

ing points with the compounds obtained in parts A and B showed no depression.

1,4,3,6-Dianhydro-L-Iditol from 2,5-Dibenzoyl-1,4,3,6-dianhydro-L-Iditol.—Ten grams of 2,5-dibenzoyl-1,4,3,6-dianhydro-L-Iditol was dissolved in 40 ml. of chloroform and chilled to 0°. A similarly chilled solution of 0.1 g. of sodium in 40 ml. of absolute methanol was then added and the solution left at 0° for twenty-three hours. Excess base was removed by passing carbon dioxide through the solution until it was acid to phenolphthalein. After filtration, the solvent was removed *in vacuo* and the residual sirup dissolved in 10 ml. of warm ethyl acetate. On cooling, there was obtained 1.46 g. (35.5%⁹) of long, white, asbestos-like needles melting at 63.8 to 64.4° and rotating in water +20.8° (c, 2.02, 24.5°) and in pyridine +33.3° (c, 2.24, 28.2°). In contrast to isosorbide and isomannide, this substance is sparingly soluble in chloroform. When mixed with these dianhydrides it caused a substantial depression of their melting points.

Anal. Calcd. for C₆H₁₀O₄: C, 49.31; H, 6.89. Found: C, 49.1, 49.1; H, 6.86, 6.84.

(9) Distillation of the residue from the mother liquors at 140° (bath) and 2 mm. pressure gave an additional 2.26 g. of substantially pure 1,4,3,6-dianhydro-L-Iditol and raised the total yield to 90.4%.

Summary

1,4,3,6-Dianhydro-L-Iditol has been prepared by the hydrogenation isomerization of both 1,4,3,6-dianhydrosorbitol and 1,4,3,6-dianhydro-D-mannitol as well as by the acid catalyzed anhydridization of L-Iditol.

These facts are best explained by the assumption that Raney nickel exerts a dehydrogenating action on these secondary alcohols, converting one or both of the free hydroxyl groups to symmetrical carbonyl groups which are subsequently reduced with the formation of a mixture of diastereoisomers.

The isolation of a dianhydro-L-Iditol in this manner from isosorbide and isomannide proves the structure of the new dianhydride as 1,4,3,6-dianhydro-L-Iditol and confirms those of isosorbide and isomannide.

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Optically Active Ketonic Beta Lactones

BY CHARLES L. BICKEL

The bromination of racemic α -phenyl- β -benzoylpropionic acid gives two β -bromo derivatives which differ markedly in the speed with which they form β -lactones. The rate of lactone formation is dependent on the configuration of the bromo acid, but Kohler and co-workers^{1,2} were not able to establish the configurations of the bromo acids in relation to those of the lactones since the opening or closing of the lactone ring may involve inversion. By using cyclic ketonic acids of fixed and known configuration, Kohler and Jansen³ later proved that the configuration of the bromo acid and the corresponding lactone was the same and that no inversion occurred.

A study of the optically active forms of α -phenyl- β -benzoylpropionic acid I, their β -bromo derivatives II and IIa, and the optically active β -lactones III and IIIa throws new light on the problem of these configurational relationships and is the subject of the present paper. The discussion is limited to one of the optically active acids and its derivatives, although identical results were obtained with the optical opposites. The racemic derivatives were also prepared in the case of compounds which had not previously been studied.

The bromination of each of the optically active acids yields two bromo acids differing considerably in specific rotation. In dilute sodium bicarbonate solution one of the bromo acids II is

rapidly converted into a β -lactone III, hereafter called the fast lactone; in sodium hydroxide solution the other bromo acid IIa is converted much more slowly into an isomeric β -lactone IIIa, the slow lactone. In both instances, the specific rotations of the bromo acid and the corresponding lactone are of the same order of magnitude. Racemization of the groups attached to the α -carbon atom does not occur since hydrogen iodide converts the fast lactone into the active acid from which it was derived, while hydrogen bromide regenerates the active bromo acid II. The conclusion of Kohler and Jansen that the formation of the lactones does not involve inversion supports, and is supported by, the polarimetric data herein described.

