

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Separation and Identification of the 9,10- and 10,9-Chlorohydrins of Methyl Oleate<sup>1</sup>BY E. JUNGERMANN<sup>2</sup> AND P. E. SPOERRI

RECEIVED MAY 2, 1953

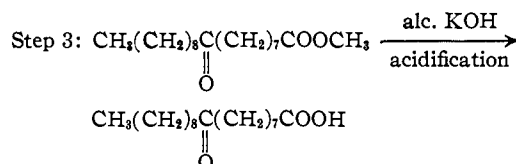
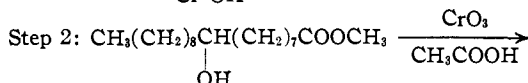
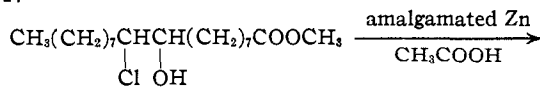
A mixture of methyl 9,10(10,9)-chlorohydroxystearates was prepared by converting methyl oleate to the epoxide and then allowing this compound to react with hydrogen chloride in diethyl ether. Low temperature fractional crystallization of the mixture yielded the two position isomers which were identified by conversion to the corresponding ketostearic acid. The chlorohydrins obtained were (1) methyl 10-hydroxy-9-chlorostearate, m.p. 25–26°, and (2) methyl 9-hydroxy-10-chlorostearate, m.p. 36.5–37.5°.

The stereochemical relationships involved in the conversion of oleic and elaidic acid to the 9,10-dihydroxystearic acids were outlined in a reaction scheme by Swern.<sup>3</sup> These transformations were effected either through the intermediate epoxy and chlorohydroxy compounds (chlorohydrins), or by oxidation with alkaline potassium permanganate. Certain assumptions had to be made, because the absolute configurations of the long chain compounds were not known. Since then, the *cis* and *trans* isomerism of oleic and elaidic acid have been confirmed by infrared spectra.<sup>4,5</sup> The configurations of the two epoxystearic acids have been established by X-ray diffraction methods.<sup>6</sup> Swern, *et al.*,<sup>7</sup> conclusively proved the configuration of the isomeric 9,10-dihydroxystearic acids by studying the formation of urea complexes.

Since the previous investigators did not separate the mixture of the 9,10- and 10,9-position isomers of the chlorohydroxy compounds, it seemed of interest to fractionate and identify these position isomers. This was effected by converting methyl oleate to the corresponding epoxide and subsequently treating this compound with hydrogen chloride in diethyl ether to yield the mixture of methyl chlorohydroxystearates. Low temperature crystallizations from methanol yielded two products; one melting at 36.5–37.5° and the other at 25–26°.

To assign definite positions to the chloro and dihydroxy groups in the two forms of methyl chlorohydroxystearate isolated, each pure position isomer was converted by unequivocal methods to the corresponding ketostearic acid. The following flow sheet shows the transformations for methyl 9-hydroxy-10-chlorostearate

Step 1:



Similarly, methyl 9-chloro-10-hydroxystearate would give 10-ketostearic acid.

After a number of unsuccessful attempts to effect the dechlorination (step 1) according to procedures suggested in the literature,<sup>8,9</sup> the complete removal of chlorine was effected by refluxing the chlorohydrin with hydrochloric acid-free amalgamated zinc and glacial acetic acid. This method resulted in the complete removal of chlorine from the compound.

The methyl hydroxystearates thus prepared were oxidized (step 2) at room temperature to the keto esters with chromic oxide in glacial acetic acid. The ketostearic acids, obtained by saponification were characterized by formation of the semicarbazones.

The ketostearic acid obtained from the chlorohydrin melting at 36.5–37.5° proved to be the 9-keto compound while the chlorohydrin melting at 25–26° yielded the 10-ketostearic acid. It followed therefore that the chlorohydrin of methyl oleate (m.p. 36.5–37.5°) was methyl 10-chloro-9-hydroxystearate, while the lower melting chlorohydrin was methyl 10-hydroxy-9-chlorostearate.

It is interesting to note that the separation of the chlorohydrin mixture yields three times as much of the methyl 10-hydroxy-9-chlorostearate than of the other position isomer. This phenomenon of opening an epoxide ring in the middle of an almost symmetrical chain to yield unequal quantities of two position isomers has also been reported by other investigators. Ross, Gebhart and Gerech<sup>10</sup> and Krems<sup>11</sup> catalytically hydrogenated methyl 9,10-epoxystearate and obtained predominantly methyl 10-hydroxystearate. McKay and Bader<sup>12</sup> brominated linoleic acid in an inert solvent at low temperature and showed that bromine added to the 12,13-carbon double bond by isolating 12,13-dibromo-9-octadecenoic acid. These authors proposed an explanation for this based on the inductive effect of the carboxyl group. A similar inductive

(1) This paper comprises parts of a thesis submitted by E. Jungermann in partial fulfillment of the requirements for the degree of Master of Science at the Polytechnic Institute of Brooklyn.

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effect might explain the reaction of hydrogen chloride with methyl 9,10-epoxystearate. The experimental data reported in this paper are in agreement with this premise. However, in spite of this correlation, further experimental investigations appear necessary to determine whether other factors are involved.

### Experimental<sup>13</sup>

**Methyl 9,10-Epoxystearate.**—Thirty grams (0.10 mole) of pure methyl oleate<sup>14</sup> was treated with 0.115 mole of peracetic acid in acetic acid at 20–25° in a similar manner as described by Swern, *et al.*<sup>15</sup>; m.p. 14–16°; yield 27 g. After four recrystallizations from acetone 16 g. (51% theoretical) of pure product was obtained, m.p. 17.1–17.8°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>36</sub>O<sub>3</sub>: oxiran O,<sup>16</sup> 5.12. Found: oxiran O, 5.02.

