ON WALDEN INVERSION.

XII. ON THE OXIDATION OF 3-THIOLVALERIC AND OF 4-THIOL-VALERIC ACIDS AND ITS SIGNIFICANCE IN CONNECTION WITH WALDEN INVERSION.

BY P. A. LEVENE AND T. MORI.*

(From the Laboratories of The Rockefeller Institute for Medical Research, New York.)

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In previous investigations of Levene and Mikeska1 and of Levene, Mori, and Mikeska2 a series of thiolcarboxylic acids has been compared with the corresponding sulfo acids with respect to their optical behavior. It was found that the undissociated acids on passing into the ionized state showed a change in rotation the direction of which was identical in the thiol and in the sulfo acids. On the basis of these observations the conclusion was formulated that the change of polarity of the substituting group does not alter the direction of rotation which the original acid displayed on passing from the unionized to the ionized state. In its turn, this conclusion furnished a way of recognizing those reactions of substitution in the simple aliphatic acids which are accompanied by a Walden inversion.

In the series of thiol- and sulfocarboxylic acids previously analyzed, only one exception was encountered. Namely, levo-3-thiolbutyric acid on passing to the mono-ion and then to the di-ion showed a change of rotation towards the right, whereas the sulfo acid derived from it on passing from the undissociated state to the mono- and then to the di-ion changed its rotation to the left. The question naturally arose as to the cause of this exceptional behavior.

* Fellow of the International Education Board.

The difference between the structure of the 3-thiolbutyric acid and the other acids which had been analyzed rests principally in the distance of the thiol group from the carboxyl. Whereas all the other acids were substituted in position (2), this one had the reactive group on carbon atom (3).

Hence, it was necessary to investigate the behavior of a larger group of acids substituted on carbon atoms (3) or (4) and possibly still more distantly from the carboxyl.

The present communication contains a report on the valeric acids substituted in positions (3) or (4).

The configurational relationships of 3- and 4-hydroxyvaleric acids to lactic acid have been established by Levene and Haller.

<table>
<thead>
<tr>
<th>Hydroxy</th>
<th>Halide</th>
<th>Thiol</th>
<th>Sulfo</th>
<th>Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Valerie acid.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free acid</td>
<td>+11.4</td>
<td>+19.9</td>
<td>+20.80</td>
<td>+14.32</td>
</tr>
<tr>
<td>Mono-salt</td>
<td>+8.0</td>
<td>+17.3</td>
<td>+13.65</td>
<td>+17.84</td>
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<tr>
<td>Di-salt</td>
<td></td>
<td></td>
<td>+19.90</td>
<td>+16.06</td>
</tr>
<tr>
<td>4-Valerie acid.</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free acid</td>
<td>+16.5</td>
<td>+7.1</td>
<td>+6.87</td>
<td>-3.53</td>
</tr>
<tr>
<td>Mono-salt</td>
<td>+3.8</td>
<td>+5.4</td>
<td>+2.43</td>
<td>-3.26</td>
</tr>
<tr>
<td>Di-salt</td>
<td></td>
<td></td>
<td>+2.40</td>
<td>-5.33</td>
</tr>
</tbody>
</table>

In Table I are given the rotations of the undissociated acids and of the anions of the hydroxy, halogen, thiol, and sulfo acids substituted in positions (3) or (4).

From Table I it is seen that levo-3-thiolvaleric acid, on passing from the undissociated acid to the mono-ion \( R \text{COO}^- \text{SH} \) shows a change of rotation to the right, and the latter on passing to the di-ion \( R \text{COO}^- \text{S}^- \) shows a change of rotation to the left. The corresponding sulfo acid is levorotatory and on passing to the

changes its rotation to the left and this on further ionization to the di-ion \( \text{R} \begin{array}{c} \text{COO}^- \\ \text{SO}_2\text{O}^- \end{array} \) changes its rotation to the right. Thus in each case the ionization of the carboxyl leads to a similar change of rotation. This behavior is identical with that of the corresponding acids substituted in position (2).

Levo-4-thiolvaleric acid, on passing to the mono-ion \( \text{R} \begin{array}{c} \text{COO}^- \\ \text{SH} \end{array} \) changes its rotation to the right and the latter on further ionization to the di-ion \( \text{R} \begin{array}{c} \text{COO}^- \\ \text{S}^- \end{array} \) does not change perceptibly. The corresponding sulfo acid is dextrorotatory and on conversion into the mono-ion \( \text{R} \begin{array}{c} \text{COOH} \\ \text{SO}_2\text{O}^- \end{array} \) changes its rotation to the left, and this on further ionization to the di-ion \( \text{R} \begin{array}{c} \text{COO}^- \\ \text{SO}_2\text{O}^- \end{array} \) changes its rotation to the right. Also in this case the behavior is identical with that of the acids substituted in position (2). Thus, the behavior of the 3-thiol- and 3-sulfobutyric acids remains the only exception.

Thus, on the basis of data on the rotations of thiol- and sulfovaleric acids, it seems to us warranted to say that the halogenation of the hydroxy acids was accompanied by a Walden inversion. Also the substitution of the halogen by the thiol group was accompanied by a Walden inversion. As regards the 3-substituted butyric acid, it seems preferable to postpone judgment until further information is obtained concerning the causes of the exceptional behavior of this substance. Work in this direction is in progress.

