Oxidation of the Fumaric Acid–Methyl Abietate Diels–Alder Adduct with Alkaline Permanganate. Terpenes. VIII[1,2]

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The alkaline permanganate oxidation of the fumaric acid–methyl abietate Diels–Alder adduct (IV) has been found to yield three products: an unsaturated γ-lactone (VI), a dihydroxylactone (IX), and a diol (X). None of the normal oxidation product, arising by hydroxylation of the C-13 double bond, was detected. The chemical transformations described demonstrate that compounds in this series possessing *cis*-β-C-15,β-C-16 dicarboxyl groups are epimerized with base to the *trans*-α-C-15,β-C-16 dicarboxyl isomers.

Recent work from this laboratory has shown that alkaline permanganate oxidation of maleopimaric acid (I) leads, unexpectedly, to the lactone II in good yield rather than to hydroxylation of the hindered double bond at C-13.[3] The hindered nature of the double bond in I and related compounds was further shown by the results of the ozonolysis of the trimethyl ester of maleopimaric acid (III).[4] In the latter reaction eight products were isolated, all resulting from oxidative attack on the isopropyl group. In a further study of the oxidation of this type of molecule we have investigated the reaction of the fumaric acid–methyl abietate Diels–Alder adduct (IV) with alkaline permanganate.

The starting compound (IV) was prepared by heating methyl abietate and fumaric acid together at 200° in a nitrogen atmosphere. The dienophile, fumaric acid, would be expected to react with the diene, methyl abietate, from the less hindered α (down) side as observed in the reaction of this diene with other dienophiles.[3] However, two products are still possible—one containing an α-C-15 carboxyl group and a β-C-16 carboxyl group and the other containing a β-C-15 carboxyl group and an α-C-16 carboxyl group. The product isolated was shown to be only one of the two possible isomers by its sharp melting point and by the gas chromatograph of its trimethyl ester (V). The chemical transformations described below show unambiguously that the isomer obtained (IV) contains an α-C-15 carboxyl group and a β-C-16 carboxyl group. An identical isomer (IV) was obtained from maleopimaric acid (I) by conversion to ester III, followed by saponification and epimerization with sodium hydroxide.[4] Harris[5] and Silver[6] have previously described the epimerization of maleopimaric acid itself.

Oxidation of IV in alkaline solution with excess permanganate at 10° gave, after acidification and ether extraction, a crude white solid which was esterified with diazomethane and chromatographed on alumina. The infrared spectrum of the first product (IV, m.p. 177–178°) to be eluted from the chromatography column showed a strong band indicative of a γ-lactone at 1775 cm.$^{-1}$ and an ester carbonyl band at 1730 cm.$^{-1}$; its n.m.r. spectrum showed that it was a dimethyl ester which was very similar to VII, the latter having been obtained by permanganate oxidation of maleopimaric acid followed by esterification with diazomethane.[3] That VI was the C-15 epimer of VII was shown by isomerization of II with alkali followed by esterification with diazomethane, in which case a mixture of VI and VII was obtained. Further evidence in support of structure VI was obtained by its ozonolysis to yield ketone VIII. The infrared spectrum showed a γ-lactone carbonyl band and its n.m.r. spectrum showed that the isopropylidene group was no longer present. It is worthwhile noting that under the same conditions VII was unaffected by ozone.[3] The lactone VI has been reported to be formed by the action of lead tetraacetate on IV, although no experimental details were provided.[7] In our hands, the reaction of IV with lead tetraacetate did not give VI, but instead two other products were isolated.[8]

Establishment of the structure of VI and the alkaline epimerization of III to V and of VII to VI show that the stable isomers have α-C-15 and β-C-16 carboxyl groups rather than the reverse arrangement, and the Diels–Alder adduct obtained from fumaric acid and methyl abietate (IV) has this configuration.

