of *2-chloro-2-(α-hydroxy-p-nitrobenzyl)-4,4-dimethyl-1-tetralone* (VIII), m.p. 188–189°, recrystallized from benzene and methanol; λ_{max}, 254 mμ (ε, 19,600); infrared spectrum with 5 mg./ml. carbon tetrachloride in a 5 mm. cell, $\gamma_{C=O}$, 1688/65 (1688/60 lithium fluoride optics), γ_{OH}, 3600/20 (3600/15 lithium fluoride optics).

Anal. $C_{19}H_{18}NClO_4$: C, 63.42; H, 5.04; Cl, 9.89. Found: C, 63.63; H, 5.08; Cl, 10.06.

When a 0.36-g. sample of the chlorohydrin VIII was dissolved in 10 ml. of methanol containing 0.1 g. of potassium hydroxide a 97% yield of the 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide was obtained.

Pyrazole formation. 1. *From 2-benzoyl-1-tetralone.* A 1.25-g. (0.05 mole) sample of 2-benzoyl-1-tetralone[18] was mixed with 0.55 g. (0.05 mole) of phenylhydrazine in 10 ml. of 1:1 ethanol-chloroform solution containing 3 drops of glacial acetic acid. After standing at room temperature for 5 hr. a 90% yield of *1,3-diphenylnaphtho(1,2-pyrazole)* (IX), was produced, m.p. 169–171°, recrystallized from benzene and hexane. A mixture of IX and 2,3-diphenylnaphtho(1,2-pyrazole) (X) (m.p.[2] 141–142°) gave m.p. 120–130°. For IX, λ_{max} 257, 270, 280, 300 sh. mμ (ε, 20,000, 20,000, 19,600, 12,000).

Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 86.06; H, 5.64; N, 8.44.

2. Attempts to obtain a pyrazole derivative from the reaction of phenylhydrazine with 2-benzal-4,4-dimethyl-1-tetralone oxide[10] or 2-hydroxy-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone[2] returned only starting materials even after refluxing in chloroform solution containing a few drops of acetic acid.

Attempted reaction of 1-hydroxy-2-benzal-tetralin oxide[2] and 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide[2] with morpholine. Refluxing these spiroepoxy alcohols with morpholine for 2 hr. returned only the starting materials.

2-(p-Dimethylaminobenzyl)-4,4-dimethyl-1-tetralone. At atmospheric pressure, in the presence of 0.15 g. of Adams catalyst, a solution of 2.0 g. (0.0065 mole) of 2-(*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone in 175 ml. of benzene absorbed 0.0057 mole of hydrogen after stirring for 15 hr. After filtration and removal of the solvent the resulting solid was crystallized from ethyl acetate and methanol providing 1.7 g. (85%) of 2-(*p*-dimethylaminobenzyl)-4,4-dimethyl-1-tetralone, m.p. 126.5–129.5°. An analytical sample was prepared by crystallization from methanol, m.p. 128.5–130°; ultraviolet (methanol) λ_{max} 252 and 292 mμ (ε, 26,600, 3620); infrared (carbon tetrachloride) $\gamma_{C=O}$ band, 1691 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.20; H, 7.84; N, 4.46.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Studies of Configuration. IX. The Preparation and Stereochemical Characterization of Some Alkyl-3-hydroxycyclohexanecarboxylic Acids[1,2]

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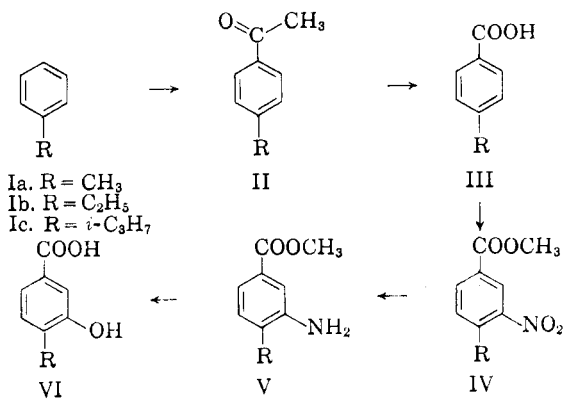
The synthesis of a series of 4-alkyl-3-hydroxycyclohexanecarboxylic acids has been carried out. The all *cis* isomers have been characterized, as well as the corresponding lactones. *trans*-5-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid and its lactone have been prepared, as well as *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid and the corresponding lactone.

In connection with a quantitative study of the γ-lactone hydroxy acid equilibrium to be discussed in the succeeding paper[4] we have examined the preparation of a variety of alkyl substituted 3-hydroxycyclohexanecarboxylic acids. Our efforts have been directed toward the stereochemical isomers in which the hydroxyl group and carboxyl group are *cis*. In this study we have clarified the stereochemical assignments of several previously reported compounds.