It may be mentioned here that difficulties were encountered in the early attempts to substitute the hydroxyl of the free acid by halogen. The difficulty was due to the ready lactonization of 3-substituted acids. To overcome the difficulty the nitrile was
Alcohol + HCl → [α] - 10.5 Levo-chloronitrile

Levo-hydroxy acid

[α] - 10.0

Concentrated HCl

[α] - 11.4 (water)

[α] - 10.6

Alcohol + HCl → Levo-hydroxy ester

α - 10.6

α - 9.9

α - 8.7

Dextro-chloro acid

[α] - 8.1

α + 6.5

α + 7.0

SOCl₂

α + 0.0

α + 5.4

Dextro-hydroxynitrile

α + 6.5

Alcohol + HCl → Dextro-bromo ester

α - 9.3

PBr₃

α + 16.1

α + 14.4

Fuming HBr

Dextro-bromo acid

[α] - 14.3

[α] + 11.0 (35 per cent alcohol)

Levo-thiol acid

[α] - 15.5 (20 per cent alcohol)

Aqueous KSH

[α] - 0.9

Ba(MnO₄)₂

[α] - 8.1

[α] - 5.1 (salt)

Levo-sulfo acid

[α] - 7.9 (salt)

Bromine

[α] - 7.9

[α] - 15.5 (20 per cent alcohol)

The rotations without solvent are all for 1 dm. tubes. Unless otherwise specified, the solvent used in determining the above rotations was ether. The levo-hydroxy acid used for the preparation of the levo-hydroxy ester was not pure.
halogenated prior to its conversion into the free acid. The chloronitrile was readily converted into the chloro ester and this again into the thiol ester, which then was oxidized to the sulfostoor ester which in the same process was hydrolyzed to the corresponding acid. There were two unsatisfactory features in this set of reactions. First, the reaction of chlorination was accompanied by a high degree of racemization. Second, the saponification of the thiol ester did not proceed satisfactorily. All difficulties, however, were overcome when the hydroxy ester was brominated and when the bromo acid was converted into the thiol acid. The entire cycle of reactions is given in the accompanying diagram.

Several points brought out on this diagram are worthy of note. First, the fact that the conversion of the hydroxy- or of the chloronitrile into the corresponding acid or ester is accompanied by a change of direction of rotation. This change of rotation is due to the change in polarity of the radicle affected by the reaction. Second, the reaction of halogenation of the nitrile, ester, or acid leads to a halogenated acid of identical configuration. Third, the halogen acid has the identical configuration regardless of the reagent employed for halogenation.

In the experiments with 4-hydroxyvaleric acid, all reactions proceeded smoothly save one; namely, on treatment of ethyl-4-chlorovalerate with potassium hydrogen sulfide, the resulting product was a mixture of the thiol ester with the thiolactone. The latter rotated in the direction opposite to that of the ester. To verify this conclusion pure 4-thiovalerolactone was prepared from 4-thiolvaleric acid.

EXPERIMENTAL.

Part I. β-Substituted n-Valeric Acids.

Levo-β-Hydroxyvaleric Acid.4—Chloromethylethyl ketone prepared by the chlorination of methylethyl ketone was converted

4 Levene, P. A., and Haller, H. L., J. Biol. Chem., 1927, lxxiv, 343. We are indebted to Dr. H. L. Haller for the chloromethylethyl ketone used in these experiments.
into hydroxymethylethyl ketone by the usual method. This compound was reduced to butylene glycol by fermenting bakers’ yeast. The best yield of the glycol was 77 gm. from 100 gm. of hydroxymethylethyl ketone. The specific rotations of the glycol were as follows:

\[
[l]_D^{\text{a}} = \frac{+ 0.87 \times 100}{1 \times 6.00} = + 14.5^\circ, \text{in absolute alcohol.}
\]

\[
[a]_D^{\text{a}} = \frac{+ 0.08 \times 100}{2 \times 17.3} = + 0.23^\circ, \text{in water.}
\]

The glycol (\([\alpha]_D^{\text{a}} = +12.4^\circ\) in alcohol) was treated with 1 equivalent of dry hydrogen bromide. From 20 gm. of the glycol 20 gm. of bromohydrin were obtained. The bromohydrin showed the following rotations.

\[
\alpha_D^{\text{a}} = - 10.31^\circ, \text{without solvent in a 1 dm. tube.}
\]

\[
[a]_D^{\text{a}} = \frac{- 0.72 \times 100}{1 \times 10.0} = - 7.2^\circ, \text{in ether.}
\]

The bromohydrin (\(\alpha_D^{\text{a}} = -5.08^\circ\) without solvent in a 1 dm. tube) was refluxed with potassium cyanide in methyl alcohol. The product, \(\beta\)-hydroxyvaleronitrile, showed the following rotations.

\[
\alpha_D^{\text{a}} = + 8.02^\circ, \text{without solvent in a 1 dm. tube.}
\]

\[
[a]_D^{\text{a}} = \frac{+ 1.00 \times 100}{1 \times 10.0} = + 10.0^\circ, \text{in ether.}
\]

The rotation of the free acid was obtained as follows: A sample of the sodium salt of \(\beta\)-hydroxyvaleric acid obtained by saponification of the nitrile (\(\alpha_D^{\text{a}} = +6.5^\circ\) without solvent in a 1 dm. tube) was treated with 1 equivalent of hydrochloric acid. This solution gave the following rotation.

\[
[a]_D^{\text{a}} = \frac{- 0.48 \times 100}{2 \times 2.11} = - 11.4^\circ.
\]
Levo-β-Chlorovaleronitrile.—Since the halogenation of the free hydroxy acid as well as of its salt was not satisfactory, the nitrile was chlorinated.

