hypoartemisin (VIII), by saponification of the lactone followed by acidification. Since such a transformation sequence when applied to the conversion of hyposantonin to isohyposantonin has been shown to involve only the lactone fusion stereochemistry,[1] a similar change can be assumed in the isohypoartemisin preparation. When the *cis*-lactone VIII was heated in glacial acetic acid in the presence of zinc, it was transformed directly to the tetralin lactone derivative IV.

In the degradation of ψ-santonin (III) and artemisin (II) to the lactone IV, three asymmetric centers, C_6, C_7 and C_{11}, of the original molecule were retained. The chemistry involved in these transformations should not have affected these three centers. Thus, the present work when coupled with the previous results[3] shows that (−)-α-santonin, artemisin and ψ-santonin possesses the same configuration at C_6, C_9 and C_{11} and that the C_7-hydroxyl group in ψ-santonin and artemisin also are of the same configuration. The stereochemical relationship of C_5 still awaits direct establishment.[5]

Experimental[6]

Hypoartemisin (VII).—To a solution of 790 mg. of artemisin oxime in 32 ml. of 90% ethanol there was added, in turn, 1.5 ml. of concd. sulfuric acid, several drops of aqueous cupric sulfate solution and 5 g. of zinc powder. The mixture was stirred at 33° for 30 hours, the zinc filtered and washed with ethanol. The combined filtrates were concentrated under reduced pressure until almost all of the solvent had been removed. The concentrated solution was cooled but no solid separated. Upon dilution with 15 ml. of water, a small amount of solid separated which was filtered and not further investigated.

The aqueous alcoholic filtrate was refluxed for 45 minutes during which time it became turbid and a crystalline solid separated. After cooling, the solid was filtered (350 mg.) and recrystallized from ethanol, m.p. 198°, $[\alpha]^{20}\text{D}$ +73° (*c* 0.5), $\lambda_{\max}^{\text{EtOH}}$ 270 mμ (log ε 2.77).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.94; H, 7.33.

Hypoartemisin Acetate.—Hypoartemisin (150 mg.) was heated for 10 hours in acetic acid with 1 g. of zinc powder. After the zinc was filtered, the filtrate was concentrated under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water, aqueous sodium carbonate and water, dried and solvent evaporated to yield 90 mg. of a crystalline solid, m.p. 160–170°. The material was recrystallized from ethanol, m.p. 173°, $[\alpha]^{20}\text{D}$ +60° (*c* 1.0); $\lambda_{\max}^{\text{EtOH}}$ 269.5 mμ (log ε 2.77), 278.5 mμ (log, ε 2.77); $\nu_{\max}^{\text{CHCl}_3}$ 1770 cm.$^{-1}$ (lactone), 1731 cm.$^{-1}$ (acetate) no hydroxyl band.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.47; H, 6.94.

Isohypoartemisin (VIII).—Hypoartemisin (300 mg.) was dissolved in 90 ml. of 90% ethanol containing 280 mg. of potassium hydroxide and the solution was refluxed for 2 hours. After cooling, the reaction mixture was acidified with 5% hydrochloric acid, the ethanol removed under reduced pressure and the residual mixture extracted with ether. The extract was washed with water, dried and the ether evaporated. The crude product (150 mg., m.p. 121–130°) was recrystallized from ethyl acetate–petroleum ether (b.p. 30–70°), m.p. 131–133°, $[\alpha]^{23}\text{D}$ −80° (*c* 1.0), $\lambda_{\max}^{\text{EtOH}}$ 271 mμ (log ε 2.93), 280 mμ (log ε 2.96).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.16; H, 7.23.

α-(**1,4-Dimethyl-7-hydroxy-5,6,7,8-tetrahydro-6-naphthyl)-propionic Acid Lactone** (**IV**).—A solution of 100 mg. of isohypoartemisin in 25 ml. of glacial acetic acid was refluxed with 2 g. of zinc powder for 10 hours. The solution was filtered, concentrated under reduced pressure and extracted with ethyl acetate. The extract was washed with water, aqueous sodium carbonate and water and the solvent evaporated to yield 20 mg. of crystalline solid. The material was recrystallized from ligroin (b.p. 70–85°), m.p. 142–144°, $[\alpha]^{25}\text{D}$ +39° (*c* 0.90, EtOH), $[\alpha]^{25}\text{D}$ +51° (*c* 1.04, chf.), $\lambda_{\max}^{\text{EtOH}}$ 267 mμ (log ε 2.61), 276 mμ (log ε 2.55). The melting point was not depressed upon mixing with an authentic sample prepared from ψ-santonin.[4] The infrared spectra of both samples were identical.

Acknowledgment.—The authors are indebted to Professor H. H. Inhoffen for kindly supplying the artemisin.

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[5] ADDED IN PROOF.—Since submission of this manuscript, W. Cocker and T. B. H. McMurry (*Proc. Chem. Soc.*, 147 (1958)) have correlated the stereochemistry of positions 6, 7 and 9 of ψ-santonin with tetrahydroalantolactone, the absolute configuration of which has been established previously.

[6] All melting points are uncorrected. Rotations were measured in ethanol.

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

Keto Fatty Acids Derived from Castor Oil. I. Unsaturated Acids[1]

BY JOSEPH NICHOLS AND EDGAR SCHIPPER

RECEIVED APRIL 21, 1958

The chromic acid and Oppenauer oxidation of ricinoleic and ricinelaidic acid to unsaturated keto acids has been investigated. The structure of the chromic acid oxidation product of 12-oxo-*cis*-9 or 12-oxo-*trans*-9-octadecenoic acid has been elucidated and the compound shown to be 9,12-dioxo-*trans*-10-octadecenoic acid.