The first group of compounds desired for our study was the 4-alkyl-3-hydroxycyclohexanecarboxylic acids. Chart I summarizes the preparation of 4-methyl-3-hydroxybenzoic acid, 4-ethyl-3-hydrobenzoic acid, and 4-isopropyl-3-hydroxybenzoic acid. The Friedel-Crafts acetylation, hypohalite oxidation, nitration, reduction, and diazotization steps have been reported previously for one or more of the compounds investigated. With attention to the appropriate modification of experimental



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(3) Dow Chemical Corp. Fellow, 1958–59.

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conditions all of these reactions proceeded in satisfactory yield.

The reduction of the aromatic ring was studied under several conditions. The most extensive study was carried out on 3-hydroxy-4-isopropylbenzoic acid (VIc). When aged Raney nickel catalyst was used at 220° (3000 p.s.i.) on the ethyl ester, reduction gave rise to a complex mixture of products. In addition to the stereoisomeric mixture of saturated hydroxy esters, there was present phenolic material (thymol), nonsaponifiable neutral material (mixed menthols), and a mixture of lactones. There was little evidence for hydrogenolysis of the phenolic hydroxyl function. By combining fractional distillation and chemical separation a mixture of the hydroxy acids was isolated. The hydroxy acids were separated into two pairs by conversion of two isomers to the lactones.

The lactone fraction prepared in this fashion was a mixture of two isomers. From reduction in ethyl acetate, the mixture proved to be rich in the desired all *cis* isomer. VIc was reduced as the sodium salt with Raney Nickel in aqueous solution.[5] The lactone fraction was predominantly the lactone of *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid. This result is another example of the well known change in the proportion of stereoisomers formed in catalytic hydrogenation when the *p*H is changed.[6]

The lactone fraction was hydrolyzed to a mixture of 4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acids, which were separated by chromatography on Florex. The lower melting isomer, m.p. 98°, is the all *cis* isomer. Purification of this isomer is attended by considerable difficulty because of its pronounced tendency to lactonize. The higher melting isomer, m.p. 114–115°, is *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid. There is a striking difference between the two isomers with regard to lactonization. The all *cis* isomer, upon boiling in water is converted to the lactone in more than 90% yield while *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid affords only 7% lactone at equilibrium.

Reduction using rhodium on alumina in acetic acid gave a fair yield of the lactone of 4-isopropyl-3-hydroxycyclohexanecarboxylic acid. The properties of this lactone were indistinguishable from those of pure *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, showing the high stereospecificity of this catalyst. The other major reduction pathway involved hydrogenolysis of the hydroxyl group.

Similar results were obtained with 4-ethyl-3-hydroxybenzoic acid. Only *cis*-4-ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid and its lactone were characterized in this study.

For the preparation of 4-*t*-butyl-3-hydroxybenzoic acid (VII), a synthetic sequence avoiding strongly acidic conditions was employed.

Commercially available 3-hydroxy-4-*t*-butyltoluene was methylated with methyl iodide and sodium ethoxide to give 3-methoxy-4-*t*-butyltoluene in 83% yield. Oxidation using potassium permanganate in pyridine afforded 3-methyl-4-*t*-butylbenzoic acid (VIII), only in mediocre yield. Ether cleavage was accomplished in 90% yield by heating VIII in 50% methanolic potassium hydroxide at 250°. This cleavage finds analogy in the work of Price and Mueller.[7] In this case reduction using rhodium on alumina afforded an excellent yield of the all *cis* isomer.

Preparation of 5-methyl-3-hydroxycyclohexanecarboxylic acid proceeded from 3-keto-5-methylcyclohex-4-ene-carboxylic acid (XII). The synthesis of XII was carried out by the procedure of Phillips and Johnson[8] from isobutylene and maleic anhydride, followed by acid catalyzed cyclization.[9] It was found that a very substantial improvement in the cyclization step resulted by substitution of polyphosphoric acid as the cyclizing reagent.

Stereochemical assignments. Configurational assignments are particularly straightforward in this series of compounds, even though the reduction of the substituted benzoic acid can give rise to four stereoisomers. One pair can be converted to lactones, showing the *cis* relationship of hydroxyl and carboxyl. If the lactones are allowed to equilibrate with the corresponding hydroxy acid in aqueous solution, the all equatorial isomer will exist almost exclusively as the hydroxy acid, while the other will exist to a major extent as the lactone.

Some of the isomers of the *x*-methyl-3-hydroxycyclohexanecarboxylic acids have been described by Perkin and his co-workers. Two of the isomers of 2-methyl-3-hydroxycyclohexanecarboxylic acid have been previously described by Baudisch and Perkin.[10] One of these (A, m.p. 150–151°) forms the lactone on heating, while the other (B, m.p. 170–172°) does not.

