[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF ETHICON, INC.]

Keto Fatty Acids Derived from Castor Oil. II. Epoxy and Hydroxy Acids[1,2]

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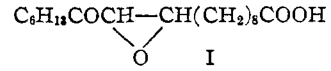
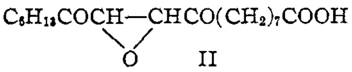
A number of epoxy and hydroxy keto acids were prepared by oxidation of 12-oxo-*cis*-9-octadecenoic acid, 12-oxo-*trans*-9-octadecenoic acid, 12-oxo-*trans*-10-octadecenoic acid and 9,12-dioxo-10-octadecenoic acid.

In the preceding paper[1] the synthesis of certain unsaturated keto fatty acids was described. It seemed of interest to utilize the ethylenic linkage for the introduction of additional oxygen into the sidechain of the fatty acid moiety. It was hoped that the resulting compounds, by virtue of their cumulative oxygen functions in the middle of the fatty acid chain, would exhibit greater solubility in hydrophilic media. Epoxidation of 12-oxo-*trans*-10-octadecenoic acid[1] and 9,12-dioxo-*trans*-octadecenoic acid[1] by means of alkaline hydrogen peroxide[3] employing magnesium chloride as a catalyst[4] gave rise to the corresponding epoxy acids, 10,11-epoxy-12-oxoöctadecanoic acid (I) and 9,12-dioxo-10,11-epoxyoctadecanoic acid (II).


$\mathrm{C_6H_{13}CO}\underbrace{\mathrm{CH{-}CH}}_{\mathrm{O}}\mathrm{(CH_2)_8COOH}$ I

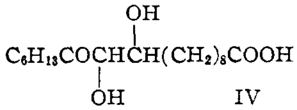

$\mathrm{C_6H_{13}CO}\underbrace{\mathrm{CH{-}CH}}_{\mathrm{O}}\mathrm{CO(CH_2)_7COOH}$ II

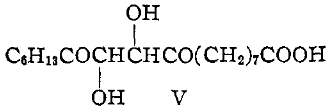
When this epoxidation procedure was applied to 12-oxo-*cis*-9-octadecenoic acid,[1] isomerization preceded oxidation and 10,11-epoxy-12-oxoöctadecanoic acid (I) was formed as the sole product. 12-Oxo-*trans*-9-octadecenoic acid[1] remained unaffected by alkaline hydrogen peroxide.

Acid-catalyzed hydrolytic cleavage of the oxido linkage of the epoxy acids proceeded slowly at room temperature (after a reaction time of 12 days the oxirane number was only 63% of theory); at elevated temperature disruption of the fatty acid chain took place. In no instance, however, could there be isolated the desired dihydroxy keto acids. These findings are in accord with previous observations on the hydrolysis of α-keto-epoxides.[3,5,6] Extensive decomposition occurred during the reaction of 12-oxo-*trans*-9-octadecenoic acid or its methyl ester with peracids and no products could be isolated. This failure confirms results reported by King.[5]

The preparation of hydroxy keto acids from the unsaturated acids was accomplished by "*cis*" hydroxylation, a procedure which does not involve epoxide formation as an intermediate step. Oxidation of 12-oxo-*cis*-9-octadecenoic acid with alkaline permanganate gave a small yield of the expected 9,10-dihydroxy-12-oxoöctadecanoic acid (III). A higher oxidation product (VI) whose structure is discussed below was obtained when 12-oxo-*trans*-9-octadecenoic acid was subjected to the same reaction conditions. A hydroxylation procedure employing *t*-butyl peroxide and osmium tetroxide (Milas reagent)[7] was found to be superior to the permanganate method and was applied to the synthesis of 10,11-dihydroxy-12-oxoöctadecanoic acid (IV) and 9,12-dioxo-10,11-dihydroxyoctadecanoic acid (V) from their respective α,β-unsaturated keto acids.


