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

THE C_4-SACCHARINIC ACIDS. IV. THE PREPARATION OF THE TWO *dl*-1,2-DIHYDROXYBUTYRIC ACIDS

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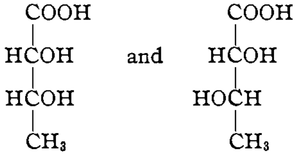
As has been stated in previous papers, the preparation of the C_4-saccharinic acids has been undertaken in order to supply data on these acids that may be of value to workers in the sugar field. Our main object, however, has been to supply these data as a preliminary to a study of the mechanism of saccharinic acid formation from the tetroses and other simple sugars, which study it is hoped to make in this Laboratory when the necessary information as to the properties of the theoretically possible products of such action has been obtained.

The work reported in this paper is a continuation of previously reported work. Of the eleven theoretically possible C_4-saccharinic acids (the dihydroxybutyric and -*iso*butyric acids), the two active 2,3-dihydroxybutyric acids,[2] the two active 1,3-dihydroxybutyric acids[3] and *dl*-1,2-dihydroxy-*iso*butyric acid,[4] have already been prepared and studied to some extent. This paper reports the preparation of the two *dl*-1,2-dihydroxybutyric acids which have the following formulas:



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{CH_3} \end{array} \quad \text{and} \quad \begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{HOCH} \\ | \\ \mathrm{CH_3} \end{array}$$

Discussion of the Literature

None of the work recorded in the literature had as its direct object the study of the acids themselves; their preparation was incidental to other work. Consequently, no thorough comparative study of the acids has been made and the literature leaves the properties and even the separate identities of the two true *dl*-1,2-dihydroxybutyric acids in doubt.

If we pass over the first three papers in the field,[5] as well as a paper by Faber and Tollens,[6] we come to two papers by Melikoff[7] in which reports

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[1] The dissertation of which this paper is a condensation was presented by Sybil Woodruff in partial fulfilment of the requirements for the degree of Doctor of Philosophy, in the University of Chicago.

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

[3] Glattfeld and Sander, *ibid.*, **43,** 2675 (1921).

[4] Glattfeld and Sherman, *ibid.*, **47,** 1742 (1925).

[5] (a) Melikoff, *Ber.*, **15,** 2586 (1882). (b) Kolbe, *J. prakt. Chem.*, **25,** 369 (1882). (c) Melikoff, *Ber.*, **16,** 1268 (1883).

[6] Faber and Tollens, *Ber.*, **32,** 2589 (1899).

[7] (a) Melikoff, *Ann.*, **234,** 197 (1886). (b) Melikoff and Petrenko-Kritschenko, *Ann.*, **266,** 358 (1891).

are made of studies of the chlorohydroxybutyric acids formed by the addition of hypochlorous acid to crotonic and *iso*crotonic acids and of the glycidic (oxygen-ring) and methylglycerinic acids which are derived therefrom. With crotonic acid as starting material, Melikoff isolated crystalline α-chloro-β-hydroxybutyric acid (m. p. 62–63°), crystalline β-methylglycidic acid (m. p. 84°) and crystalline β-methylglycerinic acid (m. p. 80°). *Iso*crotonic acid under similar treatment gave three chlorohydroxybutyric acids of which the one of m. p. 80.5° gave a liquid β-methyl*iso*glycidic acid which, in turn, gave a β-methyl*iso*glycerinic acid of m. p. 45°. Aside from an account of the preparation of the ethyl ester of β-methylglycerinic acid[8] and an abstract of a paper in the Russian Journal,[9] no other references could be found to the dihydroxybutyric acids made by the hypochlorous acid method.

One other important method of preparation has been used by two groups of workers. This involves the direct oxidation of salts of the crotonic acids by means of permanganate. Fittig and Kochs[10] obtained by this process an anhydrous dihydroxybutyric acid of m. p. 74–75° and from *iso*crotonic acid a liquid dihydroxybutyric acid. In 1904, Morrell and Hanson[11] resolved the β-methylglycerinic acid of Fittig and Kochs, and found the *l*-form to melt at 74–75° and to have a specific rotation in aqueous solution of —13.51°.

