Optical and geometric isomers of some fatty acids with vicinal hydroxy groups[1]

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Racemic *threo*-9,10-dihydroxypalmitic acid was resolved by means of the brucine salts into the optically active forms. Levorotatory *threo*-11,12-dihydroxyeicosanoic acid was obtained from the corresponding racemate by crystallization of the ephedrine salts.

The conformation of the geometric isomers of certain dihydroxy long-chain acids and their derivatives was studied by means of nuclear magnetic resonance spectra. There was a small but significant difference in the chemical shift of the CH protons in the (±)-*threo* acid as compared with those in the (±)-*erythro* acid. This was observed in 9,10-dihydroxypalmitic, 9,10-dihydroxystearic, and 11,12-dihydroxyeicosanoic acids. A similar but larger difference in the chemical shift (0.49 p.p.m.) was observed for the CH protons in the *O*-isopropylidene derivatives of the same acids. These differences are discussed and correlated with the stereochemistry of the dihydroxy acids and the corresponding 1,3-dioxolanes.

cis-(+)-12,13-Epoxyoleic acid was isolated from the seed oil of *Vernonia colorata*. (−)-*threo*-12,13-Dihydroxyoleic acid was prepared from the oil of *V. cinerea*.

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INTRODUCTION

The resolution of vicinally hydroxylated fatty acids into their optically active forms has presented difficulties to a number of investigators (1). However, McGhie *et al.* (2) were successful in resolving (±)-*threo*-9,10-dihydroxystearic acid by crystallization of the brucine salts. Certain other dihydroxyalkanoic acids could not be resolved by this method (3).

The two optically active forms of *threo*-12,13-dihydroxyoleic acid and of *threo*-12,13-dihydroxystearic acid were prepared earlier in this laboratory from the natural epoxyoleic acids (4, 5). In the present work, the direct resolution of three dihydroxy acids was undertaken, viz. *threo*-9,10-dihydroxypalmitic, *threo*-11,12-dihydroxyeicosanoic, and *threo*-4,5-dihydroxydodecanoic acids. Examination of the racemic acids and certain derivatives by nuclear magnetic resonance (n.m.r.) was also carried out to obtain data on their conformation.

RESULTS AND DISCUSSION

Resolution of Dihydroxy Acids

The resolution of (±)-*threo*-9,10-dihydroxypalmitic acid by crystallization of the brucine salts was performed by a slight modification of the general method of McGhie and his co-workers (2, 3). (+)-*threo*-9,10-Dihydroxypalmitic acid, when crystallized from aqueous acetone, had m.p. 87–88° and $[\alpha]_D^{25}$ +23.2° (in methanol). The levo isomer was obtained from the mother liquors of the alkaloidal salts. After crystallization from ethyl acetate, it had m.p. 87° and $[\alpha]_D$ −22.2°. The racemic mixture melts at 87–88° (6). The diacetate of the dextro isomer had $[\alpha]_D$ +25.1° (in methanol). The *O*-isopropylidene derivative of the levo isomer had $[\alpha]_D$ −26.8° (in methanol).

(±)-*threo*-11,12-Dihydroxyeicosanoic acid could not be resolved via the brucine salts because the separation of the diastereoisomers by crystallization was incomplete. However, crystallization of the ephedrine salts from ethyl acetate and recovery of the acid from the less-soluble salt gave pure (−)-*threo*-11,12-dihydroxyeicosanoic acid, m.p. 101.0–101.5°, $[\alpha]_D$ −21.1° (in methanol). A dextrorotatory product was isolated from the mother liquors, but it could not be obtained in an optically pure form.

(±)-*threo*-4,5-Dihydroxydodecanoic acid (7) was treated with brucine in aqueous acetone and in ethanol, but the product was not crystalline and resolution was not achieved. One fraction of the recovered acid had a specific rotation of +3.2°. The acid had a strong tendency to lactonize.

