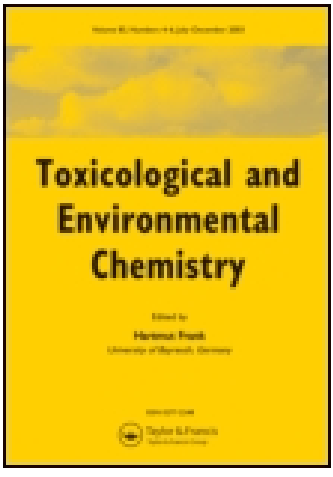

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SYNTHESES AND SPECTROSCOPIC CHARACTERIZATIONS OF OXIDATIVE METABOLITES OF 4-VINYLCYCLOHEXENE

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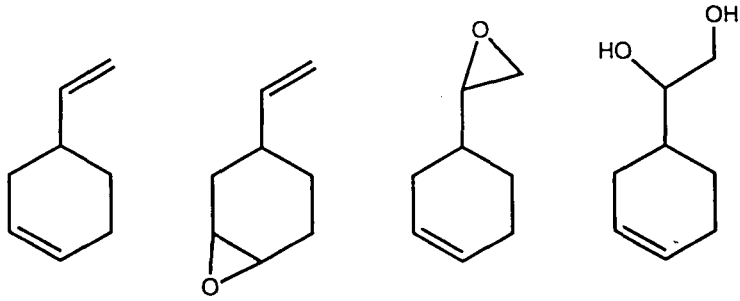
The 7,8-epoxide and 7,8-diol derivatives of 4-vinylcyclohexene were prepared and characterized spectroscopically for use as standards in toxicological studies of the oxidative metabolism of the parent hydrocarbon.

KEY WORDS: 4-vinylcyclohexene, oxidative metabolism, epoxide, spectroscopy

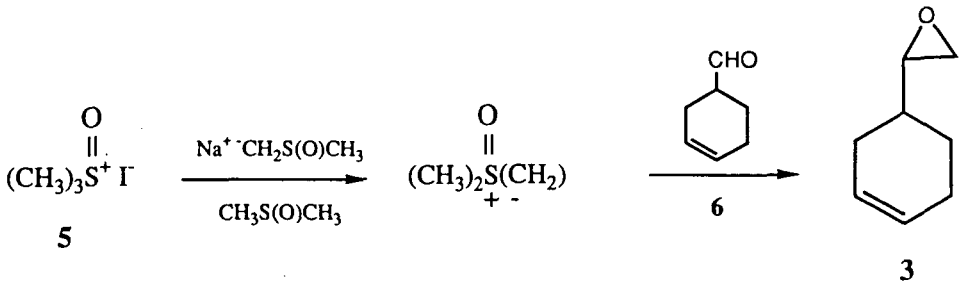
INTRODUCTION

The curing of synthetic rubber produces 4-vinylcyclohexene (**1**) from dimerization of 1,3-butadiene.[1] The curing process volatilizes the 4-vinylcyclohexene, exposing workers to this hydrocarbon by inhalation.[2] Chronic exposure of humans to 4-vinylcyclohexene may be of concern since there are indications that oxidative metabolites of **1** may be carcinogenic.[3]

The major cytochrome P450 metabolites of **1** are epoxides **2** and **3**.[4] Also of interest are diol metabolites such as **4**. We required significant amounts of these compounds for ongoing toxicological and toxicokinetic studies.[5] Epoxide **2** is commercially



1 **2** **3** **4**

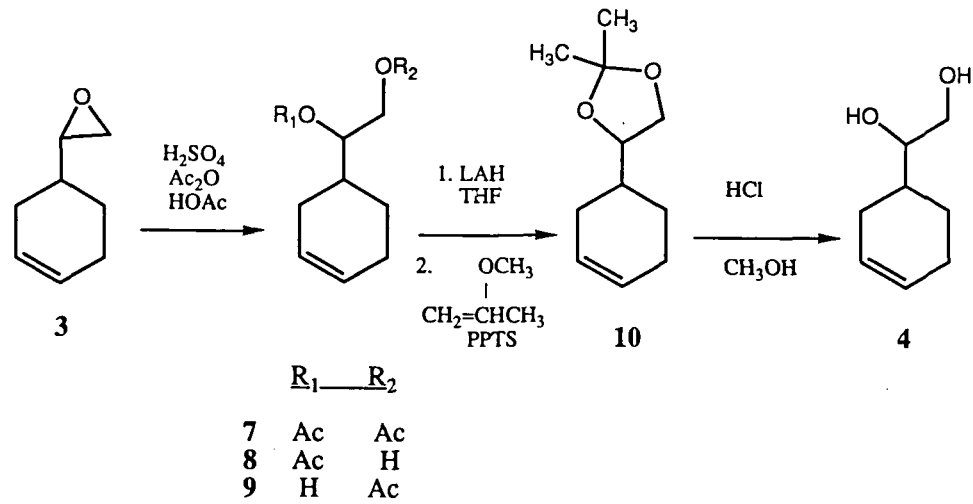


Scheme 1 Synthesis of Epoxide **3**.

available.[6] Although 4-vinylcyclohexene derivatives **3** and **4** had previously been prepared, in our hands the published three step procedure to **3** from **1** via a bromination-epoxidation-dehydrobromination sequence[7] was complicated by a lack of regioselectivity in the bromination step. Further, the water solubility of diol **4** made its isolation difficult. We have developed alternative syntheses of epoxide **3** and diol **4** which obviate the difficulties we have experienced, and describe our procedures herein.

