

[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO.]

THE C₄-SACCHARINIC ACIDS. II. THE PREPARATION AND
RESOLUTION OF dl-1,3-DIHYDROXY-BUTYRIC ACID.
SOME DERIVATIVES OF THE OPTICALLY-
ACTIVE ACIDS.

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The first two C₄-saccharinic acids to be prepared in this laboratory and studied in detail, were the two optically-active 2,3-dihydroxy-butyric acids.² The present paper is a report of the results of a similar study of the optically-active 1,3-dihydroxy-butyric acids. The object of this work is to provide material with which to study the properties of the saccharinic acids, to find means of identifying the individual acids, and to devise methods for separating them from each other in such mixtures as are obtained when sugars are treated with alkalis.

The acid under consideration has been obtained in its inactive form by Nef³ and his students in the course of their work on the effect of alkalis on the various sugars. Nef not only obtained the *dl*-acid but resolved it into the active components and proved the configuration of the *d*-acid



to be CH₂.OH.C.C.-COOH by oxidation to *d*-malic acid. He also gives



some information as to constants of the brucine salt, phenylhydrazide and lactone of the *dl*-acid, as well as the brucine salt, quinine salt and lactone of the *d*-acid and the brucine salt of the *l*-acid. His study of the *l*-acid was apparently very superficial.

The *dl*-acid and the *dl*-calcium salt have been prepared also by Raske⁴ in the course of his investigation of the action of cyanides on chlorinated aldehydes. He obtained from 2-chloro-propionaldehyde and cyanides, 1-oxy-3-chloro-butyric acid which was converted into 1,3-dihydroxy-butyric acid when boiled with water.

The above is a summary of all the work that has been published on the acid under consideration. Neither of the methods by which the acid had been prepared was considered suitable for the object of the work below. It was therefore prepared, by a method similar to Raske's, from 2-hydroxy-propionaldehyde by the addition of hydrogen cyanide and subsequent

¹ The dissertation of which this paper is a condensation was presented by Frank V. Sander as part fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Chicago. The original dissertation is on file in the University of Chicago Library.

² Glattfeld and Miller, *THIS JOURNAL*, **42**, 2314 (1920).

³ Nef, *Ann.*, **376**, 1-120 (1910). Upson, *Am. Chem. J.*, **45**, 458 (1911).

⁴ Raske, *Ber.*, **45**, 725 (1912).

hydrolysis of the nitrile. In the course of this study, Nef's entire work on this acid was repeated and the study of the *l*-acid completed.

Experimental Part.

The starting material for the synthesis was acrolein which had been prepared from dry glycerin and anhydrous magnesium sulfate, according to the method of Witzemann.⁵ The crude acrolein was introduced into a steel cylinder with 4 volumes of water⁶ and heated in a boiling water-bath for 20 hours. The solution was then subjected to complete distillation at 60° and 14 mm. in one operation by siphoning liquid into the distilling flask as fast as water distilled. The gummy residue was then distilled from an oil-bath at a low temperature and pressure. It was found that a much higher yield could be obtained when the total quantity of gummy residue was subjected to distillation in one operation than if divided into 4 portions, as suggested by Nef, and each portion subjected to distillation separately. The best results were obtained when the temperature of the oil-bath was kept about 10° above that of the vapor in the flask, and it was only by very slow and careful distillation that maximum yields could be obtained from the crude aldehyde. The yield of redistilled aldehyde of boiling range 80–86° at 14 mm. from 400 cc. of crude acrolein, averaged 95 g. The pure aldehyde can be redistilled with practically no decomposition and may be considered a fairly stable substance.

The pure aldehyde dissolved in water was treated with hydrogen cyanide, etc., in the usual manner. The hydrolysis of the nitrile was effected with conc. hydrochloric acid. The black gum which remained after subjecting the reaction mixture to complete distillation was extracted with boiling ethyl acetate and with hot ether. The acid recovered from these solutions was again extracted with hot ether. The average yield of the clear, yellow, mobile acid recovered from the ether was about 70% of the amount calculated from the pure aldehyde. The crude acid was converted into the calcium salt by means of calcium carbonate, and trituration with alcohol, etc. From 92 g. of crude acid there was obtained an average yield of 92 g. of dry powdery salt.

