sym-Oxepin Oxide

William H. Rastetter[1]

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received July 21, 1975*

Abstract: The biological relevance, synthesis, and properties of *sym*-oxepin oxide (**1**) are discussed. The synthesis of **1** has been achieved by nitrogen extrusion from the azo diepoxide **10**. The rate of degenerate Cope rerrangement for **1** is too slow to allow detection of the Cope process by ^{1}H NMR spectroscopy up to 116 °C. *sym*-Oxepin oxide (**1**) undergoes an acid-catalyzed rearrangement to 4*H*-pyran-4-carboxaldehyde (**13**) and is reduced catalytically to 4-oxepanol (**14**).

Arene oxides have received considerable attention due to the theoretical and biological relevance of this class of epoxides.[2] Of similar interest, but until recently unreported,[3,4] are the epoxides of the oxepin valence tautomers of arene oxides. The present work discusses the relevance, synthesis, and properties of one such epoxide, *sym*-oxepin oxide (**1**) (4,8-dioxabicyclo[5.1.0]octa-2,5-diene) (Scheme II).

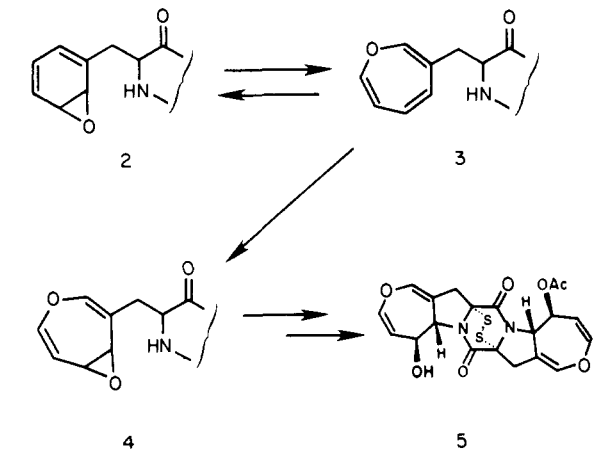
The isolation and structure determination of aranotin (**5**) (Scheme I) and related fungal metabolites (from genera *Aspergillus* and *Arachniotus*) led to the suggestion by Neuss et al.[5] that oxepin oxides might be involved in the biogenesis of naturally occurring dihydrooxepins. Based on isotopic labeling studies, the biosynthetic source of the postulated, aranotin precursor **4** is thought to be phenylalanine.[5] The generation of oxepin oxide **4** is suggested to involve monooxygenation of phenylalanine to give the arene oxide **2** and subsequent oxidation of the valence tautomer **3**. An intramolecular nucleophilic attack by nitrogen on the epoxide of **4**, with Walden inversion, would give rise to the stereochemistry observed in the aranotins. Gliotoxin, a fungal metabolite (from genera *Gliocladium* and *Trichoderma*) also from the class of sulfur-containing diketopiperazines (cf. **5**), might arise from an analogous intramolecular reaction of the arene oxide **2**.[5] While the involvement of arene oxides in the metabolism of aromatic systems is well documented,[2] and synthetic methods for the preparation of arene oxide oxepin systems have been developed,[2] the lack of precedent for **4** prompted a search for a synthetic route to oxepin oxides.

Apart from the biological relevance of oxepin oxides, the ring system is of theoretical interest. *sym*-Oxepin oxide (**1**) is expected to undergo a Cope rearrangement as demonstrated for the related bicyclo[5.1.0]octa-2,5-diene (homotropilidene) and *sym*-oxabicyclo[5.1.0]octa-2,5-dienes.[6] The anticipated Cope process for *sym*-oxepin oxide (**1**) is degenerate, interconverting two identical valence tautomers. Further, high reactivity is expected for the *sym*-oxepin oxide system. The conjugation of the epoxide of *sym*-oxepin oxide (**1**) with the bisenol ether oxygen should render **1** similar in reactivity to the seldom-isolated epoxides of enol ethers.[7] Also, by analogy to arene oxides,[8] high acid sensitivity is expected for *sym*-oxepin oxide (**1**), as protonation of the epoxide should induce cleavage to the stabilized cation **11** (Scheme III).