CHEMICAL SYNTHESES

Depicted in Scheme 1 is a one-step procedure to epoxide **3** from the commercially available starting materials, trimethylsulfoxonium iodide (**5**) and 1,2,3,6-tetrahydrobenzaldehyde (**6**). Deprotonation of **5** using dimsyl sodium in DMSO gives the



Scheme 2 Synthesis of Diol **4**.

corresponding methylide, which condenses[8] with **6** to give epoxide **3** in 78% yield after distillation.[9]

Depicted in Scheme 2 is a preparation of diol **4** from epoxide **3**. Solvolysis of **3** in a mixture of acetic anhydride and glacial acetic acid containing about 1% H_2SO_4 produced a mixture of mono- and diacetates, **7**, **8**, and **9**, along with acetylated oligomeric materials, all of which were easily extracted into ether. Reduction of the acetates using lithium aluminum hydride gave the crude diol **4**. Separation from higher oligomeric diols was most conveniently effected by conversion of **4** to the corresponding isopropylidine acetals **10**, silica gel chromatography, and acetal hydrolysis to yield diol **4**.[9]

PHYSICAL AND SPECTROSCOPIC CHARACTERIZATIONS

Thin-layer chromatographic mobility, complete proton and carbon nuclear magnetic resonance data, infrared data, and mass spectral data or elemental analysis for compounds **3** and **4** appear in the experimental section which completes this article.

Acknowledgements

We acknowledge financial assistance from the Chemical Manufacturers Association. The Midwest Center for Mass Spectrometry is partially supported by the National Science Foundation, Biology Division (Grant No. DIR9017262).

EXPERIMENTAL SECTION

All reactions were performed under a positive pressure of argon. Reaction mixtures were stirred magnetically. Hygroscopic liquids were transferred via syringe and were introduced into reaction vessels through rubber septa. DMSO was stirred over CaH_2 for 24 h, then distilled at reduced pressure. Diethyl ether was distilled from sodium/benzophenone ketyl. Analytical thin-layer chromatography was performed on Merck 0.25 mm silica gel 60 F-254 plates. Visualization of spots was effected by dipping the plate into a 2.5% solution of anisaldehyde in ethanol containing 6% H_2SO_4 and 2% acetic acid, followed by charring on a hot plate. Flash chromatography was performed using Merck 230–400 mesh silica gel 60. Standard column chromatography was performed on Merck 70–230 mesh silica gel 60. Infrared spectra were measured on a Perkin-Elmer model 1610 FT-IR spectrophotometer. ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer with tetramethylsilane (TMS) as internal standard (0 ppm). ^{13}C NMR spectra were recorded on a Brucker WM-250 spectrometer using the center line of the chloroform-*d* triplet as internal standard (77.0 ppm). Mass spectra were obtained at the Midwest Center for Mass Spectrometry. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

4-Oxiranylcyclohexene (**3**). To a 1L flame-dried flask under argon was added 6.18 g (142 mmol) of 55% sodium hydride dispersion in oil. The sodium hydride was