In recent years there has been increasing interest in the role of unsaturated fatty acids as nutritional factors, especially as related to the problem of atherosclerosis.[2] The inhibition of bacterial and fungal organisms by fatty acids and their derivatives also has received considerable attention.[3] While the exact mode of action of these fatty acids in bacterial and mammalian metabolism has not been established, sufficient evidence has accumulated which points to their involvement in important enzyme systems.[4] It seemed

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

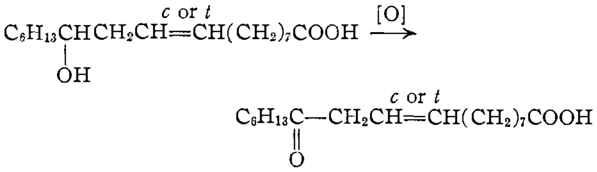
[2] A. Keys, J. T. Anderson, F. Fidanza, M. H. Keys and B. Swahn, *Clin. Chem.*, **1**, 34 (1955); J. J. Peifer and R. T. Holman, *Arch. Biochem. and Biophys.*, **57**, 520 (1955); R. T. Holman, *Svensk. Kem. Tidskr.*, **68**, 282 (1956).

[3] C. Nieman, *Bacteriol. Revs.*, **18**, 147 (1954); J. Lein, T. A. Puglisi and P. S. Lein, *Arch. Biochem. and Biophys.*, **45**, 434 (1953).

[4] H. O. Kunkel and J. N. Williams, Jr., *J. Biol. Chem.*, **189**, 755 (1951); R. W. Engel, *J. Nutrition*, **24**, 175 (1942); S. Bergström, H. Theorell and H. Davide, *Nature*, **157**, 306 (1946); V. R. Williams and E. A. Fieger, *Ind. Eng. Chem., Anal. Ed.*, **17**, 127 (1945), and subsequent papers.

of interest, therefore, to prepare fatty acid derivatives structurally similar to the natural unsaturated fatty acids, which might act as antagonists to these materials or alternately, as replacements. To this end, the synthesis of a number of long chain unsaturated keto acids was undertaken.

Ricinoleic acid and its geometrical isomer ricinelaidic acid appeared to be suitable starting materials for the synthesis of the desired keto acids. Ellis[5] showed that these acids could be oxidized to the corresponding unsaturated keto acids by means of chromic acid



$$\underset{\displaystyle |\atop \text{OH}}{\text{C}_6\text{H}_{13}\text{CH}}\text{CH}_2\text{CH}\overset{c\text{ or }t}{=}\text{CH(CH}_2)_7\text{COOH}\xrightarrow{[\text{O}]}\underset{\displaystyle \|\atop \text{O}}{\text{C}_6\text{H}_{13}\text{C}}\text{—CH}_2\text{CH}\overset{c\text{ or }t}{=}\text{CH(CH}_2)_7\text{COOH}$$

When, in contrast to the low temperature procedure of Ellis who obtained poor yields, the reaction was allowed to proceed exothermally for a very brief period, excellent yields of 12-oxo-*cis*-9-octadecenoic acid and 12-oxo-*trans*-9-octadecenoic acid were obtained.[6] A small quantity of a material I, m.p. 112–113°, usually was isolated as a by-product in this reaction. Rapid oxidation of the alkyl esters of ricinoleic and ricinelaidic acids gave rise to the corresponding keto esters, compounds which are not directly accessible from the free acids by the usual acid-catalyzed esterification procedures as these cause isomerization of the double bond.

The rapid chromic acid oxidation procedure could be well applied equally to ricinostearolic acid. 12-Oxo-9-octadecynoic acid, $\underset{\displaystyle \|\atop \text{O}}{\text{C}_6\text{H}_{13}\text{C}}\text{CH}_2\text{-C}{\equiv}\text{C(CH}_2)_7\text{COOH}$, a compound recently synthesized by Crombie and Jacklin,[7] was thus produced in good yield.

Acid-catalyzed isomerization of 12-oxo-*cis*-9- or 12-oxo-*trans*-9-octadecenoic acid gave rise to 12-oxo-*trans*-10-octadecenoic acid.[5,8] Methyl-12-oxo-*trans*-10-octadecenoate was similarly obtained from the methyl esters of the above unconjugated acids.

As part of a study of alternate oxidative methods, the Oppenauer oxidation of ricinoleic and ricinelaidic acid was investigated. The oxidation of aliphatic β,γ-unsaturated alcohols by this procedure has received little attention.[9] Although there are many examples of the Oppenauer oxidation of β,γ-unsaturated alcohol systems in steroid chemistry, the oxidation invariably is accompanied by isomerization and conjugated ketones are the sole products obtained.[10] It was found, however, that the Oppenauer oxidation of ricinoleic and ricinelaidic acid could be effected without isomerization to the conjugated ketone system. A significant difference was observed in the rate of oxidation of these two acids. On oxidation of ricinelaidic acid a maximum yield of 12-oxo-*trans*-9-octadecenoic acid was obtained after a reaction time of 18 hours. Shorter reaction periods led to mixtures containing varying amounts of starting material, while longer reaction times caused considerable decomposition. In no case could there be isolated or detected spectroscopically the conjugated 12-oxo-*trans*-10-octadecenoic acid.[5,8] When the Oppenauer procedure was applied to ricinoleic acid, the optimum yield of 12-oxo-*cis*-9-octadecenoic acid was obtained after a reaction time of 15 minutes. With increase in reaction time, partial isomerization became evident and after 12 hours essentially pure 12-oxo-*trans*-10-octadecenoic acid was obtained. When cholesterol was subjected to Oppenauer oxidation and the reaction was terminated after 15 minutes, only the usual conjugated product Δ^4-cholestene-3-one could be isolated. From these observations it would appear that the Oppenauer oxidation of a β,γ-unsaturated alcohol yields the unrearranged ketone as the primary product and that the relative rate of isomerization of this material, under the reaction conditions used, determines the constitution of the final product.