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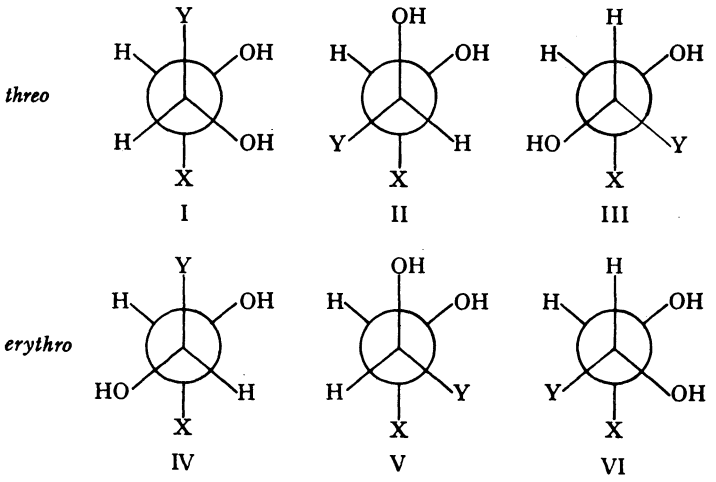
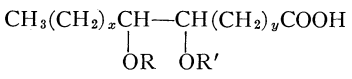


Nuclear Magnetic Resonance Spectra and Conformation of Vicinal Dihydroxy Acids

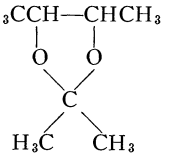
Long-chain vicinal dihydroxy acids (VII, R = R′ = H) can exist in *threo* and *erythro* forms, each of which has three possible conformations (I–III and IV–VI). The population distribution between the various rotamers in such systems can vary a great deal (8), depending upon the nature of the substituents and the solvent, and upon the existence of intramolecular hydrogen bonding.

If it is assumed that the carboxylic acid group in VII is too distant to have any conformational effect, then X and Y in structures I–VI are equivalent, and, on the basis of non-bonded interactions (8), the predominant rotamers in the *threo* and *erythro* forms will be I and IV, respectively. The stability of the *threo* rotamer I will be increased by intramolecular hydrogen bonding, but in the *erythro* form this effect will enhance the stability of the rival conformations V and VI. However, infrared studies (9) have shown that the rotamer with *trans* hydroxyl groups (IV) in the *erythro* vicinal diols is still predominant, and that intramolecular hydrogen bonding is minimal.

The n.m.r. spectra of three *threo–erythro* pairs of dihydroxy acids were measured in pyridine, and the chemical shift positions of the methine protons are given in Table I (R = R′ = H). A small but consistent difference can be noted, the *erythro* methine protons being slightly deshielded with respect to the *threo* system. This is in agreement with the rotamer distribution outlined above, since only in IV do the methine protons suffer deshielding from *cis* hydroxyl groups. The fact that the shift difference is small indicates a contribution from the other rotamers, and when the hydrogen-bonding effects are removed, as in the diacetoxy derivative (VII, R = R′ = CH_3-CO), the shift difference becomes negative as the rotamer population distribution changes.



VII



VIII

So far as the environment of the methine protons in VII is concerned, the two long-chain alkyl groups are equivalent and these methine protons will have the same chemical shift. However, they are not magnetically equivalent (10), since they are differently coupled to an adjacent methylene group, which itself consists of

two magnetically non-equivalent protons. Even if we ignore the coupling to the hydroxyl protons and 1,3 coupling to the β methylene groups, this system must be treated as an ···XYAA′Y′X′··· case and the AA′ absorption band should be characterized by five coupling constants (J_{AX}, J_{AY}, $J_{AX'}$, $J_{AY'}$, and $J_{AA'}$). No resolution of this highly complex band was in fact observed, a broad peak appearing in every case, including the isopropylidene derivatives discussed below.

