49. *The Stereochemical Relationships of the* 9 : 10-*Oxidostearic Acids and the* 9 : 10-*Dihydroxystearic Acids.*

By D. Atherton and T. P. Hilditch.

When either of the two isomeric forms of 9 : 10-oxidostearic acid is treated with an ethereal solution of hydrogen chloride, the oxido-ring is opened and chlorohydroxystearic acids are produced. The latter in presence of alkali undergo ring closure and the oxidostearic acid thus re-formed is identical with that from which the experiment commenced. It follows that the inversion, which occurs when either of the 9 : 10-dihydroxystearic acids is converted into chlorohydroxy-acids and the latter, through the oxido-compounds, into the isomeric form of the 9 : 10-dihydroxystearic acid, must take place during replacement of a hydroxyl group by chlorine.

This leads to the conclusion that no inversion takes place during the conversion of oleic and elaidic acid into the 9 : 10-dihydroxystearic acids melting at 95° and 132° respectively by means of perbenzoic, peracetic, or Caro's acid.

It has recently been demonstrated (King, J., 1942, 387) that either form of the 9 : 10-dihydroxystearic acids, m. p. 132° or 95°, when heated with hydrogen chloride at 160°, yields chlorohydrins, from which oxidostearic acids may be obtained which, on opening of the oxide ring, yield the opposite form of the dihydroxy-acids (m. p. 95° or 132°). Following Böeseken and Belinfante (*Rec. Trav. chim.*, 1926, **45**, 917) and Esafov (*J. Gen. Chem. Russia*, 1937, **7**, 1403), who have suggested that inversion always occurs when α-oxides are hydrated, King has formulated the stereochemical course of these transformations on the assumption that inversion occurs only during the opening of the oxide ring. This conclusion harmonises well with the low optical activity of the naturally-occurring 9 : 10-dihydroxystearic acid, m. p. 141°, which, since it yields the acid of m. p. 95° when submitted to the above sequence of reactions, must be an optically active form of the racemic acid of m. p. 132°; and, according to King's scheme, the latter acid would be a racemic mixture of enantiomorphs in which the rotations due to each asymmetric centre would have opposing influences.

We have sought for further experimental evidence bearing on this question and have ascertained the following facts :

(i) The oxidostearic acid obtained from the 9 : 10-dihydroxystearic acid, m. p. 95°, by King's procedure, that obtained from the chlorohydroxystearic acid produced by addition of hypochlorous acid to elaidic acid, and that obtained by perbenzoic acid oxidation of elaidic acid, are all identical.

(ii) The oxidostearic acids correspondingly obtained from the isomeric dihydroxystearic acid of m. p. 132°, and from the chlorohydroxystearic acid produced by addition of hypochlorous acid to oleic acid, are also identical with each other, but differ from those referred to under (i).

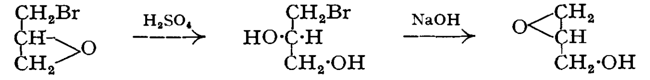
In our experience the melting points of both forms of the 9 : 10-oxidostearic acid are practically the same, namely, 55—56° in cases (i) and 56—57° in cases (ii); but mixture of either of the specimens (i) with either of the specimens (ii) produced a depression in melting point of 8—10°. It was also noticeable that the oxidostearic acid (ii) was much more soluble in organic solvents than the oxidostearic acid (i), this behaviour being parallel with the relative solubilities of the dihydroxystearic acids of m. p. 95° and 132°.

(iii) The oxide ring of both forms of the oxidostearic acids has been opened by treatment with an ethereal solution of hydrogen chloride, leading to the production of chlorohydroxystearic acids which were subsequently reconverted into oxidostearic acids. The oxidostearic acid recovered was in each case the same isomeric form as that originally employed. Thus, an oxidostearic acid (m. p. 55—56°) prepared from the product of addition of hypochlorous acid to elaidic acid yielded a chlorohydroxy-acid [Found : Cl, 9·3; OH (non-carboxylic), 4·6. $C_{18}H_{35}O_3Cl$ requires Cl, 10·6; OH (non-carboxylic), 5·1%]. This chlorohydroxy-acid gave on ring-closure an oxidostearic acid which melted at 54—55° [mixed with the original oxidostearic acid, m. p. 54—56°; mixed with the isomeric oxidostearic acid (ii), m. p. 44—46°].