9,12-Dioxo-*trans*-10-octadecenoic Acid (I).—The material melting at 112–113° formed in trace amounts on chromic acid oxidation of ricinoleic or ricinelaidic acid was identical with the compound of composition $C_{18}H_{32}O_4$ obtained by Ellis[5] as the autoxidation product of 12-oxo-*cis*-9-octadecenoic acid. This material could be obtained in good yield and on a preparative scale by controlled chromic acid oxidation of 12-oxo-*cis*-9- or 12-oxo-*trans*-9-octadecenoic acid.[11] Ellis' assignment of structure to this material as 9,10-epoxy-12-oxo-octadecenoic acid was clearly erroneous as the presence of two keto groups readily could be demonstrated.[11,12] In view of this fact and on the basis of its intense light absorption at 230 mμ, King[12] formulated the compound as 11,12-dioxo-*cis*-9-octadecenoic acid. In the absence of references in the literature to the controlled oxidation of aliphatic β,γ-unsaturated keto systems, the site of oxidative attack proposed by King appeared reasonable. Several factors, however, militated against King's structure. The assignment of a *cis* configuration seemed untenable as oxidation of either 12-oxo-*cis*-9- or 12-oxo-*trans*-9-octadecenoic acid furnished the same diketo acid. Also, the material did not absorb light in the visible region and gave no quinoxaline derivative when treated with *o*-phenylenediamine—findings which were not in accord with the α,β-dicarbonyl nature of King's formula. Furthermore, light absorption in the region of 230 mμ would not be expected to permit differentiation of such similar conjugated systems as COCOCH=CH— and COCH=CH-CO.[12,13] We, therefore, considered the possibility that the oxidation product possessed a 1,4-enedione

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[5] G. W. Ellis, *J. Chem. Soc.*, 9 (1950).

[6] J. Nichols, U. S. Patent 2,623,888 (1952).

[7] L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1740 (1955).

[8] G. King, *ibid.*, 1980 (1951).

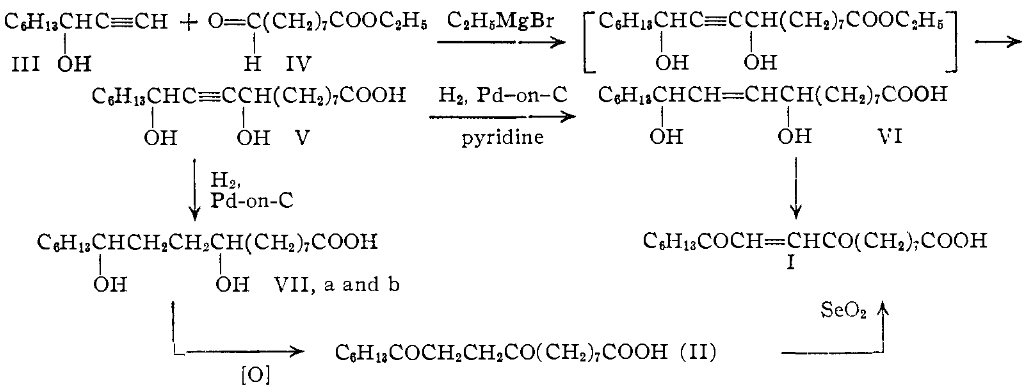
[9] N. A. Milas, S. W. Lee, E. Sakal, H. C. Wohlers, N. S. MacDonald, F. X. Grossi and H. F. Wright, THIS JOURNAL, **70**, 1584 (1948), report the oxidation of 1-(2′,6′,6′-trimethylcyclohexen-1-yl)-3-methyl-1-hexene-4-ol to the apparently non-isomerized ketone. No structural evidence is given, but the spectral data seem to indicate that total or partial conjugation had taken place.

[10] C. Djerassi, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 207.

[11] J. Nichols, U. S. Patent 2,623,889 (1952).

[12] G. King, *J. Chem. Soc.*, 2897 (1950); 1485 (1958).

[13] E. A. Braude, *ibid.*, 490 (1945).



$$\underset{\text{III}}{C_6H_{13}\underset{\text{OH}}{\text{CH}}C\equiv CH} + \underset{\text{IV}}{O=\underset{\text{H}}{C}(CH_2)_7COOC_2H_5} \xrightarrow{C_2H_5MgBr} \left[C_6H_{13}\underset{\text{OH}}{\text{CH}}C\equiv C\underset{\text{OH}}{\text{CH}}(CH_2)_7COOC_2H_5\right] \longrightarrow$$

$$\underset{\text{V}}{C_6H_{13}\underset{\text{OH}}{\text{CH}}C\equiv C\underset{\text{OH}}{\text{CH}}(CH_2)_7COOH} \xrightarrow[\text{pyridine}]{H_2,\ \text{Pd-on-C}} \underset{\text{VI}}{C_6H_{13}\underset{\text{OH}}{\text{CH}}CH=CH\underset{\text{OH}}{\text{CH}}(CH_2)_7COOH}$$

$$\text{V} \xrightarrow{H_2,\ \text{Pd-on-C}} \underset{\text{VII, a and b}}{C_6H_{13}\underset{\text{OH}}{\text{CH}}CH_2CH_2\underset{\text{OH}}{\text{CH}}(CH_2)_7COOH} \qquad \text{VI} \longrightarrow \underset{\text{I}}{C_6H_{13}COCH=CHCO(CH_2)_7COOH}$$

$$\text{VII} \xrightarrow{[O]} C_6H_{13}COCH_2CH_2CO(CH_2)_7COOH\ (\text{II}) \xrightarrow{SeO_2} \text{I}$$

structure and was 9,12-dioxo-*trans*-10-octadecenoic acid (I), $C_6H_{13}COCH{=}CHCO(CH_2)_7COOH$ (I).