Another product (IX, m.p. 123–125°) isolated by chromatography showed hydroxyl absorption at 3500 cm.$^{-1}$, γ-lactone absorption at 1780 cm.$^{-1}$, and ester carbonyl absorption at 1725–1730 cm.$^{-1}$ in its infrared spectrum. The n.m.r. spectrum of IX showed the C-14 proton at δ 4.50. Oxidation of IX with lead tetraacetate gave the same ketone VIII obtained, as mentioned above, from VI. Thus the structure depicted in formula IX can be assigned to the product of m.p. 123–125°. Compound IX undoubtedly arises in the reaction by hydroxylation of intermediate VI (as free acid) and was indeed readily prepared directly from isolated VI, after saponification, by further oxidation with permanganate followed by re-esterification. A comparison of II and VI (after saponification) in their reaction with alkaline permanganate is noteworthy. Further oxidation of II with alkaline permanganate proceeded only with great difficulty and gave a negligible yield of the dihydroxy compound epimeric with IX at C-15.[3] It can therefore be assumed that hydroxylation of VI proceeds from the less hindered side *cis* to the α-carboxy group at C-15 to give a product with the stereochemistry depicted in IX.

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(2) Terpenes. VII: L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **28**, 2037 (1963).

(3) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *ibid.*, **27**, 3535 (1962).

(4) L. H. Zalkow and N. N. Girotra, *ibid.*, **28**, 2033 (1963).

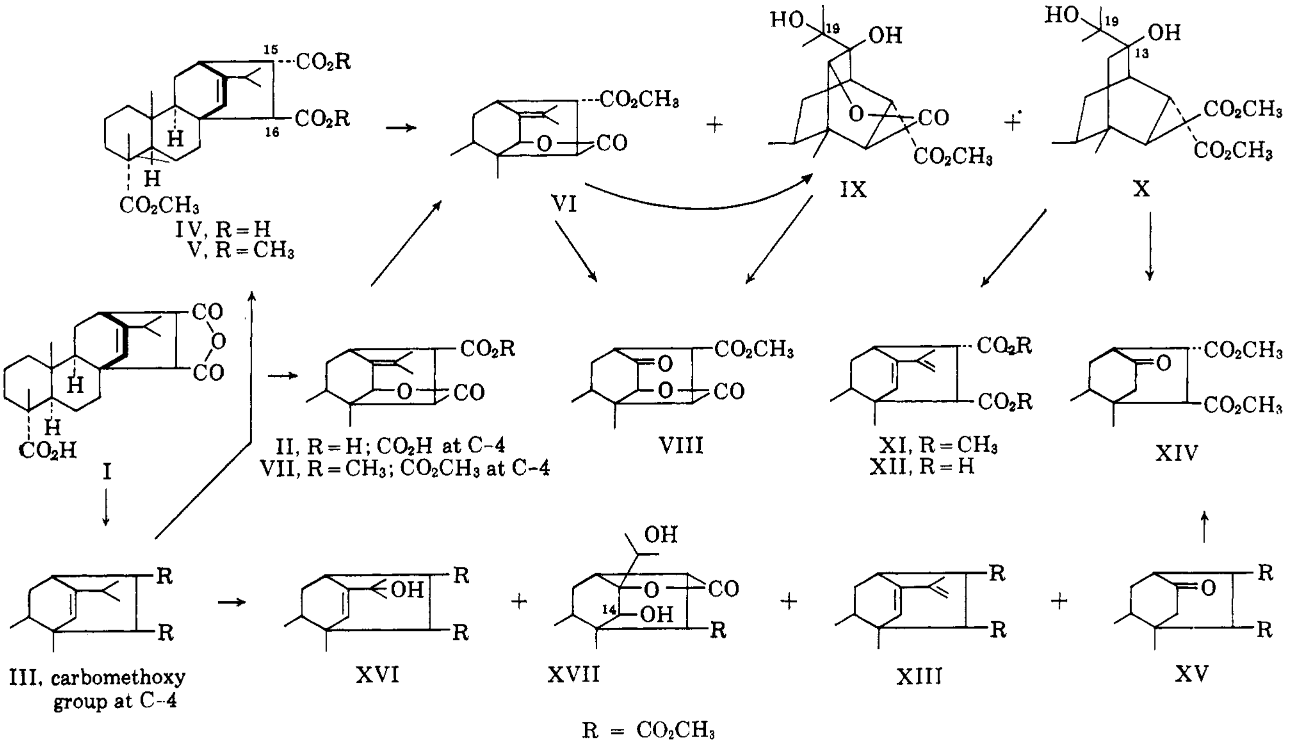
(5) G. C. Harris, U. S. Patent 2,517,563 (1950).

(6) R. P. Silver, U. S. Patent 2,522,586 (1950).

(7) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963).

(8) L. H. Zalkow and D. R. Brannon, unpublished results, Oklahoma State University.

