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Fe(II)-Induced Decomposition of Epidioxides Derived from α-Phellandrene[1]

James A. Turner and Werner Herz*

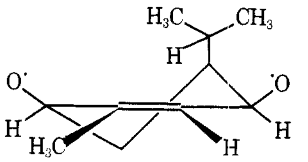
Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

Received October 15, 1976

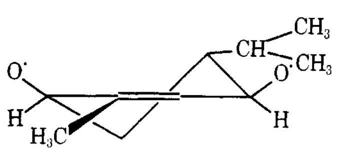
In the Fe(II)-promoted decomposition of the endoperoxides **2**, **3**, **10**, **13**, and **14** prepared from α-phellandrene, the intramolecular 1,5-hydrogen abstraction previously observed in the case of levopimaric acid epidioxide epoxide (**1**) is at best a minor pathway. Structurgs of the various products have been elucidated. A general scheme for the reactions of epidioxides with Fe(II) is presented which involves the Fe(II)–Fe(III) redox system in what superficially appears to be a series of isomerizations and provides a laboratory analogy for the PGG (or PGH) to PGF conversion.

The unexpected formation of remote oxidation products from the reaction of levopimaric acid epidioxide epoxide (**1**) with ferrous ion[2] suggested that other epidioxides might undergo similar reactions if the geometry of the peroxidic oxygen atoms were appropriate for 1,5-hydrogen transfer. Very few of the readily available epidioxides[3] fulfill this condition. In the present communication we report our results in the α-phellandrene series.

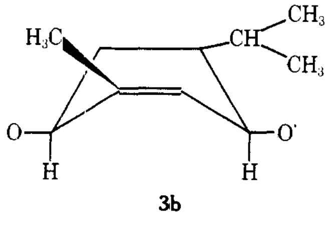
Reaction of α-phellandrene with singlet oxygen yields two epidioxides[4,5] which will be referred to as the cis peroxide **2** and the trans peroxide **3**. **3** contains a γ hydrogen (H-8) with suitable geometry and appropriate carbon–oxygen distance for abstraction by the oxygen atom on C-6 if the radical anion formed by reduction of **2**[2] could assume the half-chair conformation **2a**. The methyl hydrogens of the isopropyl side chain are available to C-3 oxygen in both half-chair and both half-boat conformers of **2**. Regardless of the conformation of the radical anion from **3**, there is no hydrogen available to the oxygen atom on C-6. But in two conformers, half-chair **3a** and half-boat **3b**, the methyl hydrogens of the isopropyl radical are accessible to the oxygen on C-3.



2a



3a

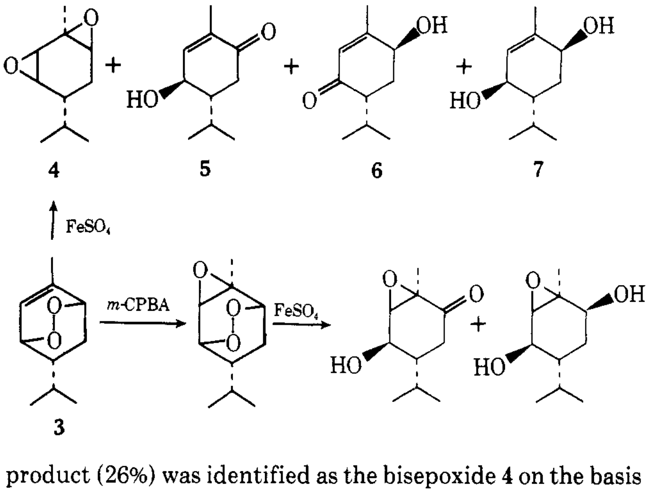


3b

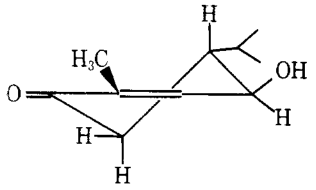
Results

Reaction of trans peroxide **3** with ferrous ion in aqueous tetrahydrofuran gave a mixture of four substances (Scheme I) which were separated by preparative TLC. The least polar product (26%) was identified as the bisepoxide **4** on the basis of the following evidence. The IR spectrum had no absorption in the carbonyl or hydroxyl region. The NMR spectrum (270 MHz) exhibited a three-proton singlet at 1.51 ppm typical of methyl attached to carbon bearing an oxygen and two methyl doublets of the isopropyl group which showed that long-range oxidation at the site of the methyl groups had not occurred. A one-proton doublet (J = 4 Hz) at 3.12 ppm and two multiplets at 2.87 and 2.91 ppm were appropriate for H-2, H-3, and H-6. Irradiation at 3.12 ppm altered the signal at 2.87 ppm and in the reverse experiment, irradiation at 2.87 ppm collapsed the doublet at 3.12 ppm to a singlet. This allowed assignment of the three peaks at 3.12, 2.87, and 2.91 ppm to H-2, H-3, and H-6, respectively.

Scheme I



The product formed in largest amount (29%) was the γ-hydroxy-α,β-unsaturated ketone **5** (IR bands at 3410 and 1670 cm^{-1}). The NMR spectrum exhibited a broadened doublet (J = 8 Hz) at 4.35 ppm which sharpened on D_2O exchange and was therefore assigned to hydrogen under hydroxyl. The chemical shift of a one-proton multiplet at 6.67 ppm was typical of the β proton of an α,β-unsaturated ketone which was allylically coupled to a vinyl methyl (1.76 ppm) at the α position. The isopropyl methyls were represented by the usual two doublets. A one-proton doublet of doublets at 2.45 ppm (J = 15.9, 3.2 Hz) was assigned to one of the two protons α to the carbonyl group. Irradiation at this frequency altered the pattern of a complex multiplet centered near 2 ppm which therefore represented the second α-keto proton. The large value of $J_{3,4}$ (8 Hz) indicated that **5** is in the half-chair conformation **5a**; this permits assignment of the 2.45-ppm resonance to H-5β. In this conformation equatorial H-5β is deshielded by the carbonyl group and the dihedral angle between H-5β and axial H-4 is consistent with the observed coupling constant of 3.2 Hz.