1. By Means of Thionyl Chloride.—To 5 gm. of dextro-β-hydroxyvaleronitrile (α₀ = + 5.98° without solvent in a 1 dm. tube) 7.2 gm. (1.2 mols) of thionyl chloride were slowly added under cooling with an ice-salt mixture. The solution was allowed to stand for 1 hour at room temperature and was then heated on the steam bath with a reflux condenser until sulfur dioxide was no longer evolved (about 15 minutes). The reaction mixture was cooled and poured into about the same quantity of crushed ice and shaken to decompose the unchanged thionyl chloride. The mixture was then extracted with ether. The ethereal extract was washed successively with ice water, with dilute sodium carbonate solution, and with water. After drying with anhydrous sodium sulfate, the ether was removed and the residue was fractionated under reduced pressure (10 mm.). The nitrile boiled at 69-70° and showed the following rotation.

\[ [\alpha]_D^{20} = \frac{-1.05\times100}{1\times10.00} = -10.5° \text{, in ether.} \]

It is soluble in ether, chloroform, and alcohol, slightly soluble in petrolic ether, and insoluble in water. It analyzed as follows:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgCl</td>
<td>Cl 30.21</td>
<td>Cl 31.66</td>
</tr>
<tr>
<td>C₆H₄NCl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.1194 gm. substance: 0.1528 gm. AgCl.

2. By Means of Phosphorus Pentachloride.—10 gm. (1.2 mols) of phosphorus pentachloride were added in small portions to 4 gm. of dextro-β-hydroxyvaleronitrile (α₀ = + 5.35° without solvent in a 1 dm. tube) under cooling with an ice-salt mixture. The reaction product was allowed to stand at room temperature until all the pentachloride had disappeared. It was then poured into ice water and the mixture was extracted with ether. The ethereal extract was treated as in the preceding preparation. The nitrile boiled at 68-70° (p = 10 mm.) and gave the following rotation.

\[ [\alpha]_D^{20} = \frac{-0.55\times100}{2\times3.4} = -8.1° \text{, in ether.} \]
The saponification of the chloronitrile and the thiolnitrile (which was prepared by adding alcoholic potassium hydrogen sulfide to the chloro compound) was unsatisfactory, although several methods were tried. Finally the chloronitrile was converted into the ester of the chloro acid as described below.

**Levo-Ethyl-β-Hydroxyvalerate.**

1. From Levo-β-Hydroxyvaleric Acid.—12 gm. of the levo-hydroxy acid (\(\left[\alpha\right]_D^{25} = -10^\circ\), in ether), obtained as a syrup by saponification of the hydroxynitrile, were treated with 40 cc. of dry ethyl alcohol containing 1.5 per cent of hydrochloric acid. The solution was gently boiled for 3 hours under a reflux condenser. An aliquot part of the solution was titrated with sodium hydroxide and the calculated amount of sodium ethylate was added to the remainder under cooling. The filtrate from sodium chloride was concentrated under diminished pressure and the residue was taken up with ether. The ethereal solution was dried over sodium sulfate. The residue from the ether was fractionated under reduced pressure. It boiled at 75.5-77° (\(p = 9.0\) mm.). It gave the following rotations.

\[
\alpha_D^{25} = -10.63^\circ, \text{ without solvent in a 1 dm. tube.}
\]

\[
\left[\alpha\right]_D^{25} = \frac{-1.56^\circ \times 100}{1 \times 10.00} = -15.6^\circ, \text{ in ether.}
\]

The ester is soluble in ether, alcohol, petrolic ether, and chloroform and very slightly soluble in water. It analyzed as follows:

4.155 mg. substance: 8.885 mg. CO₂ and 3.575 mg. H₂O.


2. From Dextro-β-Hydroxyvaleronitrile.—15 gm. of dextro-hydroxyvaleronitrile (\(\alpha_D^{25} = +7.0^\circ\), without solvent in a 1 dm. tube) were dissolved in 75 cc. of absolute (98 to 99 per cent) ethyl alcohol and the solution was saturated with dry hydrogen chloride under cooling with ice. The solution was then heated with a free flame under a return condenser. After 15 minutes ammonium chloride separated. The mixture was boiled 20 minutes longer and then cooled. To the solution some ether was
added and the ammonium chloride was filtered off. The filtrate was evaporated at as low a temperature as possible and the residue was taken up in absolute alcohol. The isolation and purification of the ester were carried out as in the preceding preparation. It boiled at 77-79° (p = 10 mm.). The yield of the crude product was 10 gm. It gave the following rotation.

\[
\left[\alpha\right]_D = \frac{-1.47 \times 100}{1 \times 10.00} = -14.7^\circ, \text{ in ether.}
\]

It analyzed as follows:

6.205 mg. substance: 13.057 mg. CO₂ and 5.335 mg. H₂O.

Depto-Ethyl-β-Chlorovalerate.

1. From Levo-β-Chlorovaleronitrile.—4 gm. of the levo-chloronitrile (α₀ = -8.30° without solvent in a 1 dm. tube) were dissolved in 32 cc. of absolute alcohol saturated with dry hydrogen chloride and the solution was refluxed for 30 minutes. After 5 minutes ammonium chloride separated. The solution was filtered from ammonium chloride and the alcohol was removed by distillation under reduced pressure. The residue was extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated under reduced pressure. During the evaporation crystals appeared in the form of plates having a mother-of-pearl luster. Petrolic ether was added and the solution was filtered. The filtrate from the crystals was concentrated and the residue was fractionated under reduced pressure. The ester boiled at 65-67° (p = 10 mm.). The yield was 2.5 gm. It gave the following rotation.

\[
\left[\alpha\right]_n = \frac{+0.35 \times 100}{1 \times 10.0} = +3.5^\circ, \text{ in ether.}
\]

It is readily soluble in ether, chloroform, petrolic ether, and alcohol, but is insoluble in water. It analyzed as follows:

0.1190 gm. substance: 0.1046 gm. AgCl.
C₇H₅O₃Cl. Calculated. Cl 21.58.
The crystals obtained above were purified by dissolving in dry ether and precipitating with petrolic ether. In this state of purity they melted at 100–102° (uncorrected) and gave the following rotation.

\[ \alpha_p^{10} = \pm \frac{0.36 \times 100}{2 \times 6.00} = +3.0^\circ \text{, in chloroform.} \]

The substance analyzed as follows:

0.0988 gm. substance: 0.1028 gm. AgCl.
7.710 mg. " : 0.8377 mg. N (micro Kjeldahl).
\( C_7H_6O_2ClN \). Calculated. Cl 26.20, N 10.33.
Found. " 25.74, " 10.86.

