THE CONFIGURATIONAL RELATIONSHIPS OF 2-HYDROXY, 3-HYDROXY, AND 4-HYDROXY ACIDS.*

II. CONVERSION OF DEXTRO-1-AMINO-3-HYDROXY BUTANE INTO DEXTRO-1,3-DIHYDROXY BUTANE.

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In previous publications the following facts and conclusions bearing on the present problem have been emphasized.

1. Dextro-3-hydroxybutyric acid was converted into dextro-1-amino-2-hydroxypropane.

2. On deamination of the above base, prepared either from 3-hydroxybutyric acid or from propylene oxide, a dextrorotatory product was obtained. The substance had the correct boiling point for propylene glycol. When larger quantities of the amine were available and the product of deamination could be fractionated, a fraction was obtained which analyzed correctly for propylene glycol.

3. From the products described in (2) a diurethane was obtained which analyzed correctly for the diurethane of propylene glycol. The rotation of the substance was in the opposite direction from that of the amine and from that of its deamination product.

4. Dextro-lactic acid was reduced to propylene glycol. The glycol was not always isolated in pure form. In every case the product rotated in the same direction as the parent acid and in every case it was unmistakably identified in the form of its diu-

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rethane which was levorotatory. In (3) it was shown that the levo-diurethane is a derivative of dextro-propylene glycol.

5. Inasmuch as from the two parent substances, dextro-3-hydroxybutyric and dextro-lactic acids, levorotatory diurethanes were obtained, and inasmuch as the reactions leading to the diurethanes did not involve any operation on the asymmetric carbon atom, it is to be concluded that the two parent substances are configurationally related.

6. Dextro-3-hydroxybutyric acid was reduced to dextro-1,3-dihydroxybutane. It was identified as its di- (phenylurethane) which was dextrorotatory.

7. Dextro-4-hydroxyvaleric acid was converted into dextro-1-amino-3-hydroxybutane, which on deamination gave a dextrorotatory product.

Points (6) and (7) were indicative of a configurational relationship between dextro-3-hydroxybutyric and dextro-4-hydroxyvaleric acids. More rigorous proof, however, was desired and such was furnished by the results of the experiments to be presented in this communication. A larger quantity of dextro-1-amino-3-hydroxybutane was prepared and this was deaminated. The product of the reaction was distilled under reduced pressure. The fraction distilling at 103–107°C and 14 mm. pressure was collected. 1,3-Dihydroxybutane described by Halpern2 boiled at 114°C and 20 mm. pressure. The product obtained by us had a specific rotation of \( \alpha = +18.5^\circ \) and analyzed as follows:

\[
\begin{align*}
\text{C} & \quad 50.82, \quad \text{H} \quad 11.08. \quad \text{Theory requires C 53.33, H 11.11.} \\
\end{align*}
\]

The yield from 10 gm. of the amine hydrochloride was about 2 gm. From this product a di- (phenylurethane) was obtained, the yield of which was nearly theoretical. It analyzed correctly and had a specific rotation of \( \alpha = +55^\circ \). Thus, a dextrorotatory diurethane of 1,3-dihydroxybutane was prepared from the reduction product of dextro-3-hydroxybutyric and from dextro-4-hydroxyvaleric acids. Inasmuch as each of the acids has only 1 asymmetric carbon atom and inasmuch as this carbon atom was not involved in the set of reactions leading to the diurethane, it is evident that the two substances are configurationally related.