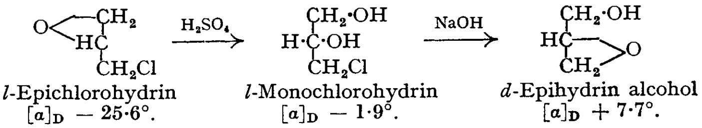
These experiments prove either that there is no inversion during either opening or closing of the oxide ring, or that inversion takes place during both these processes. It is not necessary, for the immediate purpose of our argument, to determine which of these alternatives is operative; nevertheless the following points may be mentioned which seem to suggest the absence of a Walden inversion at either stage :

(*a*) Hydrolysis of the oxido-system by alkali or by sulphuric acid (Steger and van Loon, *Rec. Trav. chim.*, 1927, **46**, 702) leads to formation of the same isomeric form of dihydroxystearic acid. Since the mechanism of ring fission in an acidic medium probably includes intermediate formation of an oxonium salt complex, it seems improbable that in this case, or in the corresponding production of a chlorohydrin from the oxido-compound by hydrogen chloride in ether, any inversion should occur.

(*b*) Moreover, Abderhalden (*Ber.*, 1915, **48**, 1847) studied the conversion of optically active epihalogenohydrins by sulphuric acid into monohalogenohydrins, and of the latter by alcoholic alkali into epihydrin alcohols with the following results :



d-Epibromohydrin $[\alpha]_D + 23·1°$. *d*-Monobromohydrin $[\alpha]_D + 4·8°$. *l*-Epihydrin alcohol $[\alpha]_D - 8·5°$.



Although in these sequences of changes the optical rotation changes in sign owing (as can be seen more clearly from three-dimensional models) to the opening of the oxido-ring on the α and β carbon atoms and subsequent production of a new oxido-ring from the β and α′ carbon atoms of the three-carbon chain, no Walden inversion has taken place, *i.e.*, there has been no spatial rearrangement of the groups attached to the middle asymmetric carbon atom.

Whether the two-fold inversions occur or not, it follows from the experiments described under (iii) above that the chlorohydrins obtained from dihydroxystearic acid have the same configuration as the dihydroxystearic acids produced therefrom through the oxidostearic acids, and therefore that the first stage of the conversion of one form of 9 : 10-dihydroxystearic acid into the other—the formation of " chlorohydrins " by the action of hydrogen chloride at 160°—must be accompanied by a Walden inversion. This, indeed, is in harmony with the views at present accepted in regard to the substitution of one anionic group for another (cf. Watson, *Ann. Reports*, 1938, **35**, 222; Kenyon and Phillips, *Trans. Faraday Soc.*, 1930, **26**, 451; Olson, *J. Chem. Physics*, 1933, **1**, 418; Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164).

This proof that inversion occurs during replacement of one of the hydroxyl groups of dihydroxystearic acid by chlorine leads to the further implications that no change in stereochemical configuration takes place during addition of hypochlorous acid to oleic or elaidic acid or during the oxidation of these acids by perbenzoic, peracetic or Caro's acid. We have made several attempts to detect the formation of oxidostearic acid in the course of the last two oxidations, but without success.* A possible explanation of the production of oxido-

Diagram 1.