SCHEME I



The third and final product (m.p. 206–207°) isolated from the permanganate reaction after esterification and chromatography has been assigned structure X on the basis of the following evidence. The infrared spectrum of X showed O–H absorption at 3500 and 3410 cm.$^{-1}$, and carbonyl absorption at 1715 and 1730 cm.$^{-1}$. Its n.m.r. spectrum showed the presence of three carbomethoxy groups and four methyl group singlets. The two singlets at highest field (δ 1.08, 1.13) could be assigned to the C-4 and C-10 methyl groups and the two singlets at next highest field (δ 1.25, 1.32) could be assigned to the two methyl groups flanking the hydroxyl group at C-19 by analogy with XVI, one of the products obtained on the treatment of the trimethyl ester of maleopimaric acid (III) with ozone.[4] That the structure of the product of m.p. 206–207° was X and not that arising by normal hydroxylation of the C-13 double bond in IV was shown by the position of the isopropyl methyl protons in the n.m.r. and by the absence of a signal in the n.m.r. corresponding to the C-14 proton. The latter signal was to be expected at about δ 4.35, the position at which the C-14 proton of XVII appears.[4] Dehydration of X with phosphorus oxychloride in pyridine gave VI. The infrared spectrum of XI showed no hydroxyl absorption and the ultraviolet spectrum showed a strong band at $\lambda_{\max}$ 245 mμ. The C-15 epimer of XI (XIII) showed strong absorption at $\lambda_{\max}$ 240 mμ.[4,9] The n.m.r. spectrum of XI showed the C-10 methyl protons at δ 0.55, thus providing additional evidence for the presence of a C-13 double bond.[4,7] The protons of the methyl group of the isopropenyl group appeared at δ 1.92, whereas the olefinic protons appeared at δ 5.86 and 6.30; both of these observations are clearly consistent with the assigned structure. Treatment of X with lead tetraacetate gave XIV. The latter compound was identified by comparison with an authentic sample, prepared as previously described[4] by isomerization of XV. The stereochemistry of the hydroxyl group at C-13 in X is assigned on the same basis as that for IX as discussed above.

The formation of VI and IX is consistent with a mechanism of the type previously proposed for the formation of II from I.[3] The formation of X is more difficult to rationalize. The C-13,C-14 double bond in IV does not rearrange to the C-13,C-19 position in the presence of alkali and in the absence of permanganate, but it is possible that the migration does occur in the oxidizing medium.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard (δ = 0). Gas chromatographs were run at 280° using a column 0.125 in. × 5 ft. of 5% SE-30 on acid-washed Chromosorb W with a hydrogen flame detector and a hydrogen flow rate of 26 cc./min. and a nitrogen flow rate of 28 cc./min. Thin layer chromatograms were run on 25-μ-thick silica gel-coated glass plates using 5:1 benzene–ethyl acetate as the mobile phase, and detection was by iodine vapors.

Preparation of Fumaric Acid–Methyl Abietate Adduct (IV).—A mixture of 50 g. of commercial methyl abietate (Eastman technical) and 20 g. of fumaric acid was stirred and heated at 200–210° in a nitrogen atmosphere for 3 hr. After washing the viscous yellow reaction mixture several times with hot water, it was poured into 300 ml. of refluxing benzene. The product IV crystallized from the cooled benzene solution in 40% yield. The analytical sample was obtained by recrystallization from glacial acetic acid and gave m.p. 294–295° after drying at 144° (0.1 mm.)[10]; $\nu_{\max}^{\mathrm{KBr}}$ 1730, 1715, and 1960 (weak) cm.$^{-1}$; $[\alpha]_D$ +36° (*c* 0.004, alcohol).

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(9) L. Ruzicka and St. Kaufman, *Helv. Chim. Acta*, **23**, 1346 (1940).

(10) L. H. Zalkow and M. L. Corser, *Proc. Oklahoma Acad. Sci.*, **42**, 190 (1962).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.13; H, 8.40.

