319. *Fatty Acids. Part IV.* The Preparation of Eight 9 : 10 : 12 : 13-Tetrahydroxystearic Acids.†*

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Naturally occurring epoxyoleic acid is proved to be an optically active *cis*-epoxide. It has been converted into *threo*- and *erythro*-12 : 13-dihydroxyoleic acid and, from these, eight optically active 9 : 10 : 12 : 13-tetrahydroxystearic acids have been prepared.

The relations between oleic and elaidic acid, the two racemic 9 : 10-dihydroxystearic acids derived from them, and various intermediates used in their preparation have now been made clear by Swern [1] who, using knowledge gained by several investigators, has been able to rationalise the stereochemistry of the processes involved. This work has opened the way to a similar explanation of the relation between linoleic acid (octadeca-*cis*-9 : *cis*-12-dienoic acid), its configurational isomers, and the tetrahydroxystearic acids derived from them. Although Swern's work removes certain theoretical difficulties concerning the relation between the tetrahydroxystearic acids and the dienoic acids, there remain several practical difficulties including that of obtaining pure linoleic acid, the fact that oxidation of linoleic acid or of its all-*trans*-isomer (linelaidic acid) always gives a mixture of two racemates separable only with difficulty and frequently giving eutectic mixtures, and the fact that direct oxidation of linoleic or linelaidic acids can give only four of the eight possible racemates so that indirect methods are required to obtain the other four racemates.

It is now accepted that linoleic acid present in seed oils is entirely the *cis-cis*-isomer,[2] that linelaidic acid is the *trans-trans*-isomer,[2] that oxidation by dilute alkaline permanganate involves *cis*-addition of hydroxyl groups to the double bond,[1] and that reaction with peracids or hydroxylation proceeding through the halogenohydrins is equivalent to *trans*-addition of hydroxyl groups.[1] The terms *cis* and *trans* used by several investigators to describe the resulting glycols are both confusing and incorrect when applied to open-chain compounds and should be replaced by *threo*- and *erythro*-. By definition *threo*-compounds result by *trans*-addition to a *cis*- or by *cis*-addition to a *trans*-ethylenic compound, whilst the *erythro*-isomers are the products of *cis*-addition to a *cis*- or *trans*-addition to a *trans*-ethylenic compound. 9 : 10 : 12 : 13-Tetrahydroxy stearic acid containing four asymmetric centres should exist in sixteen optically active forms and eight racemates. Eight stereoisomers are shown below (I—VIII), the other eight being represented by their enantiomorphs. These are obviously grouped in four pairs. It follows that *cis*-oxidation (dilute alkaline permanganate) of linoleic acid affords the two di-*erythro*-isomers which should also result from *trans*-oxidation of linelaidic acid; similarly the two di-*threo*-forms are produced from linoleic acid by *trans*-addition (performic acid) or from linelaidic acid by *cis*-addition, but the mixed *threo-erythro*-isomers (III—VI) cannot be produced directly from linoleic or linelaidic acids. In Table 1 the results obtained by several investigators are listed, the configuration of the products being determined on the basis of present views. The general agreement is immediately obvious.

Reference to the mixed *threo-erythro*-isomers is confined to reports by Kass and Burr [10] and by McKay and Bader.[13] The last authors claim to have prepared all eight racemic forms but owing to the known difficulties of working with these compounds we tried to prepare the eight racemates by an alternative procedure. We now report the preparation of eight tetrahydroxystearic acids which we consider to be optically active.

The starting materials for our oxidation experiments were the *threo*- and the *erythro*-form of 12 : 13-dihydroxyoleic acid which we obtained from 12 : 13-epoxyoleic acid (IX)

* Part III, *J.*, 1955, 3782.
† Geneva numbering, $CO_2H = 1$.

[1] Swern, *J. Amer. Chem. Soc.*, 1948, **70**, 1235.
[2] Ahlers, Brett, and McTaggart, *J. Appl. Chem.*, 1953, **3**, 433.

TABLE 1. *Di*-erythro- *and di*-threo-*tetrahydroxystearic acids.*

Date	Investigator	Reactant C_{18} acid	Reagent	M.p.s of di-*erythro*-acids		M.p.s of di-*threo*-acids	
1887	Hazura [3]	Linoleic *	$KMnO_4$	173°			
1909	Rollett [4]	,,	,,	171—173			
1912	Meyer and Beer [5]	,,	,,	173	162—163°		
1922	Nicolet and Cox [6]	,,	,,	170	153		
	,, ,,	,,	Hydrol. of halogeno-hydrin	—	—	144°	135°
1932	Smith and Chibnall [7]	,,	$KMnO_4$	172	159—160	—	—
1935	Green and Hilditch [8]	,,	,,	173	155	—	—
	,, ,,	,,	$AcOH–H_2O_2$	—	—	146	126
1937	Birosel [9]	,,	$KMnO_4$	174	164	—	—
1939	Kass and Burr [10]	Linelaidic	,,	—	—	146	122
1939	Riemenschneider *et al.* [11]	Linoleic	,,	174	163·5	—	—
1939	Hilditch and Jasperson [12]	,,	,,	173	157	—	—
	,, ,,	Linelaidic	,,	—	—	144	135
1948	McKay and Bader [13]	*erythro*-9 : 10-Dihydroxy-*cis*-12-en	,,	174	164	—	—
	,, ,,	*threo*-9 : 10-Diacetoxy-*cis*-12-en	$H·CO_2H–H_2O_2$	—	—	148	126
1954	McKay *et al.* [14]	Linoleic acid	,,	—	—	148	126
1956	Present work †	*erythro*-12 : 13-Dihydroxyoleic	$KMnO_4$	177	156	—	—
		threo-12 : 13-Diacetoxyoleic	$H·CO_2H–H_2O_2$	—	—	148	122

