THE CORRELATION OF THE CONFIGURATIONS OF 2-, 3-, AND 4-SUBSTITUTED CHLORO- AND HYDROXY-ALIPHATIC ACIDS.

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The work to be reported here is a continuation of the investigations which were the subject of three previous communications.¹,² It deals with the direction of the rotations of hydroxy acids and of the corresponding halogeno acids. Levene³ in cooperation with Mikeska and with Mori reached certain conclusions regarding these relationships by studying, on one hand, the behavior of the thiol and the corresponding sulfo acids and on the other, that of the hydroxy and halogeno acids. The conclusions obtained in this manner were in harmony with the conclusions reached by Clough and by Holmberg, but were at variance with the conclusions of Freudenberg and of Kuhn and Wagner-Jauregg. A detailed discussion of the disagreement was given in the first paper of this series.¹

The following three groups of substances have been selected for our investigations. (1) Monocarboxylic acids substituted in position 2; (2) monocarboxylic acids substituted in positions 3 or 4; and (3) substituted succinic acid.

Of the first group Levene and Mikeska and Levene, Mikeska, and Mori³ have studied seven representatives, of the second Levene and Mikeska and Levene and Mori have studied three acids, and of the third, only one substance has been studied. The conclu-

² Levene, P. A., and Haller, H. L., J. Biol. Chem., 81, 703 (1929); 82, 185 (1929).
sions of these authors have been tested now by a second and independent method and the conclusions substantiated in regard to three substances; namely, (1) 2-chloropropionic acid, (2) 3-chlorobutyric acid, (3) chlorosuccinic acid.

It was felt, however, that the experience on a greater variety of compounds was desirable for a final decision of the disputed question. All of the analyzed 2-substituted thiol and sulfo acids behaved similarly in the respect which interested us; namely, the change in direction of rotation on passing from unionized state to the ionized was in the same direction in the thiol and in the sulfo acids. The observations have been extended to two additional 2-substituted acids, namely valeric and caproic acids.

In the case of the 2-substituted valeric acids the set of reactions leading to the solution of the problem of the relationship of the hydroxy and chloro acids was the following.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 & \quad \text{CH}_2 \\
\text{COOH} & \quad \text{CH}_2 & \quad \text{CH} & \quad \text{CH} & \quad \text{COOH} \\
\text{HCOH} & \quad \text{HCOH} & \quad \text{HCOH} & \quad \text{HCl} & \quad \text{HCl} \\
\text{C}_2\text{H}_7 & \quad \text{C}_2\text{H}_7 & \quad \text{C}_2\text{H}_7 & \quad \text{C}_2\text{H}_7 & \quad \text{C}_2\text{H}_7 \\
\text{Levo.} & \quad \text{Dextro.} & \quad \text{Levo.} & \quad \text{Dextro.} & \quad \text{Levo.}
\end{align*}
\]

Thus, the conclusion is in complete harmony with that of Levene and Mikeska and of Levene, Mori, and Mikeska in regard to this pair of acids and in harmony with the conclusion regarding the 2-substituted chloropropionic acids reached by the second method.

The set of reactions and the conclusions in the case of the 2-substituted caproic acids were analogous.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 & \quad \text{CH}_2 \\
\text{COOH} & \quad \text{CH}_2 & \quad \text{CH} & \quad \text{CH} & \quad \text{COOH} \\
\text{HCOH} & \quad \text{HCOH} & \quad \text{HCOH} & \quad \text{HCl} & \quad \text{HCl} \\
\text{C}_6\text{H}_9 & \quad \text{C}_6\text{H}_9 & \quad \text{C}_6\text{H}_9 & \quad \text{C}_6\text{H}_9 & \quad \text{C}_6\text{H}_9 \\
\text{Levo.} & \quad \text{Dextro.} & \quad \text{Levo.} & \quad \text{Dextro.} & \quad \text{Levo.}
\end{align*}
\]