$\mathrm{C_6H_{13}COCH_2}\underset{\mathrm{OH}}{\mathrm{CH}}{-}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{(CH_2)_7COOH}$ III


$\mathrm{C_6H_{13}CO}\underset{\mathrm{OH}}{\mathrm{CH}}\overset{\mathrm{OH}}{\mathrm{CH}}\mathrm{(CH_2)_8COOH}$ IV

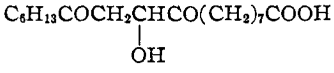

$\mathrm{C_6H_{13}CO}\underset{\mathrm{OH}}{\mathrm{CH}}\overset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CO(CH_2)_7COOH}$ V

Hydroxylation of either 12-oxo-*cis*-9 or 12-oxo-*trans*-9-octadecenoic acid by means of the Milas reagent resulted in both instances in the formation of the higher oxidation product VI. In the case of the *cis* isomer, the reaction was accompanied by much decomposition and the yield was small.

The best yields of compounds III, IV and V were obtained when hydroxylation of the unsaturated keto acids was carried out in ether solution using 90% hydrogen peroxide as oxidant and osmium tetroxide as catalyst.

9,12-Dioxo-10-hydroxyoctadecanoic Acid (VI).—Compound VI possessed an empirical formula of $C_{18}H_{34}O_5$ and its functional group analysis indicated the structure to be that of a diketo-hydroxystearic acid. Periodate oxidation proceeded with the uptake of slightly less than one equivalent of reagent pointing to the presence of an α-ketol grouping. The formation of an α-ketol in place of the expected diol has been reported to occur under certain conditions in the permanganate oxidation of oleic or elaidic acid.[8]

That VI is 9,12-dioxo-10-hydroxyoctadecanoic acid


$\mathrm{C_6H_{13}COCH_2}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CO(CH_2)_7COOH}$

and not the isomeric 9-hydroxy-10,12-dioxoöctadecanoic acid was shown by a positive pine splinter

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[1] First paper in this series, J. Nichols and E. Schipper, THIS JOURNAL, **80**, 5705 (1958).

[2] Presented in part at the 126th Meeting of the American Chemical Society in New York, N. Y., September, 1954.

[3] E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921).

[4] R. S. Wilder and A. A. Dolnick, U. S. Patent 2,431,718 (1947).

[5] G. King, *J. Chem. Soc.*, 1980 (1951), reports a similarly low oxirane number for 9,10-epoxy-12-oxoöctadecanoic acid.

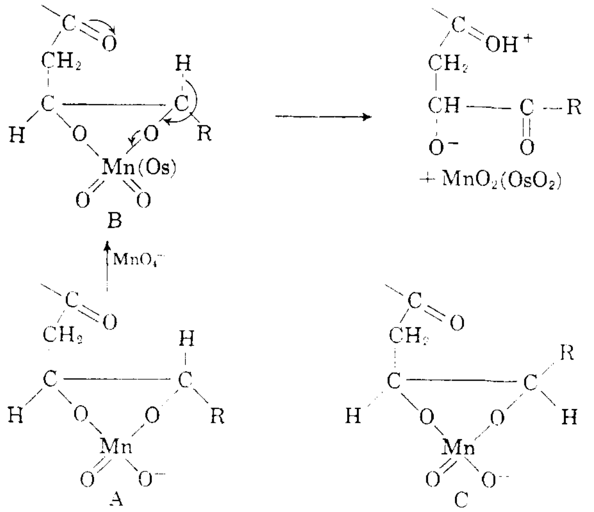
[6] D. Swern, *Chem. Revs.*, **45**, 1 (1949); J. Böeseken and A. Kremer, *Rec. trav. chim.*, **50**, 827 (1931).

