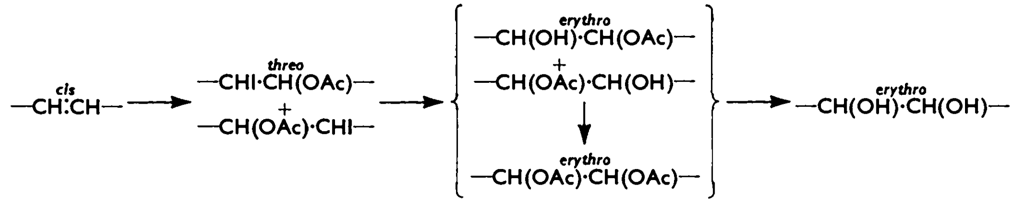
88. *Fatty Acids. Part V.* Applications of the Woodward* cis-*Hydroxylation Procedure to Long-chain Olefinic Compounds.*

By F. D. GUNSTONE and L. J. MORRIS.

Hydroxylation involving use of iodine and silver acetate in wet acetic acid is a satisfactory means of oxidising long-chain ethylenic compounds and has some advantages over other methods of *cis*-hydroxylation.

THE oxidation of olefins to the corresponding glycol is an important reaction for which several reagents are available.[1] Unsymmetrically substituted olefins when so oxidised are converted into the *threo*- and *erythro*-glycols and if stereospecific reagents are used a single isomer may be isolated. *trans*-Hydroxylation is usually effected by organic peracids,[2] by reaction with Prévost's reagent,[3] or by reaction with halogens or hypohalous acids followed by hydrolysis of the halogenated products. *cis*-Hydroxylation results from oxidation with potassium permanganate, osmium tetroxide,[4] hydrogen peroxide in *tert.*-butyl alcohol with a suitable catalyst,[5, 6] sodium or potassium chlorate with traces of osmium tetroxide,[7] or potassium manganate.[8]

The oxidation of long-chain mono-olefinic acids to the corresponding dihydroxy-acids is an important method of identifying these compounds, and *cis*- and *trans*-hydroxylation are best effected by cold dilute alkaline potassium permanganate,[9] and by performic acid,[10] respectively; both are simple procedures and give the desired dihydroxy-acid in almost quantitative yield. The reaction with permanganate, however, has some disadvantages. Following Lapworth and Mottram's procedure very dilute solutions must be used (*ca.* 1 l. per g. of acid) so that the oxidation of large quantities becomes very tedious (attempts to reduce the volume have been reported by Traynard [11]). In addition, it is less satisfactory when applied to substances which are insoluble in aqueous alkali, though acetone may then be used as solvent. Of the other methods of effecting *cis*-hydroxylation only osmium tetroxide has been widely used and a method which overcomes these difficulties and avoids the use of the expensive and toxic osmium tetroxide is therefore desirable. We have found that reaction with iodine and silver acetate in wet acetic acid followed by alkaline hydrolysis of the mixed mono- and di-acetates is a highly satisfactory procedure for the *cis*-hydroxylation of long-chain olefinic acids. The method originates from Professor



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* Part IV, *J.*, 1956, **1611**.

[1] For a review see Waters, " Organic Chemistry," Ed. Gilman, Chapman and Hall Ltd., London, 1953, Vol. IV., p. 1120.

[2] Swern, *Chem. Rev.*, 1949, **45**, **1**; " Organic Reactions," Ed. Adams, Chapman and Hall Ltd., London, 1953, Vol. VII, p. 378.

[3] Prévost, *Compt. rend.*, 1933, **196**, 1129; **197**, 1661.

[4] Criegee, *Annalen*, 1936, **522**, 75.

[5] Milas, *J. Amer. Chem. Soc.*, 1937, **59**, 2342.

[6] Milas and Sussman, *ibid.*, 1936, **58**, 1302; 1937, **59**, 2345.

[7] Hofmann, *Ber.*, 1912, **45**, 3329; Hofmann, Ehrhart, and Schneider, *ibid.*, 1913, **46**, 1657.

[8] Rigby, *J.*, 1956, 2452.

[9] Lapworth and Mottram, *J.*, 1925, **127**, 1628.

[10] Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786.

[11] Traynard, *Bull. Soc. chim. France*, 1952, 323.