O-Isopropylidene Derivatives of Vicinal Dihydroxy Acids

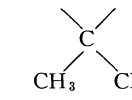
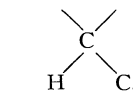
Acid-catalyzed condensation of aldehydes or ketones with vicinal diols produces substituted 1,3-dioxolanes, a reaction which has been applied to long-chain dihydroxy acids (11) without leading to any configuration assignments. We have investigated the n.m.r. spectra of a series of 2,2-dimethyl-1,3-dioxolanes (VII, R,R′ = $>C(CH_3)_2$) derived from three *threo–erythro* pairs of dihydroxy acids; the chemical shifts of the methine protons are listed in Table I. The difference between the *threo* and the *erythro* forms is about 0.5 p.p.m. This compares with 0.77 p.p.m. for the racemic and *meso* forms of 2,2,4,5-tetramethyl-1,3-dioxolane (VIII) (12).

Until recently, the 1,3-dioxolane ring was considered to be flat, but infrared (13) and n.m.r. (14, 15) investigations have shown that, like cyclopentane, it is puckered. Nuclear magnetic resonance studies, in particular, have led to calculated values of the dihedral angle (ϕ) between the groups on C_4 and C_5, estimated from the values of J_{cis} and J_{trans} for the 4,5 protons. Suggested values of ϕ are 35° for 1,3-dioxolane (15), 38° for 2-methyl-1,3-dioxolane (16), and 41° for 2,2-dimethyl-1,3-dioxolane (15), which contrast sharply with the value of 12° for the O—C—C—O angle from an X-ray study of a 1,2-*O*-isopropylidene derivative of α-D-glucose (17). These figures indicate that there is considerable deviation from a fully staggered orientation at C_4 and C_5 in 1,3-dioxolanes.

When the 2,2,4,5-tetrasubstituted-1,3-dioxolanes prepared in the present work are considered, the two conformations of the *erythro* isomer (IX and X) are equivalent (assuming that X and Y are equivalent), each with one axial and one equatorial proton, whereas the two *threo* rotamers (XI and XII) are non-equivalent and the methine protons are either both axial (XI) or both equatorial (XII). The chemical shift of the methine protons in these substituted 1,3-dioxolanes can be influenced by

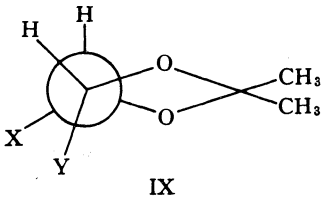
TABLE I

Chemical shift positions* of the methine protons in some dihydroxy acids (VII)

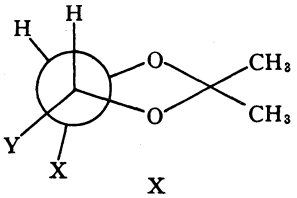
R	R′	*x*	*y*	*threo*	*erythro*	Difference†
H	H	5	7‡	6.14	6.06	0.08
H	H	7	7‡	6.14	6.05	0.09
H	H	7	9‡	6.12	6.00	0.12
CH_3CO	CH_3CO	5	7§	5.03	5.07	−0.04
		5	7§	6.46	5.97	0.49
		7	7§	6.48	6.02	0.46
		7	9§	6.46	5.94	0.52
		7	7§	6.36	—	—
Compound VIII‖				6.62	5.85	0.77

*Values are in parts per million on the τ scale with tetramethylsilane as an internal reference and are, in every case, the midpoint of a broad peak.
†*threo–erythro*.
‡In pyridine.
§In carbon tetrachloride.
‖2,2,4,5-Tetramethyl-1,3-dioxolane, without solvent; the values are taken from ref. 12.