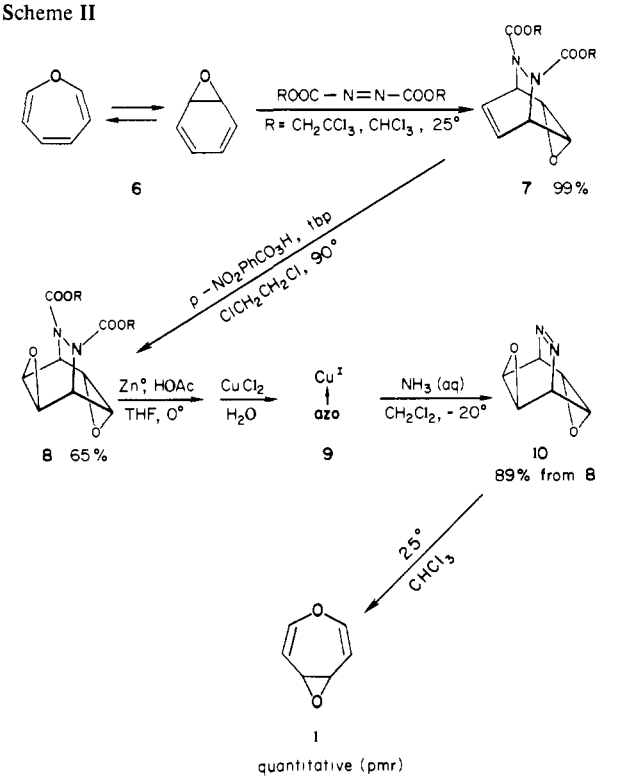
A synthetic route allowing for the generation of *sym*-oxepin oxide (**1**) under mild conditions was sought due to the anticipated sensitivity of the molecule. Generation of **1** was envisioned through the gentle thermolysis of an azo diepoxide such as **10** (Scheme II). Precedent for the desired mode of decomposition of **10**, involving nitrogen loss with concurrent opening of one epoxide, is found in the participation of cyclopropane rings in similar retrograde homo Diels–Alder reactions.[6]

The route adopted for the synthesis of *sym*-oxepin oxide (**1**) (Scheme II) achieves the preparation of the desired oxide **1** from benzene oxide–oxepin (**6**). The conversion **6** → **1** is accomplished via a protection–epoxidation–deprotection sequence which allows, in effect, the regiospecific epoxidation of the oxepin valence tautomer (**6**, triene form). The task of protection is readily accomplished by trapping the benzene oxide valence tautomer (**6**, diene form) as the Diels–Alder adduct with bis(trichloroethyl)azodicarboxylate.[9] The remaining double bond in the adduct **7** is now properly situated for the introduction of the desired epoxide moiety. After ep-

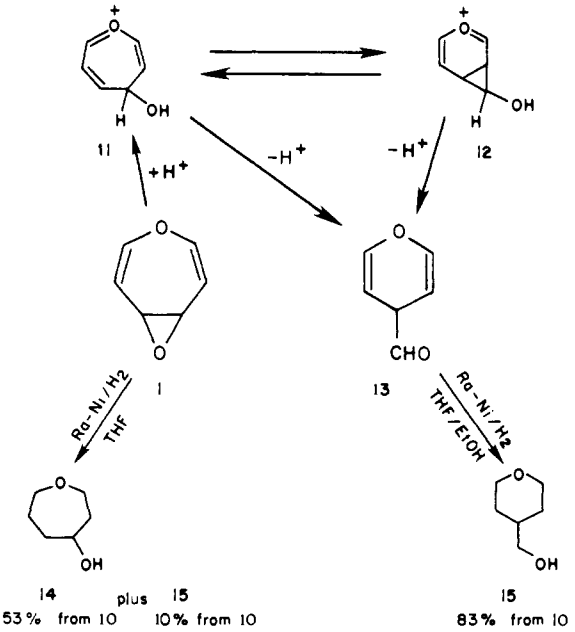
Scheme I



Scheme II



Scheme III



oxidation (**7** → **8**), deprotection is achieved via the azo cuprous complex **9** and the corresponding uncomplexed azo compound **10**.

The initial step of the synthetic sequence, the Diels–Alder addition to benzene oxide–oxepin (**6**), proceeds in a nearly quantitative fashion giving a single product (**7**). The stereochemistry assigned to the sole Diels–Alder product **7** is based on the expected direction of approach of the dienophile, bis(trichloroethyl)azodicarboxylate, to the diene, benzene oxide (**6**, diene form).[10] Epoxidation of **7** is achieved at high temperature (90 °C) by *p*-nitroperoxybenzoic acid stabilized by 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) (tbp)[11] giving the diepoxide **8** (65% yield). Reductive cleavage of the trichloroethylcarbamate esters of **8** followed by oxidation with Cu^{II} produces the stable, brick red, cuprous complex **9**. The azo diepoxide **10** is liberated from **9** at −20 °C by aqueous NH_3 and can be isolated at low temperature as a white crystalline solid (89% yield from **8**). Dissolution of **10** in aprotic solvents and warming to ambient temperature lead to the loss of nitrogen ($k^{29.8\,°C} = 9.51 \pm 0.15 \times 10^{-4}\ s^{-1}$)[12] and the quantitative (^1H NMR) formation of *sym*-oxepin oxide (**1**). The oxide **1** can be isolated as a white, crystalline solid, melting below ambient temperature. The same air sensitivity reported for γ-pyran[13] is seen for *sym*-oxepin oxide (**1**); **1** turns brown quickly after exposure to air.