* The linoleic acid is either debrominated tetrabromostearic acid or a concentrate of oleic and linoleic acid prepared from a seed oil containing high proportions of the latter.

† The products obtained here are optically active (see text) whilst all the others are racemates.

TABLE 2. *Specific rotation.*

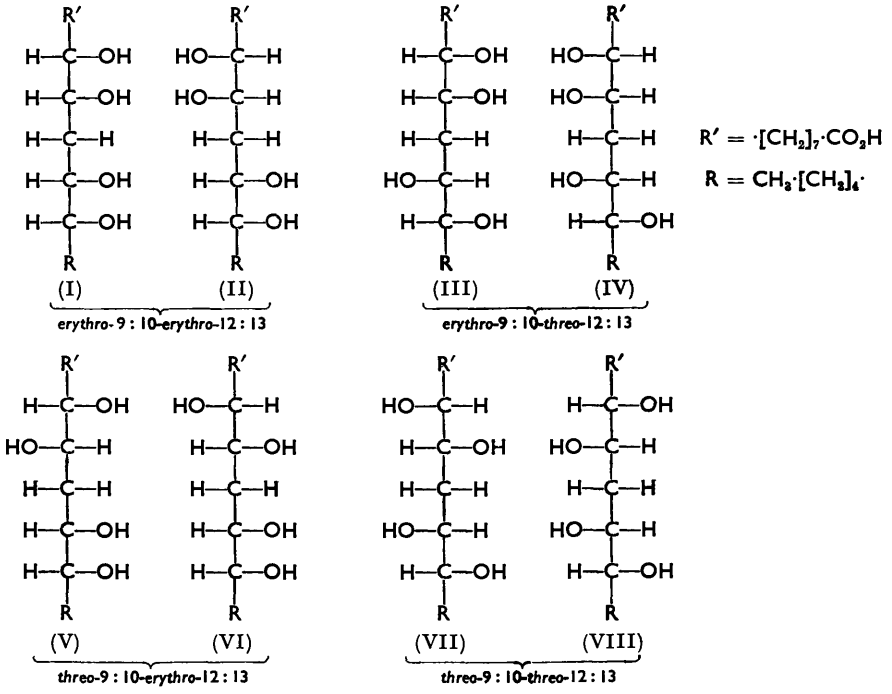
Acid	M. p.	Solvent: AcOH	Solvent: EtOH	M. p. of Me ester	Solvent: AcOH	Solvent: EtOH
threo-12 : 13-Dihydroxyoleic		**−6·8°** (19°, −0·69°)	**−5·7°** (19°, −0·51°)		—	—
erythro- ,, ...		**+1·2** (20, +0·12)	**−3·6** (20, −0·29)		—	—
threo-12 : 13-Dihydroxystearic.....		+1 (15·5, +0·01)	**−1·3** (20, −0·05)		—	—
erythro- ,, ...		+3 (16·5, +0·02)	**−1·7** (20·5, −0·03)		—	—
Tetrahydroxystearic acids :						
threo-9 : 10-*threo*-12 : 13-	148°	—	—		—	—
,, ,, ...	122	**−9** (17, −0·04)	0		0°	0°
erythro-9 : 10-*threo*-12 : 13-	165	−6 (20, −0·01)	—	136°	0	−1 (19, −0·01°)
,, ,, ...	112	—	—	—	—	—
threo-9 : 10-*erythro*-12 : 13-	156	**−44** (18·5, −0·35)	**−7** (20, −0·03)	145	**−46** (18·5°, −0·09°)	—
,, ,, ...	130	**+14** (17, +0·10)	**+5** (20, +0·03)	114	**+17** (20, +0·12)	**+22** (20, +0·08)
erythro-9 : 10-*erythro*-12 : 13-	177	**−10** (18·5, −0·04)	+6 (20, +0·01)	171	**−16** (18·5, −0·08)	**+22** (20, +0·05)
,, ,, ...	156	+14 (17, +0·02)	0	145	0	−2 (19, −0·01)
				Cephalocroton cordofanus seed oil	**+3·4** (16·5, +0·08)	—

Measurements were made with a 2 dm. tube and sodium light.

A dash (—) indicates that no measurement was made, 0 indicates a zero value.

Values in heavy type are calculated from observed rotations of 0·03° or greater (some inactive dihydroxy- and tetrahydroxy-stearic acids gave observed rotations of only 0·00° or 0·01°); figures in parentheses are temperature and the observed rotation.