While there seems to be no precedent for the formation of such oxidation products from aliphatic β,γ-unsaturated alcohols or ketones, there are examples of 1,4-enedione reaction products in steroid[14] and triterpenoid[15] chemistry. Catalytic or chemical reduction of compound I led to a diketostearic acid. This material was not affected by periodate and, in contrast to 9,10-dioxoöctadecanoic acid[16] and methylethyl glyoxal,[17] it exhibited no light absorption in the region of 400 mμ or above. Following treatment with ammonium acetate the saturated diketo acid gave a positive pine splinter test characteristic of 1,4-dicarbonyl systems.[18] It thus appeared that the reduction product of compound I was Goldsobel's 9,12-dioxoöctadecanoic acid (II),[19] $C_6H_{13}COCH_2CH_2CO(CH_2)_7COOH$. An authentic sample of this acid was prepared and its identity with the reduction product of compound I was established by mixed melting point determinations and by comparison of the infrared spectra of the respective acids, their disemicarbazones and dioximes. Consequently, compound I is 9,12-dioxo-10-octadecenoic acid. This was further substantiated by total synthesis of this substance.

Nonyne-3-ol (III) and the half aldehyde ester of azelaic acid (IV) were condensed to form an oily mixture of esters which was hydrolyzed to a mixture of solid diastereoisomeric acids (V). One of the two isomers could be obtained in a pure state by chromatography through a charcoal–Celite column. When the acetylenic acids (V) were subjected to catalytic hydrogenation, 2 moles of hydrogen was absorbed and a mixture of isomeric saturated dihydroxyoctadecanoic acids (VIIa and b) was obtained. This mixture could be separated by fractional crystallization into a high melting form (VIIa), m.p. 119–120°, and a low melting component (VIIb), m.p. 80–82°. Neither of these materials corresponds with the 9,12-dihydroxyoctadecanoic acid, m.p. 69.5°, reported by Grün[20] as the major reaction product obtained in the hydration of ricinoleic acid by sulfuric acid. In order to confirm the structure ascribed to VIIa and VIIb they were subjected separately to chromic acid oxidation. In each instance, 9,12-dioxo-octadecanoic acid (II) was obtained in good yield.

Partial hydrogenation of compound V in the presence of Lindlar's catalyst[21] or a pyridine-poisoned palladium-on-charcoal catalyst, gave a mixture of ethylenic dihydroxy acids (VI). Controlled oxidation of this material proved to be extremely difficult. After numerous attempts it was found that a 3% yield of the desired 9,12-dioxo-10-octadecenoic acid (I) could be obtained by oxidizing VI with chromic trioxide in acetic acid. Compound I could be prepared in a somewhat better yield by selenium dioxide oxidation of 9,12-dioxoöctadecanoic acid (II). Identity of 9,12-dioxo-10-octadecenoic acid prepared by the above synthetic routes with the chromic acid oxidation product of 12-oxo-*cis*-9 or 12-oxo-*trans*-9-octadecenoic acid was established by mixed melting point and by comparison of the respective ultraviolet and infrared spectra.

Although no absolute proof of the geometry of the ethylenic linkage in 9,12-dioxo-10-octadecenoic acid (I) can be offered, it seems highly probable that it possesses a *trans* structure. In the oxidation of 12-oxo-*trans*-9-octadecenoic acid to the unsaturated diketo acid I the isomerization of the *trans* structure to the thermodynamically less stable *cis* configuration would be unlikely. Selenium dioxide oxidation of a 1,4-diketone such as acetylacetone gives rise solely to a *trans* product.[22] Also, a number of attempts to isomerize compound I by methods generally employed to induce *cis*–*trans* conversion failed to give a product of different configuration.

It might be inferred from the synthetic pathway that 9,12-dioxo-10-octadecenoic acid (I) possesses the *cis* configuration as it is derived from a mixture of predominantly *cis*-ethylenic glycols. Isomerization to the *trans* structure could occur, however, on oxidation of the glycol mixture under acidic

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[14] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, 3rd ed., p. 230; L. F. Fieser, THIS JOURNAL, **75**, 4377, 4386 (1953).

[15] D. H. R. Barton, N. J. Holness, K. H. Overton and W. J. Rosenfelder, *J. Chem. Soc.*, 3751 (1952).

[16] R. T. Holman, W. O. Lundberg, W. M. Lauer and G. O. Burr, THIS JOURNAL, **67**, 1285 (1945).

[17] R. T. Holman, W. O. Lundberg and G. O. Burr, *ibid.*, **67**, 1669 (1945).

[18] 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.

[19] (a) A. G. Goldsobel, *Chem. Ztg.*, **30**, 825 (1906); (b) *Ber.*, **27**, 3121 (1894).

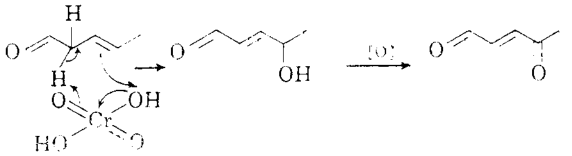
[20] A. Grün, *ibid.*, **39**, 4400 (1906).

[21] H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

[22] K. F. Armstrong and R. Robinson, *J. Chem. Soc.*, 1650 (1934); G. O. Schenck, *Ber.*, **77**, 741 (1944).

conditions. Indeed, Levisalles[23] recently isolated both geometrical forms of *sym*-diacetylethylene and observed that isomerization of the *cis* to the *trans* form occurred with great ease under acidic conditions. Furthermore, the ultraviolet absorption of 9,12-dioxo-10-octadecenoic acid (232, 320 mμ) corresponds well with that of trans-*sym*-diacetylethylene (228, 327 mμ) but not with that of the *cis* isomer (232, 282 mμ). Finally, the *trans* configuration of 9,12-dioxo-10-octadecenoic acid (I) is indicated by its infrared spectrum (*vide infra*).