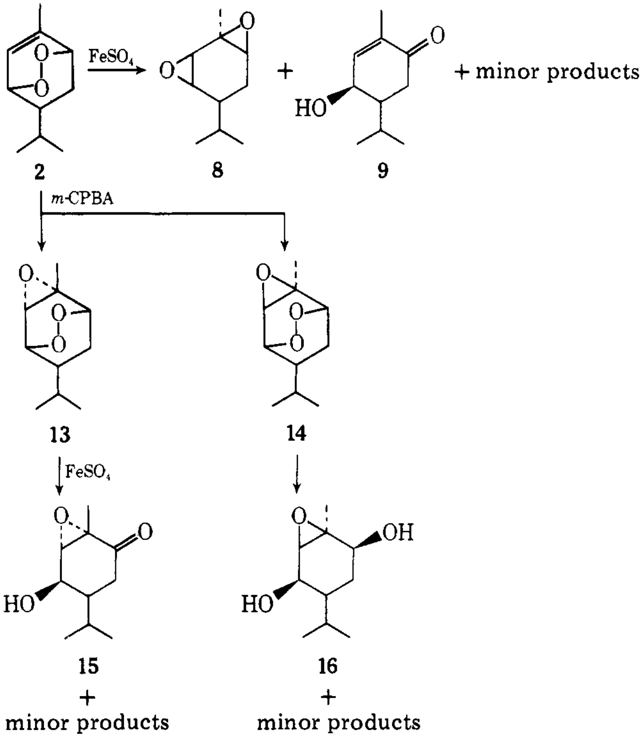
5a

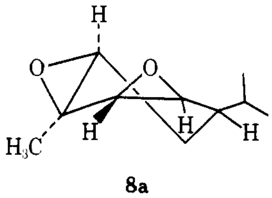
The third product (11%) was the isomeric γ-hydroxy-α,β-unsaturated ketone **6** (IR absorption at 3380 and 1655 cm^{-1}) with significant NMR signals at 5.80 (multiplet of H-Z allylically coupled to vinyl methyl at 2.01 ppm, chemical shift typical of α proton in β-alkyl-α,β-unsaturated ketone) and 4.35 ppm (multiplet of H-6). Two methyl doublets at 0.89 and 0.93 ppm showed that the isopropyl methyls had not been attacked. This substance has recently been reported as a product of the microbiological oxidation of piperitone.[6] The most polar product (18% yield) was the known[7] diol **7**.

Reaction of the cis peroxide **2** with ferrous sulfate likewise gave a mixture containing two major and two minor fractions (TLC). One of the minor fractions was formed in very small amount only and was not identified. The second minor fraction, while homogeneous on TLC, was a mixture by NMR criteria and could not be separated further. The two major products were isolated in pure form (Scheme II). The IR spectrum of the less polar substance **8** (16%) exhibited no hydroxyl or carbonyl absorptions. In the NMR spectrum (270 MHz) were found the usual two methyl doublets of the isopropyl group, a three-proton resonance at 1.46 ppm characteristic of methyl on carbon carrying single-bonded oxygen, a one-proton doublet of doublets (J = 7, 2.5 Hz) at 2.88 ppm, and an AB system centered at 3.12 ppm (J_{AB} = 5 Hz), the chemical shifts being typical of three protons under epoxidic oxygen. The value of J_{AB} indicated that the two protons in question were vicinal, not geminal; consequently the substance was identified as the diepoxide **8**. The absence of coupling between H-3 and H-4 is presumably due to conformation **8a** in which the H-3, H-4 dihedral angle is close to 90°; this conformation is also in agreement with the values of $J_{5\alpha,6}$ (7 Hz) and $J_{5\beta,6}$ (2 Hz).

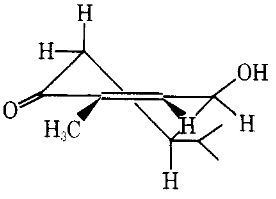
The IR spectrum of the product isolated in larger amount (28%, **9**) had hydroxyl and α,β-unsaturated ketone bands. The NMR spectrum exhibited a doublet of quartets (J = 6, 1.5 Hz) at 6.78 ppm and a narrowly split (J = 1.5 Hz) methyl doublet at 1.78 ppm typical of a β-methyl-α,β-unsaturated ketone (cf. the NMR spectrum of **5**), a complex multiplet at 4.42 ppm assigned to hydrogen under hydroxyl, and the AB part of an ABX system at 2.56 and 2.44 ppm where J_{AB} = 16.7 Hz (geminal coupling), J_{AX} = 4.3 Hz, and J_{BX} = 12.2 Hz. Clearly this system represented H-5α and H-5β of **9**; the chemical shifts and coupling constants pointed to conformation **9a**, where the larger vicinal coupling is that between H-5β at 2.44 ppm and H-5, equatorial H-5α being at lower field because of the anisotropic effect of the carbonyl group. However, H-5β is deshielded relative to H-5α of **5** because it is under the influence of a pseudoaxial hydroxyl group on C-4.