It may be said, then, that four presumably different 1,2-dihydroxybutyric acids have been reported in the literature. It is felt that the experimental work reported below definitely establishes the fact that the two *dl*-1,2-dihydroxybutyric acids are those of melting points 81.5 and 74.5°.

Experimental Part

As neither Melikoff nor Kochs records the yields obtained and as Melikoff did not even give quantities of materials used, the details of the published methods had to be worked out and the procedures found by us to give the best results are recorded below. A third method of oxidation—one which yielded the same acid as the permanganate method—was also developed. Finally, a thorough comparative study of the two acids and of some of their derivatives was made in order to establish beyond reasonable doubt the fact that the acids obtained are really different and are the two *dl*-1,2-dihydroxybutyric acids sought.

Preparation of the Acids

I. The Hypochlorous Acid Method of Preparation.—The essential steps in this method of preparation are indicated below.

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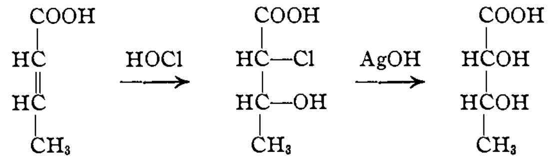
[8] Melikoff and Zelinsky, *Ber.*, **21**, 2052 (1888).

[9] Melikoff, *J. Russ. Phys. Chem. Soc.*, **1884** (I), 517–544 (*Ber.*, **17** (R), 420 (1884)).

[10] Fittig and Kochs, *Ann.*, **268**, 1 (1892).

[11] Morrell and Hanson, *J. Chem. Soc.*, **85**, 197 (1904).



$$\begin{array}{c}COOH\\ |\\ HC\\ \|\\ HC\\ |\\ CH_3\end{array} \xrightarrow{HOCl} \begin{array}{c}COOH\\ |\\ HC{-}Cl\\ |\\ HC{-}OH\\ |\\ CH_3\end{array} \xrightarrow{AgOH} \begin{array}{c}COOH\\ |\\ HCOH\\ |\\ HCOH\\ |\\ CH_3\end{array}$$

Crotonic Acid α-Chloro-β-hydroxybutyric Acid 1,2-Dihydroxybutyric Acid

Into a solution of 400 g. of crotonic acid (m. p. 71–72°) in 8 liters of water, mechanically stirred and kept at a temperature of 5–9°, was passed a slow stream of a mixture of chlorine and air (1 to 1) until the reaction mixture no longer decolorized permanganate solution and barely colored a dilute starch-iodide solution (7 to 14 hours; our experiments indicate the longer time is preferable). The solution was concentrated at 25 mm. to 2 liters and divided into 2 equal parts; the history of only one of these is important for this report. This 1 liter of reaction solution was extracted twice with 750 cc. of ether, the ether removed at atmospheric pressure and the residue (368 g. of crude chlorohydroxybutyric acid) in 500 cc. of water treated in the cold with small portions of barium carbonate until effervescence ceased (231 g. of carbonate). The mixture was heated almost to boiling and filtered; the filtrate deposited, in several crops, a total of 375 g. of crude salt (78% of theoretical calculated from crotonic acid). Thirty g. of the barium salt (after one recrystallization) was dissolved in 240 cc. of water and the solution maintained at 70–80° while a water suspension of the silver oxide from 26 g. of silver nitrate was added in very small portions followed by shaking after each addition (two hours for addition). (Great care is necessary during this stage. When most of the silver oxide has been added the silver chloride should be removed, the further addition of oxide made very carefully and the addition stopped when the first appearance of suspended free silver, which gives a pink tinge of translucency to the solution, is noted.) The barium was quantitatively removed from the filtered solution with 8 *N* sulfuric acid and the filtrate from the barium sulfate subjected to distillation to dryness at 25 mm. from a water-bath at 45°. The almost colorless sirup weighed 14.6 g. (84% calcd. from barium salt) and crystallized spontaneously after 24 hours in a desiccator.