The fast lactone III reacts with methanol⁴ to give an open-chained methoxy acid VII, the specific rotation of the methoxy acid indicating that the configuration is unchanged. Methanol and sulfuric acid react with the fast lactone to give an open-chained hydroxy ester IVa, while aqueous sulfuric acid gives the corresponding hydroxy acid Va. The specific rotations of these compounds point to inversion around the β -carbon atom and place them in the series headed by the slow lactone IIIa and the bromo acid IIa.

Both the hydroxy acid Va and the hydroxy ester IVa obtained from the fast lactone can be converted into a methoxy ester VIa and a methoxy acid VIIa which are isomeric with the meth-

(1) Kohler and Kimball, *THIS JOURNAL*, **56**, 729 (1934).

(2) Kohler, Peterson and Bickel, *ibid.*, **56**, 2000 (1934).

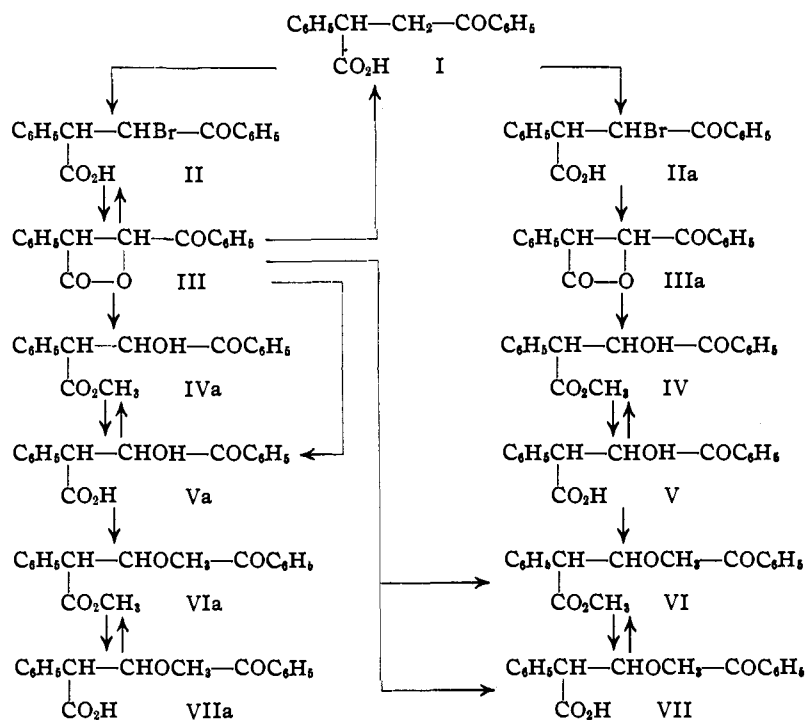
(3) Kohler and Jansen, *ibid.*, **60**, 2142 (1938).

(4) Kohler and Bickel, *ibid.*, **63**, 1531 (1941).

oxy acid VII and ester VI prepared directly from the fast lactone.

Methanol and sulfuric acid react with the slow lactone to give a hydroxy ester IV which is isomeric with the hydroxy ester IVa obtained directly from the fast lactone and which can easily be converted into the same methoxy acid VII which, in turn, is prepared directly from the fast lactone by the action of methanol. These derivatives of the slow lactone therefore have the same configuration as the fast lactone.

All of the above relationships are shown in the chart, compounds of like configuration being numbered similarly.



Basic media were avoided in the above reactions, with the exception of the preparation of the lactones. In consequence, racemization was not detected at any stage, which is evidence of the remarkable stability of these optically active centers.

Basic solutions, as well as more drastic treatment with acids, induce racemization. Racemization can in certain cases be restricted to one of the optical centers, or it may under different conditions involve both optical centers, and in a few cases the optical centers are destroyed. Examples of these processes are described below.

An earlier paper described the resistance of optically active α -phenyl- β -benzoyl propionic acid to racemization by bases.⁵ Because of the greater enolic tendency of ketones, the β -hydrogen atom of this acid and its derivatives should enolize more readily than the α -hydrogen atom

(5) Bickel, *This Journal*, 60, 927 (1938).