The ^1H NMR spectrum of **1**[14] shows no evidence of fluxional character up to 116 °C,[15] precluding a Cope rearrangement at or below this temperature *on the ^1H NMR time scale*. *sym*-Oxepin oxide (**1**) does not necessarily possess a static structure but rather may exist as identical, equilibrating valence tautomers whose interconversion is too slow to be detected by the ^1H NMR method.[16] From ^1H NMR data reported for two *sym*-oxepin oxide analogues,[6] the rates for Cope rearrangement follow the order bicyclo[5.1.0]octa-2,5-diene > *sym*-oxabicyclo[5.1.0]octa-2,5-dienes > 4,8-dioxabicyclo[5.1.0]octa-2,5-diene (**1**). Similar rate differences have been noted between *cis*-divinylcyclopropane[17] and *cis*-divinyloxirane[18] and in the bicyclo[6.1.0]nona-2,6-diene series.[19]

Treatment of **1** in aprotic solvents with trace amounts of methanesulfonic acid leads within seconds to the quantitative (^1H NMR) generation of 4*H*-pyran-4-carboxaldehyde (**13**, Scheme III). The first step in the rearrangement is assumed to be proton-induced, epoxide cleavage to the homoaromatic cation **11**. Ring contraction of **11** and proton loss might directly generate **13**. Alternatively, the conversion might occur through rearrangement of **11** to the valence tautomer **12**, with subsequent fragmentation of **12** and proton loss forming the aldehyde **13**.

sym-Oxepin oxide (**1**) and 4*H*-pyran-4-carboxaldehyde (**13**) have been transformed, each in a single step, to known compounds. Catalytic reduction of **1** (Scheme III) yields 53% of 4-oxepanol (**14**) and 10% of 4-hydroxymethyltetrahydropyran (**15**) plus several unidentified minor products. Similar reduction of **13** yields 83% of **15**. Both **14** and **15** so produced are identical in physical and spectroscopic properties with authentic samples.[20,21]

Experimental Section

^1H NMR spectra (100 MHz) were obtained on a Varian HA-100 or Varian XL-100 and ^{13}C NMR spectra (25 MHz) on a Varian XL-100 spectrometer; chemical shifts are reported downfield from internal Me_4Si in $CDCl_3$. Mass spectra were determined on an AEI MS-9 double-focusing, high-resolution mass spectrometer and infrared spectra on a Perkin-Elmer 137 spectrometer. Melting points are uncorrected and were obtained on a Kofler hot stage. All glassware used for the preparation or handling of *sym*-oxepin oxide (**1**) and of benzene oxide–oxepin (**6**) was base treated (soaked in 1 N NaOH, rinsed with distilled H_2O and then with NH_4OH, and oven-dried). Acetonitrile and all chlorinated solvents ($CHCl_3$, $CDCl_3$, $ClCH_2CH_2Cl$, $CDCl_2CDCl_2$, and CH_2Cl_2) were purified by passage through basic alumina immediately prior to use; THF was distilled from NaK benzophenone ketyl.

Diels–Alder Addition to Benzene Oxide–Oxepin (6). Preparation of Adduct 7. Benzene oxide–oxepin (**6**) was prepared by dehydrobromination of 4,5-dibromocyclohexene oxide by a modification[22] of the procedure described by Vogel et al.[2a] To 4,5-dibromocyclohexene oxide (8.00 g, 31.2 mmol) slurried in anhydrous Et_2O (53 ml) and maintained at 0 °C was added portionwise over 54 min an Et_2O (85 ml) suspension of alcohol-free potassium *tert*-butoxide (10.70 g, 95.6 mmol). The mixture was stirred for 1 h at 0 °C, then pH 7 phosphate buffer (80 ml) was added, and the mixture stirred until all suspended solids dissolved. The resulting layers were separated and the organic layer was washed with pH 7 phosphate buffer (2 × 25 ml). The aqueous layers were combined and extracted with Et_2O (2 × 10 ml); then all organic layers were combined, dried ($MgSO_4$), filtered, and concentrated (Vigreux column–steam bath). The residual orange oil was distilled bulb to bulb [70–100 °C (70 mmHg)]; the distillate, a mixture of benzene oxide–oxepin (**6**), *tert*-butyl alcohol, and Et_2O, weighed 6.90 g and contained 2.61 g (27.9 mmol) of **6** (89% yield by ^1H NMR).