In this series of 2-substituted hydroxy and chloro acids the changes in the direction of rotation in passing from the unionized to the ionized state are identical.
The problem of the configurational relationships of the 3- and 4-substituted acids was more complicated. In the case of 3-thiolbutyric acid and the 3-sulfo acid derived from it the changes of the direction of rotation were different in each acid. Thus the dextro-thiolbutyric acid passing from the unionized to the ionized state changed its rotation to the left, whereas the corresponding sulfo acid changed the direction to the right. On the basis of this conduct, it was concluded that in the pair, 3-chloro- and 3-hydroxybutyric acids, the state of affairs was similar; namely, the levo-3-chlorobutyric acid, which on passing from the unionized to the ionized state changed its rotation to the right was co-related to the dextro-hydroxybutyric acid, which on passing from the unionized to the ionized state changed its rotation to the left. In the light of this exceptional position of these acids, Levene and Mori have investigated the conduct of the 3-, and of the 4-thiol- and sulfovaleric acids. These acids behaved normally and it was then concluded that the 3- and the 4-chloro- and hydroxyvaleric acids were configurationally related when the changes in the direction of rotation on passing to the ionized state were identical for the chloro and for the hydroxy acids. These observations on the valeric acids seemed to confirm the impression of the exceptional position of 3-substituted butyric acids. However, subjecting the problem of the configuration of 4-chlorovaleric acid to test by the new method, the result obtained was as given in the following set of figures.

```
CH₂ CH₃ CH₃ CH₃
|    |    |    |
HCOH HCOH HCCl HCCl
|    |    |    |
CH₂ CH₂ CH₂ CH₂
|    |    |    |
CH₂ ← CH₂ → CH₂ → CH₂
|    |    |
COOH CH CH COOH
||    |
CH₂ CH₂
```

Dextro. Dextro. Levo. Levo.*

*[^M]_D, free acid = - 52.9° in 50 per cent alcohol.

[^M]_D, Na salt = - 43.3° in 50 per cent alcohol.

In this case then the two methods lead to different conclusions: According to the second method the levo-4-chlorovaleric acid is
correlated to dextro-4-hydroxyvaleric acid in the same manner as levo-3-chlorobutyric acid is correlated to dextro-3-hydroxybutyric acid and in both cases the changes in direction of rotation on passing to the ionized state are in the opposite directions for the hydroxy and for the chloro acids. For the present we are inclined to regard the correlation based on the second method as the correct one.

On the basis of these observations, one will have to conclude that the rule of the change of direction of rotation in passing from the unionized to the ionized state is applicable as a guide for configurational relationships only in 2-substituted acids. In 3- and 4-substituted acids, the rule is applicable to the correlation of hydroxy acids among themselves, but is unreliable in application to acids in which the hydroxyl is substituted by groups or atoms of different polarity.

It must be added that to date in our work the rotations were measured in the light of one wave-length only and at one temperature only. The rule of the change of direction of rotation may be found more comprehensive if the respective rotatory dispersions are measured. It is planned to do so in the near future.

We wish to add that we are conscious of the fact that the second method of correlating the configurational relationship of hydroxy and of halogeno acids would have gained much in weight if the unsaturated halides had been hydrogenated and if the hydrogenated products had been found identical with the halides prepared from the corresponding saturated carbinols. Our efforts to accomplish this end thus far have not been successful, although we have not abandoned the hope of accomplishing it at a future date.

**EXPERIMENTAL.**

*Hexen-(1)-ol-(3) (Vinylpropyl Carbinol).*—This carbinol was obtained on condensation of acrolein and propyl magnesium bromide in the usual manner.

*Resolution of Hexen-(1)-ol-(3).*—The acid phthalate of the carbinol was prepared in the usual way and then converted into the brucine salt in acetone. The resolution proceeded quite readily when 50 per cent alcohol was employed as a solvent. 

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4 We are indebted to Mr. R. E. Marker for the preparation of the carbinol.
attempt was made to obtain a carbinol of maximum optical activity. The usual procedure was employed for the isolation of the carbinol. It distilled at 133–134° at atmospheric pressure. It analyzed as follows:

4.750 mg. substance: 12.600 mg. CO₂ and 5.255 mg. H₂O.

In a 1 dm. tube αᵣ = −19.40°; [α]ᵣ = −23.4°.
In ether the rotation was

\[
[α]_D = \frac{-1.15° \times 100}{1 \times 9.87} = -11.7°.
\]

In absolute alcohol it had the following rotation.

\[
[α]_D = \frac{-2.15° \times 100}{1 \times 9.67} = -22.2°.
\]

_Dextro-3-Chlorohexene-(1)._—A solution of 19.5 gm. of levo-vinylpropyl carbinol (No. 1340) and 6 cc. of pyridine was dropped into 10 gm. of phosphorus trichloride. The reaction mixture was kept cold by immersion in an ice water bath and was constantly shaken. After the addition of the carbinol solution, the reaction mixture was allowed to stand for 1 hour and then the chloride was distilled under reduced pressure. p = 20 mm. The yield was 14 gm. It analyzed as follows:

0.1266 gm. substance: 0.1456 gm. AgCl.
No. 1347. C₆H₁₃Cl. Calculated. Cl 29.95. Found. Cl 29.03.