From the analysis and properties, it seems to us that this substance is \( \beta \)-chlorovaleronamide.

2. From Levo-Ethyl-\( \beta \)-Hydroxyvalerate by Means of Thionyl Chloride.—5 gm. of levo-ethyl-\( \beta \)-hydroxyvalerate (\( \alpha_p^{10} = -8.07^\circ \) without solvent in a 1 dm. tube) were treated with 4 gm. (1.2 mols) of thionyl chloride. The isolation and purification were carried out exactly as in the preceding section. It gave the following rotation.

\[ \alpha_p^{10} = +6.21^\circ \text{, without solvent in a 1 dm. tube.} \]

3. From Levo-Ethyl-\( \beta \)-Hydroxyvalerate by Means of Phosphorus Pentachloride.—5 gm. of levo-ethyl-\( \beta \)-hydroxyvalerate (\( \alpha_p^{10} = -8.7^\circ \) without solvent in a 1 dm. tube) were dissolved in 10 cc. of dry chloroform. 8.5 gm. (1.2 mols) of phosphorus pentachloride were added under cooling with an ice-salt mixture. The chloro ester was isolated as described above. It boiled at 66.5–67° (p = 10 mm.). It gave the following rotations.

\[ \alpha_p^{10} = +6.65^\circ \text{, without solvent in a 1 dm. tube.} \]

\[ [\alpha]_D^{10} = \pm \frac{0.54 \times 100}{1 \times 10.0} = +5.4^\circ \text{, in ether.} \]

The substance analyzed as follows:

0.1197 gm. substance: 0.0991 gm. AgCl.
\( C_7H_6O_2Cl \). Calculated. Cl 21.58.
Found. " 20.48.
Dextro-Ethyl-β-Bromovalerate.—This compound was prepared because the thiol compound from the chloro ester had a low activity. 10 gm. of levo-ethyl-β-hydroxyvalerate (α₀ = − 9.25° without solvent in a 1 dm. tube) were dissolved in 10 cc. of chloroform and 35.5 gm. (1.2 mols) of phosphorus pentabromide were then added in small portions under thorough cooling with an ice-salt mixture. The reaction mixture was allowed to stand at 0° with frequent shaking until all the pentabromide had disappeared. The time necessary was usually 3 hours. The bromo ester was isolated as in the preparation of the chloro body. It boiled at 74–76° (p = 10 mm.). The yield was 10 gm. It gave the following rotations.

\[ \alpha_0^o = + 16.1°, \text{ without solvent in a 1 dm. tube.} \]

\[ [\alpha]_0^o = \frac{\alpha_0^o}{1 \times 10.00} = + 10.8°, \text{ in ether.} \]

The substance analyzed as follows:

0.1052 gm. substance: 0.0964 gm. AgBr.
\[ \text{C}_7\text{H}_{13}\text{O}_2\text{Br}. \quad \text{Calculated.} \quad \text{Br 38.28.} \]
\[ \text{Found.} \quad \text{“ 38.99.} \]

It is very soluble in ether, chloroform, petrolic ether, and alcohol but insoluble in water.

Dextro-β-Bromovaleric Acid.—10 gm. of dextro-ethyl-β-bromovalerate (α₀ = + 14.35° without solvent in a 1 dm. tube) were treated with 80 cc. of fuming hydrobromic acid under cooling with an ice-salt mixture. The mixture was shaken for 3 days at 10°. It was then poured into about the same quantity of crushed ice and the resulting mixture was extracted several times with chloroform. The chloroform extract was washed with ice water and dried over sodium sulfate. The solvent was evaporated and the residue was fractionated under reduced pressure. After three refractionations the bromo acid boiled at 117–119° (p = 10 mm.). The yield was 3 gm. In another experiment in which the ester was saponified at 40°, the yield was much better, but considerable racemization occurred.

The bromo acid crystallized in glassy plates when allowed to
stand overnight at the temperature of solid carbon dioxide. It melted at about 30°. It is soluble in ether, chloroform, alcohol, and petrolic ether, but insoluble in water. It gave the following rotation.

$$[\alpha]_{D}^{n} = \frac{+0.63^\circ \times 100}{4 \times 1.50} = +11.0^\circ, [M]_{D}^{n} = +19.9^\circ, \text{in 35 per cent alcohol.}$$

To determine the rotation of the sodium salt, 0.2006 gm. of the above bromo acid, which corresponds to 0.225 gm. of sodium salt, was treated with 1 equivalent of sodium hydroxide under cooling and the volume was made up to 15 cc. The solution gave the following rotation.

$$[\alpha]_{D}^{n} = \frac{+0.51^\circ \times 100}{4 \times 1.50} = +8.5^\circ, [M]_{D}^{n} = +17.3^\circ, \text{in 35 per cent alcohol.}$$

The bromo acid analyzed as follows:

0.1226 gm. substance: 0.1306 gm. AgBr.

$$\text{CsHgOzBr. Calculated. Br 44.20.}$$

$$\text{Found. " 45.33.}$$

**Levo-Ethyl-ß-Thiolvalerate.—** 7 gm. of dextro-ethyl-ß-bromo-valerate ($\alpha_{D}^{n} = +14.25^\circ$ without solvent in a 1 dm. tube) were treated with 33 cc. (3 mols) of alcoholic potassium hydrogen sulfide solution. The mixture was allowed to stand overnight at 0° and then for 2 days at room temperature. It was then heated for 15 minutes on the steam bath to complete the reaction. It was poured into water and the thiol ester was extracted with ether. The ethereal extract was dried over sodium sulfate. After removal of the solvent the residue was fractionated under reduced pressure. It boiled at 75–76°. The yield was 2.5 gm. The residue from the distillation was a thick syrup which was dextrorotatory. The investigation of this substance was not pursued further.