erythro

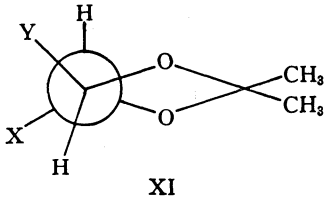


IX

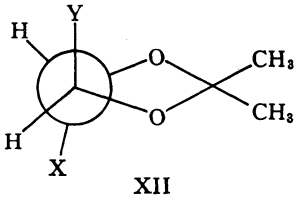


X

threo



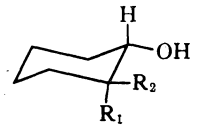
XI



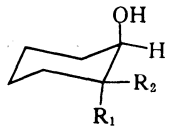
XII

three factors:[3] the groups on C_2 (18, 19), the groups on C_4 and C_5 (19), and the C—O bonds. The first effect can be neglected, since the C_2 groups are equivalent; similarly, the geminal deshielding effects of the methyl groups on C_4 and C_5 will be the same for both methine protons in all the conformations, but the vicinal effects will vary.

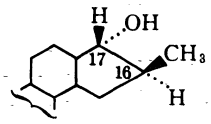
Nuclear magnetic resonance studies of the 2-methylcyclohexanols (20) have shown that, when the carbinol proton and the methyl group have an axial–equatorial (XIII, R_1 = H, R_2 = CH_3; XIV, R_1 = CH_3, R_2 = H) or an equatorial–equatorial (XIV, R_1 = H, R_2 = CH_3) relationship, then the proton is shielded, and that the proton is deshielded when these two groups are axial–axial (XIII, R_1 = CH_3, R_2 = H). A similar effect has been noted (21) in the cyclopentane ring of 17β-hydroxy steroids, where the carbinol proton (17α) is shielded by a methyl group in the 16α position (XV), a 16β-methyl group (XVI) having no effect. If we assume that a similar effect is operating in the 1,3-dioxolane system, then both protons in both *threo* rotamers (XI and XII) will be shielded, whereas only one proton in each of the *erythro* rotamers (IX and X) will be shielded. The two types of proton in the *erythro* isomer will not be separately distinguishable by n.m.r. because of rapid inversion, but the time-averaged chemical shift position will still be downfield from that of the *threo* isomer, in agreement with the observed values.



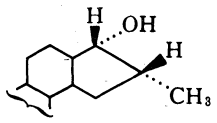
XIII



XIV



XV



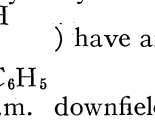
XVI

If the *threo* rotamers XI and XII have different energies and, hence, have an unequal population, the effect of the C—O bonds becomes important. By analogy with six-membered rings (22), the axial protons in XII are shielded with respect to the equatorial protons in XI, an effect similar to that of the methyl groups discussed above. Since the *erythro* rotamers have only one axial proton, the net effect of an increase of XI over XII will be to shift the *threo* methine absorption upfield from the *erythro* (in agreement with observation); of course, a shift in the opposite direction will result if the population of XII exceeds that of XI. By analogy with 1,2-dialkylcyclohexanes (8*a*, chap. 2; 8*b*, chap. 3), rotamer XI should be more stable than XII; un-

[3]Not all of the factors affecting the chemical shift of protons in cyclic systems are as yet thoroughly understood, and no unified theoretical treatment exists. Only some of the observed chemical shifts can be explained satisfactorily in terms of neighbor anisotropy effects (22 and references therein); other effects have been postulated for particular cases (26). We have made use of analogous data without attempting any *a priori* explanation.

fortunately, there are no available data on the relative stabilities of the rotamers of 1,3-dioxolanes, and this point must remain undecided. We are investigating this problem.

Whatever the explanation, the observed shift difference between the methine protons of the *threo* and *erythro* isopropylidene derivatives of vicinal dihydroxy acids offers a simple method of determining the configuration of such acids. As Baggett and his co-workers (23) have observed, the two methyl groups on C_2 of 1,3-dioxolanes derived from *erythro* or *cis* diols (cf. IX) are not equivalent and exhibit two n.m.r. peaks, whereas the corresponding *threo* or *trans* compounds have identical methyl groups with only one n.m.r. peak. Although this difference provides a means of configuration assignment for the isopropylidene derivatives of simple glycols or carbohydrates, it is of little use in the field of long-chain acids, since the peaks in question occur in a region of the spectrum (8.7–9.0 τ) which is already 'crowded' in such compounds (24).