In an attempt to elucidate the mechanism of formation of 9,12-dioxo-*trans*-10-octadecenoic acid (I) by the chromic acid oxidation of 12-oxo-*cis*-9- or 12-oxo-*trans*-9-octadecenoic acid, analogous oxidations were applied to several potential intermediates; these were 12-oxo-*trans*-10-octadecenoic acid, 12-ketoelaidic acid epoxide,[12] and *erythro*-9,10-dihydroxy-12-oxoöctadecanoic acid.[24] In no instance could 9,12-dioxo-*trans*-10-octadecenoic acid (I) be detected among the reaction products. The inability to discover an intermediate in this oxidation makes it seem likely that a mechanism similar to that proposed by Barton[15] for the oxidation of terpenoid β,γ-unsaturated alcohols to 1,4-enediones is operative. The driving force for the oxidative attack might be derived from a quasicyclic transition state between oxidant and reductant as



Infrared Spectra.—The infrared spectra of the unsaturated keto fatty acids are in good agreement with spectra reported in the literature for long chain saturated and unsaturated fatty acids.[25] Resolution of carbonyl and carboxyl C=O stretching vibrations can be observed in all of the monoketo acids but not in 9,12-dioxo-*trans*-10-octadecenoic acid. A peak at 6.04 μ, present in the spectrum of oleic acid and corresponding to the *cis* C=C stretching vibration,[26] is similarly found in the spectrum of 12-oxo-*cis*-9-octadecenoic acid. As expected, the isomeric *trans*-acid absorbs strongly at 10.4 μ. This band is shifted to 10.2 μ in the conjugated 12-oxo-*trans*-10-octadecenoic acid and to 10.04 μ in 9,12-dioxo-*trans*-10-octadecenoic acid. 12-Oxo-*trans*-10-octadecenoic acid exhibits the expected bathochromic shifts for conjugated C=O and C=C stretching vibrations to 5.98 and 6.15 μ, respectively. 9,12-Dioxo-*trans*-10-octadecenoic acid does not absorb in the conjugated C=C stretching region, possibly because of the high degree of symmetry which is imparted to the molecule by its *trans* configuration.

Acknowledgment.—The authors are indebted to Mr. E. R. Hoffmann and Miss M. G. Comfort for the analytical and spectral data reported in this paper.

Experimental[27]

12-Oxo-*cis*-9-octadecenoic Acid. (a) By Chromic Acid Oxidation.—To a vigorously stirred solution of 200 g. of ricinoleic acid[28] in 2 l. of glacial acetic acid there was added at once a solution containing 130 g. of sodium dichromate dihydrate, 160 ml. of water, 70 ml. of concd. sulfuric acid and 1.2 l. of glacial acetic acid. The temperature rose spontaneously to 50°. The reaction was maintained at this temperature for 30 seconds after which time it was terminated by the addition of 4 l. of an ice–water mixture. The precipitated crude acid was removed by filtration and was washed well with cold water. The wet precipitate was taken up in 2 l. of petroleum ether and the aqueous layer was discarded. The organic layer, containing some insoluble material (m.p. 112–113°), was filtered through a mat of sodium sulfate. The filtrate was allowed to stand at room temperature for one hour and another small quantity of the above solid was filtered off. The filtrate was cooled to −20° and the solid was collected rapidly; yield starting with pure ricinoleic acid, 150 g. (75.5%), or 120 g. when crude castor oil hydrolysate[28] was employed. The material after recrystallization from 80% ethanol melted at 40–40.5°. A semicarbazone, recrystallized from cold methanol, melted at 89–90°.

Anal. Calcd. for $C_{19}H_{35}N_3O_3$: C, 64.57; H, 9.98. Found: C, 64.39; H, 9.95.

(b) By Oppenauer Oxidation.—From a solution containing 10 g. of ricinoleic acid, 450 ml. of toluene and 100 ml. of redistilled cyclohexanone there was removed 150 ml. of distillate to ensure anhydrous conditions; 10 g. of aluminum isopropoxide was added and the mixture was refluxed for 15 minutes. The reaction mixture was cooled and washed with six 150-ml. portions of 10% sulfuric acid. The first two washings were extracted with two 100-ml. portions of benzene. The organic layers were combined and washed with water until the washings had a *p*H of 4–5. The solution was dried and the solvent was removed under reduced pressure. The residue was taken up in 50 ml. of cold 5 *N* potassium hydroxide and the basic solution was extracted with 300 ml. of ether. The ether layer was extracted with two 100-ml. portions of water and the aqueous layers were combined and neutralized with concd. hydrochloric acid. The precipitated oil was extracted with 200 ml. of ether, the ether solution was washed with water and then dried. The solvent was removed *in vacuo* and the residue was recrystallized from 60% ethanol; yield 4.2 g. (43%), m.p. 39–40°.

Methyl 12-Oxo-*cis*-9-octadecenoate.—Reaction conditions identical with those described for the chromic acid oxidation of ricinoleic acid were applied to 200 g. of methyl ricinoleate.[29] After termination of the oxidation by addition of ice-water, the oily reaction product was extracted with two 1-l. portions of petroleum ether. The extracts were combined and washed with 1 l. of 10% sodium carbonate and five 400-ml. portions of water. The solution was dried and the solvent was removed under reduced pressure leaving 162 g. of a light oil. The oil was dissolved in 400 ml. of petroleum ether, the solution was cooled to −40° and then allowed to warm to −15°. A small quantity of a solid was removed by filtration. The filtrate was subjected four times more to the cooling, warming and filtration procedure. Finally, the filtrate was cooled to −50° and the precipitate was collected rapidly. It was redissolved in 200 ml. of petroleum ether and the solution was dried. The solvent was removed leaving 120 g. (60%) of the desired keto ester, m.p. −1°, n^{20}_D 1.4592. The material had an acid number of zero and exhibited no light absorption in the region of 220–230 mμ.