Pure dl-Acid.—The acid gum obtained from the calcium salt by means of oxalic acid, etc., was first dried as completely as possible in a boiling water-bath at 14 mm. A glycerine-bath was then substituted for the water-bath and the water pump was replaced by an oil pump. A perfectly clear, mobile, and in some cases odorless, liquid distilled over, boiling point at 4 mm. 104°, and at 3 mm. 102°. The distillate was titrated with 0.1 *N* sodium hydroxide with the following results.

⁵ Witzemann, *THIS JOURNAL*, **36**, 1766 (1914).

⁶ Nef, *Ann.*, **335**, 219 (1904).

	Sample. G.	0.1 N NaOH. For free acid. ⁷ Cc.	Total required. Cc.	Calc. for C ₄ saccha- rinic acid lactone. Cc.
I	0.2462	0.05	24.18	24.14
II	0.2832	0.05	27.90	27.77

It is evident that the liquid was practically pure lactone. It is soluble in about 12 parts of warm ether.

Five g. of the lactone, with phenyl hydrazine, etc., gave 8.53 g. of crystals, m. p. 130°. The melting point was unchanged when the substance was recrystallized. As Nef reports a melting point of 130° for his *dl*-hydrazide from *l*-arabinose, these two substances were evidently identical.

The Resolution of the *dl*-1,3-Dihydroxy-butyric Acid.—To 36 g. of the acid lactone which had a boiling point of 102° at 3 mm., was added, in one liter of water, 165 g. of brucine. After the usual procedure⁸ 182 g. of crude brucine salts was obtained. A sample of this crude salt after a treatment with benzene to remove any free brucine and drying to constant weight over sulfuric acid *in vacuo*, was found to have a specific rotation of -26.73° , *i. e.*, 1 g. in 24 g. of water at approximately 20° gave $\alpha = -2.16^\circ$ in a 2 dcm. tube; sp. gr. 1.010.

The *dl*-brucine salt was now dissolved in twice its weight of hot water. The solution was allowed to stand overnight during which time crystals were deposited (Crop I from water, see below) which were removed by filtration. The filtrate was concentrated until the ratio of water to salt was again 2:1. This solution again yielded a crop of crystals. When no more crystals could be obtained in this way from water, the solution was subjected to complete distillation at 60° and 14 mm. and the residue dissolved in 10 parts of boiling absolute alcohol. When the solution had cooled, the crystals deposited (Crop I from alcohol, see below) were removed by filtration, and the filtrate concentrated until the ratio of salt to alcohol again was 1:10. This process was continued until no more crystals could be obtained. The following table shows the results. The crystals were dried to constant weight *in vacuo* over sulfuric acid, and in each case a 1g. sample was dissolved in 24 g. of water. The specific gravity was found to be 1.010 and readings were taken in a 2dcm tube at approximately 20°.

Crops I, II and III from water were united and recrystallized from 2 parts of water. This process gave 65 g. of crystals. The specific rotation was -20.79 . Six subsequent recrystallizations from 2 parts of water gave crops each of which had a specific rotation of -20.79° . This indicates that the substance was the pure brucine salt of one of the optical components of the *dl*-acid. The melting point of this brucine salt was 169°.

⁷ Ref. 2, p. 2317, footnote.

⁸ Glattfeld and Hanke, THIS JOURNAL, 40, 976 (1918), footnote.

FROM WATER.			α .		
Crop.	Parts of water used.	Weight. G.	Observed.	$[\alpha]_D^{20}$.	
I	2	49	-1.68°	-20.79°	
II	2	8	-1.71°	-21.16°	
III	1	20	-1.72°	-21.28°	
Residue		104			

FROM ABSOLUTE ALCOHOL.			α .		
	Parts of alcohol used.	Weight. G.	Observed.	$[\alpha]_D^{20}$.	
I	10	75	-2.77°	-34.28°	
II	10	18	-3.09°	-38.23°	
III	10	1	-3.18°	-39.35°	
Residue		9.2			

Crops I, II and III from alcohol were united and recrystallized from 10 parts of alcohol, and thus 78 g. of crystals was obtained with a specific rotation of -32.67° . Six subsequent recrystallizations from 10 parts of absolute alcohol gave crops each of which had a specific rotation of -32.67° . This indicates that the substance was the pure brucine salt of the other optical component of the *dl*-acid. The melting point of this acid was 169° .