Scheme II





8a



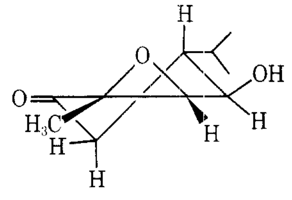
9a

Reaction of the unsaturated cis aud trans peroxides **2** and **3** with ferrous ion had thus led to the isolation only of "normal" products, i.e., rearrangement and reduction products, and had furnished no substances which might have resulted from long-range oxidation. Therefore, the epoxides of **2** and **3** were prepared to remove the influence of the double bond which permits the formation of diepoxides.

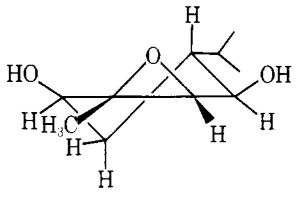
Epoxidation of **3** with m-chloroperbenzoic acid gave only one crystalline epoxide which was isolated in 76% yield and was assigned formula **10** since examination of a Dreiding model of **3** showed that the endo isopropyl group hinders attack from the α face. Reaction of **10** with ferrous sulfate furnished only two products (TLC) which were isolated in 36 and 31% yield, respectively.[8]

The less polar material **11** obtained in somewhat larger yield was a hydroxy ketone (IR bands at 3420 and 1700 cm^{-1}). The NMR spectrum exhibited in addition to the two methyl doublets of the isopropyl group and a singlet characteristic of methyl on carbon bonded to oxygen a narrowly split doublet (J = 1.5 Hz) of epoxidic hydrogen at 3.53 and a triplet at 4 ppm which sharpened to a doublet (J = 8.8 Hz) on D_2O exchange. Each half of the doublet was broadened further ($W_{1/2}$

= 4 Hz). A doublet of doublets at 2.46 ppm (J = 16.5, 3.6 Hz) was assigned to one of two protons α to the ketone group, since the larger constant was too large for vicinal coupling, the signals of the remaining two protons being superimposed in a complex multiplet centered at 2.00 ppm. The spectroscopic evidence points to conformation **11a** in which H-3 and H-4 are diaxial because of the large value of $J_{3,4}$. Equatorial H-5β at 2.46 ppm is deshielded relative to H-5α; the magnitude of $J_{4,5\beta}$ (3.2 Hz) is consonant with this arrangement (cf. NMR spectrum of **5a**).



11a

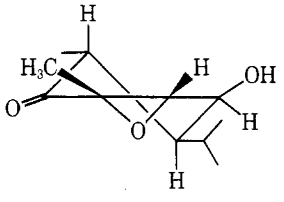


12a

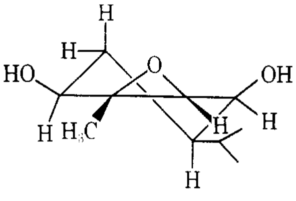
The NMR spectrum of the more polar product, whose IR spectrum indicated the absence of a carbonyl function, exhibited, in addition to the methyls of the isopropyl group and to the methyl on carbon attached to oxygen, signals of an epoxidic proton at 3.34 ppm (J = 2 Hz) and of two protons under hydroxyl on two multiplets at 3.74 and 3.84 ppm which sharpened to a broadened doublet (J = 10, 2–3 Hz) and a more narrowly split apparent triplet on D_2O exchange. Consequently this substance was the reduction product **12.** Molecular models suggested that the half-chair **12a** was the most stable conformation of this diol; the broad doublet at 3.75 ppm could then be assigned to pseudoaxial H-3 and the narrowly split triplet to pseudoequatorial H-6. Other assignments could then be made as follows. A one-proton multiplet at 1.16 ppm (J = 14.5, 12, and 4 Hz) is that of axial H-5α because of the large vicinal coupling constant to H-4 and the much smaller coupling constant to H-6. A doublet of triplets at 1.54 ppm (J = 14.5, ~3 Hz) was that of equatorial H-5β with geminal coupling to H-5α and smaller couplings to axial H-4 and pseudoequatorial H-6. The signal of H-8 was a partially obscured doublet of septets with coupling constants of 7 (to the methyl protons) and ~4 Hz to H-4 which was partially obscured by the methyl singlet at 1.46 ppm.

Epoxidation of **2** afforded two products **13** and **14.**[9] The structure assignment was based on differences in the NMR spectra. The less polar material isolated in 32% yield exhibited the methyl singlet at 1.55 and the H-2 doublet at 3.51 ppm ($J_{2,3}$ = 5 Hz), whereas the more polar product, obtained in 41% yield, displayed the same signals at 1.43 and 3.32 ppm, respectively. The chemical shifts of the more polar product are essentially identical with those of the β-epoxide **10.** Moreover, although in a molecular model of **13** H-2 and the C-1 methyl group are not particularly close to the peroxide bridge, they are certainly much closer than in molecular models of **14.** Consequently the less polar product in which the relevant signals are at somewhat lower field is identified as the α-epoxide **13** and the more polar substance as the β-epoxide **14.**

Reaction of **13** with ferrous sulfate gave a mixture containing one major product; minor substances whose presence was revealed by TLC were not present in sufficient amount to permit adequate characterization. The IR spectrum of the major product isolated in 45% yield exhibited hydroxyl and carbonyl absorption at 3375 and 1698 cm^{-1} and in the NMR spectrum H-2 was a doublet at 3.47 ppm (J = 3.8 Hz). This strongly indicated that the substance was **15** rather than the isomeric 3-keto-6-hydroxymenthane derivative. A multiplet at 4.58 ppm which sharpened to a triplet (J ~ 3 Hz) on D_2O addition could be assigned to the proton under the hydroxyl group. The A and B parts of an ABX system were visible at 2.10 and 2.48 ppm. Since J_{AB} (18.6 Hz) was characteristic of geminal coupling, and J_{AX} and J_{BX} were determined as 11.4 and 6 Hz, respectively, A was the signal of H-5β and B was the signal of H-5α in conformation **15a.** Signals of H-4 and H-8 were complex multiplets centered at 1.59 and 1.74 ppm.