The semi-solid mass was transferred to a suction filter and as much liquid as possible removed. A total of 87.0 g. of crude acid thus gave 43.9 g. of fairly dry crystals; m. p., 71–80°. Fourteen g. of these crystals in 5 cc. of water gave, in two crops, 7.3 g. of acid of m. p. 81.5° (the melting point of the acid was very sharp but, because of the very great difficulty in recrystallization, it is possible that the true melting point of the acid may be a little higher). The acid was not hygroscopic, was soluble in alcohol, glacial acetic acid and hot ethyl acetate; insoluble in cold ethyl acetate and ether. The air-dry crystals lost only 0.16% in weight when dried to constant weight over phosphorus pentoxide.

Titration. Subs., 0.2267. 0.4800; 18.94, 39.73 cc. of 0.1 *N* alkali (phenolphthalein). Calcd. for $C_4H_8O_4$: 18.88, 39.98 cc.

Anal. Subs., 0.1537, 0.1490: H_2O, 0.0918, 0.0898; CO_2, 0.2250, 0.2178. Calcd. for $C_4H_8O_4$: H, 6.71, C. 39.99. Found: 6.68, 6.74, 39.93, 39.87.

II. The Permanganate Method of Preparation.—To a solution of 20 g. of crotonic acid (m. p. 71–72°) and 22.8 g. of barium carbonate in 200 cc. of water, was added 400 cc. of a saturated solution of barium hydroxide and then 1 liter of water. The milky solution, chilled in ice water, was treated drop by drop with 2 liters of an ice-cold solution of barium permanganate which contained 43.6 g. of the salt; time of addition, three hours. The filtered reaction mixture was then concentrated to 800 cc. at reduced pressure from a water-bath at 50–55°, filtered and treated with enough 8 *N* sulfuric acid exactly to precipitate the barium. The filtrate from the barium sulfate was concentrated as above to 200 cc., twice extracted with 150cc. portions of ether, subjected to steam distillation until the distillate became neutral to litmus and subjected to distillation at 15–20 mm. (water-bath at 50–55°) as long as moisture distilled. The sirup thus obtained weighed 7 g. (25% yield) and crystallized within an hour when "seeded" with a crystal of acid made by the osmium tetroxide method (see below).

The 7 g. of acid was recrystallized from 4 cc. of water (solution chilled in ice-salt mixture) and yielded as the first crop 2.3 g. of crystals (m. p., after drying over phosphorus pentoxide, 73.5–74.5°). The air-dry acid was shown to contain 1 molecule of water of crystallization which it lost in a desiccator over phosphorus pentoxide (loss 12.67%). The acid was soluble in alcohol and hot ethyl acetate but insoluble in ether and cold ethyl acetate. The acid, dried over phosphorus pentoxide, was used in the analytical work.

Titration. Subs., 0.2873, 0.3272: 23.92, 27.25 cc. of 0.1 *N* alkali (phenolphthalein). Calcd. for $C_4H_8O_4$: 23.95, 27.27 cc.

Anal. Subs., 0.2901: H_2O, 0.1735; CO_2, 0.4241. Calcd. for $C_4H_8O_4$: **H, 6.71**; C, 39.99. Found: 6.65, 39.88.

III. The Osmium Tetroxide Method of Preparation

A solution of 100 g. of crotonic acid (m. p. 71–72°) and 189.2 g. of potassium chlorate in 1500 cc. of water, to which had been added 150 cc. of a water solution of osmium tetroxide which contained about 0.15 g. of the tetroxide, was kept in a water-bath at 50° for eight hours, when a test for completion of reaction was positive. For details of this test, as well as for a complete discussion of this method of oxidation as applied to fumaric and maleic acids, including caution as to the use of osmium tetroxide, the reader is referred to a paper by Milas and Terry.[12] The cooled solution was twice extracted with 500 cc. of benzene in order to remove the catalyst and concentrated at reduced pressure (15–20 mm.) to dryness. The residue was treated with 450 cc. of absolute alcohol, the solution filtered and again concentrated to dryness at reduced pressure. The residue was dissolved in 300 cc. of water and barium carbonate added in slight excess, the mixture heated to boiling, insoluble matter removed and the solution allowed to cool. A total of 156 g. of crude barium salt was thus obtained. Six recrystallizations of this crude salt from water were necessary to remove chloride completely; 76.2 g. of pure salt was obtained which gave, after the removal of barium in the usual way, 24 g. of sirup which crystallized completely when "seeded" (17% yield calcd. from crotonic acid).