It is noteworthy that the ratio of the specific rotation of the diurethane to that of the product of reduction of the 3-hydroxybutyric acid on one hand, and of the diurethane to the deamination product of 1-amino-3-hydroxybutane on the other hand, is the same; namely, 3:1. From this the conclusion may be drawn that the direction of rotation of the product of deamination of the hydroxy base and that the reduction product of 3-hydroxybutyric acid are determined by the direction of the rotation of the glycol. Indeed, in the series lactic acid and 3-hydroxybutyric acid a similar conclusion was drawn from the experimental results obtained. Granting that this conclusion is correct, it follows that configurationally related 1-amino-3-hydroxybutane and 1,3-dihydroxybutane rotate polarized light in the same direction. It must be added, however, that the conclusion regarding the configurational relationship of 4-hydroxyvaleric and 3-hydroxybutyric acids does not depend on the conclusions regarding the direction of the rotations of the glycols. Their configurational relationship is rigorously proven by the fact that the urethanes of the glycols prepared from them rotate in the same direction.

Thus, it is definitely established that dextro-lactic, dextro-3-hydroxybutyric, and dextro-4-hydroxyvaleric acids are configurationally related.

It is noteworthy that in all these acids the metallic salts have a lower dextrorotation than the corresponding free acids. This relationship was found previously to be the property of the 2-substituted acids belonging to the l series. This property was made a basis for a rule of differentiating between 2-substituted acids of the l and d series. The rule may be now extended also to acids substituted in positions 3 or 4.

The 1-amino-3-hydroxybutane used in the experiments described in the present communication was prepared from 4-hydroxyvaleric acid by the Curtius method. However, one step of the original process had to be modified; namely, when the symmetrical di-(hydroxybutyl) urea formed by the Curtius process was hydrolyzed by means of hydrochloric acid according to directions of Curtius, the resulting hydroxyamine was nearly entirely racemized so that it could not be used for further work. This occurrence was unexpected inasmuch as the hydrolysis with hydrochloric acid of di- (hydroxypropyl) urea was accomplished with only moderate racemization.
The extreme degree of racemization, however, was avoided when the substituted urea was hydrolyzed by means of barium hydroxide. This success may be attributed to the fact that in the alkaline hydrolysis the time and the temperature of reaction were reduced from those necessary to accomplish the same reaction by acid hydrolysis.

It may be added that this modified method of Curtius gave a better yield of the base in proportion to the parent 4-hydroxyvaleric acid than the process of Hofmann.

SUMMARY.

1. By a modification of the Curtius method it was possible to prepare a considerable quantity of dextro-1-amino-3-hydroxybutane.

2. From the deamination product of the base it was possible to obtain a product which has a boiling point approaching that of 1,3-dihydroxybutane and which rotates polarized light in the same direction as the parent amine.

3. From the product referred to in (2) a di-(phenylurethane) was obtained which rotated polarized light in the same direction as the di-(phenylurethane) obtained from the product of reduction of the dextro-3-hydroxybutyric acid.

4. The conclusion is therefore reached that dextro-3-hydroxybutyric and dextro-4-hydroxyvaleric acids are configurationally related and that both are configurationally related to dextro-lactic acid. Hence, the three substances belong to the \( l \) series.

5. The free dextro-4-hydroxyvaleric acid has a higher dextro-rotation than its metallic salts and in this respect behaves as lactic and 3-hydroxybutyric acids of the \( l \) series.

EXPERIMENTAL.

Sym-Di-(Levo-n-3-Hydroxybutyl) Urea.—This substance was obtained by the procedure previously described.\(^3\) Levo-\( \gamma \)-valerolactone \([\alpha]_D^{23} = -24.4^\circ\) was converted into the hydrazide, which was then converted into the urea derivative. In absolute alcohol it had the following rotation.

\[
[\alpha]_D^{23} = \frac{-1.35^\circ \times 100}{1 \times 3} = -45^\circ.
\]