The thiol ester gave the following rotation.

$$[\alpha]_{D}^{n} = \frac{-0.52^\circ \times 100}{1 \times 10.0} = -5.2^\circ, \text{in ether.}$$

5 The alcoholic potassium hydrogen sulfide was prepared by dissolving 20 gm. of potassium hydroxide in 100 cc. of absolute alcohol and saturating the solution with hydrogen sulfide under cooling. The total volume was 113 cc.
The thiol ester obtained from the dextro-chloro ester ([\(\alpha\)] = + 5.4° in ether) gave a rotation of only \(\alpha\) = - 0.90° without solvent in a 1 dm. tube.

2 gm. of the levo-thiol acid ([\(\alpha\)] = - 7.75° in absolute alcohol) were dissolved in 12 cc. of absolute alcohol and the solution was saturated with dry hydrogen chloride. After the solution had been allowed to stand for 3 days at 0°, the thiol ester was isolated as usual. It boiled at 71–73° (p = 10 mm.) and gave a rotation of

\[
[\alpha]_D^m = \frac{-0.99 \times 100}{1 \times 10.00} = - 9.9°, \text{ in ether}
\]

but it was not analytically pure.6

From the above result it seems to us that in the course of esterification some hydrogen sulfide was split off as in the case of the hydrolysis of the thiol ester which will be described later.

The thiol ester gives a strong nitroprusside reaction but no ferric chloride reaction. It is readily soluble in ether, petrolic ether, chloroform, and alcohol, but not in water. The substance analyzed as follows:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(<em>7)H(</em>{14})O(_3)S</td>
<td>S 19.75</td>
<td>S 19.15</td>
</tr>
</tbody>
</table>

**Levo-\(\beta\)-Thiolvaleric Acid.**—The saponification of the thiol ester was not satisfactory either by heating with water or by shaking with concentrated hydrochloric acid in the cold, since it was accompanied by the evolution of hydrogen sulfide. Hence, the thiol acid was prepared from the bromo acid by the usual method.

5.0 gm. of the dextro-bromo acid ([\(\alpha\)] = + 7.0° in ether) were treated with 10 cc. (10 mols) of 75 per cent aqueous potassium hydrogen sulfide solution. The mixture was allowed to stand for 1 day at 0° and then heated for 15 minutes on the steam bath. It was extracted with ether (when necessary) and acidified with concentrated hydrochloric acid, whereupon the thiol acid separated as an oil. It was extracted with ether and the combined ethereal extract was washed with water. After drying over

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6 C\(_7\)H\(_{14}\)O\(_3\)S. Calculated, S 19.75; found, S 16.63.
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sodium sulfate, the solvent was evaporated and the residue was fractionated. The thiol acid boiled at 112-113° (p = 10 mm.). It gave the following rotation.

\[ \alpha_D = -\frac{1.24 \times 100}{4 \times 2.00} = -15.5^\circ; [\beta_D] = -20.8^\circ, \text{ in 20 per cent alcohol.} \]

For the monosodium salt, 0.2577 gm. of the free acid, which corresponds to 0.3000 gm. of the mono-salt, was treated with 1 equivalent of sodium hydroxide and the volume was made up to 15 cc. The solution gave the following rotation.

\[ \alpha_D = -\frac{0.70 \times 100}{4 \times 2.00} = -8.75^\circ; [\beta_D] = -13.65^\circ, \text{ in 20 per cent alcohol.} \]

10 cc. of the above solution were treated with another equivalent of sodium hydroxide and the total volume was made up to 15 cc. This corresponds to 0.2282 gm. of the di-salt. The solution gave the following rotation.

\[ \alpha_D = -\frac{0.68 \times 100}{4 \times 1.52} = -11.2^\circ; [\beta_D] = -19.9^\circ, \text{ in 20 per cent alcohol.} \]

The free acid gave both a ferric chloride reaction (deep indigo blue color) and a nitroprusside reaction. It is easily soluble in ether, petrolic ether, chloroform, alcohol, and very slightly soluble in water. The free acid analyzed as follows:

0.1234 gm. substance: 0.2168 gm. BaSO₄.

C₅H₁₀O₅S. Calculated. 8 23.88.

Levo-β-Sulfovaleric Acid.

1. From Levo-Ethyl-β-Thiolvalerate.—3 gm. of the thiol ester (\(\alpha_D = -7.85^\circ\) without solvent in a 1 dm. tube) were dissolved in a mixture of 30 cc. of acetone and 3 cc. of water. To the solution 6.95 gm. of barium permanganate in 500 cc. of acetone were then added and the mixture was warmed on the steam bath near the end of the reaction. The solution was filtered from manganese dioxide and the latter was washed with acetone and with water alternately. The filtrate and the washings were combined and concentrated under reduced pressure. The residue was taken up
in a little water and extracted with ether to remove a small quantity of oily substance. The aqueous layer was made up to 50 cc. with alcohol (the resultant alcohol was 40 per cent) and this solution was treated with 7 gm. (2 mols calculated on the starting material) of Ba(OH)\(_2\)·8H\(_2\)O. The mixture was gently refluxed for 3 hours. It was then diluted with water and neutralized to litmus with dilute sulfuric acid. It was filtered from barium sulfate and the filtrate was evaporated under reduced pressure. The residue was taken up in hot water and alcohol was then added. The barium salt separated first in amorphous and then in crystalline form. After several recrystallizations it crystallized in the form of white prisms and gave the following rotation. 0.4000 gm. of dry barium salt was dissolved in water and the volume was made up to 5 cc.