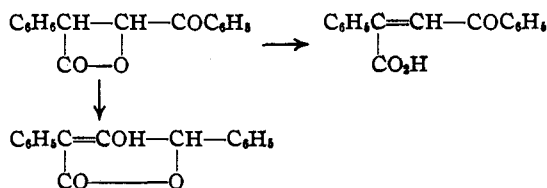
and it should therefore be possible to produce racemization at the β -carbon atom only. The only compounds suited to this study are the methoxy acids, since the hydroxy acids and the fast lactone are converted by bases into a variety of products, in most of which the β -optical center disappears and in some of which both optical centers are destroyed. In sodium hydroxide solution, each of the methoxy acids VII and VIIa gives a mixture of the two methoxy acids, and in each case methoxy acid VIIa constitutes about 65% of the mixture. These solutions in time become optically inactive and no longer yield the methoxy acids. The nature of the products has not yet been determined.

Dilute hydrobromic acid reacts with the fast lactone to give the bromo acid from which the fast lactone is formed. This process therefore occurs without racemization. A more concentrated solution of hydrobromic acid, however, converts the fast lactone into the racemic bromo acid, the result of racemization about both carbon atoms.

Dilute hydriodic acid destroys the β -carbon optical center of the fast lactone, while the α -carbon optical center is left intact without racemization. The product of this action is the active acid I. Concentrated hydriodic acid, however, also racemizes the α -carbon atom and produces the inactive acid.

Pyridine, sodium hydroxide and sodium methylate destroy both optical centers of the fast lactone. *cis*- α -Phenyl- β -ben-

zoylacrylic acid¹ is produced by pyridine and an enolic gamma lactone² by sodium hydroxide or sodium methylate.



Very dilute solutions of sodium methylate or sodium hydroxide, however, convert the fast lactone rapidly and quantitatively into the hydroxy ester IVa, a process which is free of racemization. Furthermore, the hydroxy ester gives the enolic gamma lactone when treated with more concentrated basic solutions. These relationships suggest that the enolic gamma lactone is derived from the fast lactone by way of the hydroxy ester.

Experimental

The preparation and properties of compounds I, II, IIa, III, IIIa and VII have already been reported.^{4,6} All polarimetric studies, unless otherwise stated, were carried out in methanol as described in an earlier paper.⁶

The data for the new substances are collected below in tabular form, followed by the reactions and details of preparation.

Substance ^a	Calcd., %		Found, %		[α] _D ²⁰
	C	H	C	H	
IV	71.8	5.7	71.5	5.9	+150
IVa	71.8	5.7	71.6	5.6	+92
V	71.0	5.2	71.1	5.3	+155
Va	71.0	5.2	70.8	5.5	+96
VI	72.5	6.1	72.5	6.1	+150
VIa	72.5	6.1	72.3	6.1	+100
VIIa	71.8	5.7	71.6	5.7	+98

Substance ^b	Crystal form	M. p.,	Mixed ^c
		°C.	m. p., °C.
IV	Needles	64	98
IVa	Plates	105	91
V	Rosets of needles	149	145
Va	Fine needles	143	132
VI	Stout needles	56	50
VIa	Needles	115	116
VIIa	Needles	181	153

^a The racemic compounds corresponding to VI, VIa and VIIa were also prepared by the same methods and were identified as explained in footnote c. The racemic compounds corresponding to IV, IVa, V, Va and VII have been described previously.^{1,2,4} ^b All of these substances are soluble in ether and sparingly soluble to insoluble in petroleum ether. ^c The optical opposite of each active compound derived from the dextro acid was prepared from the levo acid by identical methods. The mixed melting point in each case was the same as the melting point of the corresponding racemic compound. Moreover, the identity of each "synthetic" racemate was proved by a mixed melting point with the known racemic compound.

Reactions of the Fast Lactone, III

A. Hydrogen Iodide.—A solution of 0.2 g. of the lactone in 25 cc. of acetone and 3 cc. of 45% hydriodic acid was allowed to stand for one hour and then gave a quantitative yield of the active acid melting at 181°.

A mixture of 0.5 g. of the lactone and 20 cc. of 45% hydriodic acid was refluxed for one hour. The racemic acid, melting at 148°, was the only product.

B. Hydrogen Bromide.—The conversion of the lactone into the active bromo acid II was reported in an earlier paper.⁴

After standing for twenty-four hours, a solution of one gram of the lactone in 15 cc. of methanol and 7.5 cc. of concentrated hydrobromic acid gave the racemic bromo acid melting at 208°.