Dextro-3-Hydroxybutyl Amine. 7.0 gm. of the above urca derivative were dissolved in 125 cc. of water and 14 gm. of hydrated barium hydroxide added. The mixture, in a round bottom flask under a return condenser, was brought to the boiling point during the course of 10 minutes. Gentle boiling was then maintained for 5 minutes. The mixture was cooled to 5°C. and filtered on a Buchner funnel. The filtrate was again treated with barium hydroxide (7 gm.), the mixture cooled, and carbon dioxide passed into it until precipitation of the barium carbonate was completed. After filtering, the solution was made acid to Congo red with hydrochloric acid and concentrated under diminished pressure to a thick syrup. For purification, the substance was converted into the chloroplatinate, which, after one recrystallization from methyl alcohol, melted with decomposition at 206°C. It analyzed as follows:

\[
0.1024 \text{ gm. substance} : 0.0631 \text{ gm. CO}_2 \text{ and } 0.0388 \text{ gm. H}_2\text{O.}
\]

\[
0.1012 \quad " : 0.0334 \quad " \text{ Pt.}
\]

\[
\text{C}_9\text{H}_2\text{O}_2\text{N}_2\text{PtCl}_4 \cdot 2\text{HCl. Calculated. C 16.33, H 4.08, Pt. 33.1. Found. " 16.80, " 4.24, " 32.94.}
\]

In water it had the following rotation.

\[
[\alpha]_D = +1.55^\circ \times \frac{100}{2 \times 9.0} = +8.6^\circ.
\]

Dextro-1,3-Dihydroxybutane.—15.6 gm. of the above 3-hydroxybutylamine chloroplatinate were dissolved in 150 cc. of water and the platinum was precipitated with hydrogen sulfide. After filtering, the solution was concentrated under diminished pressure to 45 cc. It contained 0.639 gm. of nitrogen, all of which was present as amino nitrogen. This solution had the following rotation.

\[
[\alpha]_D = +3.15^\circ \times \frac{100}{2 \times 13.3} = +11.8^\circ.
\]

The above solution was deaminated with potassium nitrite. The nitrite, dissolved in a small amount of water, was slowly added to the solution which was vigorously shaken and at first was kept cold (5°C.). After 2 equivalents of nitrite had been introduced, the solution was warmed to room temperature and the addition of nitrite continued until 6 equivalents had been added. The solution was warmed on the water bath, cooled to room tempera-
ture, 2 equivalents of hydrochloric acid added, and then 2 equivalents of potassium nitrite. The solution was then free of amino nitrogen and was acid to litmus paper but not to Congo red. It was evaporated to dryness under diminished pressure and the residue extracted with a solution of 2 parts of alcohol and 1 part of ether. After removal of the solvent, the glycol was distilled. It boiled at 103–107°C. (p = 14 mm.).

In absolute alcohol it had the following rotation.

\[
\left[\alpha\right]_D^{25} = \frac{1.85 \times 100}{1 \times 10} = +18.5^\circ.
\]

0.1028 gm. substance: 0.1916 gm. CO₂ and 0.1018 gm. H₂O.
C₄H₁₀O₂. Calculated. C 53.33, H 11.11.
Found. “ 50.82, “ 11.08.

Diurethane of 1,3-Dihydroxybutane.—1 part of the above glycol and 3 parts of phenylisocyanate in a flask provided with a calcium chloride tube were heated in a metal bath at 100°C. for 45 minutes. The reaction mixture crystallized on standing overnight. It was washed several times with petroleum ether and then recrystallized from 80 per cent alcohol. The recrystallized substance melted at 122–123°C. and analyzed as follows:

0.0984 gm. substance: 0.2374 gm. CO₂ and 0.0554 gm. H₂O.
0.1000 “ “ : required 6.05 cc. 0.1 N HCl.

In absolute alcohol it had the following rotation.

\[
\left[\alpha\right]_D^{25} = \frac{1.70 \times 100}{1 \times 3.1} = +54.8^\circ.
\]

Since this paper has been submitted for publication, we have prepared dextro-β-butylene glycol from acetaldol by reduction with yeast, as described by Neuberg and Kerb. The glycol thus obtained was converted into a di-(phenylurethane) which was dextrorotatory. The ratio of the specific rotation of the urethane derivative to the specific rotation of the glycol was approximately 3:1. Thus, the above conclusions are further substantiated.

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