\[
[a]_D = \frac{-0.81^\circ \times 100}{2 \times 8.00} = -5.06^\circ, \quad [\mathcal{M}]_D = -16.06^\circ, \text{ in water.}
\]

1 equivalent of hydrochloric acid was added and the solution was diluted to 10 cc. This corresponds to 0.314 gm. of monobarium salt. The solution gave the following rotation.

\[
[a]_D = \frac{-0.45^\circ \times 100}{2 \times 3.14} = -7.16^\circ, \quad [\mathcal{M}]_D = -17.84^\circ, \text{ in water.}
\]

To determine the rotation of the free acid, 0.6768 gm. of dry barium salt was treated with 2 equivalents of hydrochloric acid and diluted to 5 cc with water. This corresponds to 0.4000 gm. of free acid. The solution gave the following rotation.

\[
[a]_D = \frac{-1.26^\circ \times 100}{2 \times 8.00} = -7.87^\circ, \quad [\mathcal{M}]_D = -14.32^\circ, \text{ in water.}
\]

The barium salt has no melting point. It is quite soluble in water, but insoluble in alcohol. It analyzed as follows:

0.1000 gm. substance: 0.0106 gm. H\(_2\)O.

C\(_4\)H\(_6\)O\(_4\)Ba·2H\(_2\)O. Calculated. Water of crystallization 10.18.

Found. 10.60.

0.0894 gm. substance: 0.0654 gm. BaSO\(_4\) (for Ba).

0.0887 “ “ : 0.0642 “ “ ( “ S “).


Found. 43.05, 9.94.
2. From Levo-β-Thiolvaleric Acid.—1 gm. of the levo-thiol acid was dissolved in 37 cc. (2 equivalents) of 0.4 N barium hydroxide and 9 gm. of barium carbonate (6 equivalents) were then added. The mixture was treated with 4 gm. (a slight excess) of bromine under cooling with ice. The filtrate from the excess of barium carbonate was concentrated to a small volume and alcohol was then added slowly, whereupon the barium sulfonate crystallized out. It was purified by dissolving in a little hot water and precipitating with alcohol. The purified barium salt showed the following rotation.

\[
[a]_D^{\infty} = \frac{-1.20^\circ \times 100}{2 \times 7.58} = -7.92^\circ, \text{ in water.}
\]

It analyzed as follows:

| 0.0943 gm. substance: 0.0688 gm. BaSO₄ (for Ba). |
| 0.1426 " " : 0.0930 " " ( " S ). |
| Found. " 42.93, " 8.96. |

Part II. γ-Substituted n-Valeric Acids.

Levo-Ethyl-γ-Chlorovalerate.—Levulinic acid was first prepared and this was reduced to γ-valerolactone according to the directions of Losanitsch.⁷ The γ-valerolactone was resolved into its enantiomers by means of cinchonidine as described by Levene and Haller.⁸ The γ-bromo acid was easily obtained from γ-valerolactone by heating with fuming hydrobromic acid in an autoclave. However, the preparation of the thiol acid from the bromo acid was not successful, although attempted by several methods. The reaction product was always the original substance, i.e. γ-valerolactone. Therefore an attempt was made to convert the chloro acid, prepared from its ester as described below, into the thiol acid, inasmuch as the chlorine atom is not so reactive as bromine. Even this reaction was accompanied by the hydrolysis of the chlorine atom. Finally the chloro ester was

⁷ Losanitsch, M. S., Monatsh. Chem., 1914, xxxv, 303.
⁸ Levene, P. A., and Haller, H. L., J. Biol. Chem., 1926, lxix, 165. We are indebted to Dr. H. L. Haller for the active γ-valerolactone used in these experiments.
prepared essentially according to the directions of Noyes\(^9\) for the corresponding racemic form.

35 gm. of levo-\(\gamma\)-valerolactone (\(\alpha_0^\circ = -20.32^\circ\) without solvent in a 1 dm. tube) were dissolved in 140 cc. of absolute ethyl alcohol and the solution was saturated with dry hydrogen chloride under cooling with ice. After standing first at 0\(^\circ\) and subsequently at room temperature each for 1 day in a stoppered bottle, the solution was poured on crushed ice, whereupon the ester separated as an oil. It was extracted with petrolic ether and the extract was dried over sodium sulfate. The residue from the ether was fractionated under reduced pressure. It boiled at 71–73\(^\circ\) (\(p = 9\) mm.) and gave the following rotation.

\[
[a]_D^\circ = \frac{-0.79^\circ \times 100}{1 \times 4.00} = -19.7^\circ, \text{ in ether.}
\]

The chloro ester obtained from the dextro-lactone (\(\alpha_0^\circ = +4.5^\circ\) without solvent in a 1 dm. tube) gave a rotation of \(\alpha_0^\circ = +4.33^\circ\) without solvent in a 1 dm. tube and analyzed as follows:

\[
\begin{align*}
0.1046 \text{ gm. substance} & : 0.0920 \text{ gm. AgCl.} \\
C_7H_{13}O_2Cl. & \text{ Calculated.} \quad \text{Cl 21.58.} \\
& \text{Found.} \quad " \quad \text{21.76.}
\end{align*}
\]