The 24 g. of crude crystalline product was recrystallized from 10 cc. of water and yielded 13 g. of acid as a first crop. This acid contained 1 molecule of water of crystallization which it lost to the air in six days (loss 12.82%). The acid, after drying to constant weight in a desiccator over phosphorus pentoxide, melted at 73.5–74.5°. Titration and analysis for carbon and hydrogen gave, in duplicate, results almost identical with those for the acid obtained by the permanganate method.

Derivatives of the Acids

In order to save space the dihydroxybutyric acids prepared by the three different procedures outlined above will be referred to henceforth in this paper as Acid-HOCl, Acid-MnO_4 and Acid-OsO_4, respectively.

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[12] Milas and Terry, This Journal, **47, 1412** (1925).

DERIVATIVES OF ACID-HOCL. **Phenylhydrazide,**[13] $C_{10}H_{14}O_3N_2.H_2O$.—A mixture of 2 g. of acid (*m.* p. 81.5°) and 3 g. of phenylhydrazine in 2 cc. of absolute alcohol, warmed for half an hour at 75°, yielded 3.4 g. of crude crystals; twice recrystallized from absolute alcohol these yielded 2 g. of vacuum-dry substance of m. p. 103°. This compound was an ivory-white, granular powder even when it separated slowly from alcohol. Calcd. for $C_{10}H_{14}O_3N_2.H_2O$: N, 12.28; H, 7.07; C, 52.61. Found: 12.47, 12.25, 7.27, 51.98.

o-Tolylhydrazide, $C_{11}H_{16}O_3N_2.H_2O$.—This compound was made in the same way as the phenylhydrazide: 2 g. of acid and 3.4 g. of *o*-tolylhydrazine (m. p. 59°) in 4 cc. of absolute alcohol gave 2.9 g. of product; twice recrystallized from 15 cc. of absolute alcohol, this crude product yielded 0.5 g. of substance, m. p. 103°. The compound separated in recrystallizations as a powder. Calcd. for $C_{11}H_{16}O_3N_2.H_2O$: N, 11.57. Found: 11.52, 11.57.

Barium Salt $(C_4H_7O_4)_2Ba$.—Three g. of recrystallized acid (m. p. 81.5°) in 7 cc. of water was treated in the cold with 2.4 g. of barium carbonate; the filtered solution was concentrated at reduced pressure to 3 cc. and poured into 25 cc. of absolute alcohol. The precipitated salt was rendered crystalline by trituration in absolute alcohol; 3.5 g. of powdery salt (desiccator-dry) was thus obtained. It could not be recrystallized from water. The salt was dried at 110°. Calcd. for $(C_4H_7O_4)_2Ba$: Ba, 36.58. Found: 36.16, 36.11.

Silver Salt, $C_4H_7O_4Ag$.—Three g. of acid (m. p. 81.5°) in 25 cc. of hot water was treated with 3.3 g. of silver carbonate. As the hot filtrate cooled, it deposited 2 g. of white powder. The salt decomposes somewhat if its aqueous solution is heated. Calcd. for $C_4H_7O_4Ag$: Ag, 47.53. Found: 47.44, 47.42.