15a



16a

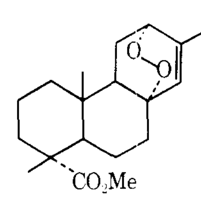
Treatment of **14** with ferrous sulfate in aqueous THF also gave a mixture containing one major and several minor products. The major product could be isolated in 42% yield; its IR spectrum indicated the absence of carbonyl functions and the presence of at least one hydroxyl group. The NMR spectrum retained the doublet of H-2 at 3.38 ppm (J ~ 5 Hz) and exhibited two multiplets at 3.76 and 4.11 ppm which sharpened to a doublet of doublets (J = 11, ~5.5 Hz) and a triplet (J ~ 4 Hz) on D_2O exchange. Consequently we were dealing with epoxy diol **16** whose most stable conformation would be expected to be **16a.** In this conformer the signal at 3.76 ppm would be that of pseudoaxial H-6 which is coupled to axial H-5β (large J) and equatorial H-5α (smaller J) and the signal at 4.11 ppm that of pseudoequatorial H-3 with two smaller coupling constants to H-2 and H-4.

Discussion

Long-range oxidation products were not isolated from the reactions of either the unsaturated peroxides **2** and **3** or the saturated peroxides **10, 13,** and **14** with ferrous sulfate. They were not formed at all from **3** and **10** and if formed from the others, they escaped isolation. Although **2, 13,** and **14** yielded mixtures which might well have included some materials resulting from intramolecular hydrogen transfer, the unidentified fractions which must include substantial amounts of reduction and/or rearrangement products represented rather small proportions of the total product (in no case more than about 20% by TLC).

Failure of **2, 13,** and **14,** peroxides in which a priori hydrogen transfer from C-8 to the oxygen atom on C-6 seemed possible, to undergo preferential intramolecular hydrogen abstraction may be due to the circumstance that such hydrogen transfers require transition states analogous to **2a** in which the isopropyl group is axial. On the other hand, it should also be pointed out that the alternative intramolecular hydrogen abstraction process and the only one possible in **3** and **10,** i.e., hydrogen transfer from one of the methyl groups to C-3 oxygen, could easily have escaped detection for the following reason. Reduction by Fe(II) of the primary radical resulting from such a transfer is likely to be faster than oxidation by Fe(III)[10] and the products of such reduction would be the same as the products formed by reduction of the oxygen radical by Fe(II). On the whole, then, it appears in retrospect that the α-phellandrene peroxides were not particularly good candidates for the reaction we wished to observe and our results do not provide a satisfactory answer to the question whether Fe(II)-promoted decomposition of epidioxides can induce long-range oxidation reactions in relatively flexible molecules.

Diepoxides have now been observed as products in all reactions of unsaturated endoperoxides with ferrous ion which have so far been examined (i.e., **2, 3, 17,**[11,12] and **18**[2]) except in the case of ascaridole (**19**). The structure of ascaridole glycol, the major product of the reaction of **19** with $FeSO_4$,[13]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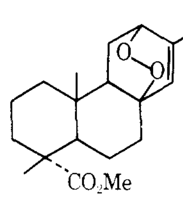
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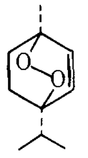
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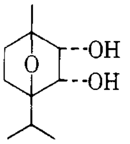
appears to have been reasonably well established as **20** by Jacob and Ourisson,[14] who used the then controversial,[1] but now well-established,[15,16] formula **21** (rather than **22**) for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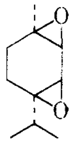
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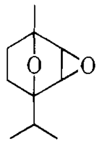
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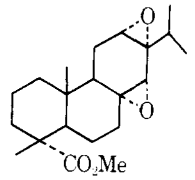
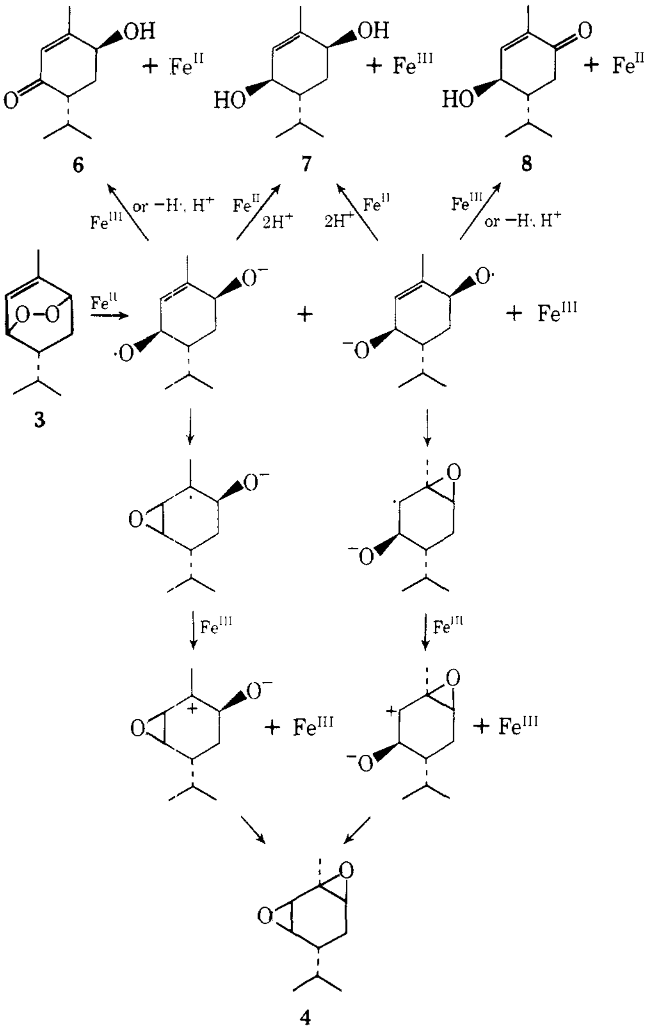