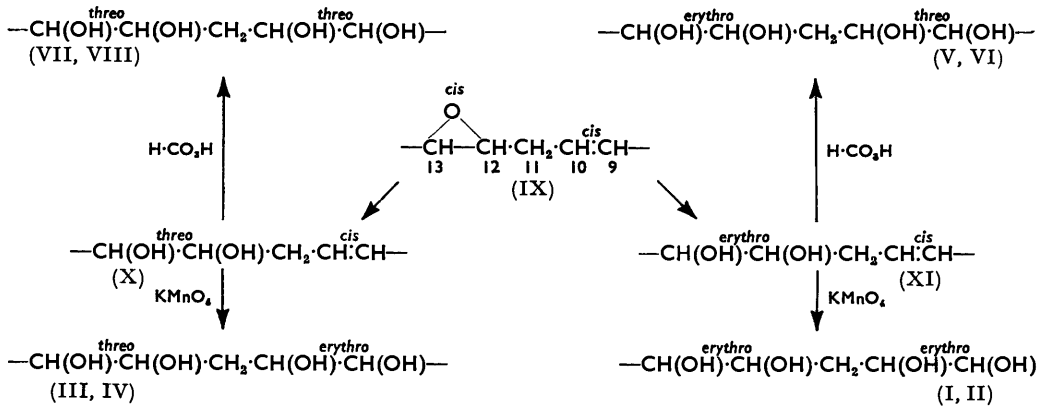
known to occur in quantity among the component acids of *Vernonia anthelmintica* [15] (74%) and *Cephalocroton cordofanus* [16] (66%) seed oils. One isomer (X), m. p. 54°, resulted when the epoxy-acid was treated with acetic acid and then with alkali. This has been proved to be a 12 : 13-dihydroxyoleic acid [15a] and was considered to be the *threo*-form since on hydrogenation it afforded a 12 : 13-dihydroxystearic acid (m. p. 95—96°) of similar m. p. (96·5—97°) to that of the known racemic *threo*-compound [17] and very different from that of the racemic *erythro*-isomer [17] (119—120°). We now find, however, that the unsaturated dihydroxy-acid is optically active (see Table 2) and, presumably, the saturated acid also,



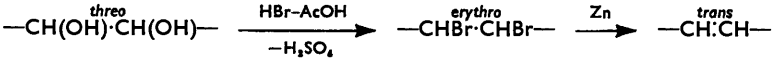
despite the low observed rotation; the identity of melting point between the racemic *threo*- and our dihydroxyoleic acid is thus inadequate proof of the *threo*-configuration of the latter and we now offer independent proof of this by the partial synthesis from it of octadec-*trans*-12-enoic acid.

The dihydroxyoleic acid (X), when converted into the dibromide by Bowman's procedure [18] and subsequently debrominated, gave octadec-*trans*-12-enoic acid. This is quite certain since the melting point of this acid and of the two dihydroxystearic acids obtained from it agree with those expected of the *trans*-acid. Since the bromination occurs with inversion and debromination is a *trans*-elimination the dihydroxy-compound

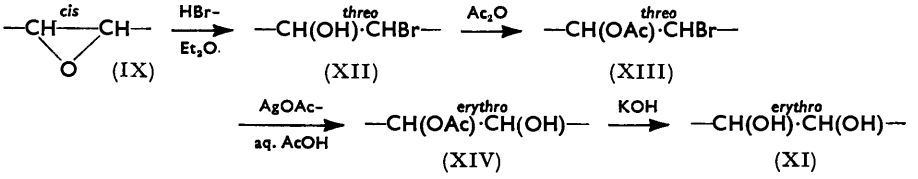
[3] Hazura, *Monatsh.*, 1887, **8**, 147; 1888, **9**, 180.
[4] Rollett, *Z. physiol. chem.*, 1909, **62**, 410.
[5] Meyer and Beer, *Monatsh.*, 1912, **33**, 311.
[6] Nicolet and Cox, *J. Amer. Chem. Soc.*, 1922, **44**, 144.
[7] Smith and Chibnall, *Biochem. J.*, 1932, **26**, 218.
[8] Green and Hilditch, *ibid.*, 1935, **29**, 1552.
[9] Birosel, *J. Amer. Chem. Soc.*, 1937, **59**, 689.
[10] Kass and Burr, *ibid.*, 1939, **61**, 1062.
[11] Riemenschneider, Wheeler, and Sando, *J. Biol. Chem.*, 1939, **127**, 391.
[12] Hilditch and Jasperson, *J. Soc. Chem. Ind.*, 1939, **58**, 233.
[13] McKay and Bader, *J. Org. Chem.*, 1948, **13**, 75.
[14] McKay, Levitin, and Jones, *J. Amer. Chem. Soc.*, 1954, **76**, 2383.
[15] (*a*) Gunstone, *J.*, 1954, 1611; (*b*) Bharucha and Gunstone, *J. Sci. Food Agric.*, 1955, **6**, 373.
[16] Bharucha and Gunstone, unpublished observation.
[17] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.
[18] Ames and Bowman, *J.*, 1951, 1079.