DERIVATIVES OF ACID-MNO4. **Phenylhydrazide,** $C_{10}H_{14}O_3N_2.H_2O$.—From 2 g. of acid (m. p. 73.4–74.5°) 3.7 g. of white, fluffy, fine needles was obtained; m. p. of purified product, 129.5°. This compound could be recrystallized from 5 parts of absolute alcohol, whereas only 1 part of absolute alcohol could be used with the phenylhydrazide of Acid-HOCl. Calcd. for $C_{10}H_{14}O_3N_2.H_2O$: N, 12.28; H, 7.07; C, 52.61. Found: 12.31, 12.64; 7.27; 51.53.

o-Tolylhydrazide, $C_{11}H_{16}O_3N_2.H_2O$.—One and five-tenths g. of acid (m. p. 73.5–74.5°) gave 3.0 g. of product as ivory-white, glistening leaflets. Two recrystallizations from 15 cc. of absolute alcohol gave 1.3 g. of product; m. p., 111.5°. Calcd. for $C_{11}H_{16}O_3N_2.H_2O$: N, 11.57; H, 7.49; C, 54.52. Found: 11.57, 7.63, 53.69.

DERIVATIVES OF ACID-OSO4. **Phenylhydrazide,** $C_{10}H_{14}O_3N_2.H_2O$.—The results of this preparation were identical with those of the preparation of the phenylhydrazide of the Acid-MnO_4 as regards properties of product, behavior and yield. The purified phenylhydrazide melted at 129.5°. Calcd. for $C_{10}H_{14}O_3N_2.H_2O$: N, 12.28. Found: 12.86, 12.57.

o-Tolylhydrazide, $C_{11}H_{16}O_3N_2.H_2O$.—This derivative was also similar in method of preparation, yield and properties to that made from the Acid-MnO_4. It melted at 111.5°. Calcd. for $C_{11}H_{16}O_3N_2.H_2O$: N, 11.57; H, 7.49; C, 54.52. Found: 11.42, 11.39, 7.59, 53.80.

Barium Salt, $(C_4H_7O_4)_2Ba$.—Five g. of acid (m. p. 74.5°) in 15 cc. of cold water was treated with 4 g. of barium carbonate in portions. The thick paste was heated; the hot filtrate deposited 5 g. of white, needle-like crystals. These were dried at 110°. Calcd. for $(C_4H_7O_4)_2Ba$: Ba, 36.58. Found: 36.51, 36.62.

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[13] The "phenylhydrazide" obtained here, and likewise from the acids made by the other two procedures, may have been the phenylhydrazine salt of the acid and not the true phenylhydrazide with one molecule of water of crystallization. Because of the stability and general properties of the product, we are inclined to think it was the true phenylhydrazide.

Silver Salt, $C_4H_7O_4Ag$.—A hot solution of 4 g. of acid (m. p. 74.5°) in 50 cc. of water was treated with 4.5 g. of silver carbonate in small portions. The hot filtrate deposited 2 g. of large, glistening, silver-white leaflets. Calcd. for $C_4H_7O_4.Ag$: Ag, 47.53. Found: 47.53, 47.64.

Comparison of the Properties of the Acids Made by the Three Different Methods and of their Derivatives

So far as the properties of the Acid-MnO_4 and the Acid-OsO_4 and their derivatives were studied, there is every indication that these acids are identical.

COMPARISON OF MELTING POINTS

Compound	Acid-MnO_4	Acid-OsO_4	Mixture of the two
Acid	73.5–74.5°	73.5–74.0°	73–74°
Phenylhydrazide	129.5°	129.5°	129.5°
Tolylhydrazide	111.5°	111.5°	111.0°

The freshly-prepared Acid-MnO_4 lost 12.67% of its weight, the Acid-OsO_4 12.82%, as water of crystallization; this corresponds to 1 mole.

In a similar way the Acid-OsO_4 and the Acid-HOCl may be compared and shown to have very different properties.

COMPARISON OF MELTING POINTS

Compound	Acid-OsO_4	Acid-HOCl	Mixture of the two
Acid	73.5–74.0°	81.5°	63–74°
Phenylhydrazide	129.5°	103.0°	109–122°
Tolylhydrazide	111.5°	103.0°	99–105°

The Acid-HOCl lost only 0.16% in weight in drying to constant weight and hence contained no water of crystallization. The Acid-OsO_4 was noticeably less soluble in cold water than was the Acid-HOCl. This difference in solubility was sufficiently marked to be of practical importance in the recrystallization of the two acids from water.