23

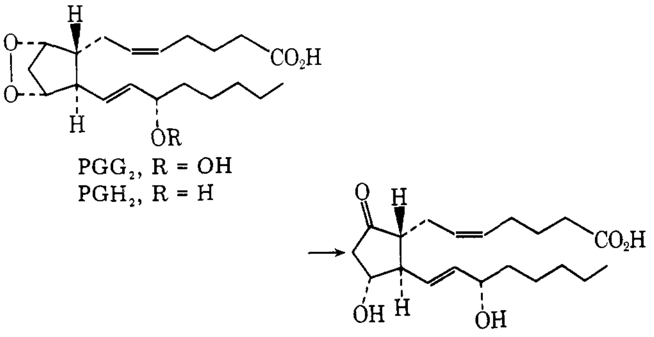
isoascaridole (ascaridole glycol anhydride), a substance which is the thermal rearrangement product of **19** and from which ascaridole glycol is also accessible by hydration.[17,18]

Because of the controversy surrounding the structure of isoascaridole, ascaridole glycol was prepared from ascaridole and ferrous sulfate and its NMR spectrum was recorded at 270 MHz. Two doublets of doublets at 3.79 and 3.56 ppm (J = 5, 9 Hz) which sharpened to an AB pattern at 3.77 and 3.57 ppm (J_{AB} = 9 Hz) with fine coupling (J = 1 Hz) on D_2O exchange were assigned to two hydrogens under two vicinal hydroxyl groups. The large coupling indicates that the hydrogens are cis (dihedral angle ~0°). The small coupling must be due to "W" coupling between H-2 and H-6, on the one hand, and H-3 and H-5 on the other. The relatively large chemical shift difference (0.2 ppm) between the H-2 and H-3 signals is somewhat surprising, but nevertheless, the NMR spectrum is consistent with formula **20**. Since glycol **20** can also be prepared by hydrolysis of diepoxide **21**, the ferrous ion reaction of ascaridole **19** must proceed through the intermediate nonisolable diepoxide **21**.

Scheme III



As regards the mechanism of formation of the substances described in this report, diols **7**, **12**, and **16** are obviously produced by reduction of epidioxides **3**, **10**, and **14** with 2 equiv of Fe(II). On the other hand, the formation of **23** from **17** proceeds in 90% yield when only 0.376 molar equiv of $FeSO_4$ is employed.[12] Therefore, just as in the remote oxidations discussed earlier,[2] the mechanism of the epidioxide–diepoxide rearrangement requires a step in which Fe(III) serves as an oxidant. This step is included in Scheme III, which presents a mechanism for diepoxide formation as well as a unified picture for the reactions of unsaturated epidioxides with Fe(II).[19] The trans peroxide **3** which best typifies the diverse pathways open to these substances is used as an example, although not all pathways may not operate in each instance.[21] Of particular interest is the conclusion that just like the isomerization **3** → **4**, the Fe(II)-induced isomerizations **3** → **6** or **3** → **8** involve the Fe(II)–Fe(III) redox system. Thus the Fe(II)-induced rearrangement of epidioxides to ketols may serve as a model for the transformation of prostaglandin G or H to prostaglandin E in vivo under the influence of Fe(II)-based enzyme systems.