must be the *threo*-form. This reaction also provides proof that the epoxide has the *cis*-configuration since ring opening is accompanied by inversion.[1]



The preparation of *erythro*-12 : 13-dihydroxyoleic acid from the *cis*-epoxide requires a reaction sequence involving no inversion or an even number of inversions. This has been achieved by adaptation of some work of Winstein and Buckles [19] who, in investigations of neighbouring-group participation in replacement reactions, showed that interaction of silver acetate in dry acetic acid with several acetoxy-bromides proceeds with predominant retention of configuration, but that the presence of water in the solvent causes inversion to occur to an increasing extent, almost complete inversion taking place when one equivalent of water is present. We converted the *cis*-epoxide into the *threo*-bromohydrin (XII) which after acetylation gave the *erythro*-monoacetate (XIV) by reaction with



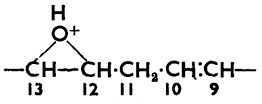
silver acetate in wet acetic acid, and this on hydrolysis afforded the required *erythro*-glycol (XI). The high overall yield of glycol resulting from this four-stage process (78% crude, 69% pure)—which also involves in the final stage removal of the other acids originally present in the oil—and the ease with which the glycol is obtained pure are evidence of the high stereospecificity of these reactions. We have simplified the procedure of Winstein and Buckles by reducing the reaction period with silver acetate from 8 to 2 hours and by effecting the reaction with silver nitrate in wet alcohol (cf. Bevan, Malkin, and Smith [20]).

The *erythro*-dihydroxyoleic acid was a crystalline solid with m. p. (88°) greater than that of the *threo*-isomer (54°), like many similar compounds. Hydrogenation gave *erythro*-12 : 13-dihydroxystearic acid with a higher m. p. (126°) than that (119—120°) previously recorded for the racemic isomer.[17] This difference is due to the fact that our compound is optically active; the observed rotation is very small, but it is larger for its unsaturated precursor. The structures of the saturated and the unsaturated *erythro*-dihydroxy-acid were confirmed by oxidation.

Before considering how far the optical activity of these dihydroxy-acids is to be expected it is necessary to remark that optical activity of long-chain compounds is

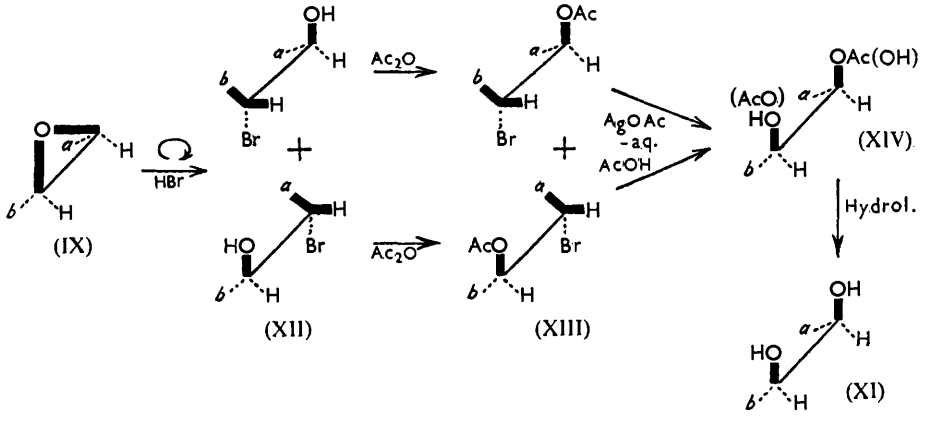
[19] Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780, 2787.
[20] Bevan, Malkin, and Smith, *J.*, 1955, 1043.

frequently so small that it cannot be measured and in the present instance this difficulty was sometimes increased by low solubilities (Baer and Fischer [21] showed that certain triglycerides which should be optically active lack observable rotatory power but are optically active when one or more of the usual aliphatic acyl groups is replaced by an aromatic acyl group). Epoxyoleic acid contains two asymmetric centres and the naturally occurring acid may be expected to be an enantiomorphic form and indeed must be if it is to give rise to optically active derivatives. We have now observed a small dextrorotation with *Cephalocroton cordofanus* seed oil. Consideration of the reaction mechanism involved in the preparation of the *erythro*-dihydroxyoleic acid suggests that an optically active epoxide should give an active glycol (see scheme). On the other hand, the active epoxide will give an active *threo*-glycol only if the conjugate acid (XV) is attacked unequally at $C_{(12)}$ and $C_{(13)}$ by the acetate ion: an attack equally distributed between these two centres would give a racemic glycol. Although the specific rotation of these two acids is fairly small the observed rotations are definite (see Table 2). The values for the corresponding saturated acids are less definite, but as hydrogenation does not affect the active centres racemisation would not be expected to occur; further the m. p. of the saturated *erythro*-isomer differs appreciably from that of the racemic compound.