[7] N. A. Milas and S. Sussman, THIS JOURNAL, **58**, 1302 (1936); N. A. Milas, *ibid.*, **59**, 2342 (1937); N. A. Milas, S. Sussman and H. S. Mason, *ibid.*, **61**, 1844 (1939); N. A. Milas, U. S. Patent 2,402,566 (1946).

[8] G. King, *J. Chem. Soc.*, 1788 (1936); R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955); J. E. Coleman, C. Ricciuti and D. Swern, THIS JOURNAL, **78**, 5342 (1956).

test on treatment with ammonium acetate[9] and, more conclusively, by its conversion to the known 9,12-dioxoöctadecanoic acid[10] by reduction with stannous chloride.

The difference in products obtained on permanganate oxidation of *cis* and *trans* 12-oxo-9-octadecenoic acid and similarly on osmium tetroxide catalyzed hydrogen peroxide oxidation can be explained as shown in the chart.[11]



(from *trans*-acid) (from *cis*-acid)

The Mn(V) in the initial oxidation product A of the *trans*-acid is oxidized by permanganate to Mn(VI).[12] In this transition state (B) the carbonyl group oxygen may act as an internal base and participate in the further oxidation to the ketol through a six-membered cycle. In the case of the *cis*-acid this participation of the carbonyl oxygen is precluded on steric grounds and there is no specific impetus for ketol formation. The major oxidation product of the *cis*-acid is, therefore, the diol III.[13]

Experimental[14]

10,11-Epoxy-12-oxoöctadecanoic Acid (I).—To a stirred solution containing 100 g. of 12-oxo-*trans*-10-octadecenoic acid,[1] 19 g. of potassium hydroxide, 4 g. of magnesium chloride and 8 l. of methanol were added simultaneously over a period of 15 minutes 174 ml. of 30% hydrogen peroxide and a solution containing 38 g. of potassium hydroxide, 166 ml. of water and 420 ml. of methanol. The reaction mixture was maintained at −5° during the addition and then was stirred at room temperature for 90 minutes. After standing at 0° for two days the solution was acidified with 10 l. of 0.1 *N* hydrochloric acid. Sufficient water was added to increase the total volume to 40 l. The white precipitate was collected by filtration, washed with water and recrystallized from ethanol; yield 74 g. (70%), m.p. 69.5–70°. When 12-oxo-*cis*-9-octadecenoic acid was oxidized in the same manner, the epoxy acid I was obtained in a yield of 38%. Only starting material could be recovered on epoxidation of 12-oxo-*trans*-9-octadecenoic acid.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.33; equiv. wt., 312.5; oxirane number,[15] 5.12. Found: C, 69.26; H, 10.44; equiv. wt., 314.5; oxirane number, 3.25.

The semicarbazone, recrystallized from abs. ethanol, showed m.p. 131–132°.

Anal. Calcd. for $C_{19}H_{35}N_3O_4$: C, 61.76; H, 9.54. Found: C, 62.29; H, 9.59.

9,12-Dioxo-10,11-epoxyoctadecanoic Acid (II).—The epoxidation procedure described above was applied to 100 g. of 9,12-dioxo-*trans*-10-octadecenoic acid. In this case, however, the reaction mixture was allowed to stand at 0° for one hour only, as longer periods were found to result in lowered yields; yield, after recrystallization from ethanol, 45 g. (43%), m.p. 99.5–100°.

Anal. Calcd. for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26; equiv. wt., 326.5; oxirane number,[15] 4.98; % carbonyl 17.1.[16] Found: C, 66.31; H, 9.17; equiv. wt. 330.5; oxirane number, 2.24; % carbonyl, 16.6.

Attempted Hydrolytic Cleavage of the Epoxide Ring.—A solution containing 0.5 g. of 10,11-epoxy-12-oxoöctadecanoic acid, 20 ml. of glacial acetic acid and 1 ml. of concd. sulfuric acid was allowed to stand for one hour at room temperature and then was poured onto 50 g. of crushed ice. The brown precipitate was filtered off and dissolved in 10 ml. of a 1 *N* potassium hydroxide solution. The solution was allowed to stand at room temperature for two days. On neutralization, a brownish oil appeared which resisted all attempts at purification. When the above ketoepoxy acid was refluxed for 16 hours with 0.1 *N* hydrochloric acid negative results again were obtained; a small quantity of starting material could be recovered.