PGG_2, R = OH
PGH_2, R = H

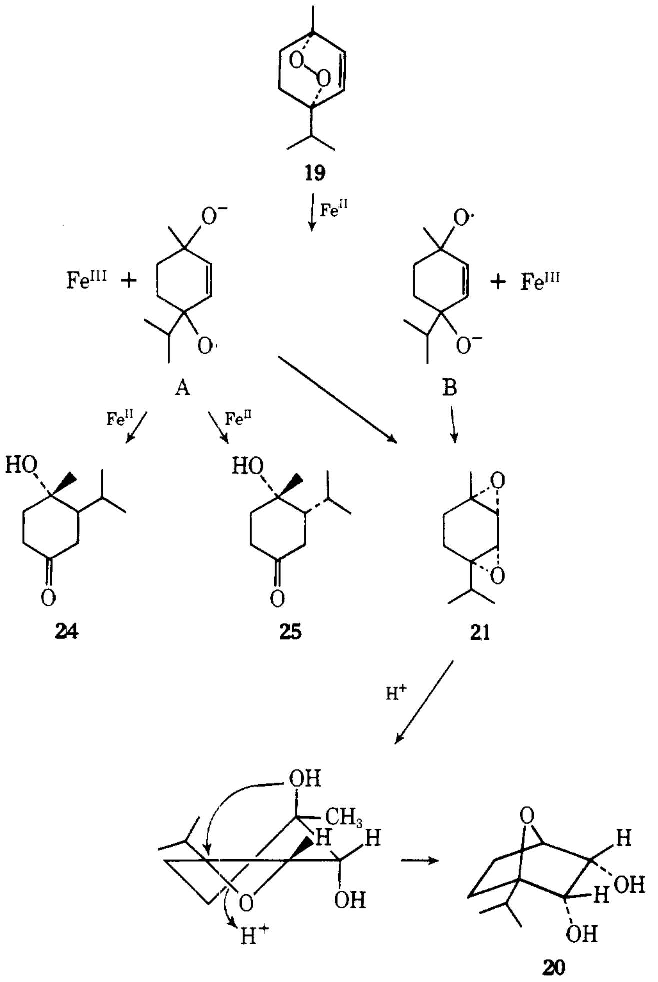
PGE

On the basis of this scheme, a mechanism can also be written for the reaction of ascaridole (**19**) with ferrous ion (Scheme IV) which takes into account that the 1,2-epoxide of isoascaridole (**21**) is more reactive than the 3,4-epoxide[15] and incorporates the observations of Brown et al.[18] that the reaction of ascaridole with $FeSO_4$ is accompanied by formation of **24** and **25**. These substances are presumably formed by expulsion of an isopropyl radical from anion radical A and recombination in Michael fashion at the β position of an α,β-unsaturated ketone.[21a]

Experimental Section

Preparation of 2 and 3. These substances were prepared from commercial α-phellandrene by the literature method.[4,5] The crude reaction mixture was difficult to separate because of the presence of a small amount of ascaridole presumably formed from α-terpinene, which is an impurity in commercial α-phellandrene that cannot be separated by distillation. The crude product was chromatographed over silica gel, a procedure which resulted in the separation of p-cymene from the peroxidic product. The fraction containing **2** and **3** and some ascaridole was separated into its constituents by high-pressure liquid chromatography on a 12-ft Porasil column using 8% ether–hexane as eluent. The cis peroxide **2**, which was a liquid at room temperature but crystallized in the refrigerator, displayed NMR signals (270 MHz) at 6.31 dq (H-2, $J_{2,3}$ = 7, $J_{2,7}$ = 2 Hz), 4.52 dbr

Scheme IV



(H-2), 4.32 m (H-6), 1.90 d (C-1 methyl), 0.96 and 0.98 ppm d ($J \sim 6.5$ Hz, isopropyl methyls). The trans peroxide **3**, mp 37–40 °C, had NMR signals (270 MHz) at 6.17 m (H-2, $W_{1/2}$ = 12 Hz), 4.58 m (H-3), 4.42 m (H-6), 1.91 d ($J_{2,7}$ = 2 Hz, C-6 methyl), and 0.87 ppm dbr (isopropyl methyls).

Reaction of 3 with FeSO$_4$. A solution of 0.910 g of $FeSO_4 \cdot 7H_2O$ in 15 mL of water was added in one portion to 0.500 g of **3** in 20 mL of THF. A moderately exothermic reaction ensued. The mixture was stirred for 1 h, diluted with 100 mL of water, and thoroughly extracted with $CHCl_3$. The washed and dried extract was evaporated at reduced pressure, and the residue was taken up in a small volume of $CHCl_3$ and filtered to remove 31 mg of crystalline **7**. The filtrate was subjected to preparative TLC (eluent 3:2 ether–hexane). This resulted in four fractions which were isolated and characterized.

The gummy, least polar material was **4** (124 mg, 26%) whose NMR spectrum (270 MHz) had signals at 3.12 d ($J_{2,3}$ = 4 Hz, H-2), 2.91 m (H-6), 2.87 m (H-3), 1.51 (C-1 methyl), 0.99 d and 0.94 ppm d (J = 6.5 Hz, isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.90; H, 9.67.

The second gummy fraction was **5** which had IR absorption at 3410 and 1670 cm^{-1}; NMR signals (270 MHz) at 6.67 m (H-2), 4.35 dbr (J = 8 Hz, simplified on addition of D_2O, H-3), 2.45 dd (J = 3.2, 15.9 Hz, H-5β), 1.76 d ($J_{2,7}$ = 2 Hz, C-1 methyl), 0.95 d and 0.88 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: mol wt, 168.1149. Found: mol wt (MS), 168.1158.

The third gummy fraction was **6**[6] (55 mg, 11%) which had IR absotion at 3380 and 1655 cm^{-1}; NMR signals at 5.80 m (H-2), 4.35 m (H-6), 2.03 d $J_{2,7}$ = 1.5 Hz, C-1 methyl), 0.93 d and 0.89 ppm d (isopropyl methyls).

The most polar fraction was crystalline **7**[7] (62 mg, total yield 93 mg, 18%), mp 164–166 °C. The NMR spectrum tallied with that reported in ref 7.

Reaction of 2 with FeSO$_4$. Reaction of 0.400 g of **2** with 0.828 g of $FeSO_4 \cdot 7H_2O$ in the manner described above required only 15 min for completion. After the usual workup, the crude, gummy product was subjected to preparative TLC (first development with 1:1 ether–hexane, second development with 13:7 ether–hexane). The least polar fraction, wt 41 mg, was still somewhat impure and was not further investigated. The two most polar fractions 4 and 5, wt 50 and 58 mg, were mixtures by NMR criteria and were also discarded. Fraction 2, wt 64 mg (16%), was a gum (**8**) and had NMR signals (270 MHz) at 3.14 d and 3.10 d (AB system of H-2 and H-3, J_{AB} = 4.5 Hz), 2.88 dd (H-6, J = 7, 2.5 Hz), 1.47 (C-1 methyl), and 0.97 ppm d (superimposed isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: mol wt, 168.1149. Found: mol wt (MS), 168.1186.