To the benzene oxide–oxepin (**6**), *tert*-butyl alcohol, and Et_2O mixture, diluted with $CHCl_3$ (20 ml) and magnetically stirred, was added portionwise during 1 h a solution of bis(trichloroethyl)azodicarboxylate[9] (8.51 g, 22.4 mmol) in $CHCl_3$ (20 ml).[23] The Diels–Alder addition was monitored conveniently by ^1H NMR spectroscopy; after addition of the dienophile solution, an excess of **6** (d, δ 5.25) was seen vs. dienophile (s, δ 5.20). After adding additional bis(trichloroethyl)azodicarboxylate (1.21 g, 3.18 mmol) as the crystalline solid (total dienophile added = 9.72 g, 25.6 mmol) the reaction solution contained a small excess of **6** (^1H NMR); the mixture was stirred overnight.

Rotary evaporation of the nearly colorless reaction mixture gave a white, foamy residue. Trituration of the foam with Et_2O induced crystallization; recrystallization ($CHCl_3$–Et_2O) yielded white, microcrystalline, solid adduct **7** [11.94 g, 99% based on bis(trichloroethyl)azodicarboxylate]: ir (KBr) 1760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) temperature-dependent spectrum, at 30 °C, δ 6.35 (1 H, br t), 6.09 (1 H, br t), 5.37 (2 H, br s), 4.82 (4 H, br m), 3.78 (1 H, br s), 3.56 (1 H, br s); ^1H NMR at 110 °C δ 6.21 (2 H, t), 5.36 (2 H, m), 4.81 (4 H, AB q), 3.63 (2 H, m); uv (CH_3CN) no λ_{max} above 216 nm; mass spectrum (70 eV) parent six Cl cluster, *m/e* 472, 474, 476, 478, 480, 482, 484; mp 145–147 °C. Anal. Calcd for $C_{12}H_{10}Cl_6N_2O_5$: C, 30.35; H, 2.12; Cl, 44.79; N, 5.90. Found: C, 30.41; H, 2.25; Cl, 45.00; N, 5.83.

Epoxidation of Adduct 7. Preparation of Diepoxide 8. A thick-walled glass tube was charged with adduct **7** (2.39 g, 5.03 mmol), 85% *p*-nitroperoxybenzoic acid[24] (Aldrich) (4.30 g, 19.95 mmol, active oxygen), 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) (tbp)[11] (43.2 mg,

1 wt % vs. peracid), and $ClCH_2CH_2Cl$ (7.5 ml) and was sealed under an argon atmosphere. The tube was heated[25] in an oil bath at 90 °C for 2.5 h, cooled in an ice bath, and opened. The contents, a slurry of pale yellow solid, were transferred to a separatory funnel with $CHCl_3$ (50 ml). The organic layer was washed with 15% aqueous $NaHSO_3$ (50 ml) and separated from the resulting aqueous suspension. The aqueous layer was diluted by the cautious addition of saturated, aqueous $NaHCO_3$ (50 ml) and, after gas evolution ceased, was extracted with $CHCl_3$ (2 × 25 ml). The organic layers were combined and filtered to remove suspended solids and then washed with 15% aqueous $NaHSO_3$ (25 ml) and with saturated, aqueous $NaHCO_3$ (2 × 25 ml). Drying ($MgSO_4$), filtration, and rotary evaporation gave a white to yellow foam which crystallized upon trituration with Et_2O. Recrystallization ($CHCl_3$–Et_2O) yielded white, microcrystalline, solid diepoxide **8** (1.61 g, 65% based on adduct **7**): ir (KBr) 1775, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 5.05 (2 H, m), 4.84 (4 H, 2 AB q), 3.72 (2 H, m), 3.40 (2 H, m); mass spectrum (70 eV) parent six Cl cluster, *m/e* 488, 490, 492, 494, 496, 498, 500; mp 187 °C. Anal. Calcd for $C_{12}H_{10}Cl_6N_2O_6$: C, 29.36; H, 2.05; Cl, 43.33; N, 5.71. Found: C, 29.52; H, 2.18; Cl, 43.11; N, 5.67.

Deprotection of Diepoxide 8. A. Preparation of Cuprous Complex 9. Zinc dust (30.01 g, 0.460 g-atom) was washed in a Schlenk filter flask, under a nitrogen atmosphere, with 5% aqueous HCl (48 ml) for 60 s and then the aqueous layer was removed by pressure filtration. In a similar fashion, the zinc dust was rinsed sequentially with 5% aqueous HCl (3 × 36 ml), H_2O (5 × 36 ml), absolute ethanol (4 × 36 ml), and anhydrous Et_2O (5 × 36 ml). The activated zinc[26] after drying in vacuo weighed 28.44 g.