Woodward's laboratory and has been described for a few individual compounds all containing the ethylenic group in an alicyclic system.[12]

The reaction occurs in three stages.[13] In the first iodine and silver acetate interact to form a product which quickly reacts with the olefin giving an iodo-acetate by *trans*-addition. These changes occur when the reagents in acetic acid are shaken at room temperature; the American workers add the iodine portion-wise but we have found this to be unnecessary. The second stage involves replacement of the halogen by a hydroxyl group which may become acetylated; this is effected by silver acetate in acetic acid. Winstein and Buckles [14] have shown that by using anhydrous solvent this reaction occurs with predominant retention of configuration but that the presence of water causes inversion to an increasing extent, almost complete inversion taking place when one equivalent of water is present; these authors have explained these observations in terms of neighbouring-group participation. (We had already used this highly stereospecific solvolysis for the conversion of a *cis*-epoxide into an *erythro*-glycol [15]). This reaction is carried out after addition of the required amount of water and with our olefins refluxing for 1 hr. is as satisfactory as 3 hr. on the water-bath as recommended in the American papers. Finally the mixture of mono- and di-acetates is isolated and hydrolysed.

By our modified procedure we have oxidised a number of olefinic compounds (see Table). With pure starting materials the products are obtained in high yield and readily purified. Though most of these oxidations were effected on 2—3 g. of olefin similar yields were obtained in one experiment on ten times this scale. The method is a little more tedious than Lapworth and Mottram's but it gives equally good yields of pure product, works just as well with neutral compounds, and may be conveniently effected on a larger scale than is usual with the permanganate method.

EXPERIMENTAL

Ethylenic Compounds.—Olive oil and castor oil were good-quality commercial materials; oleic acid, *cyclo*hexene, and acenaphthylene were those available from chemical suppliers, and methyl undecenoate was prepared from purchased undecenoic acid. Methyl hexadecenoate was derived from a concentrate of unsaturated C_{16} esters isolated from crocodile oil and consisting mainly of hexadec-9-enoate; methyl linoleate had also been prepared previously from 9 : 10 : 12 : 13-tetrabromostearic acid.

Pure methyl oleate was prepared from the mixed acids of olive oil: saturated acids were removed by crystallisation at −20° and polyethenoid acids remained in solution at −50°; the monoethenoid concentrate was then esterified and distilled, and appropriate fractions combined. Some of the ester was hydrolysed and the acid, when isomerised [16] by heating it with selenium at 220—225°, afforded elaidic acid (m. p. 43—44°) a part of which was converted into the methyl ester. Reduction (lithium aluminium hydride) of oleic and elaidic acid gave the corresponding alcohols.[17]

Oxidation.—The following method applies to the oxidation of esters. The ethylenic compound (0·01 mole), silver acetate (0·022 mole), and iodine (0·01 mole) in glacial acetic acid (65 ml.) are shaken for 30 min. at room temperature. Wet acetic acid (10 ml. containing 0·2 ml., 0·011 mole, of water) is then added and the mixture is refluxed for 1 hr. After cooling the precipitated silver salts are filtered off and washed with a little acetic acid, and the solvent then removed from the combined filtrate and washings by distillation at 100° under reduced pressure. The residue is diluted with water and extracted with ether, and the extract washed with concentrated ammonia and then with water. The solvent is next removed and the product hydrolysed by boiling it with excess of 3N-aqueous alcoholic potassium hydroxide for 1 hr.; the mixture is then diluted and acidified (hydrochloric acid). The crude oxidation product is dried in a vacuum desiccator (containing concentrated sulphuric acid and potassium hydroxide) and crystallised. Methanol was used in these experiments except where otherwise stated.

[12] (*a*) Woodward, U.S. 2,687,435/1954; (*b*) Ginsberg, *J. Amer. Chem. Soc.*, 1953, **75**, 5746; (*c*) Barkley, Farrar, Knowles, Raffelson, and Thompson, *ibid.*, **76**, 5014; (*d*) Jefferies and Milligan, *J.*, 1956, 2363.

[13] *Ann. Reports*, 1954, **51**, 178.

[14] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780, 2787.

[15] Bharucha and Gunstone, *J.*, 1956, 1611.

[16] Swern and Scanlan, *Biochem. Prepns.*, 1953, **3**, 118.

[17] Ligthelm, von Rudloff, and Sutton, *J.*, 1950, 3187.

In the oxidation of olefinic acids the (partially) acetylated glycol cannot be washed with ammonia and therefore after acetic acid has been removed and water and ether added, the mixture is treated with dilute hydrochloric acid, and the precipitated silver salts are removed and washed with ether. The ether solutions are combined and washed with water, the solvent removed, and the residue hydrolysed.

With neutral products there is no need to acidify the final hydrolysate: the product usually separates when the diluted solution is cooled.

The results of several oxidations are summarised in the Table and some additional information is added below.