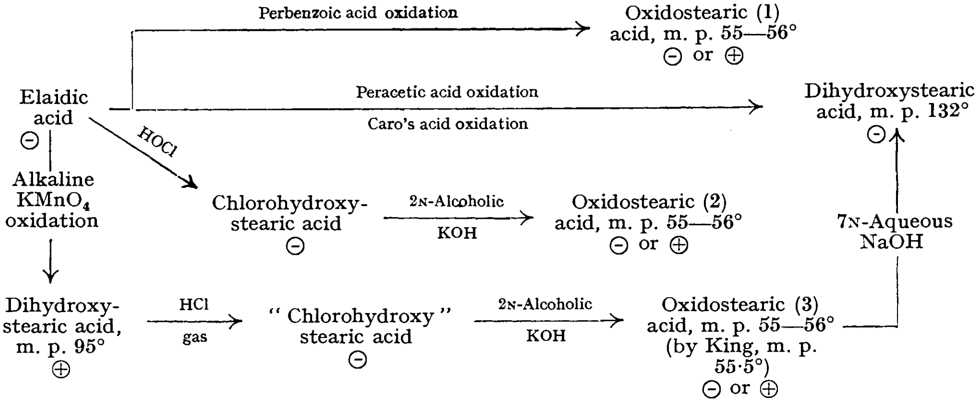
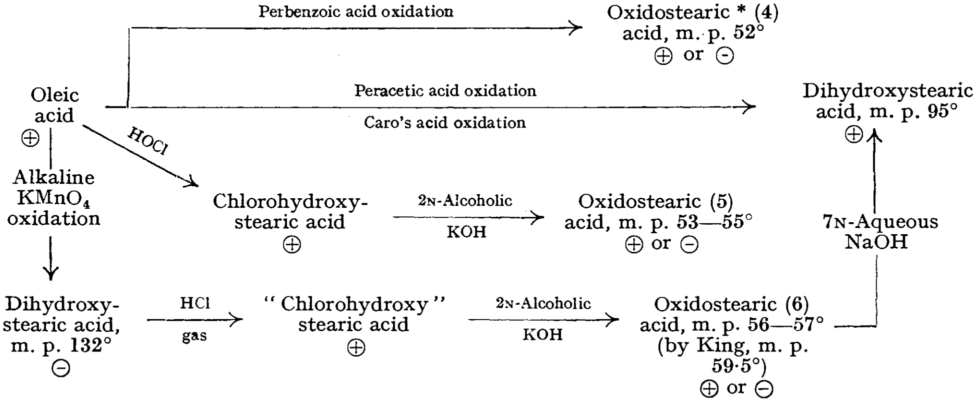


Diagram 2.



Oxidostearic acids (1), (2) and (3) depress the m. p.'s of oxidostearic acids (5) and (6).
Mixtures of (1) and (2) and (3), or (5) and (6), melt without depression.
* Böeseken and Belinfante, *Rec. Trav. chim.*, 1926, **45**, 917.