In a 1 dm. tube without solvent αᵣ = +17.85°.
In absolute alcohol the rotation was

\[
[α]_D = \frac{+2.13° \times 100}{1 \times 11.86} = +18.0°.
\]

In ether it had the following rotation.

\[
[α]_D = \frac{+1.85° \times 100}{1 \times 9.86} = +18.8°.
\]
Levo-2-Chlorovaleric Acid.—The chloride (No. 1347) obtained as described above was ozonized in chloroform solution in 3 gm. lots in the usual manner. The decomposition of the ozonide and the oxidation of the resulting aldehyde was effected by the procedure previously described for other unsaturated chloro derivatives. The acid distilled at 80–84°, p = 1 mm. It analyzed as follows:

0.1190 gm. substance: 0.1324 gm. AgCl.
0.1480 gm. substance required 10.95 cc. 0.1 N NaOH. Calculated. 10.84 cc.

C₇H₉O₂Cl. Calculated. Cl 26.0. Found. Cl 27.52.

In ether it had the following rotation.

\[ [\alpha]_D^{25} = \frac{-0.79^\circ \times 100}{1 \times 6.82} = -11.6^\circ. \]

0.431 gm. substance dissolved in 5 cc. of 50 per cent alcohol had the following rotation.

\[ [\alpha]_D^{19} = \frac{-1.44^\circ \times 100}{2 \times 8.62} = -8.4^\circ. \]

To 4.0 cc. of the above solution were added 2.6 cc. of 1.0 N NaOH; the rotation was observed immediately.

For the sodium salt,

\[ [\alpha]_D^{19} = \frac{-0.36^\circ \times 100}{2 \times 6.04} = -3.0^\circ. \]

Dextro-Hexanol-(3) (Ethylpropyl Carbinol).—3.5 gm. of levo-vinylpropyl carbinol (No. 1340) were dissolved in a solution of 15 cc. of glacial acetic acid and 5 cc. of water and reduced with hydrogen in the presence of colloidal palladium as catalyst. After reduction had been completed the acid was neutralized with 25 per cent sodium hydroxide and the carbinol was extracted with ether. The ether extract was dried over anhydrous potassium carbonate and after removal of the ether, the carbinol was dis-

tilled. It boiled at 130–132° at atmospheric pressure. It analyzed as follows:

4.225 mg. substance: 10.910 mg. CO₂ and 5.125 mg. H₂O.
C₆H₁₄O. Calculated. C 70.59, H 13.72.

In a 1 dm. tube without solvent αₚ = +2.75°.
In ether it had the following rotation:

\[
\alpha_p^{\text{°}} = \frac{+0.68 \times 100}{1 \times 13.1} = +5.2°.
\]

In absolute alcohol the rotation was

\[
\alpha_p^{\text{°}} = \frac{+0.45 \times 100}{1 \times 10.9} = +4.1°.
\]

**Dextro-3-Chloroheptene-(1).—**This substance was prepared in the same manner as described for dextro-3-chlorohexene-(1). The hepten-(1)-ol-(3)⁹ employed was levorotatory. \([\alpha]_p^{\text{°}} = -22.2°\) without solvent.

The chloride analyzed as follows:

0.1144 gm. substance: 0.1190 gm. AgCl.

In a 1 dm. tube without solvent αₚ = +14.60°.
In ether it had the following rotation.

\[
\alpha_p^{\text{°}} = \frac{+0.98 \times 100}{1 \times 6.10} = +16.1°.
\]

In absolute alcohol the rotation was

\[
\alpha_p^{\text{°}} = \frac{+0.98 \times 100}{1 \times 6.06} = +16.2°.
\]

**Levo-2-Chlorocaproic Acid.—**The chloride (No. 1383) obtained as described above was oxidized to the chloro acid employing the procedure described for 2-chlorovaleric acid. The acid distilled at 80–95°, p = 1 mm. It analyzed as follows:

0.1084 gm. substance: 0.1044 gm. AgCl.
C₆H₁₁O₂Cl. Calculated. Cl 23.58. Found. Cl 23.82.