(XV)

The two dihydroxyoleic acids have been oxidised with dilute alkaline potassium permanganate and with performic acid. In each case the product is a mixture which has been separated by an extensive series of crystallisations. Some general comments are made before discussing the results.



a = $CH_3\cdot[CH_2]_4\cdot$ $\quad$ b = $\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$

(i) In the performic acid oxidation of *threo*-dihydroxyoleic acid the main product was a low-melting, ether-soluble compound which accompanied the desired tetrahydroxyacids. Two individual compounds were isolated from this product (m. p.s 77·5—78°, 94—95°) but these were not identified. Similar products have been isolated by other investigators,[8,14] whilst Paul and Tchelitcheff [22] have reported that furan compounds are formed in the hydrolysis of 1 : 2 : 4 : 5-diepoxypentane. We found little or none of these products when we oxidised diacetoxyoleic acid and this became our standard procedure.

(ii) The separation of the two products obtained in each reaction involves many crystallisations. The higher-melting isomer being the less soluble is generally the more easily isolated; purification of the lower-melting isomer was more difficult and we are less confident of the homogeneity of the latter though in all cases the products were crystallised to constant melting point.

[21] Baer and Fischer, *Chem. Rev.*, 1941, **29**, 287.
[22] Paul and Tchelitcheff, *Compt. rend.*, 1954, **239**, 1504.

(iii) McKay and his colleagues [14] report that the two tetrahydroxy-acids are more easily separated as their methyl esters and in some cases we have checked our results by separation of both acids and esters with subsequent hydrolysis of the separated esters.

(iv) We emphasise the purity of our starting materials. Both 12 : 13-dihydroxyoleic acids are crystalline solids, readily purified and available in quantity from the sources already mentioned. This is in contrast to much of the previous work on this problem which has been undertaken with impure starting materials. Many investigators have used a concentrate of linoleic acid obtained from a suitable source and containing appreciable quantities of oleic acid. Alternatively, linoleic acid has been prepared by debromination of tetrabromostearic acid and is known then to contain small quantities of conjugated isomers and larger quantities of goemetrical isomers of linoleic acid. In either case the desired product is contaminated with closely related compounds. McKay and Bader [13] used *threo-* and *erythro*-9 : 10-dihydroxyoctadec-12-enoic acid, prepared from linoleic acid by partial bromination at the 12 : 13-positions, oxidation of the 9 : 10-double bond by permanganate or per-acid, and subsequent debromination. We consider these acids, isomeric with our dihydroxyoleic acids, should be solid, though McKay and Bader obtained only the *erythro*-isomer as a solid. Although their oily *threo*-compound was hydrogenated to *threo*-9 : 10-dihydroxystearic acid we consider it unlikely that it was pure.

Details of the oxidations are given in the Experimental section and the results are summarised in Tables 2 and 3. The high yield from the performic acid oxidation is in accordance with that usually obtained with monoethenoid compounds [23] and is greater

TABLE 3. 9 : 10 : 12 : 13-*Tetrahydroxystearic acids.*

	threo-9 : 10-*threo*-12 : 13- (VII, VIII)		*erythro*-9 : 10-*threo*-12 : 13- (III, IV)		*threo*-9 : 10-*erythro*-12 : 13- (V, VI)		*erythro*-9 : 10-*erythro*-12 : 13- (I, II)	
Yield of mixed tetrahydroxystearic acids (%)	82		61		92		59	
Yield of separated acids :								
(i) separated as acids (%) *	8	34	17	6	21	41	24	13
(ii) separated as esters (%) *	—	—	20	1·1	25	25	26	17
Acid, m. p.	147·5—148·5°	121—122°	164—165°	**112—113°**	**156·5—157°**	**129·5—131°**	176·5—177°	**155·5—156·5°**
C (%) †	62·1	62·0	62·0	62·2	62·1	61·9	62·2	62·1
H (%) †	10·5	10·3	10·6	10·1	10·6	10·6	10·4	10·5
Methyl ester, m. p.	—	—	135·5—136°	—	144·5—145·2°	113·5—115°	**170·5—171°**	143—146°
C (%) ‡	—	—	62·8	—	62·8	63·0	62·8	63·1
H (%) ‡	—	—	10·3	—	10·6	10·8	10·7	10·3
Racemic compound : [13, 14]								
acid, m. p.	148°	126°	164°	126°	164°	142°	174°	164°
ester, m. p.	118°	95°	—	—	—	—	157°	145·5°

* Based on the total theoretical yield. † $C_{18}H_{36}O_6$ requires C, 62·0, H, 10·4%.
‡ $C_{19}H_{38}O_6$ requires C, 63·0; H, 10·6%.
M. p.s in heavy type differ appreciably from those quoted for the racemic compound.

than in the oxidation of linoleic acid.[14, 24] The yields of separated tetrahydroxy-acids are much higher than those reported by McKay and Bader.[13]

We consider our products to be optically active for three reasons. The starting materials are active and it is believed that oxidation will not affect the asymmetric centres present; thus, the 9 : 10 : 12-trihydroxystearic acids obtained by oxidation of ricinoleic acid are optically active.[25] Several, though not all, of our tetrahydroxystearic acids show significant optical rotation (this refers to the observed rotation rather than to the calculated values of specific rotation). In some cases there is a marked difference in m. p. between the active and the inactive forms (see Table 3). The last may not be very strong

[23] Swern, " Organic Reactions," Vol. VII, p. 398, J. Wiley and Sons Inc., 1953.
[24] Swern and Dickel, *J. Amer. Chem. Soc.*, 1954, **76**, 1957.
[25] Kass and Radlove, *ibid.*, 1942, **64**, 2253.

evidence in all the instances cited since we consider some of the values quoted by McKay and Bader to be unsatisfactory, but one case is particularly strong, *viz.*, the high-melting form of methyl *erythro*-9 : 10-*erythro*-12 : 13-tetrahydroxystearate. We have confirmed McKay's value of 157° for the racemate whilst our active form has m. p. 171°.