Anal. Calcd. for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.42; H, 11.14.

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[23] J. Levisalles, *Bull. soc. chim. France*, 997 (1957).

[24] See paper II in this series, THIS JOURNAL, **80**, 5711 (1958).

[25] R. T. O'Connor, *J. Am. Oil Chemists' Soc.*, **33**, 1 (1956).

[26] J. W. McCutcheon, M. F. Crawford and H. L. Welsh, *Oil and Soap*, **18**, 9 (1941).

[27] All melting points are uncorrected.

[28] In practice it was convenient to replace pure ricinoleic acid by a crude castor oil hydrolysate obtained by heating to reflux a mixture of 1 kg. of castor oil, 400 g. of potassium hydroxide, 2 l. of ethanol and 300 ml. of water. Upon acidification, the oily layer was washed with water and dried over anhydr. sodium sulfate. The preparation contained *ca.* 85% of ricinoleic acid.

[29] P. S. Skell and S. B. Radlove, *Ind. Eng. Chem., Anal. Ed.*, **18**, 67 (1946).

Ethyl 12-oxo-*cis*-9-octadecenoate was prepared by the preceding oxidation procedure from 200 g. of ethyl ricinoleate.[29] The colorless keto ester was obtained in a yield of 88 g. (44%), m.p. −7 to −6°, $n^{31}D$ 1.4542.

Anal. Calcd. for $C_{20}H_{36}O_3$: C, 74.02; H, 11.18. Found: C, 73.78; H, 11.17.

12-Oxo-*trans*-9-octadecenoic Acid. (a) By Chromic Acid Oxidation.—An oxidation mixture containing 160 g. of sodium dichromate dihydrate, 60 ml. of concd. sulfuric acid, 160 ml. of water and 1.3 l. of glacial acetic acid was added with vigorous stirring to a solution of 200 g. of ricinelaidic acid[30] in 1.6 l. of glacial acetic acid. The temperature of the reaction mixture rose to 52° and the mixture was maintained at this temperature for 1.5 minutes. The reaction was terminated with ice-water and the recovered precipitate was washed well with water. The crude reaction product, after successive recrystallizations from petroleum ether and ethanol, melted at 72–72.5°; yield 162 g. (82%).

(b) **By Oppenauer Oxidation.**—To a solution containing 10 g. of ricinelaidic acid, 100 ml. of acetone (purified by two distillations over fused potassium hydroxide and one distillation over potassium permanganate) and 100 ml. of dry and redistilled benzene was added 10 g. aluminum *t*-butoxide dissolved in 200 ml. of hot benzene. The solution was refluxed for 18 hours and the reaction mixture was washed with six 100-ml. portions of 10% sulfuric acid. The first two washings were extracted with two 100-ml. portions of benzene. The organic layers were combined and washed with water to a *p*H of 4–5. The solution was dried and the solvent was removed under reduced pressure. The residue was recrystallized once from 70% ethanol to give 5.4 g. (55%) of desired product; m.p. 71–72°.

Methyl 12-Oxo-*trans*-9-octadecenoate.—Reaction conditions identical with those employed in the chromic acid oxidation of ricinelaidic acid were applied to 200 g. of methyl ricinelaidate.[29] The crude reaction product was taken up in 2 l. of warm petroleum ether and the solution was washed with successive portions of 10% sodium carbonate and water. The organic solution was dried and cooled to −30°. The ester, m.p. 24–25°, was collected by rapid filtration; yield 148 g. (75%).

Anal. Calcd. for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.84; H, 10.93.

12-Oxo-9-octadecynoic Acid.—To a solution of 200 g. of ricinostearolic acid[31] in 1.6 l. of glacial acetic acid was added a mixture containing 160 g. of sodium dichromate dihydrate, 160 ml. of water, 50 ml. of concd. sulfuric acid and 1.3 l. of glacial acetic acid. After a two-minute reaction time the oxidation was terminated by addition of 4 l. of ice-water. The precipitated product was filtered, washed with water and recrystallized twice from 1.8-l. portions of petroleum ether; yield 190 g. (95%), m.p. 63–64°.

12-Oxo-*trans*-10-octadecenoic Acid.—A solution containing 25 g. of 12-oxo-*cis*-9-(or 12-oxo-*trans*-9)-octadecenoic acid, 500 ml. of glacial acetic acid and 1 ml. of concd. sulfuric acid was refluxed for 5 minutes. The brown reaction mixture was poured into 1 l. of ice-water and the precipitate was filtered off, air-dried and taken up in 600 ml. of hot petroleum ether. The solution was allowed to stand at room temperature for 1 hour and a small quantity of insoluble material was removed by filtration. The filtrate was cooled to −30° and the precipitate was collected. After several recrystallizations from 70% ethanol, it melted at 50–50.5°; yield 10 g. (40%).

Methyl 12-Oxo-*trans*-10-octadecenoate.—A solution containing 25 g. of methyl 12-oxo-*cis*-9-octadecenoate, 500 ml. of glacial acetic acid and 1 ml. of concd. sulfuric acid was refluxed for 5 minutes. The reaction mixture was poured into 1 l. of ice-water and the oil was extracted with 200 ml. of petroleum ether. The extract was washed with successive portions of 10% sodium carbonate and water. The washed solution was dried and concentrated to a volume of 150 ml. The concentrate was cooled to −40° and the crystalline product was collected by rapid filtration. After several low temperature recrystallizations from petroleum ether the material melted at 12–13°, yield 8 g. (32%).

Anal. Calcd. for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.76; H, 11.03.