Fraction 3, wt 112 mg (28%), was also a gum (**9**) which crystallized on drying and then melted at 40–42 °C. It had IR bands at 3400 and 1660 cm^{-1}; NMR signals (270 MHz) at 6.78 dg ($J_{2,7}$ = 1.5, $J_{2,3}$ = 6 Hz, H-6), 4.42 m (H-3), 2.56 dd (J = 16.7, 4.3 Hz, H-5α) 2.44 dd (J = 16.7, 12.2 Hz, H-5β), 1.78 br (C-1 methyl), 1.02 d and 0.95 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.55.

Epoxidation of 2. A solution of 0.500 g of **2** and 0.700 g of *m*-chloroperbenzoic acid in 50 mL of $CHCl_3$ was stirred for 2 days, washed with dilute KI, sodium thiosulfate, saturated $NaHCO_3$, and water, dried, and evaporated. The residue was *rapidly* chromatographed by preparative TLC (eluent ether–hexane, 1:3) approximately two-thirds up the plate. The less polar product **13** was recrystallized from pentane and had mp 86–88°C; wt 133 mg (32%); NMR signals at 4.26 m, 4.14 m (H-3 and H-6), 3.51 d (J = 5 Hz, H-2), 1.55 (C-1 methyl), 0.95 d and 0.92 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.69.

The more polar product **14** was recrystallized from $CHCl_3$: mp 83–85 °C; wt 224 mg (41%); NMR signals at 4.42 m and 4.13 m (H-3 and H-6), 3.32 d (J = 3.5 Hz, H-2), 1.43 (C-1 methyl), 1.07 d and 1.00 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97; H, 8.67.

Epoxidation of 3. A solution of 0.500 g of **3** and 1 g of *m*-chloroperbenzoic acid in 50 mL of $CHCl_3$ was stirred for 2 days and worked up as described in the previous paragraph. The crude product which exhibited only one spot on TLC was recrystallized from $CHCl_3$–pentane to give 0.356 (65%) of **10**. The melting point of this substance was not determined for fear of explosion but was over 110 °C. The NMR spectrum had signals at 4.40 dd (J = 3, 6 Hz) and 4.18 m ($W_{1/2}$ 10 Hz, H-3 and H-6), 3.33 dd (J = 1, 3 Hz, H-2), 1.43 (C-1 methyl), and 0.98 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.56.

Reaction of 10 with FeSO$_4$. Reaction of 0.370 g of **10** with 0.600 g of $FeSO_4 \cdot 7H_2O$ followed by the usual workup gave a crude product which showed only two spots on TLC. Preparative TLC (17:3 ether–hexane) gave 96 mg (26%) of the less polar product **11** and 78 mg (21%) of the more polar product **12**. In a second run, when THF was removed at reduced pressure before workup, 0.300 g of **3** yielded 0.109 g of **11** (36%) and 92 mg of **12** (31%).

Recrystallization from $CHCl_3$–pentane furnished **11**: mp 76–78 °C; IR bands at 3420 and 1670 cm^{-1}; NMR signals (270 MHz) at 4.00 d (after D_2O exchange, J = 8.8 Hz, H-3), 3.53 d (J = 1.5 Hz, H-2), 2.46 dd (J = 16.6, 3.6 Hz, H-5β), 1.43 (C-1 methyl), 0.93 d and 0.84 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.87; H, 8.67.

Recrystallization from $CHCl_3$–pentane gave **12**, mp 115–117 °C, which had an IR band at 3290 cm^{-1} and NMR signals (270 MHz) at 3.88 t (after D_2O exchange, J = 4 Hz, H-6), 3.74 dbr (after D_2O exchange, J = 10 Hz), 3.34 d (J = 2 Hz, H-2), 2.05 d sept (J = 4, 7 Hz, H-8), 1.54 dt (J = 14.5, 2.5 Hz, H-5β), 1.48 (C-1 methyl), 1.16 ddd (J = 14.5, 4, 12 Hz, H-5β), 0.93 d and 0.80 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.45; H, 9.89.

Reaction of 13 with FeSO$_4$. Reaction of 0.300 g of **13** with 0.500 g of $FeSO_4 \cdot 7H_2O$, removal of THF at reduced pressure, and workup in the usual fashion gave a gum. TLC showed 5–6 spots but only one product was formed in appreciable amount. Preparative TLC (3:2 ether–hexane) and recrystallization of this substance from $CHCl_3$–pentane gave **15**: mp 102–103 °C; wt 134 mg (45%); IR absorption at 3375 and 1698 cm^{-1}; NMR signals (270 MHz) at 4.58 t (after D_2O exchange, J = 3 Hz, H-3), 3.47 d (J = 3.8 Hz, H-2), 2.48 dd (J = 6, 18.6 Hz, H-5α), 2.10 dd (J = 11.4, 18.6 Hz, H-5β), 1.74 m and 1.59 m (H-4 and H-8), 1.45 (C-1 methyl), 1.00 d and 0.92 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.83; H, 9.12.