**Levo-\(\gamma\)-Chlorovaleric Acid.**—15 gm. of the levo-chloro ester (\(\alpha_0^\circ = -5.37^\circ\) without solvent in a 1 dm. tube) were mixed with 150 cc. of fuming hydrochloric acid and the mixture was shaken at 10\(^\circ\) until solution was complete (2 days). The solution was then allowed to stand for 2 days at 40\(^\circ\). After cooling, the same quantity of crushed ice was added and the solution was extracted with chloroform. The chloroform extract was washed once with ice water and dried over sodium sulfate. After three refractionations the chloro acid boiled at 108–111\(^\circ\) (\(p = 10\) mm.). It gave the following rotation.

\[
[a]_D^\circ = \frac{-0.62^\circ \times 100}{2 \times 6.00} = -5.17^\circ, [M]_D^\circ = -7.06^\circ, \text{ in 25 per cent alcohol.}
\]

0.2584 gm. of the same sample of the chloro acid was neutralized with 1 equivalent of sodium hydroxide and the volume was made

up to 5 cc. under cooling. This corresponds to 0.3000 gm. of sodium salt. The solution gave the following rotation.

$$\left[ \alpha \right]_D = -\frac{0.41^\circ \times 100}{2 \times 0.00} = -3.42^\circ, \left[ M \right]_D = -5.42^\circ, \text{in 25 per cent alcohol.}$$

The free acid analyzed as follows:

0.1078 gm. substance: 0.1144 gm. AgCl.

C\text{\textsubscript{5}}H\text{\textsubscript{9}}O\text{\textsubscript{2}}Cl. Calculated. Cl 26.01


5 gm. of the levo-chloro acid ($\alpha_D = -6.60^\circ$ without solvent in a 1 dm. tube) were added to 25 cc. of aqueous potassium hydrogen sulfide and the mixture was allowed to stand for 3 days at 0\textdegree. An oily substance which separated was extracted with ether and the ethereal extract was dried over sodium sulfate. The residue from the ether was fractionated under reduced pressure. It boiled at 75.5-77\textdegree (p = 9 mm.). It contained neither halogen nor sulfur and was found to be y-valerolactone. It gave the following rotation.

$$\left[ \alpha \right]_D = -\frac{0.46^\circ \times 100}{1 \times 10.0} = -4.6^\circ, \text{in ether.}$$

It analyzed as follows:

5.265 mg. substance: 11.650 mg. CO\text{\textsubscript{2}} and 3.825 mg. H\text{\textsubscript{2}}O.

C\text{\textsubscript{5}}H\text{\textsubscript{9}}O\text{\textsubscript{2}}. Calculated. C 60.00, H 8.00.

Found. " 60.34, " 8.12.

Dextro-Ethyl-\gamma-Thiolvalerate.—30 gm. of the levo-chloro ester ($\alpha_D = -4.5^\circ$ without solvent in a 1 dm. tube) were treated with 145 cc. (2½ mols) of alcoholic potassium hydrogen sulfide solution. After standing at 0\textdegree and at room temperature each for 1 day, the mixture was heated at 150\textdegree for 2½ hours in a pressure bottle. The solution was cooled and poured into ice water. The ester was extracted with ether. On removal of the ether, a light yellow mobile oil remained which was fractionated under a pressure of 10 mm. The rotations given below are all for 1 dm. tubes.

<table>
<thead>
<tr>
<th></th>
<th>Weight</th>
<th>$\alpha_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F I</td>
<td>5 gm.</td>
<td>$-4.95^\circ$</td>
</tr>
<tr>
<td>F II</td>
<td>13 &quot;</td>
<td>$-3.96^\circ$</td>
</tr>
<tr>
<td>F III</td>
<td>5 &quot;</td>
<td>$0^\circ$</td>
</tr>
</tbody>
</table>
F III was redistilled.  
F I' 78-79°  
F II' 79-80°  
F III' 80-83°  
F III' was again redistilled.  
F I' 77-80°  
F II' 81-82°  
Weight = 1 gm.  
\[
\left[\alpha\right]_D = \frac{+0.17^\circ \times 100}{1 \times 10.0} = +1.7^\circ, \text{ in ether.}
\]

As above, we obtained dextro- and levorotatory substances which were both neutral to litmus. From the results of analyses and the behavior toward iodine solution the levorotatory substance is the thiolactone and the dextrorotatory is the thiol ester, although the thiolactone was not isolated in a pure state from the above preparation. To make this conclusion certain, the pure thiolactone was prepared from the thiol acid as described later.

The substances analyzed as follows:

- F I 0.1146 gm. substance: 0.1913 gm. BaSO₄. Found. S 23.28.
- F I' 0.1174 " " : 0.2024 " " " 23.68.
- F II' 0.1037 " " : 0.1554 " " " 20.59.

\[
\text{C}_7\text{H}_4\text{OS (lactone). Calculated. S 27.59.}
\]
\[
\text{C}_7\text{H}_8\text{O}_3\text{S (ester). " " 19.75.}
\]

The thiol ester has a quite unpleasant odor and gives a strong nitroprusside reaction but no ferric chloride reaction. It is easily oxidized by iodine; i.e., it decolorizes iodine solution. It is readily soluble in ether, petrolic ether, chloroform, and alcohol, but not in water.