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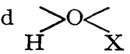
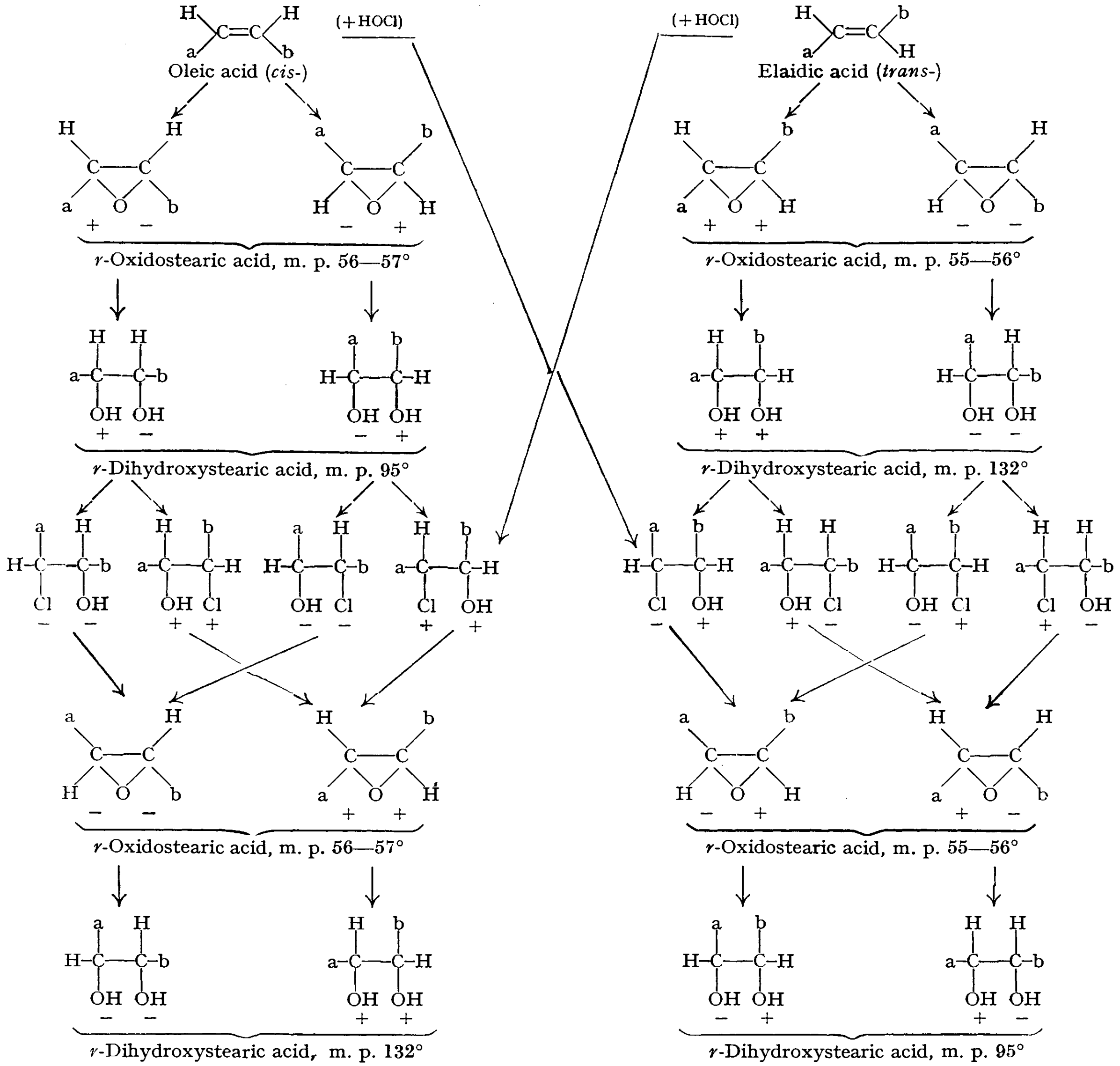
* Since this paper was submitted, King (this vol., p. 37) has shown that, under restrained conditions of oxidation with hydrogen peroxide and acetic acid, elaidic acid furnishes the oxidostearic acid, m. p. 55·5°, in 25—30% yield. He has also observed that both oxidostearic acids, on prolonged standing with cold acetic acid, are converted into monoacetyl derivatives of the corresponding dihydroxystearic acids. In presence of acetic acid, oleic acid epoxide undergoes ring fission, to the monoacetyl derivative of the dihydroxystearic acid, m. p. 95°, much more readily than elaidic acid epoxide, which is partly resolved into the monoacetyl derivative of the dihydroxystearic acid, m. p. 132°.

stearic acids when perbenzoic acid is oxidant, and of dihydroxystearic acids exclusively when peracetic acid or Caro's acid is used, may be that in all cases an oxonium addition-compound  $\underset{H}{>}O\underset{X}{<}$ (–CH——CH–) is formed with the peracid but in the latter two instances (in which, moreover, the action proceeds in an acid solution) the presence of the stronger acid—sulphuric or acetic—causes instantaneous opening of the oxide ring, which, however, resists rupture in the less strongly acidic conditions of oxidation by perbenzoic acid in a neutral solvent.

We believe that, in the light of the present results, the changes operating in these various actions are accurately summarised in diagrams 1 and 2 (p. 205), in which the signs (+) and (−) are arbitrarily given to oleic and elaidic acid in order to correlate the configurational relationships (the signs of course have no reference to optical rotations). To indicate the uncertainty as to whether inversion occurs during closure and fission of the oxide ring, or in neither case, the oxidostearic acids are given both (+) and (−) signs.