Reaction of 14 with $FeSO_4$. Reaction of 0.300 g of **14** with 0.500 g of $FeSO_4 \cdot 7H_2O$ for 1 h, followed by removal of THF and the usual workup, gave a gum. TLC showed several spots but only one product was formed in substantial amount. Preparative TLC (17:3 ether–hexane) resulted in isolation of this substance **16** in semicrystalline form, wt 125 mg (42%). Its IR spectrum showed strong hydroxyl absorption at 3380 cm^{-1}; the NMR spectrum (270 MHz) after D_2O exchange had signals at 4.11 t (J = 4 Hz, H-3), 3.76 dd (J = 5.5, 11 Hz, H-6), 3.38 d (J = 5 Hz, H-2), 1.47 (C-1 methyl), 0.99 d and 0.92 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.40; H, 9.74. Found: C, 64.45; H, 9.89.

Registry No.—**2**, 61616-15-7; **3**, 61616-16-8; **4**, 61570-80-7; **5**, 61570-81-8; **6**, 55955-53-8; **7**, 61664-34-4; **8**, 61616-17-9; **9**, 61570-82-9; **10**, 61570-83-0; **11**, 61570-84-1; **12**, 61570-85-2; **13**, 61617-12-7; **14**, 61616-18-0; **15**, 61616-19-1; **16**, 61616-20-4; α-phellandrene, 99-83-2; $FeSO_4$, 19468-88-3.

References and Notes

(1) Supported in part by a grant from the National Science Foundation (GP-12582).

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(8) The relatively poor yield of isolated products was probably due to the difficulty in extracting the two highly polar substances from aqueous solution.

(9) Difficulty was encountered in isolating the more polar epoxide **14** because of its decomposition on silica gel. The procedure given in the Experimental Section relies on rapid preparative TLC of the mixture and crystallization. The decomposition on silica gel is the subject of separate study: J. A. Turner and W. Herz, *J. Org. Chem.*, note in this issue.

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(19) The reaction should not be confused with the now well-known thermal rearrangement of epidioxides to diepoxides. The thermal reaction requires higher temperatures and is carried out in a nonpolar solvent. Similarly, the base-catalyzed rearrangement[20] of epidioxides to γ-hydroxy-α,β-unsaturated ketones, etc., differs fundamentally from the transformations described in this report.

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(21) When the double bond is absent and the epidioxide bridge is attached to at least one tertiary center, stabilization of the initial oxidation products may occur by intramolecular hydrogen transfer followed by oxidation at the remote site as in the case of **1**,[2] or by loss of an alkyl radical which undergoes subsequent oxidation as in the case of dihydroascaridole epidioxide.[18] Therefore an alternative to the direct oxidation of the anion radicals by Fe(II) to give **5** and **6** may be loss at a hydrogen atom which is subsequently oxidized by Fe(III).[21a] (a) **Note Added in Proof.** The possible implications of the Fe(II)-induced decomposition of such epidioxides for prostacyclin and thromborane biosynthesis are discussed in a separate report: J. A. Turner and W. Herz, *Experientia*, in press.

(22) Experimental details have been specified in ref 2.

Fe(II)-Induced Decomposition of Unsaturated Cyclic Peroxides Derived from Butadienes. A Simple Procedure for Synthesis of 3-Alkylfurans

James A. Turner and Werner Herz*

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

Received October 15, 1976

3,6-Dihydro-1,2-dioxins, prepared by reaction of 2-substituted 1,3-butadienes with singlet oxygen, furnish 3-alkylfurans in high yield when treated with ferrous sulfate. The mechanism and limitations of the reaction are discussed. The overall sequence, particularly the last step which involves a redox reaction under extremely mild conditions, may be a model for the biogenesis of naturally occurring 3-alkylfurans.

Fe(II)-induced decomposition of the epidioxide 1 resulted in the unexpected formation of remote oxidation products as the result of intramolecular hydrogen abstraction by the initially formed anion radical.[2] In an attempt to extend this reaction to other substrates with geometries suitable for 1,5-hydrogen transfer[3] we have studied the reaction of Fe(II) with several epidioxides derived from terpenoids which incorporate a 2-alkyl-1,3-butadiene residue. While the original objectives were not realized we have discovered a simple method for making 3-substituted furans which is synthetically useful and may mimic the path by which such substances are formed in nature.

The formation of epidioxides by reaction of homo- and semiannular 1,3-dienes with singlet oxygen is well known,[4] but the preparation of unsaturated cyclic peroxides (3,6-dihydro-1,2-dioxins) from acyclic 1,3-dienes is a relatively new development.[5-7] Very recently, Matsumoto and Kondo[8] examined the reaction of singlet oxygen with a number of acyclic monoterpenoid 1,3-dienes and suggested the following order of reactivity of olefins toward singlet oxygen: trisubstituted monoolefin > 1,3-diene with alkyl substituent at the 2 position > 1,1-disubstituted olefins. Since singlet oxygen is an electrophilic reagent and since mono- and disubstituted olefins react very sluggishly with singlet oxygen,[4] the order of reactivity of olefins toward singlet oxygen suggested by Matsumoto and Kondo[8] can probably be extended as follows: tetrasubstituted monoolefins > trisubstituted monoolefins > 1,3-diene ≫ disubstituted monoolefin and monosubstituted olefin.

Results

As initial substrates for the reaction with ferrous ion we selected the dioxides 3 and 6 from β-myrcene (2) and the epoxide 5.[8,9] Treatment of 3 with ferrous sulfate in aqueous tetrahydrofuran surprisingly furnished only one product (TLC analysis) which was isolated in 81% yield. The IR spectrum displayed hydroxyl absorption as well as bands at 1500 and 880 cm^{-1} characteristic of furans. The 270-MHz