In all cases of recrystallization from alcohol, the mother liquors when concentrated *in vacuo* at 60° yielded second crops of crystals, the specific rotations of which were much higher than -32.67° , the invariable rotation of the first crops. That this was due to free brucine was shown as follows. When separate samples from Crops I, II and III, from alcohol, $[\alpha]_D^{20}$ -34.28 , -38.23 , -39.35 , respectively, were refluxed for 2 hours with benzene, the specific rotations of the extracted brucine salts fell in each case to -32.67° and the benzene was shown to contain brucines. Hydrolysis was not observed in the case of recrystallization of the pure brucine salt of low rotation from water. This salt is apparently perfectly stable in water solution. Furthermore the specific rotation of this salt was not changed after it had been boiled for 2 hours with benzene under a reflux condenser.

The Optically-active 1,3-Dihydroxy-butyric Acids.—The active acids were obtained by the usual method⁹ from the pure brucine salts by treatment with barium hydroxide, etc. The crude acid was distilled at 3 mm. and the distillate in each case was a perfectly colorless, transparent, mobile, odorless liquid with a boiling point of 96° . The yield from 100 g. of brucine salt $[\alpha]_D^{20} -20.79^\circ$, was 18.0 g. and from 100 g. of brucine salt $[\alpha]_D^{20} -32.67^\circ$, was 17.8 g.

The specific rotations of the two acids were now determined with the following results. In each case an exactly 4% solution was used in a 2 dcm. tube. The specific gravity was 1.010 and observations were made at approximately 20° .

The figures show that equilibrium between free acid and lactone was reached in water solution at ordinary temperatures in 7 days. Experi-

⁹ Ref. 8, p. 981, footnote.

	α . Obs. 5 min.	α . Obs. 7 days.	α . Obs. 12 days.	$[\alpha]_D^{20}$. 5 min.	$[\alpha]_D^{20}$. 7 days.	$[\alpha]_D^{20}$. 12 days.
Acid from -20.79° brucine salt.....	+1.64°	+1.21°	+1.21°	+20.29°	+14.97°	+14.97°
Acid from -32.67° brucine salt.....	-1.62°	-1.20°	-1.20°	-20.05°	-14.86°	-14.86°

ments with these acids showed that equilibrium was reached at 100° in water solution in 4 hours.

Samples of the two acids were titrated with the following results.

	Sample. G.	0.1 N NaOH.		Calculated for C ₆ -sac- charinic acid. Cc.
		For free acid. Cc.	Total re- quired. Cc.	
Acid from -20.79° brucine salt I.....	0.3759	0.05	36.87	36.85
II.....	0.2531	0.10	24.74	24.81
Acid from -32.67° brucine salt I.....	0.3117	0.05	30.48	30.56
II.....	0.2001	0.05	19.48	19.62

The above results show that the acids were practically entirely in the form of lactone.

Proof of Configuration of the Optically-active Acids.—Although Nef¹⁰ had already proved the configuration of the acid of positive rotation, which he obtained from *l*-arbinose, by oxidizing it to *d*-malic acid, his work was repeated and the acid of negative rotation also oxidized. The procedure outlined by Glattfeld and Miller in the first paper,² was followed. In each case 5 g. of the optically-active acid was oxidized, and the experimental data thus obtained are tabulated below. An exactly 4% solution was observed in a 2cm. tube at approximately 20° . The specific gravity was determined as 1.010.

Oxidation of acid.	Insoluble calcium salt obt. G.	Cryst. acid obt. from calcium salt. G.	α . Observed of cryst- allized acid.	$[\alpha]_D^{20}$ of cryst- allized acid.	M. p. of cryst. acid. ° C.
1. Positive ro- tation.....	3.42	2.37	+ .27°	+3.34°	101
2. Negative ro- tation.....	3.24	2.17	- .26°	-3.22°	101

The following results were obtained by titration of the 2 crystalline acids obtained as oxidation products of the 2 dihydroxy acids.