**Methyl 9,10-(10,9)-Chlorohydroxystearate.**—Methyl 9,10-epoxystearate (3.12 g., 0.01 mole) was allowed to react with hydrogen chloride in absolute diethyl ether at room temperature in a similar manner as described by Swern<sup>3</sup>; yield 3.30 g. (97%) of methyl 9,10-(10,9)-chlorohydroxystearate, m.p. 23–25.5°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>37</sub>O<sub>3</sub>Cl: Cl, 10.20. Found: Cl, 10.13.

**Separation of the 9,10- and 10,9-Isomers of Methyl Chlorohydroxystearate.**—In a three-necked round-bottom flask equipped with stirrer and low temperature thermometer, 15.7 g. of the mixed methyl chlorohydroxystearates were dissolved in 62 ml. of methanol. The solution was cooled (Dry Ice–acetone) slowly to –30 to –35° at which point a triangular fractional crystallization was carried out. Two distinct fractions were obtained: (1) 10.1 g. of isomer melting at 25–26°; recrystallization of this fraction from methanol yielded five crops of crystalline material, each melting at 25–26°; all of the starting material was recovered. (2) 3.3 g. of isomer melting at 36.5–37.5°; recrystallization of this fraction from methanol yielded three crops (total recovery 95%) of crystalline material; m.p. of each crop

36.5–37.5°. The final mother liquor still contained 0.6 g. of oily residue which was not purified.

**Methyl Hydroxystearates.**—Methyl chlorohydroxystearate (1.7 g., 5 mmoles) was dissolved in 100 ml. of glacial acetic acid and 5 g. of amalgamated zinc was added. The mixture was refluxed for six hours. The solution was cooled, filtered, diluted with water and extracted with diethyl ether. The extracts were washed and dried, and on removing the solvent 1.4 g. (90% yield) of crystalline solid was obtained. Analysis for chlorine indicated that all of the chlorine was removed.

*Anal.* Calcd. for C<sub>19</sub>H<sub>36</sub>O<sub>3</sub>: sapon. equiv., 314. Found: sapon. equiv., 311.

**Ketostearic Acids.**—Methyl hydroxystearates (1 g., 3.2 mmoles) were oxidized with 25% excess of chromic oxide in glacial acetic acid at 30–35°, yield 0.8 g. Saponification of this intermediate with alcoholic potassium hydroxide followed by acidification and extraction with diethyl ether yielded the ketostearic acids.

The 9-ketostearic acid derived from methyl 10-chloro-9-hydroxystearate was obtained in 70% yield, m.p. 80° (reported m.p. 81.5°<sup>10,17,18</sup>).

*Anal.* Calcd. for C<sub>18</sub>H<sub>34</sub>O<sub>3</sub>: neut. equiv., 298. Found: neut. equiv., 296.

The semicarbazone was prepared in the usual manner; m.p. 117–119° (reported m.p. 118–120°<sup>10</sup>).

*Anal.* Calcd. for C<sub>19</sub>H<sub>37</sub>O<sub>3</sub>N<sub>3</sub>: N, 11.83. Found: N, 11.80.

The 10-ketostearic acid derived from methyl 9-chloro-10-hydroxystearate was obtained in 75% yield; m.p. 72° (reported m.p. 72°<sup>10,17,18</sup>); a mixed melting point with the 9-keto compound was 66–69°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>34</sub>O<sub>3</sub>: neut. equiv., 298. Found: neut. equiv., 295.

The semicarbazone was prepared in the usual manner; m.p. 100.5–102° (reported m.p. 101–103°<sup>10</sup>).

*Anal.* Calcd. for C<sub>19</sub>H<sub>37</sub>O<sub>3</sub>N<sub>3</sub>: N, 11.83. Found: N, 11.65.

**Acknowledgment.**—The authors wish to thank the Colgate–Palmolive–Peet Co. for use of their laboratory facilities.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

## Synthesis of *erythro*- and *threo*- $\alpha$ -Amino- $\beta$ -hydroxystearic Acids<sup>1</sup>

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RECEIVED MAY 2, 1953

The two DL- $\alpha$ -amino- $\beta$ -hydroxystearic acids have been synthesized and characterized as the *threo* and *erythro* forms on the basis of physical and chemical properties.

Dihydrosphingosine has been characterized as one of the four 1,3-dihydroxy-2-aminoöctadecanes<sup>4</sup> and the amino carbon atom has been shown to have the D-configuration.<sup>5</sup> In order to complete the stereochemical characterization of dihydrosphingosine we

have synthesized the two racemic forms by reduction of the corresponding *threo*- and *erythro*-DL- $\alpha$ -amino- $\beta$ -hydroxystearic acids.<sup>6</sup> The preparation of the latter compounds is described in the present paper.

Attempts to prepare the  $\alpha$ -amino- $\beta$ -hydroxystearic acids from octadecanoic acid by procedures applicable to the synthesis of the threonines were not promising. Since Attenburrow, Elliott and Penny<sup>7</sup> had reported excellent results in the preparation of threonine and allothreonine by a procedure involving the condensation of acetic an-

(1) This investigation was supported in part by a research grant (RG 2031) from the National Institutes of Health, Public Health Service. Part of the material in this paper was taken from the thesis submitted by J. B. Harrison to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(2) AEC fellow in Chemistry, 1951–1952.

(3) On leave of absence from Weizmann Institute of Science, Rehovoth, Israel.

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