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Chloro- and Hydroxyaliphatic Acids

In ether the rotation was

\[ [\alpha]_D = - \frac{0.22^\circ \times 100}{1 \times 10.3} = -2.1^\circ. \]

In 50 per cent alcohol it had the following rotation.

\[ [\alpha]_D = - \frac{0.25^\circ \times 100}{1 \times 14.2} = -1.8^\circ. \]

**Dextro-Heptanol-(3) (Ethylbutyl Carbinol).**—The relationship of levo-vinylbutyl carbinol to dextro-ethylbutyl carbinol has been described.

**Dextro-Hexen-(1)-ol-(5).**—The preparation and the resolution of the carbinol was carried out in the same manner as previously described. The carbinol distilled at 138–139° at atmospheric pressure. It analyzed as follows:

3.715 mg. substance: 9.865 mg. CO₂ and 4.035 mg. H₂O.
Found. C 72.41, H 12.15.

In a 1 dm. tube without solvent \( \alpha_D = +12.25^\circ \).

In absolute alcohol the rotation was

\[ [\alpha]_D = + \frac{1.85^\circ \times 100}{1 \times 12.3} = +15.0^\circ. \]

In ether the rotation was

\[ [\alpha]_D = + \frac{2.25^\circ \times 100}{1 \times 12.8} = +17.6^\circ. \]

**Dextro-Hexanol-(2) (Methylbutyl Carbinol).**—5 gm. of hexen-(1)-ol-(5) (No. 1209) were reduced in ether solution in the usual manner. The reduced carbinol distilled at 136–138° at atmospheric pressure.

It analyzed as follows:

3.095 mg. substance: 8.065 mg. CO₂ and 3.915 mg. H₂O.
Found. C 71.01, H 14.15.

In a 1 dm. tube without solvent \( \alpha_D = +8.25^\circ \).
In ether the rotation was

\[ [\alpha]_D = \frac{+1.50^\circ \times 100}{1 \times 10.6} = +14.1^\circ. \]

In absolute alcohol the rotation was

\[ [\alpha]_D = \frac{+1.70^\circ \times 100}{1 \times 15.6} = +10.9^\circ. \]

**Levo-5-Chlorohexene-(I).**—50 gm. of dextro-hexen-(1)-ol-(5) (No. 1200) were dissolved in 100 cc. of dry ether and gradually added to a suspension of 115 gm. of phosphorus in 250 cc. of dry ether. The subsequent procedure was the same as that described for the chlorination of penten-(1)-ol-(4).\(^\text{10}\) On distillation at atmospheric pressure a fraction was collected which distilled at 119–122\(^\circ\). This analyzed as follows:

0.1016 gm. substance: 0.1226 gm. AgCl.

No. 1219. C\(_3\)H\(_{11}\)Cl. Calculated. Cl 29.95. Found. Cl 29.84.

In a 1 dm. tube without solvent \( \alpha_D = -38.75^\circ \).

In ether the rotation was

\[ [\alpha]_D = \frac{-3.50^\circ \times 100}{1 \times 8.08} = -43.3^\circ. \]

In absolute alcohol it had the following rotation.

\[ [\alpha]_D = \frac{-4.30^\circ \times 100}{1 \times 9.84} = -43.7^\circ. \]

**Levo-4-Chlorovaleric Acid.**—The chloride (No. 1219) obtained as described above was ozonized in chloroform solution. The procedure was the same as described under 2-chlorovaleric acid. The acid distilled at 95–100\(^\circ\), \( p = 1 \) mm.

It analyzed as follows:

0.1276 gm. substance: 0.1452 gm. AgCl.


0.1855 gm. substance required 12.80 cc. 0.1 N NaOH. Calculated. 13.6 cc.

Chloro- and Hydroxyaliphatic Acids

In ether the rotation was

\[
\left[\alpha\right]_b^\circ = \frac{-9.00^\circ \times 100}{2 \times 11.0} = -40.9^\circ.
\]

0.397 gm. substance was dissolved in 5 cc. of 50 per cent alcohol. For the free acid

\[
\left[\alpha\right]_b^\circ = \frac{-6.17^\circ \times 100}{2 \times 7.94} = -38.9^\circ.
\]

To 3 cc. of the above solution were added 1.75 cc. of 1.0 N NaOH and 0.6 cc. of absolute alcohol. For the sodium salt

\[
\left[\alpha\right]_b^\circ = \frac{-2.83^\circ \times 100}{2 \times 5.17} = -27.4^\circ.
\]
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