The reductive cleavage of the carbamate esters of **8** was carried out in a three-neck round-bottom flask; one neck was sealed with a serum cap and the remaining necks connected the flask to a vacuum manifold and, by means of Gooch tubing, to a vessel containing the activated zinc. To diepoxide **8** (3.54 g, 7.22 mmol) in the reaction vessel was added glacial acetic acid (169 ml). The mixture was frozen by brief application of a liquid nitrogen bath; then the system was evacuated and refilled with argon several times (including the vessel containing the activated zinc by a separate connection to the vacuum manifold). THF (128 ml) was added to the argon-filled system by injection through the serum cap; the mixture was allowed to thaw. Once a homogeneous solution was obtained, an ice bath was applied and the activated zinc (28.44 g, 0.436 g-atom) was added in one portion via the Gooch tubing. The reaction mixture was magnetically stirred at 0 °C for 1 h 25 min and then cooled with an ethylene glycol–H_2O–CO_2(s) cooling bath to temperatures between −30 and −40 °C for 30 min. The cold reaction mixture was filtered under argon in a Schlenk apparatus giving a colorless filtrate and a cake of zinc-gray solids. A minor portion of the reductive cleavage products[27] was obtained by rotary evaporation of the filtrate in high vacuum with gentle warming (30 °C); the white to yellow solid residue was stored under an argon atmosphere. Separation of the major portion of the desired product from the zinc-gray solids in the Schlenk apparatus was achieved by thorough washing of the cake under an argon atmosphere with H_2O (6 × 10 ml); pressure filtration gave a colorless, aqueous solution of the reductive cleavage products.

The cuprous complex **9** was formed by the addition of Cu^{II} to the aqueous filtrate containing the reductive cleavage products. Thus, to the magnetically stirred filtrate (initial pH 3.1) was added 2 N aqueous $CuCl_2$ (7.2 ml, 14.4 mmol) causing the immediate precipitation of **9** (pH after addition of $CuCl_2$, 2.1). The pH of the aqueous suspension was raised to 5.0 by the dropwise addition of NH_4OH (7.4 ml of 5 N NH_4OH plus 10.5 ml of 15 N NH_4OH was required), and collection of the precipitated cuprous complex was achieved by centrifugation and decantation of the supernatant. Finally, the product was washed sequentially with cold 20% aqueous NH_4Cl (2 × 12 ml), cold H_2O (2 × 12 ml), cold absolute EtOH (2 × 12 ml), and with anhydrous Et_2O (3 × 16 ml) (product centrifuged and supernatant decanted after each wash). Preliminary drying of the product in a stream of nitrogen gave the cuprous complex **9** (1.78 g) as a brick red, microcrystalline solid.

Dissolution of the minor portion of the reductive cleavage products (obtained by rotary evaporation of the HOAc–THF filtrate, vide supra) in H_2O, followed by similar treatment with $CuCl_2$, and washing and drying in a nitrogen stream gave an additional portion of cuprous complex **9** weighing only 67.4 mg. After drying in high vacuum overnight, the combined portions of **9** weighed 1.70 g: ir (KBr) 1465 cm^{-1}; mp 132–135 °C dec.

B. Isolation of Azo Diepoxide 10. The azo diepoxide **10** was liberated immediately prior to use from the stable, cuprous complex **9.** In a typical preparation, cuprous complex **9** (288 mg, corresponding to 1.22 mmol of diepoxide **8**) was placed in a stoppered, tapered-bottom, centrifuge tube; the tube was cooled briefly in an acetone–CO_2(s) bath. To the tube was added 20% aqueous NH_3 (2.5 ml), just above its melting point, plus CH_2Cl_2 (2.5 ml). Extraction of the azo diepoxide **10** into the organic layer was achieved by shaking the cold, stoppered tube until the brick red, solid, cuprous complex was consumed (ca. 1 min); periodically the tube was dipped into an acetone–CO_2(s) bath to maintain the temperature of the mixture just above the freezing point of the aqueous layer (ca. −20 to −30 °C). Rapid separation of the cold organic and aqueous layers was effected by centrifugation and the organic layer was drawn off and stored at −78 °C. The aqueous layer was extracted further with CH_2Cl_2 (2 × 2.5 ml) and the organic layers were combined and washed with H_2O (2.0 ml) at 0 °C. While still cold, the organic layer was dried ($MgSO_4$) and filtered into a flask maintained at −20 to −30 °C [HO-CH_2CH_2OH–H_2O–CO_2(s) bath] with a CH_2Cl_2 (4 × 1.5 ml) rinse. The CH_2Cl_2 solution was rotary evaporated in high vacuum at −20 to −30 °C giving azo diepoxide **10** (150 mg, 89% based on diepoxide **8**) as a white, crystalline solid. Compound **10** is stable at −20 °C in $CDCl_3$ solution and the ^1H NMR spectrum shows δ 6.08 (2 H, m), 3.50 (2 H, MM′XX′ half spectrum), and 3.40 (2 H, AA′XX′ half spectrum); ^1H decoupling irr at δ 6.08 gives 3.50 (2 H, s), 3.40 (2 H, s); irr at δ 3.45 gives 6.08 (2 H, s); mp 51–80 °C dec.