In view of the frequency with which the m. p.s of active and inactive compounds of this type resemble one another it is interesting to relate our results to some conclusions by Kass and Burr [10] which have been questioned by McKay and Bader.[13] Kass and Burr obtained, from elaidinised linoleic acid, linelaidic acid and a liquid isomer considered to be the *trans*-9 : *cis*-12-acid from which they prepared two tetrahydroxystearic acids (m. p. 156—158°, 126—127°) by oxidation with dilute alkaline permanganate, presumably the *threo*-9 : 10-*erythro*-12 : 13-acids. McKay and Bader, however, report 164° and 142° for these acids (these were prepared from the *liquid* dihydroxyoctadecenoic acid and the higher-melting acid did not depress the m. p. of the higher-melting form of the *erythro*-9 : 10-*threo*-12 : 13-acid though the two are reported to have different crystalline properties) and consider that Kass and Burr's products are the *erythro*-9 : 10-*threo*-12 : 13-acids (m. p. 164°, 126°) which would be derived from the *cis*-9 : *trans*-12-octadecadienoic acid. On the other hand, our results (156°, 130°) suggest that Kass and Burr's original view may be correct, but since our products are enantiomorphic and theirs racemic this is not certain.

Experimental

threo-12 : 13-*Dihydroxyoleic Acid* (X).—This was isolated from *Vernonia anthelmintica* or *Cephalocroton cordofanus* seed oil by treatment with (i) acetic acid and (ii) alcoholic alkali as previously described.[15a] The dihydroxy-acid (m. p. 52—55°; 57% based on epoxy-acid present) was isolated by crystallisation from ether–light petroleum (b. p. 40—60°; 1 : 1) and then from ethyl acetate.

Partial Synthesis of Octadec-trans-12-*enoic Acid.*—*threo*-12 : 13-Dihydroxystearic acid [15a] (5 g.) was kept at room temperature for 16 hr. with a solution of hydrogen bromide in acetic acid (50 ml.; *d* 1·25) and concentrated sulphuric acid (5 ml.) and then heated to 100° for 8 hr., further hydrogen bromide reagent (5 ml.) being added after 4 hr. The solution was then cooled, diluted with water, and extracted with light petroleum (b. p. 60—80°). The crude *dibromide* (6·73 g., 97%) was purified by crystallisation from light petroleum (b. p. 40—60°) (5·13 g., 74%), m. p. 47·5—48·5° (Found : C, 49·0; H, 7·4; Br, 36·4. $C_{18}H_{32}O_2Br_2$ requires C, 48·9; H, 7·75; Br, 36·1%).

The dibromostearic acid (4·0 g.) was added to a mixture of zinc dust (8·7 g.), methanol (45 ml.), and aqueous hydrogen bromide (50%; 0·8 ml.) which had been refluxed for 5 min. and the whole boiled for 1 hr. in a nitrogen atmosphere. The filtered solution was extracted with ether; the extract, after being washed with alkali, contained only 0·07 g. of material, showing that practically no esterification had occurred. The alkaline solution when acidified and extracted gave the crude *trans*-acid (1·66 g., 65%) which after several crystallisations from methanol and acetone had m. p. 52—53° (lit.,[17] 52—53°) (Found : C, 76·6; H, 12·1. Calc. for $C_{18}H_{34}O_2$: C, 76·5; H, 12·1%).

This was converted into *threo*-12 : 13-dihydroxystearic acid, m. p. 96—97° (lit.,[17] 96·5—97°), by dilute alkaline permanganate and into the *erythro*-isomer, m. p. 117—118° (lit.,[17] 119—120°), by performic acid (Found : C, 68·1; H, 11·5. Calc. for $C_{18}H_{36}O_4$: C, 68·3; H, 11·5%).

erythro-12 : 13-*Dihydroxyoleic Acid* (XI).—*Cephalocroton cordofanus* seed oil (53 g.) was kept overnight in ether (1·5 l.) saturated with hydrogen bromide, and the solution was then washed with water and dried, and the solvent removed. The resulting bromohydrin (62 g.) was acetylated by boiling acetic anhydride (300 ml.) for 3 hr. and then heated with water (200 ml.) for a further 30 min., the product (64 g.) being isolated by ether-extraction. Silver acetate [prepared by slow addition of a solution of potassium acetate (20·8 g. in 75 ml. of water) to one of silver nitrate (32·8 g. in 75 ml. of water) and by subsequent washing of the precipitate with cold water and then with acetic acid] was added to the oily acetoxy-bromide (59 g.) dissolved in acetic acid (325 ml.) containing a little water (3·3 ml.) and refluxed for 8 hr. After filtering, the cold reaction mixture was diluted with water and extracted with ether, and the solvent removed from the extract after it had been washed and dried. The residue (54 g.) was finally hydrolysed with N-alcoholic potassium hydroxide (1·5 l.), and the mixed acids (45 g.)

were recovered by ether-extraction and then crystallised from ether. The erythro-12 : 13-*dihydroxyoleic acid* (21·3 g., 69% overall yield based on epoxy-acid originally present) was practically pure after the first crystallisation (m. p. 87—88°) (Found : C, 68·5; H, 10·8. $C_{18}H_{34}O_4$ requires C, 68·75; H, 10·9%).