The methine protons of the benzylidene derivative of *threo*-9,10-dihydroxystearic acid (Table I, R,R′ = ) have an n.m.r. peak about 0.1 p.p.m. downfield compared with that of the corresponding isopropylidene derivative, as a result of the deshielding influence of the aromatic ring (19*b*). The benzyl proton has a single peak at 4.2 τ, as would be expected for a racemic mixture (25).

Optically Active Acids from Seed Oils

cis-(+)-Epoxyoleic acid was isolated from the seed oil of *Vernonia colorata* Drake. A preliminary report of this work has been made (4). The specific rotation of the acid was +0.2° (in ethanol). It had m.p. 30–31°, but when mixed with the levo isomer (from *Hibiscus cannabinus* (27)), the racemic mixture melted at 34–35°. Krewson and Luddy (28) reported *cis*-(+)-epoxyoleic acid from another source, m.p. 32.5°, $[\alpha]_D$ +2.0° (in hexane). Osbond found m.p. 35–36° for the synthetic (racemic) acid, *cis*-(±)-epoxyoleic acid (29).

(−)-*threo*-12,13-Dihydroxyoleic acid was prepared in a pure form from the seed oils of *Vernonia colorata* and *V. cinerea*, by hydration of the epoxy acid therein. The oil content of these seeds (10.4 and 10.8%, respectively) was considerably higher than that found for the same species by Badami and Gunstone (3.1 and 3.8%) (30). The epoxy acid content of the oils (65.0 and 33.3%) was also much higher. These differences may be attributed to a difference in the environment during growth of the plants or during storage of the seeds.

EXPERIMENTAL

Specific rotations were measured with sodium light at a temperature of 24 ± 1°. Nuclear magnetic resonance spectra were determined at 60 Mc/s on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard; the dihydroxy acids were dissolved in pyridine and the other acids in carbon tetrachloride.

cis-11-Eicosenoic acid was synthesized by the method of Carroll (31). *threo*-Dihydroxyalkanoic acids were prepared from the corresponding monoenoic acids by reaction with performic acid (32), and the *erythro* acids by reaction with alkaline permanganate (33).

Resolution of threo-9,10-Dihydroxypalmitic Acid

The kernel oil of *Macadamia ternifolia* was converted into methyl esters by transesterification, and the mixed esters were distilled through a spinning-band column. The fraction distilling at 104–108° and 0.5 mm was methyl *cis*-9-hexadecenoate. It was hydrolyzed and the acid was treated with performic acid by Swern's procedure (32) to give (±)-*threo*-9,10-dihydroxypalmitic acid, m.p. 87–88° (lit. m.p. 87–88° (6)).

The dihydroxy acid (16 g) and (−)-brucine (28 g) were dissolved by gentle heating in a mixture of acetone (50 ml) and water (100 ml). The solution was allowed to stand for 2 days at 0°, and the precipitated salt (33 g) was collected and crystallized three times from acetone–water (1:2 by volume), yielding 15 g of the brucine salt, m.p. 51°, $[\alpha]_D$ −22.2° (*c*, 1.1 in EtOH). It was decomposed by boiling with 2 *N* hydrochloric acid (25 ml), and the resulting solid was crystallized from aqueous acetone to yield (+)-*threo*-9,10-dihydroxypalmitic acid (2.3 g), m.p. 87–88°, $[\alpha]_D$ +23.2° (*c*, 0.9 in MeOH).

Anal. Calcd. for $C_{16}H_{32}O_4$: C, 66.63; H, 11.18. Found: C, 66.45; H, 10.89.