Generation and Isolation of *sym*-Oxepin Oxide (1). Dissolution of the azo compound **10** in aprotic solvents ($CHCl_3$, $CDCl_3$, CH_2Cl_2, CD_2Cl_2, $CDCl_2CDCl_2$, THF, or CH_3CN) and warming to ambient temperature led to the generation of *sym*-oxepin oxide (**1**). The formation of **1** from the azo compound **10** ($k^{29.8°C} = 9.51 \times 10^{-4}\ s^{-1}$)[12] was quantitative ($^1H$ NMR) and at 30 °C was virtually complete after 1.5 h. *sym*-Oxepin oxide (**1**) was isolated as an air-sensitive, white, crystalline solid, melting below ambient temperature, by vacuum transfer [25 °C (0.02 mmHg)] of a methylene chloride solution, followed by low temperature (−30 to −40 °C) evaporation of the solvent: ir ($CDCl_3$) 1670, 1650, 1320, 1170, 1100, 990, 840 cm^{-1}; ^1H NMR[14] ($CDCl_3$, 100 MHz) δ 6.33 (2 H, d), 5.14 (2 H, m), 3.33 (2 H, m); ^{13}C NMR ($CDCl_3$, 25 MHz) δ^C (Me_4Si) 146.4 (d, J_{CH} = 190.5 Hz), 103.7 (d, J_{CH} = 158.1 Hz), 51.2 (d, J_{CH} = 174.7 Hz); uv (CH_3CN) λ_{max} (shoulder) 227 nm (ε 980); mass spectrum (70 eV) *m/e* parent 110, base 81.

Reduction of 1 to 4-Oxepanol (14). The catalytic reduction of **1** to 4-oxepanol (**14**) was achieved in aprotic medium (THF) over Raney nickel catalyst. To prepare the catalyst, NaOH (4.99 g) was dissolved in H_2O (20 ml); when the temperature of the aqueous alkali dropped to 50 °C, Raney nickel catalyst powder (Grace No. 2813) (4.02 g) was added portionwise at a rate to maintain the temperature at 50 ± 2 °C (ca. 1.5 h required for addition). The mixture was stirred and allowed to digest at 50 °C for 52 min and then the supernatant was decanted. The metal was washed with H_2O until the rinses remained neutral (650 ml of H_2O in ca. 40-ml rinses) and then was washed with THF (4 × 40 ml). The pyrophoric catalyst was stored under THF at −20 °C until used.

sym-Oxepin oxide (**1**) used for the preparation of **14** was generated from azo compound **10** (147 mg, 1.06 mmol) by the dissolution and warming of **10** to ambient temperature in THF (7.0 ml). To the solution of **1** was added a Raney nickel–THF slurry (130 μl); the mixture was shaken under H_2 (47 psig) for 41 h. Filtration of the reaction mixture through Celite with an Et_2O rinse, evaporation of the solvents (Vigreux column–steam bath), and preparative gas–liquid chromatography (8 ft × 0.25 in. Carbowax 20M, 10% on 80–100 Diatoport S, 152 °C) gave 4-oxepanol (**14**) (65.3 mg, 53% based on **10**) and 4-hydroxymethyltetrahydropyran (**15**) (11.8 mg, 10% based on **10**), plus several unidentified minor products. 4-Oxepanol **14**, produced by catalytic reduction of **1**, was found to be identical with an authentic sample[20] by GLC coinjection (Carbowax 20M and SE-30), by mixture melting point of the phenylurethane derivatives, and by comparison of the ir, ^1H NMR, and mass spectra. Exact mass of **14** prepared via **1**: calcd for $C_6H_{12}O_2$, 116.0837; found, 116.0840. The 4-hydroxymethyltetrahydropyran (**15**) produced via **1** was found to be identical with an authentic sample[21] and to **15** produced by catalytic reduction of 4*H*-pyran-4-carboxaldehyde (**13**) (vide infra) by GLC coinjection (Carbowax 20M) and by comparison of the ir, ^1H NMR, and mass spectra.