The reaction proceeded equally smoothly with *V. anthelmintica* seed oil and we found (i) that the period of heating with silver acetate could be reduced to 2 hr. with an increase in yield (82%) and (ii) that a similar reaction occurred (45% in a single experiment) when the acetoxy-bromide was refluxed for 1 hr. with its own weight of silver nitrate in aqueous alcohol (10 ml. per g. of acetoxy-bromide).

The following derivatives were prepared by standard procedures : *methyl ester*, m. p. 56—57·5° (Found : C, 69·2; H, 11·2. $C_{19}H_{36}O_4$ requires C, 69·5; H, 11·1%); *ethyl ester*, m. p. 52—53° (Found : C, 70·1; H, 11·3. $C_{20}H_{38}O_4$ requires C, 70·1; H, 11·2%); p-*bromophenacyl ester*, m. p. 116—117° (Found : C, 61·1; H, 7·6; Br, 15·8. $C_{26}H_{39}O_5Br$ requires C, 61·1; H, 7·7; Br, 15·6%).

When hydrogenated over 5% palladium–charcoal the *erythro*-dihydroxyoleic acid (100 mg.) gave erythro-12 : 13-*dihydroxystearic acid* (90 mg.), m. p. 125—126° raised only to 125·5—126·5° after three crystallisations from ethanol and from ethyl acetate (Found : C, 68·3; H, 11·3. $C_{18}H_{36}O_4$ requires C, 68·3; H, 11·5%). The following esters were prepared : *methyl*, m. p. 102—103° (Found : C, 69·2; H, 11·6. $C_{19}H_{38}O_4$ requires C, 69·1; H, 11·6%); *ethyl*, m. p. 97—98° (Found : C, 69·7; H, 11·5. $C_{20}H_{40}O_4$ requires C, 69·7; H, 11·7%); p-*bromophenacyl*, m. p. 136·5—137·5° (Found : C, 60·6; H, 8·1; Br, 15·5. $C_{26}H_{41}O_5Br$ requires C, 60·8; H, 8·1; Br, 15·6%).

Oxidised [15a] with potassium permanganate in acetic acid solution at 45—50° *erythro*-12 : 13-dihydroxyoleic acid (1·80 g.) gave hexanoic acid (0·59 g.) (*p*-bromophenacyl ester, m. p. and mixed m. p. 70·5—71·5°; 63—64° when mixed with the ester of heptanoic acid), and azelaic acid (0·59 g.), m. p. and mixed m. p. 105—106°.

erythro-12 : 13-Dihydroxystearic acid (1·01 g.), similarly treated, afforded hexanoic acid (0·16 g.) (*p*-bromophenacyl ester, m. p. and mixed m. p. 71·5—72°; 62—63° when mixed with the ester of heptanoic acid), and dodecanedioic acid (0·23 g.), m. p. and mixed m. p. 129—131° (112—114° when mixed with sebacic acid).

erythro-9 : 10-threo-12 : 13-*Tetrahydroxystearic Acids* (III, IV).—*threo*-12 : 13-Dihydroxyoleic acid (5 g.), oxidised with dilute alkaline permanganate (potassium permanganate, 5·5 g.; sodium hydroxide, 5·0 g.) according to the procedure of Lapworth and Mottram,[26] gave crude tetrahydroxystearic acids (3·36 g.), insoluble in light petroleum (b. p. 40—60°).

A portion of these (1·60 g.) was separated by utilising the lower solubility of the higher-melting *acid* in ethyl acetate. This (437 mg.), after crystallisation from ethanol, melted at 164—165° (*methyl ester*, m. p. 135·5—136°). The lower-melting isomer, after repeated crystallisation from ethyl acetate and finally acetone, melted at 111—113°.

The remainder of the mixed acids (1·7 g.) was methylated (methanolic hydrogen chloride) and the methanol solution on progressive concentration gave several fractions of the higher-melting ester (576 mg.), m. p. 135—135·5°. The mother-liquors gave a small amount of solid, hydrolysed to the *acid* melting at 112—113°.

threo-9 : 10-threo-12 : 13-*Tetrahydroxystearic Acids* (VII, VIII).—*threo*-12 : 13-Dihydroxyoleic acid (6 g.) was boiled for 4 hr. with acetic anhydride (50 ml.) and for a further 2 hr. after the addition of water (50 ml.), and the product (7·23 g.) was isolated by ether-extraction. (The original dihydroxyoleic acid could be recovered in good yield after alkaline hydrolysis.) The diacetoxyoleic acid (5·4 g.), oxidised with formic acid (98%; 13 ml.) and hydrogen peroxide (25%; 2 ml.) by Swern's procedure,[23] gave a mixture of the di-*threo*-acids (4·54 g.) of which the greater part (3·87 g.) was insoluble in ether. This was extracted with acetone (6 × 50 ml.), and the last two extracts deposited, at room temperature, material (402 mg.) of m. p. 144—146° which was raised to 147·5—148·5° by several crystallisations from acetone and from ethyl acetate. The first two extracts gave crystals (2·12 g.) of m. p. 119—123° raised to 121—122° (1·59) by repeated crystallisation from acetone and from ethyl acetate.

