alcohol **10** (160 mg, 0.889 mmol) in dimethylformamide (0.7 mL) was added NaH (ca. 40 mg, 1.7 mmol). When evolution of H_2 ceased, MeI (55 μL, 0.89 mmol) was added and the mixture was stirred overnight. Removal of solvent, extractive workup, and preparative TLC gave the methyl ether derived from **10** (158 mg, 92%).

The methyl ether (147 mg, 0.757 mmol) was converted to sulfonium salt **12** by treatment with $Me_3O^+ BF_4^-$ (117 mg, 0.793 mmol) in CH_2Cl_2 (0.9 mL) over a period of 30 h. Removal of solvent and trituration with Et_2O yielded sulfonium salt **12** (167 mg, 75%) as light purple crystals (mp 147–148 °C).

Similar steps produced sulfonium salt **13** (mp 82–83 °C) from thioether alcohol **11**.

Acknowledgment is made to the National Institutes of Health for support of this work. We also thank Dr. C. E. Costello for mass spectra.

Registry No. **1**, 70897-83-5; **2**, 7567-68-2; *anti*-**3**, 70897-84-6; *syn*-**3**, 70954-00-6; **4**, 70897-85-7; **5**, 70897-86-8; **6**, 70897-87-9; **7**, 51927-77-6; **8**, 70897-88-0; **9**, 70897-89-1; **10**, 70897-90-4; **11**, 70897-91-5; **12**, 70897-93-7; **13**, 70897-95-9.

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Preparation and Purification of Arachidonic Acid Hydroperoxides of Biological Importance

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Singlet oxygen oxidation of arachidonic acid (5,8,11,14-eicosatetraenoic acid) leads to eight hydroperoxides that may be separated by high-pressure liquid chromatography. The hydroperoxides result from allylic oxidation of one of the double bonds of the polyene fatty acid, a trans double bond being formed in the process. 12-(Hydroperoxy)eicosatetraenoic acid, 12-HPETE, a biologically important hydroperoxide formed from arachidonic acid and a lipoxygenase enzyme present in blood platelets, may be prepared by this approach.

Arachidonic acid (5,8,11,14-eicosatetraenoic acid, 20:4) reacts with molecular oxygen in reactions catalyzed by two distinctly different enzymes found in platelets (Figure 1). The first enzyme, cyclooxygenase, converts arachidonic acid into the prostaglandin (PG) endoperoxides, PGG_2 and PGH_2.[1,2] The PG endoperoxides are enzymatically converted to the thromboxanes[3] and other nonperoxidic PG's,[4] and these prostaglandins and thromboxanes play an important role in the chemistry associated with the aggregation of platelets.

A second enzymatic pathway of arachidonic acid in platelets was revealed when it was shown that a platelet lipoxygenase converts arachidonic acid into 12-(hydroperoxy)eicosatetraenoic acid, 12-HPETE.[5,6] Although the biological function of 12-HPETE has not been completely defined, lipid hydroperoxides such as 12-HPETE have been recently shown to be important mediators of diverse

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