***erythro*-9,10-Dihydroxy-12-oxoöctadecanoic Acid** (III). (a) **By Oxidation with 90% Hydrogen Peroxide.**—To a stirred solution of 100 g. of 12-oxo-*cis*-9-octadecenoic acid in 3 l. of abs. ether there was added in rapid succession 100 ml. of 90% hydrogen peroxide and 200 ml. of a 1% ethereal osmium tetroxide solution. The reaction mixture was maintained at −10° during the addition and was then allowed to stand at 0° for 12 hours. The precipitate was collected by filtration, suspended in 1 l. of water and the suspension was stirred vigorously for one hour. It was heated to 50°, sufficient ethanol was added to dissolve all the material and the solution, after filtration, was diluted with water to three times its volume. The precipitate was removed by filtration and was dissolved in 1 l. of ether. The ether solution was dried, cooled to −20°, and two liters of petroleum ether was added. The precipitate was collected and recrystallized from ethyl acetate; yield 48 g. (43%), m.p. 107–108°.

Anal. Calcd. for $C_{18}H_{34}O_5$: C, 65.42; H, 10.37; equiv. wt., 330.5. Found: C, 65.41; H, 10.52; equiv. wt., 330.0.

The semicarbazone, recrystallized from ethanol, had m.p. 123–125°.

Anal. Calcd. for $C_{19}H_{37}N_3O_5$: C, 58.89; H, 9.63. Found: C, 59.19; H, 9.93.

(b) **By Permanganate Oxidation.**—To a stirred solution containing 5 g. of 12-oxo-*cis*-9-octadecenoic acid, 1.6 g. of potassium hydroxide and 860 ml. of water there was added over a period of 10 minutes a solution of 5.3 g. of potassium permanganate in 330 ml. of water. During the addition the temperature of the reaction mixture was kept below 10°. After addition of 16.6 g. of sodium bisulfite and 83 ml. of 8 *N* sulfuric acid a white precipitate appeared which was collected by filtration. The product was immediately[17] taken

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[9] E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 386.

[10] A. G. Goldsobel, *Ber.*, **27**, 3121 (1894).

[11] We are indebted to Dr. John S. Showell, Eastern Utilization Research and Development Division, U. S. Department of Agriculture, Philadelphia, Penna., for suggesting this mechanism and for helpful discussion in its regard.

[12] K. B. Wiberg and K. A. Saegebarth, THIS JOURNAL, **79**, 2822 (1957).

[13] The formation of a small amount of ketol (VI) in the osmium tetroxide-hydrogen peroxide oxidation of the *cis* acid may be the result of a non-specific oxidative attack of the intermediate osmate ester. Theoretically, this oxidation should result in equal formation of the isomeric ketols, VI and 9-hydroxy-10,12-dioxo-octadecanoic acid. However, the latter compound, a β-diketone, would not be expected to survive under the oxidative conditions employed.

[14] All melting points are uncorrected. The microanalyses were performed by Mr. Erik Hoffmann and Miss Mary Grace Comfort.

[15] The procedure of D. Swern, T. W. Findley, G. N. Billen and J. T. Scanlan, *Ind. Eng. Chem., Anal. Ed.*, **19**, 414 (1947), was used but the reaction time was increased to 12 days.

[16] S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 16.

[17] The material was found to be quite unstable when wet.

up in ether, the ether solution was washed with water and dried. After removal of the solvent under reduced pressure the residue was recrystallized from ethyl acetate; yield 1.9 g. (34%), m.p. 107–108°.