The adduct IV was converted into the corresponding trimethyl ester V by treatment with ethereal diazomethane. The triester could not be crystallized but was shown to be homogeneous by gas chromatography, a single peak being obtained in its gas chromatogram with a retention time of 8.7 min. The infrared and n.m.r. spectra of V were identical with those of the product obtained by epimerization of III.[2]

Oxidation of Adduct IV with Alkaline Permanganate.—The adduct IV (10 g.) was added to a solution prepared by dissolving 3 g. of sodium hydroxide in 400 ml. of water. After cooling to 10°, a cold 0.165 *M* aqueous permanganate solution was added to the alkaline solution dropwise until the permanganate color persisted for 3 hr. During the addition of the permanganate solution the reactants were maintained at $\leq 10°$. The precipitated manganese dioxide was removed by filtration and gaseous sulfur dioxide was passed through the aqueous solution until the permanganate color disappeared. Acidification (pH 1) with dilute hydrochloric acid gave 5.5 g. of crude crystalline products, and continuous ether extraction (12 hr.) of the aqueous filtrate gave an additional 2.1 g. of products. The combined products were esterified with ethereal diazomethane and separated by column chromatography as described below.

Isolation of VI.—The crude esterified product (1.58 g.), mentioned above, was chromatographed on 125 g. of Merck acid-washed alumina (activity III) and elution with 15:85 ether–benzene gave 0.320 g. of VI as a gum which was crystallized from isooctane at −40°. Recrystallization from 1:4 water–methanol and drying at 144° (0.1 mm.) gave VI of m.p. 177–178°, positive tetranitromethane test, single peak in gas chromatography with retention time of 9.8 min., single spot in thin layer chromatography with R_f 0.625; ν_{max}^{KBr} 1775 and 1730 cm.$^{-1}$; n.m.r. (carbon tetrachloride) δ 0.70 (3 protons), 1.12 (3), 1.78 (6), 3.62 (3), 3.74 (3), and 4.89 (1).

Conversion of II to VI.—The lactone II (90 mg.) prepared as previously described[3] was refluxed in 10 ml. of a 5% sodium hydroxide solution containing 0.5 ml. of methanol for 4 hr. After removal of the solvent with a rotary evaporator the cooled residue was acidified with dilute hydrochloric acid (pH 1) whereupon a white precipitate was obtained. After filtration, the solid product was treated with ethereal diazomethane, and removal of the ether gave a viscous gum which could not be crystallized. An n.m.r. spectrum of this gummy product showed that it was a mixture of VI and VII by the presence of two peaks at high field, δ 0.70 (C-10 methyl protons in VI) and 0.75 (C-10 methyl protons in VII) and by the presence of peaks at δ 3.62 and 3.74. In VI the two carbomethoxy groups give signals at δ 3.62 and 3.74 whereas in VII only one signal (δ 3.62) is observed for the two carbomethoxy groups. The gummy product after dissolving in 0.5 ml. of methanol was again refluxed with 10 ml. of a 10% potassium hydroxide solution for 60 hr. The n.m.r. spectrum of the product after re-esterification with diazomethane showed the presence of 40% of VI. Thin layer chromatography also showed the presence of VI (R_f 0.625) and VII (R_f 0.583).

Isolation of X.—The second product (X) to be eluted in the chromatography of the esterified oxidation product was eluted in 1:1 ether–benzene, whereupon 0.309 g. was obtained from 1.58 g. of the crude esterified product. This product was crystallized from isooctane and the analytical sample was obtained by recrystallization from methanol, m.p. 206–207° after drying at 100° (0.1 mm.); ν_{max}^{KBr} 3500, 3410, 1715, and 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_8 \cdot CH_3OH$[8]: C, 63.85; H, 8.80. Found: C, 63.92; H, 8.56.

Isolation of IX.—The third and final product isolated from the esterified oxidation mixture was eluted from the chromatography column with 99:1 ether–methanol, 0.716 g. being obtained from 1.58 g. of the crude product. Two recrystallizations from isooctane gave the analytical sample, m.p. 123–125°; ν_{max}^{KBr} 3500, 1780, and 1725–1730 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{38}O_8$: C, 65.24; H, 8.01. Found: C, 64.87; H, 8.05.