9,12-Dihydroxy-10-octadecynoic Acid (V).—A solution of 14 g. of nonyne-3-ol (III)[32] in 250 ml. of dry ether was cooled to 10–15°. Stirring was started and 125 ml. of a 1.66 *M* ethylmagnesium bromide solution was added dropwise. The solution was refluxed for 3 hours and then was cooled to 0°. A solution of 22 g. of ethyl η-formylcaprylate (IV)[33] in 50 ml. of anhydr. ether was added dropwise to the stirred reaction mixture. Stirring was continued for two hours at room temperature and the white suspension was cooled to −30°. A solution containing 250 ml. of 30% ammonium acetate was added dropwise and the mixture was allowed to separate into two layers by standing overnight. The ether layer was washed with water and dried over sodium sulfate. The ether was removed and the residual oil (27 g.) was saponified by refluxing for 5 minutes with a solution containing 10 g. of potassium hydroxide, 7.5 ml. of water and 50 ml. of ethanol. The solution was neutralized with 4 *N* hydrochloric acid and was diluted with 200 ml. of water. The oily substance was extracted with 200 ml. of ether, the ether solution was washed with water, dried over sodium sulfate and the solvent removed under reduced pressure. The residual oil crystallized after standing for several days. After freeing the crystals from adhering oily material by trituration with petroleum ether, 13 g. of a crude mixture of isomers, m.p. 55–65°, was obtained. This mixture was purified by chromatography over Darco-Celite, petroleum ether, ether and ethyl acetate being employed as eluents. The yield of purified substance, m.p. 62–65°, was 8 g. (28%). This material was used as such for further experiments. One of the isomers could be obtained pure by repeated low temperature crystallizations from 1:4 mixtures of ether and petroleum ether; m.p. 64–65°.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.02; H, 10.48.

9,12-Dihydroxy-10-octadecenoic Acid (VI).—A solution containing 3 g. of 9,12-dihydroxy-10-octadecynoic acid (V), 50 ml. of ethanol and Lindlar catalyst,[21] or a pyridine-poisoned palladium-on-charcoal catalyst,[34] was hydrogenated at an initial pressure of 1 atm. After the uptake of a molar equivalent of hydrogen the reaction was stopped. Removal of catalyst and solvent left an oily residue which was dissolved in 25 ml. of a 1:4 mixture of ether and petroleum ether. The solution was cooled to −10° and 2.1 g. of a solid, m.p. 65–72°, was obtained. After several low temperature recrystallizations from ether, the material melted at 75–79°. The isolation of a pure isomer was not possible.

9,12-Dihydroxyoctadecanoic Acid (VIIa and b).—A suspension containing 3 g. of crude 9,12-dihydroxy-10-octadecynoic acid (V), 0.1 g. of platinum oxide and 200 ml. of 95% ethanol was subjected to hydrogenation at an initial pressure of 3 atm. The catalyst and reaction solvent were removed and the solid residue was dissolved in 400 ml. of hot ether. The solution was cooled to −20° and 1.5 g. of crude VIIa, m.p. 100–112°, was obtained by filtration. The filtrate was condensed to a volume of 100 ml. and 200 ml. of petroleum ether was added. The precipitate VIIb melted at 70–73°, yield 1.5 g. Crude VIIa was purified by successive recrystallizations from ethanol and ether; m.p. 119–121°.

Anal. Calcd. for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47; equiv. wt., 316.5. Found: C, 68.49; H, 11.54; equiv. wt., 315.7.

Crude VIIb was purified by several recrystallizations from 1:4 mixtures of ether and petroleum ether; m.p. 80–82°.

Anal. Calcd. for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47. Found: C, 68.59; H, 11.28.

9,12-Dioöxoctadecanoic Acid (II). (a) By Oxidation of 9,12-Dihydroxyoctadecanoic Acid (VIIa or b).—A solution containing 1.5 g. of VIIa, 50 ml. of glacial acetic acid, 10 ml. of water and 1 g. of chromium trioxide was allowed to stand overnight at room temperature. The precipitate obtained on addition of 400 ml. of water was filtered off and washed well with water. Recrystallization from ethanol gave 1.2 g. (80%) of 9,12-dioxoöctadecanoic acid (II), m.p. 95–96°. When the lower melting isomer VIIb was treated in an identical manner 1.3 g. (87%) of the diketo acid II was isolated. A dioxime melted at 112–113°.[19b] A

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[32] F. Moulin, *Helv. Chim. Acta*, **34**, 2416 (1951).

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disemicarbazone (recrystallized from 50% methanol) melted at 135–136°.[35]

Anal. Calcd. for $C_{20}H_{38}N_3O_4$: C, 56.31; H, 8.98. Found: C, 56.38; H, 9.04.

(b) **By Catalytic Reduction of 9,12-Dioxo-*trans*-10-octadecenoic Acid** (I).—A suspension containing 12 g. of 9,12-dioxo-*trans*-10-octadecenoic acid, 0.5 g. of 2.5% palladium-on-alumina catalyst and 200 ml. of warm abs. ethanol was hydrogenated at an initial pressure of 3 atm. Hydrogen uptake was complete after several minutes. The catalyst was removed by filtration and the filtrate was cooled to −10°. The precipitate, consisting of 7.4 g. (61%) of 9,12-dioxoöctadecanoic acid, m.p. 96–96.5°, was collected by filtration.

(c) **By Chemical Reduction of 9,12-Dioxo-*trans*-10-octadecenoic Acid** (I).—To a refluxing solution consisting of 90 ml. of glacial acetic acid and 72 ml. of concd. hydrochloric acid there was added 49 g. of stannous chloride. After several minutes of further refluxing, 15 g. of 9,12-dioxo-*trans*-10-octadecenoic acid was added to the clear solution. Boiling was continued for 5 minutes and the red reaction mixture was poured into 350 ml. of water. The yellow precipitate was collected and recrystallized from 80% ethanol; yield 13 g. (86%), m.p. 95–96°.

