

On the Absolute Configuration of 3-Cyclohexene-1-carboxylic Acid

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3-Cyclohexene-1-carboxylic acid, *1*, has been resolved with brucine and dextrorotatory *1* has been converted to *R*-(+)-1,2,4-butanetricarboxylic acid, *4*.

Ozonolysis of (+)-3-cyclohexene-1-methanol, *2*, followed by oxidative work-up, yielded after esterification the levorotatory methyl ester of 3-hydroxymethylhexanedioic acid γ -lactone, *5*.

3-Cyclohexene-1-carboxylic acid,* *1*, is a chiral compound which is commercially available in racemic form. The title compound was of interest as a potential starting material for the synthesis of optically active, α -alkylated dicarboxylic acids.¹ For this purpose we needed *1* of high optical purity and of known absolute configuration.

3-Cyclohexene-1-carboxylic acid has been resolved into enantiomeric forms by Goldberg and Lam² who also proposed that dextrorotatory *1* has *R*-configuration by converting it to 3-methylhexanedioic acid, *3*, which had earlier been related to *R*-glyceraldehyde.³ Goldberg and Lam's interconversions are outlined in Fig. 1 along with optical purity data (O.P.) for pertinent compounds. In one series of experiments (*cf.* Fig. 1) they resolved 3-cyclohexene-1-methanol, *2*, and converted the dextrorotatory enantiomer to *R*-(+)-3-methylhexanedioic acid, *3*, with a quoted optical purity of *ca.* 16%. In a second series of experiments (*cf.* Fig. 1) they partially resolved *1* and reduced both enantiomers with lithium aluminium hydride to (+)- and (-)-3-cyclohexene-1-methanol, (+)-*2* and (-)-*2*, respectively, with, as they report,² an optical purity of *ca.* 7%. Assuming that this reduction occurs without racemization, 3-cyclohexene-1-carboxylic acid should possess the same optical purity and one could estimate its absolute rotation⁴ at the sodium D-line to be about 20°. Although the proposed assignments of absolute configuration² seemed to be correct, the low optical yield obtained in the resolution of *1*

* Sometimes called 4-carboxycyclohexene or 1,2,3,6-tetrahydrobenzoic acid.

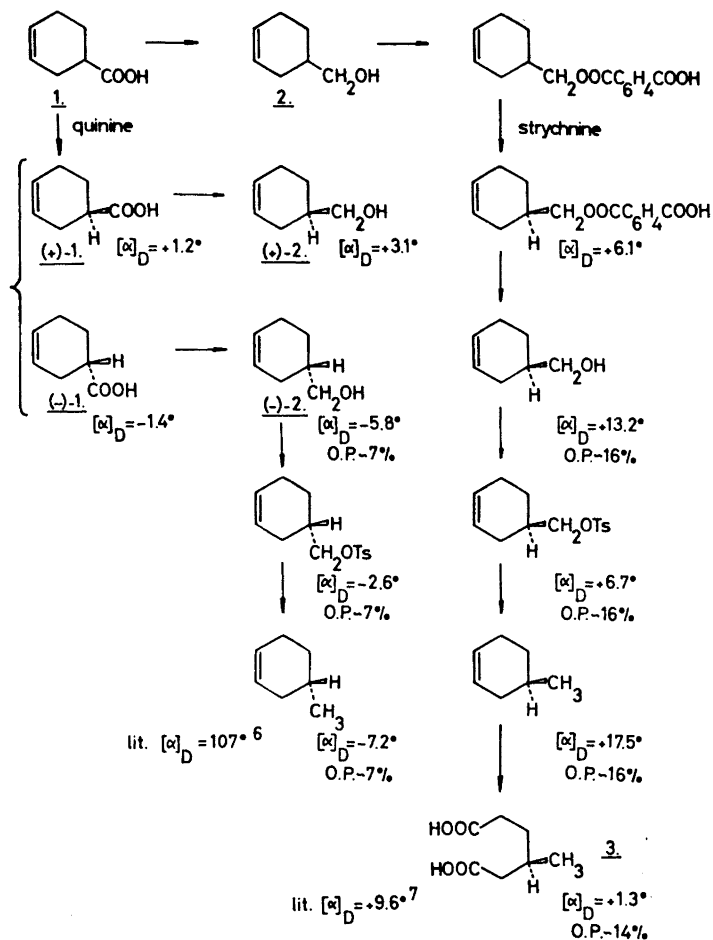


Fig. 1.

with quinine, and the discrepancy in the reported rotations when the enantiomeric forms of *1* were reduced to the corresponding alcohols *2* (cf. Fig. 1) made a reinvestigation desirable. Accordingly, we needed a more efficient method of resolution.