The mother liquors from the crystallization of the brucine salt were combined and cooled to give a second crop of the salt, $[\alpha]_D$ −40° (*c*, 1.0 in EtOH); this was discarded. The filtrate was evaporated to dryness, leaving an oil which solidified after 2 days. This solid was dissolved in acetone and cooled. The small crop of crystals that formed was discarded. Evaporation of the filtrate gave an oil that did not

crystallize, $[\alpha]_D$ −55° (*c*, 1.3 in EtOH). It was decomposed by hydrochloric acid in the same way as the dextro isomer. The solid product was dissolved in ethyl acetate and a little unchanged brucine salt was removed. The levo acid crystallized when the filtrate was cooled. It was crystallized once more from ethyl acetate, giving (−)-*threo*-9,10-dihydroxypalmitic acid (1.1 g), m.p. 87°, $[\alpha]_D$ −22.2° (*c*, 1.0 in MeOH).

Anal. Found: C, 66.94; H, 11.34.

Resolution of threo-11,12-Dihydroxyeicosanoic Acid

The racemic acid (10.0 g) was treated with (−)-ephedrine hydrate (5.3 g) in a mixture of ethanol (40 ml) and water (20 ml). The salt that deposited (9.6 g) had m.p. 95–100° and $[\alpha]_D$ −26° (*c*, 2.0 in EtOH). After three crystallizations from ethyl acetate, it had $[\alpha]_D$ −27.9° (*c*, 1.3 in EtOH), unchanged by further crystallization. It was decomposed by heating with a mixture of methanol and 5 *N* hydrochloric acid (1:1), and the methanol was removed on the steam bath. The product deposited from the aqueous residue. It was crystallized from aqueous methanol and then from ethyl acetate, giving (−)-*threo*-11,12-dihydroxyeicosanoic acid, m.p. 101.0–101.5°, $[\alpha]_D$ −21.1° (*c*, 1.2 in MeOH).

Anal. Calcd. for $C_{20}H_{40}O_4$: C, 69.72; H, 11.70. Found: C, 69.68; H, 11.68.

(+)-threo-9,10-Diacetoxypalmitic Acid

(+)-*threo*-9,10-Dihydroxypalmitic acid (0.27 g) was heated in acetic anhydride (3 ml), with refluxing, for 3 h. Water (10 ml) was added and the heating was continued for 1 h. The solution was cooled, diluted with water, and extracted with ether. After evaporation of the ether, the residue was dissolved in cyclohexane and decanted from the unchanged dihydroxy acid. The product, (+)-*threo*-9,10-diacetoxypalmitic acid, was an oil, $[\alpha]_D$ +25.1° (*c*, 3.13 in MeOH); ν_{max} 1 700 (COOH) and 1 740 (OAc) cm^{-1}, no OH absorption at 3 400 − 3 600 cm^{-1}.

(±)-*erythro*-9,10-Diacetoxypalmitic acid was prepared in the same way. The CH protons of these two compounds had chemical shifts of 5.03 and 5.07 τ in the *threo* and *erythro* forms, respectively (in CCl_4 solution).

O-Isopropylidene Derivatives of Long-Chain Dihydroxy Acids

(−)-*threo*-9,10-Dihydroxypalmitic acid (0.2 g) was suspended in dry acetone (15 ml), and sulfuric acid (10 drops) was added. The solution was allowed to stand for 2½ h and was then neutralized with solid sodium carbonate. After the mixture was filtered, the acetone was evaporated and the residue was dissolved in cyclohexane and refiltered. Evaporation of the cyclohexane gave the oily product, (−)-*threo*-9,10-*O*-isopropylidenepalmitic acid, $[\alpha]_D$ −26.8° (*c*, 3.4 in MeOH).