9,12-Dioxo-*trans*-10-octadecenoic Acid (I). (a) **From 12-Oxo-*cis*-(or *trans*)-9-octadecenoic Acid.**—An oxidizing solution of 40 g. of sodium dichromate dihydrate, 200 ml. of water, 100 ml. of glacial acetic acid and 20 ml. of concd. sulfuric acid was added to a stirred solution of 25 g. of 12-oxo-*cis*-(or *trans*)-9-octadecenoic acid in 100 ml. of glacial acetic acid. The reaction mixture was stirred for one hour at 40–45°, one liter of water was added and the precipitate was filtered off. It was washed free of chromous salts and air-dried. After recrystallization from 250 ml. of 90% ethanol the material melted at 112–113°; yield 15 g. (57%).

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.65; H, 9.74; equiv. wt., 310.4. Found: C, 69.41; H, 10.07; equiv. wt., 310.9.

(b) **From 9,12-Dihydroxy-10-octadecenoic Acid** (VI).—A solution containing 0.5 g. of compound VI, 0.3 g. of chromium trioxide, 17 ml. of glacial acetic acid and 33 ml. of water was allowed to stand at room temperature for two hours. The mixture was diluted with 100 ml. of water and the oil was extracted with two 100-ml. portions of ether. The ether extract was washed with water and dried. The solvent was removed and the residual oil was allowed to crystallize over a period of two weeks. The crystals were triturated with petroleum ether and after filtration they were recrystallized from ether; yield 0.015 g. (3%), m.p. 112–113°.

(c) **From 9,12-Dioxoöctadecanoic Acid** (II).—A suspension containing 3.5 g. of 9,12-dioxoöctadecanoic acid, 2.5 g. of selenium dioxide, 12.5 ml. of water, 50 ml. of glacial acetic acid and 75 ml. of dioxane was heated at 80–90° for 6 hours. The reaction mixture was diluted with 600 ml. of water. The precipitate (2.8 g.) was collected and dried; m.p. 96–98°. It was chromatographed through a Darco-Celite column employing petroleum ether, ether and ethyl acetate as eluents. The fractions were examined for their ability to decolorize neutral permanganate. The petroleum ether and ether eluates contained mostly starting material. The ether–ethyl acetate and ethyl acetate eluates decolorized permanganate and from these fractions 0.3 g. (9%) of 9,12-dioxo-*trans*-10-octadecenoic acid (I) was isolated. After recrystallization from ether the product melted at 112–113°.

Methyl 9,12-Dioxo-*trans*-10-octadecenoate.—A solution containing 20 g. of methyl 12-oxo-*cis*-9-octadecenoate, 32 g. of sodium dichromate dihydrate, 160 ml. of water, 260 ml. of glacial acetic acid and 16 ml. of concd. sulfuric acid was stirred and heated at 70–80° for 2.5 minutes. One liter of water was added and the precipitate was removed by filtration. It was washed with water, air-dried and dissolved in 400 ml. of petroleum ether. A small quantity of insoluble material was filtered off and the filtrate was washed with successive portions of 10% potassium carbonate and water. The petroleum ether solution was dried and condensed to half its original volume under reduced pressure. The solution was cooled to −30° and the solid recovered by filtration was recrystallized from petroleum ether; yield 6.2 g. (30%), m.p. 58–59°.

Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.34; H, 9.94. Found: C, 70.20; H, 9.95.

Experiments Performed in the Determination of the Structure of 9,12-Dioxo-*trans*-10-octadecenoic Acid (I). (a) **Attempted Periodate Oxidation.**—A solution containing 1.55 g. of periodic acid dihydrate, 100 ml. of *N* sulfuric acid and 100 ml. of water was added to a solution of 2 g. of compound II in 400 ml. of ethanol. The reaction mixture was heated briefly at 45° to effect complete solution and then was allowed to stand at room temperature for 48 hours. After the addition of 100 ml. of *N* potassium hydroxide, the solution was steam distilled. The residue from the steam distillation was filtered and the solid material was triturated with petroleum ether. The insoluble material (0.6 g.) proved to be unreacted starting material. By cooling the petroleum ether solution to −20°, 0.4 g. of a neutral substance, m.p. 54–55°, was obtained. The material proved to be ethyl 9,12-dioxoöctadecanoate.

Anal. Calcd. for $C_{20}H_{35}O_4$: C, 70.54; H, 10.66. Found: C, 70.32; H, 10.34.

(b) **Attempted Quinoxaline Formation.**—A solution containing 3.1 g. of compound I, 1.2 g. of *o*-phenylenediamine and 100 ml. of ethanol was refluxed for 3.5 hours. The reaction mixture was cooled to −10° and a precipitate, m.p. 98–99°, was obtained. It was acidic in nature and contained no nitrogen. Its constitution was not determined.

(c) **Isomerization Attempts.**—9,12-Dioxo-*trans*-10-octadecenoic acid (I) was dissolved in an excess of 3 *N* ethanolic potassium hydroxide (or sodium ethoxide) and the solution was allowed to stand for two minutes. After neutralization of the reaction mixture with 3 *N* hydrochloric acid only an oily substance appeared. The extreme lability of compound I toward basic reagents thus was demonstrated.

Compound I was heated for three hours with an excess of selenium dioxide at 100°, or with selenium powder at 140° for 15 minutes. The organic material was extracted with ether. From the ether extract starting material could be recovered almost quantitatively.

One gram of I was dissolved in 50 ml. of ethanol and a few crystals of iodine were added. The solution was exposed to sunlight for 24 hours. After removal of the solvent only starting material was obtained.

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(35) Goldsobel (see ref. 19b) reports a melting point of 163° for the disemicarbazone. However, when we prepared this disemicarbazone from the 9,12-dioxoöctadecanoic acid obtained by Goldsobel's procedure, the melting point coincided with that of the disemicarbazone of our 9,12-dioxoöctadecanoic acid.