It will be observed that, according to this scheme, the production of dihydroxystearic acid by alkaline permanganate oxidation of the ethenoid acid must involve an inversion. It has been suggested (Hilditch, J., 1926, 1828; Hilditch and Lea, J., 1928, 1576) that this is connected in some way with the marked excess of alkali which Lapworth and Mottram (J., 1925, **127**, 1628) showed to be essential for the production of good yields of dihydroxystearic acid by this procedure. Even with excess of alkali as recommended by Lapworth and Mottram, the stable *trans*-isomeride elaidic acid affords definitely lower yields of the dihydroxystearic acid,



$a = CH_3\cdot[CH_2]_7-$ $b = -[CH_2]_7\cdot CO_2H$.

m. p. 132°, than the almost quantitative yields of the acid, m. p. 95°, obtainable from oleic acid by aqueous alkaline permanganate (Saytzew, *J. pr. Chem.*, 1886, **34**, 315; Hilditch, *loc. cit.*). These observations support the view that the alkalinity of the medium determines the configurational course taken during the conversion of the double bond in monoethenoid higher aliphatic acids into a glycol by oxidation.

As pointed out by King (*loc. cit.*), occurrence of inversion during replacement of hydroxyl by chlorine, instead of solely at the stage when oxidostearic acid is converted into dihydroxystearic acid, would involve different configurational formulæ for the products produced in the later stages of his reaction from those which he formulated (*loc. cit.*, p. 388). According to our present results, this scheme takes the form shown on p. 206 (where an inversion during replacement of hydroxyl by chlorine is allowed for, and closure and opening of the oxide ring are assumed to take place without inversion).

According to this scheme the active 9 : 10-dihydroxystearic acid, m. p. 141°, which King has shown to be one of the components of the racemic acid of m. p. 132° would be a diastereoisomeride of the form *d*A*d*B and might therefore be expected to exhibit stronger rotatory power than has been observed. Although this feature is apparently in conflict with the rest of the evidence discussed above, it may be pointed out that there is little knowledge available whereby the probable order of rotatory power of such a compound might be predicted. Further work on the resolution of both racemic dihydroxystearic acids, m. p. 132° and 95°, on which data hitherto recorded are not in agreement (Freundler, *Bull. Soc. chim.*, 1895, **13**, 1053; Inoue and Suzuki, *Proc. Imp. Acad. Tokyo*, 1931, **7**, 261; Toyama and Ishikawa, *Bull. Chem. Soc. Japan*, 1936, **11**, 735), appears to be necessary before this point can be settled.

EXPERIMENTAL.

Interconversion of the 9 : 10-*Dihydroxystearic Acids.*—The results obtained by King (*loc. cit.*) were substantially reproduced, except that, as already mentioned, the m. p.'s of the oxidostearic acids differed somewhat from those recorded by King. Further, the products of the action of hydrogen chloride at 160° on the dihydroxystearic acids were found by analysis to consist not of chlorohydroxystearic acids, but almost wholly of chloro-esters, or, rather, chloro-estolides, one of the hydroxyl groups of the dihydroxystearic acid having been esterified, under the conditions employed, with a carboxyl group (the latter probably from a different molecule of the acid).

9 : 10-Dihydroxystearic acid, m. p. 132° (5 g.), was heated for 4 hours at 160° in an open tube in a current of dry hydrogen chloride. The product, after solution in ether, washing with water and recovery from solvent, was a brown viscous oil (4·8 g.) [Found : Cl, 10·1; OH (carboxylic), 0·6; OH (non-carboxylic), 0·6%. $C_{18}H_{33}OCl$ requires Cl, 11·2%; OH, nil %].

The chloro-estolides (4·1 g.) were refluxed for 2 hours with 2N-alcoholic potassium hydroxide (50 c.c.) and yielded 3·8 g. of solid acids which, on crystallisation, gave 0·7 g. of impure dihydroxystearic acid, m. p. 87°, and 2 g. of oxidostearic acid (No. 6, diagram 2), which after repeated crystallisation from methyl alcohol and acetone melted at 55—57°. This oxidostearic acid yielded the dihydroxystearic acid, m. p. 93—94°, after heating with excess of 7N-aqueous sodium hydroxide in a closed tube at 170°.