Three racemic *threo* dihydroxy acids were treated with acetone in the same way to give the respective isopropylidene compounds: (±)-*threo*-9,10-*O*-isopropylidenepalmitic acid, (±)-*threo*-9,10-*O*-isopropylidenestearic acid, and (±)-*threo*-11,12-*O*-isopropylidene-eicosanoic acid. The corresponding *erythro* dihydroxy acids gave the *erythro* forms of these three isopropylidene compounds. All were liquids. Their infrared spectra had C—O stretching bands between 1 040 and 1 110 cm^{-1}. In the *threo* isomers, the band at 1 095 cm^{-1} was more intense than that at 1 040 – 1 050 cm^{-1}. The n.m.r. spectra have been discussed.

(±)-threo-9,10-O-Benzylidenestearic Acid

(±)-*threo*-9,10-dihydroxystearic acid (0.2 g) was treated with an excess of benzaldehyde (2 ml) in the presence of sulfuric acid (4 drops), allowed to stand for 3 h, neutralized, and diluted with carbon tetrachloride. The excess benzaldehyde was allowed to oxidize to benzoic acid as the solvent evaporated. The residue was washed with dilute alkali and dried, giving (±)-*threo*-9,10-*O*-benzylidenestearic acid. Its infrared spectrum showed no free OH group (ca. 3 400 cm^{-1}).

12,13-Epoxyoleic Acid

The isolation of (−)-12,13-epoxyoleic acid, m.p. 29–30°, from the seed oil of *Hibiscus cannabinus* has been described (27). The dextro isomer was isolated from the oil of *Vernonia colorata* Drake as follows. Air-dried seed was ground and extracted with petroleum ether, yielding 10.4% of an oil, n_D^{25} 1.4806, iodine value 115.0, unsaponifiable matter 11%, oxirane oxygen (HCl method) 3.51%, glycerol yield 7.4%.

Twelve grams of the oil was hydrolyzed with alcoholic KOH in the cold, and the epoxy acid was concentrated by solvent partitioning as described for the levo isomer (27). The concentrate (4.0 g) was crystallized from acetone at −50° and again at −25°, giving *cis*-(+)-12,13-epoxyoleic acid, m.p. 30–31°.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88; equiv. wt. 296.4; oxirane O, 5.40. Found: C, 72.99, 73.15; H, 10.50, 10.56; equiv. wt. 297.3; oxirane O, 5.29.

The acid had a small positive rotation in ethanol. When mixed with *cis*-(−)-12,13-epoxyoleic acid, prepared from the oil of *Hibiscus cannabinus*, the racemic mixture melted at 34–35°.

Epoxidation of (+)-12,13-epoxyoleic acid with peracetic acid gave 9,10;12,13-diepoxystearic acid, m.p. 78–79° after several crystallizations from acetone. Osbond (29) reports m.p. 76.5–77.5° for the diepoxy acid prepared from (±)-12,13-epoxyoleic acid.

(−)-threo-12,13-Dihydroxyoleic Acid

Acetolysis of (+)-12,13-epoxyoleic acid from *V. colorata*, followed by hydrolysis and fractional crystallization of the product (4), gave (−)-*threo*-12,13-dihydroxyoleic acid, m.p. 61.0–61.5°, $[\alpha]_D^{24}$ −19.0° (*c*, 10.0 in EtOH).

Anal. Calcd. for $C_{18}H_{34}O_4$: C, 68.75; H, 10.89. Found: C, 68.55; H, 10.74.

The same enantiomer was obtained by Scott and his co-workers (34) by direct acetolysis of the seed oil of *V. anthelmintica*. Their product had m.p. 62.5–63.0° and $[\alpha]_D$ −18.6°.

(−)-*threo*-12,13-Dihydroxyoleic acid was also prepared by us from the seed oil of *V. cinerea* by

direct acetolysis of the oil. The dihydroxy acid melted at 60–61°, alone and when mixed with the authentic acid from *V. colorata*. Catalytic hydrogenation of this acid gave (−)-*threo*-12,13-dihydroxystearic acid (34), m.p. 96.5–97.0°, $[\alpha]_D$ −23.8° (*c*, 2.5 in EtOH), equiv. wt. 317.6 (theoretical 316.5).

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