**Dextro-\(\gamma\)-Thiolvaleric Acid.**—20 gm. of the mixture of the dextro-thiol ester and the levo-thiolactone \(\left(\alpha_D = -19.82^\circ\right)\) without solvent in a 1 dm. tube were dissolved in 200 cc. of 90 per cent alcohol containing 20 gm. of potassium hydroxide and the solution was heated on the steam bath for 2 hours under a reflux condenser. The excess of alcohol was removed by distillation under reduced pressure. The residue was diluted with ice water and acidified with concentrated hydrochloric acid under cooling, whereupon the thiol acid separated as an oil. It was then extracted with ether and the ethereal extract was dried over sodium sulfate. The thiol acid boiled at 121-122°. These operations should be
performed as quickly as possible after acidifying. It gave the following rotations.

\[ [\alpha]_{D}^{20} = \frac{+0.50^\circ \times 100}{2 \times 4.00} = +6.25^\circ, \text{in ether.} \]

\[ [\alpha]_{D}^{20} = \frac{+0.42^\circ \times 100}{2 \times 4.09} = +5.14^\circ, [M]_{D}^{20} = +6.87^\circ, \text{in 20 per cent alcohol.} \]

For the rotation of the mono-salt, 0.5000 gm. of the same sample was treated with 1 equivalent of sodium hydroxide solution and the volume was made up to 5 cc. This corresponds to 0.582 gm. of the acid salt. The solution gave the following rotation.

\[ [\alpha]_{D}^{20} = \frac{+0.37^\circ \times 100}{2 \times 11.6} = +1.56^\circ, [M]_{D}^{20} = +2.43^\circ, \text{in 20 per cent alcohol.} \]

To the above solution another equivalent of sodium hydroxide was added and the volume was made up to 10 cc. This corresponds to 0.664 gm. of disodium salt. The solution gave the following rotation.

\[ [\alpha]_{D}^{20} = \frac{+0.18^\circ \times 100}{2 \times 6.64} = +1.36^\circ, [M]_{D}^{20} = +2.40^\circ, \text{in 20 per cent alcohol.} \]

The thiol acid is very soluble in ether and alcohol, but very slightly soluble in water. It analyzed as follows:

0.1052 gm. substance: 0.1828 gm. BaSO$_4$.

\[ \text{C}_4\text{H}_6\text{O}_2\text{S}. \text{ Calculated.} \quad \text{S 23.88.} \]

\[ \text{Found.} \quad \text{S 23.74.} \]

*Levo-\(\gamma\)-Thiovalerolactone.*$^{10}$—3 gm. of dextro-\(\gamma\)-thiolvaleric acid (\(\alpha_n = +4.87^\circ\) without solvent in a 1 dm. tube) were added to 30 cc. of 10 per cent sulfuric acid and the mixture was shaken for 2 days at 40°. It was then extracted with ether and the ethereal extract was washed with water and dried first with sodium sulfate and subsequently with anhydrous potassium carbonate. After removal of the ether, the thiolactone was fractionated under reduced

$^{10}$ The inactive substance was prepared by Fries from valerolactone and phosphorus pentasulfide. Fries, K., and Mengel, H., *Ber. chem. Ges.*, 1912, xlv, 3410.
pressure. It boiled at 69-70° (p = 10 mm.). It gave the following rotation.

\[
[a]_D = \frac{-7.83 \times 100}{1 \times 10.00} = -78.3°, \text{ in ether.}
\]

The thiovalerolactone has a not unpleasant odor. It is neutral to litmus, does not decolorize iodine solution, gives no ferric chloride reaction, but gives a nitroprusside reaction. It is soluble in ether, petrolic ether, glacial acetic acid, chloroform, and alcohol, but insoluble in water. The substance analyzed as follows:

0.1015 gm. substance: 0.2144 gm. BaSO₄.
C₆H₄OS. Calculated. S 27.60.
Found. S 29.02.

*Levo-γ-Sulfovaleric Acid.*—3 gm. of the dextro-γ-thiol acid \([\alpha]_b^\circ = +6.25°, \text{ in ether}) were dissolved in 75 cc. (1 equivalent) of 0.3 N barium hydroxide and 26 gm. of barium carbonate (6 equivalents) were added. The mixture was treated with 10 gm. (6 equivalents) of bromine in small portions under cooling. The filtrate from the excess of barium carbonate was concentrated to a small volume under reduced pressure. To the solution alcohol was added, whereupon the barium sulfonate was precipitated as an amorphous substance. The precipitate was purified by dissolving in a little hot water and precipitating with alcohol. This treatment was repeated four times. The barium salt gave the following rotation.

\[
[a]_D = \frac{-0.67 \times 100}{2 \times 20.0} = -1.68°, [M]_D = -5.33°.
\]

3.0573 gm. of the same sample of barium salt were dissolved in 1 equivalent of hydrochloric acid and the volume was made up to 15 cc. This corresponds to 2.400 gm. of mono-salt. The solution gave the following rotation.

\[
[a]_D = \frac{-0.84 \times 100}{4 \times 16.0} = -1.31°, [M]_D = -3.26°.
\]

For the free sulfo acid, 4.1812 gm. of the same substance were treated with 2 equivalents of hydrochloric acid. This corresponds
Walden Inversion. XII

to 2.400 gm. of free acid. The solution gave the following rotation.

\[ [\alpha]_D^{20} = \frac{-1.24^\circ \times 100}{4 \times 16.0} = -1.94^\circ, \quad [\beta]_D^{20} = -3.53^\circ. \]

The barium salt is very soluble in water but not in alcohol. It has no melting point. It analyzed as follows:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Weight (gm)</th>
<th>Ba %</th>
<th>S %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0908</td>
<td></td>
<td>42.25</td>
<td>10.06</td>
</tr>
<tr>
<td>0.0919</td>
<td></td>
<td>42.25</td>
<td>10.09</td>
</tr>
</tbody>
</table>

C\textsubscript{4}H\textsubscript{6}O\textsubscript{5}SBa. Calculated. Ba 43.22, S 10.09. Found. " 42.25, " 10.06.
ON WALDEN INVERSION: XII. ON THE OXIDATION OF 3-THIOLVALERIC AND OF 4-THIOLVALERIC ACIDS AND ITS SIGNIFICANCE IN CONNECTION WITH WALDEN INVERSION
P. A. Levene and T. Mori


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