It would appear likely from the method of preparation that isomer A is *trans*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid. This suggested assignment is amply confirmed by our results. Reduction of 2-methyl-3-hydroxybenzoic acid, prepared by the method of Fieser and Lothrop,[11] was hydrogenated over 5% rhodium on alumina to afford a mixture of crude 2-methyl-*cis*-3-hydroxy-

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cyclohexanecarboxylic acid lactones in satisfactory yield. Equilibration of this mixture in water afforded a pure sample of *cis*-2-methyl-*cis*-3-hydroxycyclohexane carboxylic acid lactone, m.p. 39.6–40.2°. The acid generated on hydrolysis melts at 136.2–137.0°. Thus it would appear that the isomer C which Baudisch and Perkin[10] had in hand was an impure sample of the all *cis* isomer.

Meldrum and Perkin[12] have described two of the isomers of 4-methyl-3-hydroxycyclohexanecarboxylic acid, one (A, m.p. 130–132°) convertible to a solid lactone (m.p. 30–33°), and the other (B, m.p. 161°) not. More recently Lehmann and Paasche[13] reported a lactone, m.p. 69°, obtained as a byproduct in the Diels-Alder reaction of isoprene and acrylic acid. They assigned this material the structure of 4-methyl-3-hydroxycyclohexanecarboxylic acid lactone. A more likely structure is suggested by the observation[14] that the lactone of 4-methyl-4-hydroxycyclohexanecarboxylic acid melts at 68–68.7°.

The isomer (m.p. 140–141°) prepared in this study is *cis*-4-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid, as shown by the high equilibrium proportion of lactone upon equilibration in water. Thus the isomer A of Meldrum and Perkin is *trans*-4-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid.

In the case of 5-methyl-3-hydroxycyclohexanecarboxylic acid, the situation is less clear. Meldrum and Perkin[15] report two isomers, m.p. 139°, one of which has the *cis* orientation of hydroxyl and carboxyl, and the other the *trans* arrangement. We have characterized *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (m.p. 142–143°) and its lactone (m.p. 40–41°), and also *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (m.p. 134–136°) and its lactone.

The isomers are distinctive in their behavior upon equilibration in boiling water; the all *cis* isomer gives only 5% lactone, the *trans*-5-methyl isomer giving 50% lactone.[4]

EXPERIMENTAL[16]

Methyl 3-nitro-4-methylbenzoate (IVa) was prepared according to the procedure of Kamm and Segur[17] in 80% yield, after crystallization from methanol, m.p. 49–50° (lit.[18] m.p. 49–50°). Catalytic reduction[19] afforded 95% *methyl 3-amino-4-methylbenzoate* (Va), m.p. 111–112°. After crystallization from ethanol, the purified sample melts at 114.5–115.2°.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.72; H, 6.52; N, 8.24.

The *benzamide* was prepared in the usual manner, m.p. 159–160° after crystallization from ethanol.

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.29. Found: C, 71.51; H, 5.43; N, 5.29.

3-Hydroxy-4-methylbenzoic acid (VIa). Methyl 3-amino-4-methylbenzoate (186 g.) was dissolved in 650 ml. of warm 40% sulfuric acid. Crushed ice was added with vigorous stirring, and the resulting mixture was cooled rapidly to 0°. The slurry (of the hydrogen sulfate of the amine) was diazotized with 68 g. of sodium nitrite dissolved in about 250 ml. of water. After destroying the excess nitrous acid with urea, the diazonium salt was decomposed by adding the solution dropwise to a boiling solution of 850 g. of sodium sulfate, 650 ml. of water, and 600 ml. of concentrated sulfuric acid.

After evolution of nitrogen had ceased, the mixture was cooled and worked up in the usual manner to afford crude 3-hydroxy-4-methylbenzoic acid as a dirty brown solid, which was difficult to purify.

Ethyl 3-hydroxy-4-methylbenzoate. The crude acid was esterified with absolute ethanol and sulfuric acid to afford 134.5 g. (66%) of ethyl 3-hydroxyl-4-methylbenzoate, b.p 140° (2 mm.), m.p., after crystallization from benzene-pentane, 75.6–76.0° (lit.[20] m.p. 74–75°).

Ethyl 3-hydroxy-4-ethylbenzoate. Ethylbenzene was converted to *p*-ethylacetophenone,[21] b.p. 115–118° (30 mm.), n_D^{25} 1.5277 (lit.[22] b.p. 125° (20 mm.), n_D^{25} 1.5269), in 89% yield. Hypohalite oxidation[23] afforded *p*-ethylbenzoic acid, which was converted to methyl *p*-ethylbenzoate. Methyl *p*-ethylbenzoate was nitrated[17] in good yield to give *methyl 3-nitro-4-ethylbenzoate*, m.p. 40–42°. The analytical sample melts at 43.5–44° after several crystallizations from methanol.