C. Sodium Methylate or Sodium Hydroxide.—A solution of one gram of the lactone in 30 cc. of methanol, containing 0.007 g. of sodium methylate or an equivalent quantity of sodium hydroxide, was allowed to stand for 15 minutes and then poured into cold dilute hydrochloric acid. The hydroxy ester IVa was the only product.

When the above was repeated using 0.15 g. of sodium methylate or an equivalent quantity of sodium hydroxide, the enolic gamma lactone, melting at 205°, was obtained.

D. Methyl Iodide and Silver Oxide.—A solution of 0.5 g. of the lactone in 25 cc. of anhydrous ether was refluxed for eight hours with one cc. of methanol, 0.5 g. of silver

oxide and 1 g. of methyl iodide. The filtered solution gave a quantitative yield of the methoxy ester VI.

E. Methanol and Sulfuric Acid.—After standing for 24 hours, a solution of 2 g. of the lactone in 20 cc. of methanol and 2 g. of sulfuric acid gave a quantitative yield of the hydroxy ester IVa.

F. Aqueous Sulfuric Acid.—One gram of the lactone, refluxed for five hours with 50 cc. of 10% sulfuric acid, gave the hydroxy acid Va.

Preparation of the Hydroxy Ester, IV.—A solution of one gram of the lactone IIIa in 15 cc. of methanol and 1.2 cc. of sulfuric acid, after standing for thirty hours, gave a good yield of the hydroxy ester.

Hydrolysis of the Esters.—This procedure was applied to the following conversions: VI \rightarrow VII, VIa \rightarrow VIIa, IV \rightarrow V, and IVa \rightarrow Va. A solution of one gram of the ester in 25 cc. of acetic acid, 30 cc. of water and 2 cc. of sulfuric acid, refluxed for five hours, gave a good yield of the corresponding acid.

Esterification of the Acids.—This procedure was applied to the following conversions: V \rightarrow IV, Va \rightarrow IVa, VII \rightarrow VI, and VIIa \rightarrow VIa. A good yield of the ester was realized by allowing a solution of one gram of the acid in 25 cc. of methanol and 1.5 cc. of sulfuric acid to stand for twenty-four hours.

Methylation of the Hydroxy Acids and Hydroxy Esters.—This procedure was applied to the following conversions: V \rightarrow VI, Va \rightarrow VIa, IV \rightarrow V, and IVa \rightarrow VIa. Two grams of the hydroxy acid or ester in 50 cc. of anhydrous ether was refluxed for 12–15 hours with 2 g. of silver oxide and 4 g. of methyl iodide. The filtered solution gave a good yield of the corresponding methoxy ester.

Sodium Hydroxide on the Hydroxy Ester, IVa.—A solution of 0.5 g. of the hydroxy ester in 25 cc. of methanol, containing 0.2 g. of sodium hydroxide, was refluxed for ten minutes. The enolic gamma lactone, melting at 205°, was obtained in good yield.

Racemization of the Methoxy Acids, VII and VIIa.—One gram of the methoxy acid VII was dissolved in 40 cc. of 2% aqueous sodium hydroxide and the solution was allowed to stand for four days. The mixture of products, VII and VIIa, was separated by fractional crystallization from ether and petroleum ether, the higher melting acid VIIa being more insoluble and constituting about 65% of the mixture.

A repetition of the above, starting with methoxy acid VIIa, gave the same results.

Polarimetric studies of this racemization indicated a complete loss of activity in about three months. In one such study, 0.7 g. of the methoxy acid VII was dissolved in 11.4 cc. of 2% aqueous sodium hydroxide. After ten days, beautiful transparent crystals appeared in the polarimeter tube and were allowed to grow for one week. The filtered crystals became opaque within a few minutes and decomposed with bubbling at about 80°. When shaken with hydrochloric acid and ether, the crystals yielded the pure methoxy acid VIIa. The solid is undoubtedly the sodium salt of the methoxy acid VIIa which is less soluble in sodium hydroxide solution than is the sodium salt of the isomeric methoxy acid VII.

Summary

The configurations of two isomeric optically active ketonic beta lactones are related to their derivatives and also to the bromo acids from which they are formed.

The effect of various basic and acidic media on the optical centers of these substances is also described.

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