Preparation of IX from VI.—A solution prepared by dissolving VI (320 mg.) in 10 ml. of 5% potassium hydroxide and 0.5 ml. of methanol was refluxed for 1 hr., then concentrated to 5 ml. with a rotary evaporator. After cooling to room temperature, a 0.165 *M* aqueous potassium permanganate solution was added until an excess of permanganate remained. The precipitated manganese dioxide was removed by filtration and gaseous sulfur dioxide was passed through the solution as previously described. The resulting solution was acidified (pH 1) and continuously extracted with ether for 12 hr. The ether extract was dried over magnesium sulfate, concentrated, and finally treated with ethereal diazomethane. Removal of the ether gave 163 mg. of a gummy residue whose n.m.r. spectrum showed very little of the signal at δ 1.78 arising from the isopropylidene protons thus showing that the double bond had reacted. Chromatography of this residue on 55 g. of Merck acid-washed alumina (activity III) gave 80 mg. of pure IX (m.p. 123–125°) in the 99:1 ether–methanol eluent. The diol IX thus obtained was identical with IX (isolated as previously described) in infrared and n.m.r. spectra and the mixture melting point was undepressed.

Ozonolysis of VI. Preparation of VIII.—A stream of oxygen containing ozone (~3%) was passed through a solution, prepared by dissolving 125 mg. of VI in 15 ml. of glacial acetic acid, at room temperature for 10 hr. Zinc dust (250 mg.) and water (5 ml.) were then added to the acetic acid solution and stirring was continued for 6 hr. After removal of the zinc by filtration the solution was concentrated with a rotary evaporator and then extracted with four 50-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and concentrated to give a resinous solid. Chromatography on 40 g. of Merck acid-washed alumina (activity III) gave 90 mg. of ketone VIII in the 6:4 benzene–ether eluent. The analytical sample was prepared by recrystallization from methanol and gave m.p. 170–172.5°, single spot in thin layer chromatography with R_f 0.580; ν_{max}^{KBr} 1790 and 1730–1740 cm.$^{-1}$; n.m.r. (carbon tetrachloride) δ 0.70 (C-10 methyl protons) and 4.14 (C-14 proton).

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.70; H, 7.26.

Preparation of VIII from IX.—Diol IX (200 mg.) and 275 mg. of dry lead tetraacetate were refluxed in 15 ml. of glacial acetic acid for 24 hr.; an additional 275 mg. of lead tetraacetate was added and refluxing was continued for 36 hr. After removal of the acetic acid on a rotary evaporator, 10 ml. of water was added to the residue and the aqueous solution was extracted with three 20-ml. portions of ether. After drying over magnesium sulfate, the ether was removed to give 160 mg. of brown noncrystalline material which was chromatographed on 9 g. of Merck acid-washed alumina (activity III). Elution with 6:4 benzene–ether gave 80 mg. of VIII, m.p. 168–170°, identical in thin layer chromatography and infrared and n.m.r. spectra with VIII prepared as described above.

Dehydration of X. Preparation of XI and XII.—Diol X (150 mg.) was heated on a steam bath with 2 ml. of phosphorus oxychloride and 5 ml. of dry pyridine for 6 hr. After cooling, 5 ml. of water was cautiously added to the reaction mixture which was then extracted with five 20-ml. portions of ether. The combined ether extract was washed with water, dried over magnesium sulfate, and concentrated to give 110 mg. of noncrystalline residue which was then chromatographed on 10 g. of Merck acid-washed alumina (activity III). Diene XI (75 mg.) was eluted in 9:1 benzene–ether as a viscous gum which could not be crystallized. Thin layer chromatography showed one spot with R_f 0.58; ν_{max}^{film} 1730 and 1745 cm.$^{-1}$; λ_{max}^{EtOH} 235 mμ (log *E* 4.15). The n.m.r. spectrum (carbon tetrachloride) showed signals at δ 0.55 (3 protons), 1.10 (3), 1.92 (3), 3.60 (3), 3.67 (3), 3.74 (3), 5.86, and 6.30.

Preparation of XIV from X.—Diol X (20 mg.) and dry lead tetraacetate (50 mg.) were refluxed in 15 ml. of glacial acetic acid for 12 hr. After removal of the acetic acid with a rotary evaporator, 20 ml. of water was added and the aqueous solution was extracted with three 25-ml. portions of ether. The combined ether extract was washed with water, then dried over magnesium sulfate. Removal of the ether gave a gummy residue which was chromatographed on 8 g. of acid-washed alumina (activity III). Ketone XIV (12 mg.) was eluted in 9:1 benzene–ether and was crystallized from methanol, m.p. 145°. Thin layer chromatography showed one spot, R_f 0.65; XIV thus obtained was identical in all respects with a sample of XIV prepared as previously described.[4]