***threo*-10,11-Dihydroxy-12-oxoöctadecanoic Acid (IV).** (a) **By Oxidation with 90% Hydrogen Peroxide.**—Seventy-five milliliters of 90% hydrogen peroxide and 150 ml. of a 1% ethereal osmium tetroxide solution were added to a stirred solution of 150 g. of 12-oxo-*trans*-10-octadecenoic acid in 3 l. of abs. ether. The reaction temperature was maintained at 15–20° and stirring was continued at this temperature for 15 minutes after completed addition. The mixture was allowed to stand at 0° for 12 hours and the white precipitate was collected by filtration. It was combined with the precipitate which formed on dilution of the filtrate with 12 l. of petroleum ether and cooling to −20°. The combined precipitate was suspended in 1 l. of water and the mixture was stirred for one hour. After filtration, the solid was dissolved in 500 ml. of ethanol and the solution was decolorized with Darco. Upon addition of 600 ml. of water a precipitate was obtained which after recrystallization from a 4:1 mixture of petroleum ether and ether melted at 98–100°; yield 39 g. (23%).

Anal. Calcd. for $C_{18}H_{34}O_5$: C, 65.42; H, 10.37; equiv. wt., 330.5; % carbonyl, 8.5. Found: C, 65.48; H, 10.32; equiv. wt., 327.0; % carbonyl, 8.2.

The semicarbazone, recrystallized from abs. ethanol, showed m.p. 160–162°.

Anal. Calcd. for $C_{19}H_{37}N_3O_3$: C, 58.89; H, 9.63. Found: C, 59.39; H, 9.33.

(b) **By Oxidation with the Milas Reagent.**—To a stirred solution of 5.2 g. of 12-oxo-*trans*-10-octadecenoic acid in 20 ml. of anhydrous *t*-butyl alcohol was added rapidly 12 ml. of the Milas reagent[7] (analyzing for 5% peroxide) and 4 ml. of a 1% ethereal osmium tetroxide solution. The temperature was allowed to rise to 50°. The reaction mixture was cooled to 35° and was stirred for one hour. After standing overnight at room temperature, the mixture was diluted with 250 ml. of ice-water and was then extracted with two 100-ml. portions of ether. The combined extracts were dried and the solvent was removed under reduced pressure. The residue was recrystallized from a 4:1 mixture of petroleum ether and ether; yield 0.8 g. (13%), m.p. 99–100°.

9,12-Dioxo-*threo*-10,11-dihydroxyoctadecanoic Acid (V). (a) **By Oxidation with 90% Hydrogen Peroxide.**—To a stirred solution of 50 g. of 9,12-dioxo-*trans*-10-octadecenoic acid in 2 l. of abs. ether at 0° was added 75 ml. of 90% hydrogen peroxide and 125 ml. of a 1% ethereal osmium tetroxide solution. The stirred reaction mixture was allowed to warm gradually to room temperature and after total solution had occurred (2 to 3 hours) the reaction flask was transferred to an ice chest. The solution was allowed to stand at 0° for 12 hours and the mixture was filtered. The precipitate and filtrate were worked up by the process described above for the preparation of compound IV by the 90% hydrogen peroxide oxidation procedure. The recrystallization solvent was 90% ethanol. There was obtained 31.2 g. (56%) of 9,12-dioxo-*threo*-10,11-dihydroxyoctadecanoic acid (V), m.p. 103–104°.

Anal. Calcd. for $C_{18}H_{32}O_6$: C, 62.76; H, 9.37; % carbonyl, 16.4. Found: C, 62.64; H, 9.16; % carbonyl, 16.0.

When the reaction mixture was stirred at room temperature for but one hour, a material was obtained on filtration which melted at 131–132°. It analyzed as an addition complex between one mole of V and two moles of hydrogen peroxide. Upon brief heating with 50% methanol it was converted quantitatively into compound V.