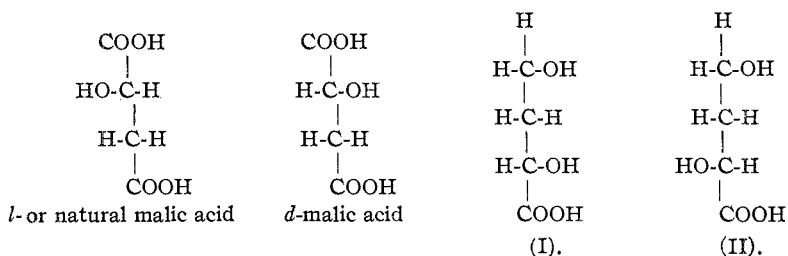
	Sample. G.	0.2 N NaOH.	
		Used. Cc.	Calculated for malic acid. Cc.
+3.34° acid I.....	0.5106	38.21	38.11
II.....	0.4987	37.10	37.18
-3.22° acid I.....	0.3061	22.90	22.84
II.....	0.3893	29.21	29.05

When natural or *l*-malic acid was purified in the same way as the acid obtained above by the oxidation of the dihydroxy-butyric acid of negative

¹⁰ Nef, *Ann.*, **376**, 36 (1910).

rotation, it was found to have a specific rotation of -3.34° and a melting point of 101° . These constants are practically the same as those of the crystalline acid from the oxidation of the dihydroxy-butyrac acid of negative rotation. That the two acids were identical was finally shown by a mixed-melting-point determination. A mixture of the 2 acids melted at 101° .

The above facts show that the acid having $[\alpha]_D^{20} - 14.86^\circ$ gives natural or *l*-malic acid which has the following configuration, as was shown by Fischer.¹¹



Of the two 1,3-dihydroxy-butyrac acids only the one with the configuration I (above) can give *l*-malic acid. This must then be the configuration of the dihydroxy-butyrac acid $[\alpha]_D^{20} - 14.86^\circ$ and it must be called *l*-1,3-dihydroxy-butyrac acid. In the same way Configuration II (above) must be the configuration of the acid $[\alpha]_D^{20} + 14.97$ since it gives by oxidation *d*-malic acid, and it must be called *d*-1,3-dihydroxy-butyrac acid

Some Derivatives of the Active Acids.

The Strychnine Salts.—The strychnine salts were obtained as well defined crystals from alcohol, but seemed to be hydrolyzed quickly by water.

The Quinine Salts.—The quinine salts were made from the pure *d*- and *l*-acids in the usual manner except that the solutions were extracted with chloroform instead of benzene to remove free quinine. The quinine salt of the *d*-acid crystallized from 2 parts of absolute alcohol and the salt of the *l*-acid from 4 parts of absolute alcohol. Thus the solubilities of these 2 salts are the reverse of those of the brucine salts, a fact which may be of value in some cases of separation. The following constants were determined.

	Quinine salt.	α . Observed.	$[\alpha]_D^{20}$	M. p. ° C.
(a)	<i>d</i> -acid	-4.30°	-106.4°	149
(b)	<i>l</i> -acid	-9.93°	-122.9°	149

(a) 0.3000 g. present in 7.5 g. of water. The angle of rotation was observed in a 1dcm. tube at approximately 20° ; sp. gr. taken as 1.010.

(b) 1.000 g. present in 25.00 g. of water. The angle of rotation was observed in a 2dcm. tube at approximately 20° ; sp. gr. taken as 1.010.

The Calcium Salts.—The calcium salts of the pure *d*- and *l*-acids were

¹¹ Fischer, *Ber.*, 29, 1378 (1896).

made. After treatment with excess calcium carbonate, filtration, and complete distillation of the clear filtrate *in vacuo*, a solid porous white mass was obtained, whereas with the *dl*-acid a clear yellow gum was obtained at this point. The crude salts were recrystallized from water. When 2 parts of water were used a moist pliable mass of interwoven needle-like crystals was obtained, while in 3 parts of water very few crystals were formed.

From 5 g. of *d*-1,3-dihydroxy-butyric acid, there was obtained from water 5.57 g. of a beautifully crystalline salt which after several recrystallizations from 2 parts of water gave a constant specific rotation of $+17.08^\circ$, *i. e.*, an exactly 4% aqueous solution in a 1dcm. tube at approximately 20° gave $\alpha + 0.69^\circ$; sp. gr. taken as 1.010. This salt decomposes when heated at $220\text{--}225^\circ$.