washed with pentane (3 × 50 mL) to remove the oil, and the last traces of pentane were removed under vacuum. Dimethylsulfoxide (100 mL) was added to the flask slowly via syringe. The mixture was stirred and heated to 65°C for two hours while hydrogen gas was evolved. The resulting clear brown solution was cooled to room temperature and trimethylsulfoxonium iodide (**5**) (29.8 g, 135 mmol) was added portionwise. After 30 min a solution of 1,2,3,6-tetrahydrobenzaldehyde (**6**) (14.2 g, 129 mmol) in DMSO (20 mL) was added dropwise via addition funnel over one hour. The addition funnel was rinsed with DMSO (10 mL). When the aldehyde had been consumed (TLC, CH_2Cl_2), the reaction was quenched by addition of water (50 mL). The clear yellow solution was poured into water (900 mL) and extracted with pentane (5 × 200 mL). The combined pentane extracts were washed with saturated NaCl solution (100 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and the pentane removed by distillation at atmospheric pressure through a 30 cm Vigreux column. The resulting yellow liquid was distilled at aspirator pressure (40 mm Hg) to yield epoxide **3**[9] as a clear colorless liquid. bp_{40} 95–100°C, R_f 0.37 (CH_2Cl_2); yield 12.4 g (100 mmol, 78%); IR (CH_2Cl_2) cm^{-1} 3026, 2922, 2840, 1652, 910, 876, 855; ^1H NMR (250 MHz, $CDCl_3$) δ 1.29–1.60 (2 H, m), 1.70–2.28 (5 H, m), 2.55 (1 H, dd, J = 5 Hz, 3 Hz), 2.74 (1 H, dd, J = 9Hz, 5 Hz), 2.78–2.90 (1 H, m), 5.60–5.75 (2 H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) mixture of diastereomers: δ 24.0, 24.4, 24.6, 25.2, 26.9, 27.8, 35.9, 36.2, 45.4, 46.0, 55.6, 55.9, 125.1, 125.4, 126.7, 127.1. Mass spectrum (70 eV) m/z (rel. intensity) 124 (0.5), 123 (1), 109 (4), 106 (10), 105 (8), 95 (4), 94 (6), 93 (44), 92 (9), 91 (87), 81 (16), 80 (52), 79 (100), 78 (63), 77 (53), 70 (18), 69 (8), 68 (6), 67 (17), 66 (15), 65 (10), 55 (11), 54 (25), 53 (21), 51 (9); exact mass calcd for $C_8H_{12}O$ 124.08886, obsd 124.08868.

4-(1,2-Dihydroxyethyl)cyclohexene (**4**). To a solution of epoxide **3** (3.94 g, 31.7 mmol) in glacial acetic acid (20 mL) and acetic anhydride (50 mL) at 0°C under argon was added a solution of concentrated H_2SO_4 (0.5 mL) in acetic acid (20 mL) slowly via an addition funnel. After 15 min additional H_2SO_4 (0.5 mL) was added as a solution in acetic acid (5 mL). The mixture was warmed to room temperature, and TLC (20% ethyl acetate/hexanes) indicated that the epoxide had been consumed. The reaction mixture was diluted with anhydrous diethyl ether (500 mL) and the acids present were neutralized by rapid addition of 10% aqueous Na_2CO_3 solution (2 L). The aqueous layer was extracted with ether (3 × 250 mL), the ether extracts were combined, washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution. The ether extracts were then dried over anhydrous $MgSO_4$, filtered, and the solvent removed to yield 6.59 g of a yellow-brown oil which was a mixture of mono- and diacetates **7–9** and oligomeric materials. Pure diol **4** was obtained from this mixture as described below.

To a flame-dried 1 L flask under argon was added lithium aluminum hydride (1.75 g, 46.1 mmol) and diethyl ether (100 mL). A solution of the oil from the previous paragraph in ether (10 mL) was added via addition funnel over one hour. The addition funnel was rinsed with ether (5 mL). The reaction mixture was heated to reflux for one hour, then cooled to 0°C and quenched by careful successive additions of water (1.75 mL), 4 N NaOH solution (1.75 mL), and water (5.25 mL). The mixture

was stirred until all the gray solid had turned white. The reaction mixture was filtered, and the white solid extracted with ether continuously for five hours. The filtrate and extracts were combined, and the ether was removed to give the crude diol as a yellow oil (3.84 g). Following one pass through flash silica gel, the diol was purified by one of the two methods described herein: (1) repeated column chromatography using 50% ethyl acetate/hexanes; or (2) reaction with methyl isopropenyl ether in the presence of catalytic pyridine *p*-toluenesulfonate. The isopropylidene ketal **10** so formed was easily separated from polar oligomeric diol impurities by flash chromatography. The isopropylidene group was subsequently removed by stirring in 3% methanolic HCl at room temperature. Column chromatography using 50% ethyl acetate/hexanes then gave the pure diol **4**[9] as a colorless oil, R_f 0.17 (50% ethyl acetate/hexanes), R_f 0.24 (80% ethyl acetate/hexanes). IR (neat) cm^{-1} 3361(br), 3022, 2915, 2838, 1653, 1436, 1076, 1046; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20–1.46 (1 H, m), 1.56–2.18 (6 H, m), 3.40–3.60 (2 H, m), 3.65–3.76 (1 H, m), 4.70 (variable, 2 H, s), 5.59–5.75 (2 H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) mixture of diastereomers δ 24.4, 24.8, 25.0, 26.9, 27.7, 36.3, 36.4, 64.6, 64.7, 125.5, 126.0, 126.7, 127.2.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.25; H, 10.19.

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5. Results of the toxicological studies will be reported elsewhere.
6. From Aldrich Chemical Company (in the Alfred Bader Collection of Rare Chemicals).
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9. Epoxide **3** and diol **4** are obtained as mixtures of all possible stereoisomers. It is unknown at this time whether or not biological epoxidation of **1** is enantiomer-selective or stereoselective.