The salts of the Acid-HOCl and Acid-OsO_4 exhibited marked differences in behavior. The barium salt of the Acid-HOCl could not be crystallized from water; the barium salt of the Acid-OsO_4, on the other hand, crystallized from hot water as finely matted, glistening needles. The silver salts of Acid-HOCl and Acid-OsO_4 could both be recrystallized from hot water; the salt of the Acid-OsO_4 consisted of large, glistening, silver-white leaves, however, whereas the salt of Acid-HOCl was obtained as a dull white powder.

The hydrazides (both the phenyl and *o*-tolyl) of the Acid-OsO_4 consisted of definite, large crystals which were sparingly soluble in hot absolute alcohol. The hydrazides of the Acid-HOCl were coarse powders which were markedly more soluble in alcohol than were the hydrazides of the other acid.

Summary

This paper is a report (a) of the repetition, with some modifications, of the preparation of the two *dl*-1,2-dihydroxybutyric acids reported by Melikoff and Fittig and Kochs; (b) of the preparation of one of these acids by a new procedure; (c) of the preparation of two new derivatives (phenylhydrazides and *o*-tolylhydrazides) of each of the two acids; (d) of a careful comparative study of the properties of the acids produced by the three procedures and of a few of their derivatives; and (e) of the con-

clusion that the two theoretically possible *dl*-1,2-dihydroxybutyric acids have melting points of 73.5–74.5 and 81.5°.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE PREPARATION OF TETRAPHENYL LEAD[1]

BY HENRY GILMAN AND JACK ROBINSON

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There are, at present, two general methods for the preparation of tetraphenyl lead. One, by Polis,[2] is the protracted heating of an ethyl acetate solution of bromobenzene with sodium-lead alloy. The other, by Pfeiffer and Truskier,[3] is commonly represented by the following reaction.[4]

$$2PbCl_2 + 4C_6H_5MgBr \longrightarrow (C_6H_5)_4Pb + Pb + 2MgCl_2 + 2MgBr_2 \qquad (1)$$

The method using the Grignard reagent has been widely employed[5] because of its greater convenience and better yields. In connection with the application of organolead compounds as antiknock reagents and in the treatment of cancer and some plant diseases, tetraphenyl lead is being used as one of the types for the preparation of variously substituted derivatives. The present study reports the effect of various factors on the yield of tetraphenyl lead as prepared by the Grignard reaction. Using Pfeiffer and Truskier's technique we have not succeeded in equaling their yields. However, the quantity of phenylmagnesium bromide required to give a yield that closely approximates theirs has been significantly decreased below that which they used. Our present maximum yield of about 50% points strongly to a series of reactions more complex than that illustrated in Reaction (1). Experiments have shown that lead chloride cannot be effectively replaced by lead bromide, lead iodide or lead dioxide in this method of preparation. It is possible that better yields may be realized by treating the phenylmagnesium bromide with zinc chloride prior to the addition of lead chloride. Such a method, involving the intermediate formation of organozinc compounds, has been

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[1] A preliminary report was read at the meeting of the Iowa Academy of Sciences held at Iowa City on May 6, 1927.

[2] Polis, *Ber.*, **20**, 717 (1887).

[3] Pfeiffer and Truskier, *Ber.*, **37**, 1125 (1904).

[4] A recent excellent survey of organolead compounds has been made by Calingaert, *Chem. Reviews*, **2**, 43 (1925).

[5] (a) Hofmann and Wölfl, *Ber.*, **40**, 2425 (1907). (b) Möller and Pfeiffer, *Ber.*, **49**, 2443 (1916). (c) Jones and Werner, THIS JOURNAL, **40**, 1257 (1918). (d) Krause and Schmitz, *Ber.*, **52**, 2165 (1919). (e) von Hevesy and Zechmeister, *Ber.*, **53**, 410 (1920). (f) Richards, King and Hall, THIS JOURNAL, **48**, 1530 (1926). (g) Ebert, *Ion*, **2**, 277 (1910). (h) Staehling, *Compt. rend.*, **157**, 1430 (1913). (i) Dillon, Clarke and Hinchy, *Sci. Proc. Roy. Dublin Soc.*, **17**, 53 (1922).