Brucine was chosen as the resolving base. The brucine salt of *1* was recrystallized seven times from acetone to give a product with constant specific rotation. After acidification it yielded free acid with $[\alpha]_D = +94.5^\circ$. The dextrorotatory acid was ozonized and, on oxidative work-up, yielded dextrorotatory 1,2,4-butanetricarboxylic acid, *4*, (cf. Fig. 2) which has been related to *R*-glyceraldehyde.³ This result supports the earlier assignment² of the absolute configuration for dextrorotatory *1* (cf. also footnote 5 in Ref. 2). The specific rotations for the free acid *4*, $[\alpha]_D = +26.9^\circ$, and its trimethyl

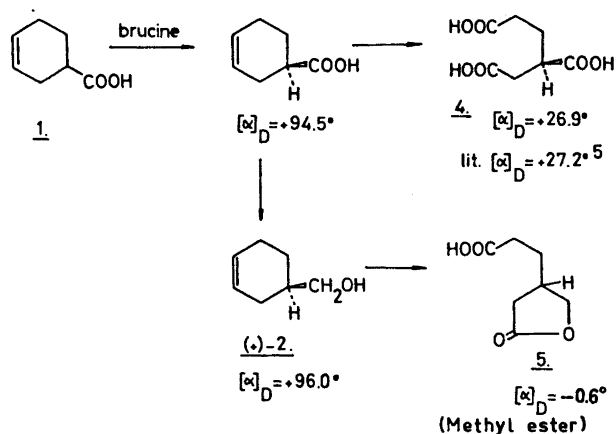


Fig. 2.

ester, $[\alpha]_D = +20.0^\circ$, are very close to the values reported earlier, $[\alpha]_D = +27.2^\circ$, and $[\alpha]_D = +16.2^\circ$, respectively.⁵ We therefore believe that our dextrorotatory 3-cyclohexene-1-carboxylic acid has an optical purity close to 100 %. The value we obtained for its specific rotation indicates that Goldberg and Lam's sample had an optical purity of only 1.5 %.

In a second series of experiments (*cf.* Fig. 3) levorotatory 3-cyclohexene-1-carboxylic acid of lower optical purity (*ca.* 47 %) was converted to (-)-3-

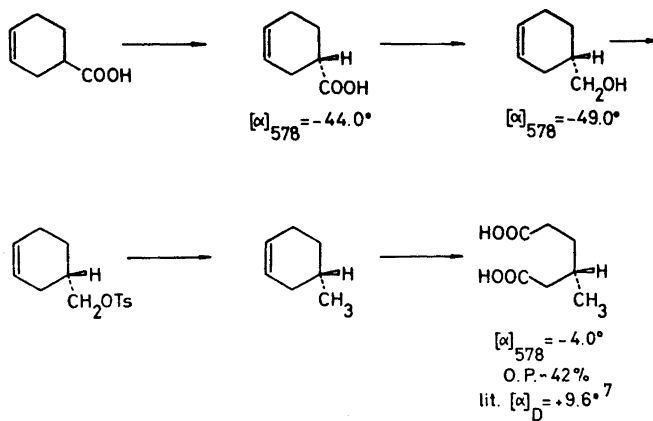


Fig. 3.

methylhexanedioic acid, 3, with Goldberg and Lam's method. The specific rotation of 3 was 42 % of the reported value⁷ thus confirming the conclusions concerning the optical purity of our 3-cyclohexene-1-carboxylic acid.

We also transformed (*cf.* Fig. 2) 3-cyclohexene-1-methanol, **2** ($[\alpha]_D = +96.0^\circ$) by ozonolysis followed by oxidative work-up with hydrogen peroxide in formic acid, to the five-membered ring lactone **5**, which was to be the key intermediate in the synthetic routes to optically active, α -alkylated dicarboxylic acids. The methyl ester of lactone **5** proved to have very low specific rotation, $[\alpha]_D = -0.6^\circ$. In a subsequent paper it will be shown that this is due to low absolute rotation and not to partial racemization during the oxidative work-up.

EXPERIMENTAL

The ozonization experiments were performed according to the following general procedure: The reaction solution was kept at -60° by a Dry Ice-ethanol bath. A mixture of 3% of ozone in oxygen produced by a Welsbach Model T-23 ozonator was passed through the solution at a rate of 70 ml/min. The reaction was continued until elemental iodine was liberated from a 1% aqueous solution of potassium iodide through which the effluent gases were passed. Excess of ozone was then removed by passing a stream of nitrogen through the solution for 15 min.