9 : 10-Dihydroxystearic acid, m. p. 95° (5·2 g.), was similarly treated with hydrogen chloride at 160° and yielded a dark brown oil (5·1 g.) [Found : Cl, 10·6; OH (carboxylic), 0·5; OH (non-carboxylic), 0·6%]. The oil (4·6 g.) was converted by refluxing with 2N-alcoholic potassium hydroxide into solid acids, which after repeated crystallisation gave oxidostearic acid (No. 3, diagram 1), m. p. 55—56° [depressed to 46—47° on admixture with the preceding oxidostearic acid (No. 6), unchanged when mixed with oxidostearic acid (No. 1) from perbenzoic acid oxidation of elaidic acid]. The oxidostearic acid No. 3 was much less soluble in light petroleum, methyl alcohol and acetone than the acid No. 6.

Chlorohydroxystearic Acids from Oleic and Elaidic Acids.—These were prepared by dissolving the fatty acid (20 g.) in water (200 c.c.) containing sodium hydroxide (3 g.) and mechanically stirring the solution, through which carbon dioxide was passed during the slow addition of sodium hypochlorite solution (70 c.c. containing 9% of NaOCl). The resulting solution was made acid with dilute sulphuric acid, and the product recovered by extraction with ether.

Elaidic acid thus yielded a semi-solid mixture of chlorohydroxystearic acids [Found : I.V. (Wijs), 8·3; Cl, 9·8; OH (non-carboxylic), 3·5. $C_{18}H_{35}O_3Cl$ requires Cl, 10·6; OH (non-carboxylic), 5·1%]. On crystallisation of the semi-solid acids a small amount of a solid chlorohydroxystearic acid was obtained, m. p. 58°. The semi-solid chlorohydroxystearic acids (8 g.) gave, on refluxing with 2N-alcoholic potassium hydroxide (100 c.c.), a solid product (7·2 g) which on crystallisation gave 0·3 g. of impure dihydroxystearic acid, m. p. 132°, and 3·6 g. of oxidostearic acid (No. 2, diagram 1) which after repeated crystallisation melted at 55—56° (unchanged when mixed with oxido-acids No. 1 and No. 3, depressed to 43—46° when mixed with oxido-acid No. 5, diagram 2).

Oleic acid, which reacted more completely than elaidic acid with hypochlorous acid, gave a solid product [Found : I.V. (Wijs), 1·4; Cl, 10·7; OH (non-carboxylic), 4·0%]. The latter (8 g.), refluxed with 2N-alcoholic potassium hydroxide (50 c.c.), gave a viscous oil (7·7 g.) which solidified after standing in an exsiccator for 2 days. It was crystallised only with difficulty and furnished 0·5 g. of impure dihydroxystearic acid, m. p. 95°, and 0·6 g. of oxidostearic acid (No. 5, diagram 2), m. p. 54° (unchanged when mixed with oxido-acid No. 6, depressed to 48—52° when mixed with oxido-acid No. 1).

The yield of oxido-acid was much improved by first converting the chlorohydroxy-acids into chloro-estolides. The chlorohydroxystearic acids (16·0 g.) from oleic acid were heated at 160—170° for some hours in presence of a trace of camphor-β-sulphonic acid and in an atmosphere of carbon dioxide. The product (15·4 g.) was a dark viscous oil [Found : Cl, 9·9; OH (non-carboxylic), 0·7%], 14·7 g. of which, on refluxing with 2N-alcoholic potassium hydroxide, gave a semi-solid product (12·8 g.), from which 0·4 g. of impure dihydroxystearic acid, m. p. 91·5—93°, and 6·4 g. of crude oxidostearic acid were isolated. The latter, on repeated crystallisation gave 2 g. of oxidostearic acid, m. p. 52—53° (mixed with the preceding oxido-acid No. 5, m. p. 52—54°).

Opening and Re-closing of the Oxide·Ring in the Oxidostearic Acids.—The oxidostearic acid No. 2 (from elaidic acid through chlorohydroxystearic acid) (3·1 g.) was dissolved in a saturated solution of dry hydrogen chloride in ether (100 c.c.) and kept for 18 hours; it was then refluxed for 1 hour with 10 c.c. of water (Nicolet and Poulter, *J. Amer. Chem. Soc.*, 1930, **52**, 1180). The solid product (3·4 g.) [Found : Cl, 9·3; OH (non-carboxylic), 4·6%] gave on repeated crystallisation from light petroleum a small amount of acid, m. p. 64—65° [mixed with the original chlorohydroxy-acid (m. p. 58°), m. p. 59—62°].