The cis-*hydroxylation of some ethylenic compounds.*

Olefin	Crude product, yield (%)	Crude product, m. p.	Pure product, yield (%)	Pure product, m. p.	M. p. (lit.)
Pure olefins:					
Methyl oleate	99	126—128°	89	130—132°	132 [a]
Methyl elaidate	97	92—93	91	93·5—94·5	95 [a]
Elaidic acid	89	92—94	85	94—94·5	95 [a]
Oleyl alcohol	100	123—125	81	126	126 [b]
Elaidyl alcohol	94	82—84	79	82·5—83·5	82 [b]
*cyclo*Hexene	66	—	41	94—97	98 [c]
Acenaphthylene	89	180—204	28	203—208	213 [d]
Crude olefins:					
Olive oil	87	—	83 *	131—132	132 [a]
Olive oil †	94	112—125	97 *	125—132	132 [a]
Castor oil	95	—	30 * 7 *	108—111 135—137	112 138 [e]
Methyl undecenoate	49	74—77	42	84—87·5	85—86 [f]
Methyl hexadecenoate	93	—	62	126—128	129 [g]
Methyl linoleate	95	—	14 15	173 163—165	174 164 [h]
Oleic acid	95	—	56	123—127	132 [a]

* These percentages are based on the assumption that olive oil contains 75% of oleic acid and castor oil 90% of ricinoleic acid.

† All oxidations were effected on about 0·01 mole of olefinic compound except in this case where 0·1 mole was used.

[a] Hilditch, " The Chemical Constitution of Natural Fats," Chapman and Hall Ltd., London, 1956, 3rd Edn., p. 498. [b] Hilditch, *op. cit.*, p. 564. [c] Ref. 20. [d] Ref. 21. [e] Kass and Radlove, *J. Amer. Chem. Soc.*, 1942, **64**, 2253. [f] Ref. 18. [g] Hilditch, *op. cit.*, p. 516. [h] Hilditch, *op. cit.*, p. 529.

Comments on Some Oxidations.—(a) *Castor oil.* The crude oxidation product after crystallisation from ethyl acetate was separated into fractions soluble and insoluble in hot chloroform. After crystallisation from ethanol these gave the low-melting and the high-melting isomer, respectively. Similar yields (28% and 8%) resulted from oxidation of acetylated castor oil.

(b) *Methyl undecenoate.* The above procedure afforded only 8% of dihydroxy-acid but the yield was raised to 42% by shaking the initial reactants overnight and then refluxing them with wet acetic acid for 2·5 hr. (The double bond in this compound is known to be less reactive; performic acid for example requires a longer time of reaction than usual and gives a 44% yield [10] whilst oxidation with permanganate affords the diol in 31% yield.[18])

(c) *Methyl linoleate.* Because this ester contains two double bonds the quantity of iodine, silver acetate, and water was doubled. The crude oxidation product was first crystallised from 30% acetic acid and then boiled with acetone (200 ml. per g.). The insoluble fraction, after crystallisation from 50% ethanol, gave the higher-melting isomer; the soluble acids crystallised on concentration of the acetone solution and were recrystallised from 50% ethanol to give the lower-melting isomer.[19]

(d) cyclo*Hexene.* The standard procedure gave only 20% of the *cis*-diol but this yield was doubled when the reactants were shaken for 4·5 hr. and the product worked up : after hydrolysis the solution was neutralised (concentrated hydrochloric acid) and evaporated to dryness, and the residue extracted with chloroform; this extract gave the diol on crystallisation from ethyl acetate (Clarke and Owen [20] obtained yields of 46% with sodium chlorate and osmium tetroxide and 33% with potassium permanganate and magnesium sulphate).

[18] Hazura and Grüssner, *Monatsh.*, 1888, **9**, 947.

[19] Riemenschneider, Wheeler, and Sando, *J. Biol. Chem.*, 1939, **127**, 391.

[20] Clarke and Owen, *J.*, 1949, 318.

(e) *Acenaphthylene.* The first stage of the reaction was prolonged to 2 hr. The crude product was decolorised with charcoal in acetic acid solution and then recrystallised from the same solvent (Found : C, 77·0; H, 5·5. Calc. for $C_{12}H_{10}O_2$: C, 77·4; H, 5·4%). Previously this diol has been prepared from acenaphthylene by bromination and subsequent hydrolysis,[21] by reduction of the diketo-compound,[21] or by osmium oxidation of the olefin;[4] the first two methods give mixtures of the *cis*- and the *trans*-diol.

We were unable to oxidise tetramethylethylene, phenanthrene, methyl ximenynate, methyl ricinstearolate, and stearolic acid; there was some evidence of reaction but only very small yields of unsatisfactory products were isolated.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY OF ST. ANDREWS. [*Received, September,* 12*th* 1956.]

[21] Jack and Rule, *J.*, 1938, 188.