Infrared spectra were determined with a Beckman IR 9 spectrophotometer and nuclear magnetic resonance spectra with a Varian A-60 instrument. Vapor phase chromatographic analyses were performed with a Perkin-Elmer 800 Gas Chromatograph using a $1/8" \times 2$ m SE-30 column. Optical rotations were measured at 22° with a Perkin-Elmer 141 Polarimeter using a microcell. Melting points were determined with a Reichert melting point microscope and are uncorrected.

Resolution of 3-cyclohexene-1-carboxylic acid (1). To a suspension of 50 g of brucine in 400 ml of acetone was added 16 g of racemic 3-cyclohexene-1-carboxylic acid. The resulting solution was refluxed for 30 min, filtered, and allowed to cool. The crystals which had formed were filtered to yield 31 g of a white salt, m.p. = $125-135^\circ$, $[\alpha]_{578} = -13.0^\circ$ (CH_3OH ; $c=3$). The salt was recrystallized seven times from acetone providing 5.0 g of material with a melting point of $138-141^\circ$ and $[\alpha]_{578} = +2.0^\circ$ (CH_3OH ; $c=5$). The salt was then dissolved in 25 ml of 2.5 M hydrochloric acid, and the solution was extracted three times with ether. The combined ether layers were washed with water and with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 1.1 g of dextrorotatory 3-cyclohexene-1-carboxylic acid, $[\alpha]_D = +94.5^\circ$ (CH_3OH ; $c=7$). The first mother liquor was evaporated to dryness and treated with 2.5 M hydrochloric acid. It was then extracted with ether, washed with water and with sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. After evaporation of the ether, 6.0 g of levorotatory **1**, $[\alpha]_{578} = -44.0^\circ$ (CH_3OH ; $c=4$), remained.

Conversion of R-(+)-3-cyclohexene-1-carboxylic acid to R-(+)-1,2,4-butanetricarboxylic acid (4) by ozonolysis. A solution of 0.5 g of the dextrorotatory 3-cyclohexene-1-carboxylic acid, $[\alpha]_D = +94.5^\circ$, in 15 ml of methanol was ozonized at -60° . After the reaction was completed the methanol was removed under reduced pressure. The residual colorless syrup was treated with 1.2 ml of 90% formic acid and 0.6 ml of 30% hydrogen peroxide. The resulting mixture was heated gently on a water-bath and at 80° a vigorous reaction set in. Heating was continued at 90° for 30 min. All volatile components were then removed at 0.5 torr. The crystalline material that remained, 0.5 g, was dissolved in 5 ml of acetone, and 5 ml of benzene was added. Crystallization was accomplished by distilling off solvent until a volume of 3 ml remained. The resulting white crystals were filtered to yield 300 mg of R-(+)-1,2,4-butanetricarboxylic acid, m.p. $94-96^\circ$, and $[\alpha]_D = +26.9^\circ$ (acetone; $c=2$), lit. m.p. $102-103^\circ$ and $[\alpha]_D = +27.2^\circ$ (acetone; $c=4$).⁵

Trimethyl ester of R-(+)-1,2,4-butanetricarboxylic acid. R-(+)-1,2,4-butanetricarboxylic acid (100 mg) dissolved in ether was treated with an ether solution of diazomethane. Evaporation of the solvent gave 100 mg of the dextrorotatory trimethyl ester of 1,2,4-butanetricarboxylic acid, $[\alpha]_D = +20.0^\circ$ (acetone; $c=3$), lit. $[\alpha]_D = +16.2^\circ$ (acetone; $c=12$).⁵