Generation of 4*H*-Pyran-4-carboxaldehyde (13). Treatment of

sym-oxepin oxide (**1**) in aprotic solvents ($CDCl_3$, CH_2Cl_2, CD_2Cl_2, THF, or CH_3CN) with catalytic amounts of $MeSO_3H$ led within seconds to the generation of **13.** In $CDCl_3$ the addition of $MeSO_3H$ (0.1 mol %) catalyzes the quantitative (^1H NMR) rearrangement of **1** to **13:** ir ($CDCl_3$) 1725, 1680, 1620, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 9.51 (1 H, d), 6.50 (2 H, m), 4.90 (2 H, m), 3.64 (1 H, m); uv (CH_3CN) λ_{max} 246 (ϵ 590), 310 (110); mass spectrum (70 eV) *m/e* parent 110, base 81. Exact mass of *p*-nitrophenylhydrazone: calcd for $C_{12}H_{11}N_3O_3$, 245.0800; found, 245.0797.

Reduction of 13 to 4-Hydroxymethyltetrahydropyran (15). The catalytic reduction of **13** to 4-hydroxymethyltetrahydropyran (**15**) was achieved in THF–EtOH over Raney nickel catalyst. The catalyst was prepared as for the reduction of **1** to **14,** except that the metal was both washed and stored under EtOH rather than THF.

sym-Oxepin oxide (**1**) used for the preparation of **13** was generated from azo compound **10** (150.2 mg, 1.09 mmol) by the dissolution and warming of **10** to ambient temperature in THF (4.7 ml). To the solution of **1** was added 2% $MeSO_3H$ in Et_2O (23 μl); the mixture was stirred for 23 min. A portion of $CaCO_3$ (Merck, precipitated) (41 mg) was added and the suspension was stirred briefly and filtered with an EtOH (4.7 ml) rinse. To the resulting solution of **13** was added a Raney nickel–EtOH slurry (120 μl); the mixture was shaken under H_2 (47 psig) for 40 h. Filtration of the reaction mixture through Celite with an Et_2O rinse, evaporation of the solvents (Vigreux column–steam bath), and preparative gas–liquid chromatography (8 ft × 0.25 in. Carbowax 20M, 10% on 80–100 Diatoport S, 157 °C) gave 4-hydroxymethyltetrahydropyran (**15**) (104.8 mg, 83% based on **10**). The sample of **15** produced by catalytic reduction of **13** was found to be identical with an authentic sample[21] by GLC coinjection (Carbowax 20M and SE-30), by mixture melting point of the phenylurethane derivatives, and by comparison of the ir, ^1H NMR, and mass spectra. Exact mass of **15** prepared via **13:** calcd for $C_6H_{12}O_2$, 116.0837; found, 116.0840.

Acknowledgments. I am indebted to Professor R. B. Woodward for his generous support and guidance and to Professor J. E. Baldwin for his valuable discussions and continuing interest. I gratefully acknowledge an NSF predoctoral fellowship (1972–1975).