When the dihydroxyoleic acid (5 g.) was similarly oxidised without prior acetylation the crude product (4·6 g.) gave a large ether-soluble fraction (2·53 g.; m. p. 63—68°) from which two products were isolated by fractional crystallisation : (*a*) m. p. 77·5—78·5° (Found : C, 65·2; H, 10·1. Calc. for $C_{18}H_{34}O_5$: C, 65·4; H, 10·4%); and (*b*) m. p. 94—95° (Found : C, 65·1; H, 10·0%). Our product (*b*) depressed the m. p. of compound A [14] (m. p. 95·5—96°) to 82—84° and of compound B [14] (m. p. 90—91°) to 81—83°.

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

erythro-9 : 10-erythro-12 : 13-*Tetrahydroxystearic Acids* (I, II).—*erythro*-12 : 13-Dihydroxyoleic acid (3 g.), dissolved in water (300 ml.) containing sodium hydroxide (3 g.), was diluted with 2·4 l. of water and then oxidised at 10° with potassium permanganate solution (1%; 290 ml.). After 5 min. the solution was decolorised with sulphur dioxide and, when acidified, gave crude tetrahydroxystearic acids (2·04 g.) of which the greater part (1·97 g.) was ether-insoluble. This was dissolved in ethanol and that part which crystallised at room temperature (1·39 g.), after several extractions with ethyl acetate and with acetone in which the *acid* is insoluble, was finally crystallised from aqueous ethanol, m. p. 176·5—177° (780 mg.); the *methyl ester* had m. p. and mixed m. p. with sample described below 170·5—171°. The low-melting *acid* was obtained from the ethanol mother-liquors and from the ethyl acetate and acetone extracts; a long series of crystallisations from ethyl acetate, aqueous alcohol, water, chloroform–acetic acid, acetone, and ethanol did not raise the m. p. above 155·5—156·5° (440 mg.). This was depressed to 145—150° on admixture with a sample of the *threo*-9 : 10-*erythro*-12 : 13-acid (m. p. 157°).

A sample of the mixed tetrahydroxy-acids (3·6 g.) was methylated by boiling it with methanolic hydrogen chloride. The product in methanol (150 ml.) deposited a large fraction at room temperature (2·14 g.; m. p. 159—165°) and a further fraction at 0° (0·96 g.; m. p. 143—144°). The m. p. rose sharply to 169—171° (1·50 g.) when the former was recrystallised from the same solvent and remained unchanged when the ester was washed with alkali; hydrolysis afforded the di-*erythro*-acid, m. p. 176·5—177·5°. The low-melting *ester* was unchanged in m. p. after several crystallisations or after washing with alkali; hydrolysis gave the low-melting di-*erythro*-acid.

The two racemic di-*erythro*-acids (m. p. 171·5—172·5°, 154—156°) were prepared by oxidation of linoleic acid; the methyl ester of the higher-melting acid had m. p. 157—157·5° confirming the value given by McKay *et al.*[14]

threo-9 : 10-erythro-12 : 13-*Tetrahydroxystearic Acid* (V, VI).—*erythro*-12 : 13-Dihydroxyoleic acid (5 g.) was acetylated and the product (6·23 g.) oxidised with performic acid, as already described. The greater part (5·02 g.) of the product (5·13 g.) was insoluble in ether.

A portion of the acids (2·5 g.), extracted with acetone and then with ethyl acetate, gave the high-melting *acid* as an insoluble fraction (574 mg.), m. p. 155—158° which became 156·5—157° after crystallisation from ethanol and repeated extraction with acetone and with ethyl acetate. The crystals which separated from the first acetone extracts were combined (1·27 g.; m. p. 128—131°). After repeated crystallisation from ethyl acetate and from ethanol this *acid* had m. p. 129·5—131°.

The remaining acids were esterified with cold methanolic hydrogen chloride, and the solution, when concentrated, gave crystals of *ester* (792 mg.), m. p. 142—145° raised to 144·5—145·5° after crystallisation from acetone, ethyl acetate, and methanol. Hydrolysis gave the higher-melting acid, m. p. and mixed m. p. 155·5—157°. Further concentration of the original methanol solution gave crude samples (1·63 g.) of the low-melting *ester*, purified by crystallisation from acetone, ethyl acetate, and methanol to m. p. 113·5—115° (720 mg.). Hydrolysis gave the low-melting acid, m. p. and mixed m. p. 130—131°.

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