(b) **By Oxidation with the Milas Reagent.**—A slurry of 5.6 g. of 9,12-diketo-*trans*-10-octadecenoic acid and 35 ml. of the Milas reagent was warmed slightly and 5 ml. of a 1% ethereal osmium tetroxide solution was added with stirring. A spontaneous reaction occurred and the temperature was allowed to reach 70° before a cooling bath was applied. The mixture was allowed to stand overnight at room temperature and was worked up in the same manner as described above for the preparation of compound IV. After several recrystallizations from ether and ethanol there was obtained 1.2 g. (19%) of product melting at 103–104°.

9,12-Dioxo-10-hydroxyoctadecanoic Acid (VI). (a) **By Oxidation with the Milas Reagent.**—To a stirred solution of 10 g. of 12-oxo-*trans*-9-octadecenoic acid in 100 ml. of anhydrous *t*-butyl alcohol was added rapidly 60 ml. of the Milas reagent and 12 ml. of a 1% ethereal osmium tetroxide solution. The temperature was allowed to rise to 50°. The reaction mixture was cooled to 35° and stirred at this temperature for one hour. After standing at room temperature overnight, the mixture was diluted with 500 ml. of ice-water and was extracted with 200-ml. portions of ether. The combined extracts were dried, the solvent was removed under reduced pressure and the residue triturated with 100 ml. of petroleum ether. The insoluble material was collected by filtration and recrystallized from 50% ethanol; yield 2.5 g. (22%), m.p. 90–91°.

Anal. Calcd. for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82; equiv. wt., 328.5; % carbonyl, 17.1. Found: C, 66.01; H, 9.73; equiv. wt., 328.0; % carbonyl, 17.4.

When the above procedure was applied to 12-oxo-*cis*-9-octadecenoic acid much decomposition occurred and compound VI was isolated in a yield of only 3%.

(b) **By Permanganate Oxidation.**—On oxidation of 5 g. of 12-oxo-*trans*-9-octadecenoic acid with alkaline permanganate by the procedure described above for the preparation of *erythro*-9,10-dihydroxy-12-oxoöctadecanoic acid (III) there was obtained, after several recrystallizations of the reaction product from 50% ethanol and from a 1:1 mixture of ether and petroleum ether, 0.5 g. (9%) of 9,12-dioxo-10-hydroxyoctadecanoic acid (VI), m.p. 90–91°.

Methyl 9,12-Dioxo-10-hydroxyoctadecanoate.—A solution containing 0.75 g. of 9,12-dioxo-10-hydroxyoctadecanoic acid, 72 ml. of methanol and 3 ml. of concd. hydrochloric acid was allowed to stand at room temperature for 24 hours. The solvent was removed under reduced pressure and the residue was diluted with 100 ml. of water. The oil was extracted with 100 ml. of ether and the ether solution was washed with a 10% potassium carbonate solution and then with water. The ether solution was dried and the solvent was removed. The residue was recrystallized from a petroleum ether solution cooled to −30°. The solid obtained (0.55 g.) melted at 45–47°.

Anal. Calcd. for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.54; H, 10.02.

Reduction of 9,12-Dioxo-10-hydroxyoctadecanoic Acid.—One gram of 9,12-dioxo-10-hydroxyoctadecanoic acid was added to a boiling solution containing 5 g. of stannous chloride, 9 ml. of glacial acetic acid and 7 ml. of concd. hydrochloric acid. The mixture was heated for 3 minutes on a steam-bath and poured onto 50 g. of crushed ice. The precipitate was collected by filtration and was washed with water. After successive recrystallizations from ethanol and ether, a material, m.p. 95–96°, was obtained in a yield of 0.4 g. It gave a positive pine splinter test following treatment with ammonium acetate.[9] Identity of the product with 9,12-dioxoöctadecanoic acid[1,10] was established by comparison of infrared spectra and by mixed melting point determination of the acids and of their respective dioximes.

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