Conversion of S-(-)-3-cyclohexene-1-carboxylic acid to S-(-)-3-methylhexanedioic acid (3). To a suspension of 2.4 g (63 mmol) of lithium aluminium hydride in 50 ml of anhydrous ether was added a solution of 3.8 g (30 mmol) of levorotatory 1, $[\alpha]_{578} = -44.0^\circ$, in 50 ml of ether. The reaction mixture was refluxed for 3 h and excess hydride was destroyed with water. The ether layer was separated and the aqueous layer was extracted three times with ether. The combined ether layers were dried over anhydrous magnesium sulfate and evaporated to dryness. The yield of pure (VPC) levorotatory 3-cyclohexene-1-methanol, 2, $[\alpha]_{578} = -49.0^\circ$ (CH_3OH ; $c=3$), 3.0 g, was used as follows. To a solution of 2.9 g (26 mmol) of levorotatory 2 in 20 ml of dry pyridine was added 4.9 g (26 mmol) of *p*-toluenesulfonyl chloride. During the addition the solution was maintained at -5° . After standing at $+4^\circ$ for 24 h, the reaction mixture was poured onto 70 g of ice and extracted with two 80 ml portions of ether. The ether extracts were washed with cold water, cold 1 M hydrochloric acid, and again with cold water, and then dried over anhydrous magnesium sulfate and evaporated. The yield of colorless 3-cyclohexene-1-methyl-*p*-toluenesulfonate, $[\alpha]_{578} = -27.0^\circ$ (CH_3OH ; $c=4$), was 4.0 g. The oily material did not crystallize, probably due to small amounts of pyridine in the sample. The material was utilized without further purification as follows. A solution of 4.0 g (15 mmol) of levorotatory 3-cyclohexene-1-methyl-*p*-toluenesulfonate in 15 ml of dry diglyme was added to a suspension of 1.8 g (47 mmol) of lithium aluminium hydride in 20 ml of diglyme. The reaction mixture was kept at 120° for 1 h, and then allowed to cool before excess hydride was destroyed with ethyl acetate. The entire reaction mixture was fractionated on a Vigreux column. An optically active fraction (20 ml) was collected at $90^\circ/760$ torr. Attempts to isolate 4-methylcyclohexene by preparative VPC from this fraction, which also contained ethanol and ethyl acetate, proved unsuccessful. The fraction was therefore directly ozonized at -50° . After removal of the solvents under reduced pressure 0.1 g of material remained, to which was added 0.5 ml of 90 % formic acid and 0.5 ml of 30 % hydrogen peroxide. The reaction mixture was heated on a water-bath at 70° whereupon a vigorous reaction started. Heating was continued for 30 min. Evaporation under reduced pressure yielded an oil which gradually became crystalline after standing in a desiccator over potassium hydroxide. The crystals were recrystallized from benzene to yield 50 mg of levorotatory 3-methylhexanedioic acid, m.p. $83-85^\circ$, $[\alpha]_{578} = -4.0^\circ$ (CHCl_3 ; $c=2$), lit. m.p. = $85-87^\circ$, $[\alpha]_{\text{D}} = 9.6^\circ$ (CHCl_3 ; $c=4$).⁷ For analytical purposes, this material was converted to its dimethyl ester and subjected to VPC analysis (SE-30 column, temp. 80°). The retention time was identical to that of the dimethyl ester of authentic, racemic 3-methylhexanedioic acid (Aldrich Chemical Co.) and the chromatogram indicated a purity of $>98\%$.

Ozonolysis of R-(+)-3-cyclohexene-1-methanol to 3-hydroxymethylhexanedioic acid γ -lactone (5). Dextrorotatory 3-cyclohexene-1-methanol (1.7 g), $[\alpha]_{\text{D}} = +96.0^\circ$ (CH_3OH ; $c=3$), obtained by lithium aluminium hydride reduction of dextrorotatory 3-cyclohexene-1-carboxylic acid, $[\alpha]_{\text{D}} = +94.5^\circ$ (CH_3OH ; $c=7$), as described above for the levorotatory enantiomer, was dissolved in 30 ml of methanol and ozonized at -60° . The solvent was evaporated under reduced pressure, and to the resulting colorless syrup 12.5 ml of 90 % formic acid and 6.5 ml of 30 % hydrogen peroxide were added. The solution was heated on a water-bath at 70° whereupon a vigorous reaction started. The heating was continued for 45 min. Evaporation of the reaction mixture under reduced pressure yielded 2.0 g of 3-hydroxymethylhexanedioic acid γ -lactone, 5. For analytical purposes the lactone was converted to its methyl ester by treatment with an ether solution of diazomethane. The ester was subjected to spectroscopic analyses with the following results: $[\alpha]_{\text{D}} = -0.6^\circ$ (CH_2Cl_2 ; $c=7$). IR: -OH absent, C=O at 1780 cm^{-1} . NMR (CDCl_3): $\delta=3.7$ (singlet, 3H), $\delta=3.6-4.6$ (multiplet, 2H), $\delta=1.5-2.9$ (multiplets, 7H). Mass; $\text{M}^+ = 172.0741$, calc. for $\text{C}_8\text{H}_{16}\text{O}_4 = 172.0736$, $\text{M}^+ - \text{CH}_3\text{O}$ ($\text{C}_7\text{H}_{15}\text{O}_3$) = 141.0538 , calc. 141.0551 , $\text{M}^+ - \text{CH}_3\text{OH}$ ($\text{C}_7\text{H}_{14}\text{O}_3$) = 140.0460 , calc. 140.0473 .

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