The calcium salt of the *l*-acid was made in exactly the same way as that of the *d*-acid. This salt was made twice from the lactones of $[\alpha]_D^{20} -20.91^\circ$ and -20.05 , the rotation of each lactone being taken after 5 minutes in solution. The first crops from 2.5 parts of water had specific rotations of -8.66° and -3.80 . Evidently these crops were not the normal salts of the acid.¹² The filtrates from these first crops of crystals were concentrated and the residues dried completely at 100° and 14 mm. The gummy residues were then made crystalline by trituration with absolute alcohol. The salts so obtained were apparently the normal salts of the acid as was shown by their specific rotations -17.33° and -17.01° , respectively.

An analysis of the calcium salts of the *d*- and *l*-acids was made. The salts were ignited to constant weight in a platinum crucible with the following results.

Calcium salt. Rotation.	Sample, G.	Constant wt. dried at 100° . G.	Loss of water %.	Constant wt. of ash. G.	CaO. %.
$+17.08^\circ$	0.3503	0.3103	11.42	0.0627	17.89
-17.33°	0.3169	0.2806	11.45	0.0568	17.92
Calc. for $\text{Ca}(\text{C}_4\text{H}_7\text{O}_4)_2 \cdot 2\text{H}_2\text{O}$			11.46		17.83

The cinchonine and barium salts and the phenylhydrazides of the two pure acids were made but all proved to be gums.

Summary.

dl-1,3-Dihydroxy-butyric acid has been prepared from 2-hydroxy-propionaldehyde. The resolution of the *dl*-acid, by means of brucine, into the optical components is reported. Configurations are assigned to the two forms of the acid and proofs of the correctness of these configurations are given. The following constants for the *d*- and *l*-forms of the acid, and some of the derivatives, are given.

¹² The exact nature of these salts has not been determined. A thorough investigation of the calcium salt formation in these cases will be taken up as soon as opportunity offers.

	After 5 min. [α] _D ²⁰ .	At equilibrium. [α] _D ²⁰ .	B. p. at 3 mm. ° C.	Brucine salts. [α] _D ²⁰ .	M. p. ° C.	Quinine salts. [α] _D ²⁰ .	M. p. ° C.	Calcium salts. [α] _D ²⁰ .
<i>d</i> -Acid	+20.29°	+14.97°	96	-20.79°	169	-106.4°	149	+17.08
<i>l</i> -Acid	-20.05°	-14.86°	96	-32.67°	169	-122.9°	149	-17.33

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[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO.]

THE PREPARATION OF OPTICALLY-ACTIVE HYDRAZINES.
 II. THE PREPARATION OF *dl-p*-SECONDARY-BUTYL-PHENYLHYDRAZINE. THE RESOLUTION OF
dl-p-SECONDARY-BUTYL-ANILINE.

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As stated in the first paper² of this series these attempts to prepare some optically-active phenylhydrazines have been undertaken in order to supply another set of reagents to supplement the alkaloids in the resolution of such *dl*-hydroxy acids as the saccharinic acids.³ Furthermore the hope has been entertained that methods of preparation might be found which would make some of the optically-active hydrazines much less expensive than the alkaloids ordinarily used. In the previous attempt only the *dl-p*-trimethylethyl-phenylhydrazine was prepared, such attempts as were made to obtain one of the active forms having failed. In the work reported below it was again found impossible in the time at hand to isolate the active forms of the hydrazine prepared (*sec*-butyl-phenylhydrazine) although the hydrazine was obtained in the *dl* form and the active forms of the corresponding aniline were isolated. In the light of our work up to the present time, it does not seem impossible ultimately to succeed in obtaining some of the active phenylhydrazines and our attempts will therefore continue. In the present paper we report as briefly as seems possible those results of our work that appear to us to be of some general interest or importance.

The plan for the preparation of the optically-active *p-sec*-butyl-phenylhydrazines included first the preparation of *dl-sec*-butyl-aniline, then the resolution of this compound into the two optical isomers, and finally the preparation from these, of the active phenylhydrazines.

In order to prepare *dl-p-sec*-butyl-aniline it was necessary first to pre-

¹ The dissertation of which this paper is a condensation was presented by E. Wertheim as part fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Chicago. The original dissertation is on file in the University library.

² Glattfeld and Milligan, *THIS JOURNAL*, **42**, 2322 (1920).

³ Glattfeld and Miller, *ibid.*, **42**, 2314 (1920).