The chlorohydroxystearic acid (2·7 g.) thus produced, refluxed with 2N-alcoholic potassium hydroxide for 4 hours, was converted into crude oxidostearic acid which, on crystallisation, yielded 0·1 g. of impure dihydroxystearic acid,

m. p. 132°, and 0·4 g. of oxidostearic acid. m. p. 54—55° [mixed with the original oxidostearic acid No. 2 used in the experiment, m. p. 54—56°; mixed with oxidostearic acid No. 5 (from the chlorohydroxy-acid from oleic acid), m. p. 44—46°].

Similarly, the oxidostearic acid No. 5 (from oleic acid through chlorohydroxystearic acid) (3·1 g.) was converted by dry hydrogen chloride in ether into semi-solid chlorohydroxy-acids [Found : Cl, 8·0; OH (non-carboxylic), 5·3%], which, when refluxed with 2N-alcoholic alkali gave, after crystallisation of the solid product, 0·2 g. of dihydroxystearic acid, m. p. 95°, and 1·2 g. of crude oxidostearic acid which after repeated crystallisation melted at 52—54° [mixed with the original oxidostearic acid No. 5 used in this experiment, m. p. 52—53°; mixed with oxidostearic acid No. 2 (from the chlorohydroxy-acid from elaidic acid), m. p. 40—46°].

Oxidation of Elaidic Acid with Perbenzoic Acid.—Elaidic acid (6·8 g.) was oxidised in chloroform solution (15 c.c.) with perbenzoic acid as described by Böeseken (*Rec. Trav. chim.*, 1926, **45**, 917). From the product (8·2 g.) there were obtained by crystallisation 0·3 g. of dihydroxystearic acid, m. p. 130°, and 1·6 g. of oxidostearic acid (No. 1, diagram 1), m. p. 55°. The methyl-alcoholic mother-liquors from the oxidostearic acid, on hydrolysis in the cold with N/2-alcoholic potassium hydroxide, gave a large yield of dihydroxystearic acid, m. p. 132°.

Oxidation of Elaidic Acid with Peracetic Acid.—Elaidic acid, when oxidised with perhydrol in glacial acetic acid (Hilditch, *loc. cit.*; Scanlan and Swern, *J. Amer. Chem. Soc.*, 1940, **62**, 2304), gave the dihydroxystearic acid, m. p. 132°, in almost theoretical yield and no evidence of the presence of oxidostearic acid could be detected.

A partial oxidation was then carried out in the following manner in the hope of isolating the oxido-acid; elaidic acid (5 g.) was refluxed for 3 hours in acetone solution (50 c.c.) with an excess of peracetic acid (4 c.c. of 30% hydrogen peroxide with 4·25 c.c. of glacial acetic acid). The product (5·5 g.) gave on crystallisation 0·54 g. of dihydroxystearic acid, m. p. 126—128°, and 0·9 g. of unchanged elaidic acid. The soluble portion was refluxed with N/2-alcoholic potassium hydroxide (50 c.c.) in order to hydrolyse any acetylated products; the recovered acids gave a further 0·4 g. of dihydroxystearic acid, m. p. 128°, and 2 g. of an oily residue (I.V. 47·5). No oxidostearic acid was detected.

Partial Oxidation of Elaidic Acid with Caro's Acid.—Elaidic acid (5 g.) was dissolved in acetone (50 c.c.) containing 1·95 c.c. of sulphuric acid and 2·1 c.c. of 30% hydrogen peroxide. No reaction set in in the cold and the solution was refluxed for 1 hour and the acids were then recovered. On crystallisation a very small amount (0·1 g.) of the dihydroxystearic acid, m. p. 132°, was obtained together with unchanged elaidic acid, but no oxidostearic acid could be detected.

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