References and Notes

(1) Address correspondence to this author at the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass. 02139.
(2) Reviews: (a) E. Vogel and H. Günther, *Angew. Chem., Int. Ed. Engl.*, **6**, 385 (1967); (b) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, **28**, 1129 (1972); (c) D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1**, 267 (1973); (d) D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974).
(3) W. H. Rastetter, *J. Am. Chem. Soc.*, **97**, 210 (1975).
(4) H. Klein and W. Grimme, *Angew. Chem., Int. Ed. Engl.*, **13**, 672 (1974).
(5) (a) N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Lett.*, 4467 (1968); (b) N. Neuss, L. D. Boeck, D. R. Brannon, J. C. Cline, D. C. DeLong, M. Gorman, L. L. Huckstep, D. H. Lively, J. Mabe, M. M. Marsh, B. B. Molloy, R. Nagarajan, J. D. Nelson, and W. M. Stark, *Antimicrob. Agents Chemother.*, 213 (1968).
(6) See D. D. Haas and W. H. Rastetter, *J. Am. Chem. Soc.*, following paper in this issue, and references cited therein.
(7) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 314–315.
(8) See, e.g., G. J. Kasperek and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 198 (1972).
(9) A sample was kindly provided by Dr. W. T. Borden and Y. C. Toong. Later a literature preparation appeared: D. Mackay, C. W. Pilger, and L. L. Wong, *J. Org. Chem.*, **38**, 2043 (1973).
(10) The stereochemical assignment is corroborated by an isotopic labeling study (see ref 6) which indicates that the epoxide fused anti with respect to the azo bridge of **10** is derived from the epoxide of benzene oxide.
(11) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. Chem. Soc., Chem. Commun.*, 64 (1972).
(12) Determined from a single kinetic run by the ^1H NMR method described in ref 6; error limit is the standard deviation determined by least-squares fitting of the values of **10** at eight times during the nitrogen extrusion reaction.
(13) (a) S. Masamune and N. T. Castellucci, *J. Am. Chem. Soc.*, **84**, 2452 (1962); (b) J. Strating, J. H. Keijer, E. Molenaar, and L. Brandsma, *Angew. Chem., Int. Ed. Engl.*, **1**, 399 (1962).
(14) An extensive treatment of the ^1H NMR spectrum of **1** is given in ref 6.
(15) High-temperature ^1H NMR spectra were determined in $CDCl_2CDCl_2$ solution; thermal instability of **1** prevents observation at higher temperatures.
(16) The rate of the Cope rearrangement for the *sym*-oxepin oxide system has been measured by an isotopic labeling study; see ref 6.
(17) J. M. Brown, B. T. Golding, and J. J. Stofko, Jr., *J. Chem. Soc., Chem. Commun.*, 319 (1973).
(18) (a) E. L. Stogryn, M. H. Gianni, and A. J. Passannante, *J. Org. Chem.*, **29**, 1275 (1964); (b) J. C. Pommelet, N. Manisse, and J. Chuche, *Tetrahedron*, **28**, 3929 (1972).
(19) W. Grimme and K. Seel, *Angew. Chem., Int. Ed. Engl.*, **12**, 507 (1973).
(20) S. Olsen and R. Bredoch, *Chem. Ber.*, **91**, 1589 (1958).
(21) A. Burger, L. B. Turnbull, and J. G. Dinwiddie, Jr., *J. Am. Chem. Soc.*, **72**, 5512 (1950).
(22) A similar procedure utilizing potassium *tert*-butoxide in Et_2O at 0 °C was kindly provided by Dr. W. Lever.
(23) The Diels–Alder addition is exothermic; ice bath cooling was utilized in large-scale preparations of adduct **7.**
(24) The use of *p*-nitroperoxybenzoic acid achieves the epoxidation of **7** under significantly milder conditions than those required with *m*-chloroperoxybenzoic acid; *m*-chloroperoxybenzoic acid gave tarry reaction products requiring tedious chromatographic purification and gave yields of **8** not exceeding 30%.
(25) Adequate shielding should be used during high-temperature epoxidatiion by *p*-nitroperoxybenzoic acid and the reaction temperature should be carefully regulated; D. F. Debenham, A. J. Owen, and E. F. Pembridge, *J. Chem. Soc. B*, 213 (1966), report that *p*-nitroperoxybenzoic acid, as the solid, in the absence of radical inhibitors, detonates at 100 °C.
(26) The activated zinc was protected from contact with air during all manipulations.
(27) The reductive cleavage products are assumed to include zinc salts and the hydrazinium acetate salt corresponding to azo diepoxide **10.**

Proton Magnetic Resonance Studies of *sym*-Oxepin Oxide

Daniel D. Haas and William H. Rastetter*[1]

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, and the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received April 9, 1976*

Abstract: Proton magnetic resonance studies have yielded information concerning the conformation and the degenerate Cope rearrangement of *sym*-oxepin oxide (**1**). Proton–proton coupling constants derived from a computer simulation of the high-resolution ^1H NMR spectrum of **1** indicate that the preferred or average conformation of *sym*-oxepin oxide (**1**) is significantly flatter than the transoid conformation **1a.** The specific generation of *sym*-2,7-dideuteriooxepin oxide (**9**) from the dideuterioazo compound **8** has provided a means to study the equilibrium subsequently established between **9** and its Cope rearrangement product *sym*-4,5-dideuteriooxepin oxide (**10**). Activation parameters have been obtained for the nitrogen extrusion reactions, **8** → **9** and **8** → **10,** and for the Cope rearrangement, **9** ⇄ **10.**

The structural similarity of *sym*-oxepin oxide[2] (**1**) (4,8-dioxabicyclo[5.1.0]octa-2,5-diene) to the hydrocarbon homotropilidene (**2**) (bicyclo[5.1.0]octa-2,5-diene) and to the half oxygenated analogues, the *sym*-oxabicyclo[5.1.0]octa-2,5-dienes (**3**), raises questions about the conformation and possible fluxional structure of **1.** Results obtained by Heil-