Anal. Calcd. for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.67; H, 5.41; N, 6.92.

Catalytic reduction[19] afforded *methyl 3-amino-4-ethylbenzoate*, m.p. 53–54° after crystallization from ethanol.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.01; H, 7.31; N, 7.82. Found: C, 66.88; H, 7.32; N, 7.75.

The *benzamide* was prepared in the usual fashion and crystallized from ethanol, m.p. 133.0–133.6°.

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.12; H, 6.08; N, 4.97.

Methyl 3-amino-4-ethylbenzoate was converted to 3-hydroxy-4-ethylbenzoic acid by the procedure described above for the conversion of methyl 3-amino-4-methylbenzoate to 3-hydroxy-4-methylbenzoic acid. The crude acid was esterified directly. After working up in the usual fashion ethyl 3-hydroxy-4-ethylbenzoate was obtained in 68% yield, based upon methyl-3-amino-4-ethylbenzoate. Crystallization from ligroin afforded pure material, m.p. 89–90°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.10; H, 7.35.

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Ethyl 3-hydroxy-4-isopropylbenzoate. By the same sequence of reactions, *p*-isopropylbenzoic acid was converted to methyl 3-nitro-4-isopropylbenzoate, m.p. 60.5–63° (lit.[24] m.p. 64°), and thence to methyl 3-amino-4-isopropylbenzoate, m.p. 50–51° (lit.[24] m.p. 51–52°). Diazotization was carried out as described above, and the diazonium salt was decomposed to give crude 3-hydroxy-4-isopropylbenzoic acid which was esterified directly with ethanol to give ethyl-3-hydroxy-4-isopropylbenzoate, m.p. 71.0–72.5° (lit.[25] m.p. 73–75°). The yield from *p*-isopropylbenzoic acid was 47%.

3-n-Butoxy-4-t-butylbenzoic acid. To a solution of 38.2 g. of potassium permanganate in 400 ml. of pyridine and 100 ml. of water was added 16.6 g. of 3-*n*-butoxy-4-*t*-butyltoluene.[26] The resulting mixture was heated under reflux for 3 hr. The cooled solution was filtered to remove manganese dioxide, and the filter cake was washed with 1 l. of water. After concentration of the filtrate, acidification with concentrated hydrochloric acid precipitated the desired 3-*n*-butoxy-4-*t*-butylbenzoic acid. Crystallization from hexane afforded 7.0 g. (38%) of 3-*n*-butoxy-4-*t*-butylbenzoic acid, m.p. 133.5–134.6°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; neutralization equivalent, 250.32. Found: C, 71.82; H, 8.97; neut. equiv., 251.

Similarly 3-methoxy-4-*t*-butyltoluene was oxidized to afford *3-methoxy-4-t-butylbenzoic acid*, m.p. 151–152° (lit.[26] m.p. 150–151°) in 20% yield.

3-Hydroxy-4-t-butylbenzoic acid. A mixture of 10.0 g. of 3-methoxy-4-*t*-butylbenzoic acid, 50 ml. of methanol and 50 g. of potassium hydroxide was heated in a steel bomb for 48 hr. at 250°. After cooling, the bomb was opened cautiously (considerable pressure, probably due to dimethyl ether) and the contents removed. Isolation in the usual fashion afforded a nearly quantitative yield of crude 3-hydroxy-4-*t*-butylbenzoic acid, m.p. 189–190°, 8.5 g. (91%).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.26; neut. equiv., 194.22. Found: C, 67.91; H, 7.14; neut. equiv., 194.

Hydrogenation studies. (a) Using rhodium on alumina catalyst. cis-4-t-Butyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. A mixture of 7 g. of 3-hydroxy-4-*t*-butylbenzoic acid and 2 g. of 5% rhodium on alumina catalyst in 100 ml. of glacial acetic acid was reduced with hydrogen at an initial pressure of 3 atm. The theoretical amount of hydrogen was absorbed in 28 hr. Filtration of the suspended catalyst, followed by distillation under reduced pressure afforded 5.8 g. (85%) of the crude lactone, b.p. 140°/6 mm., which solidified immediately. The crude lactone, m.p. 88–89°, was dissolved in ether, washed with cold dilute sodium bicarbonate and water. The lactone, after removal of the ether, was crystallized from hexane, m.p. 90.2–91.1°.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.52; H, 9.96. Found: C, 72.54; H, 9.86.

A saponified sample of the lactone of *cis*-4-*t*-butyl-*cis*-3-hydroxycyclohexanecarboxylic acid was converted to the *p*-phenylphenacyl ester, m.p. 174.6–175.0°, after four crystallizations from ethanol.

Anal. Calcd. for $C_{25}H_{30}O_4$: C, 76.11; H, 7.67. Found: C, 76.22; H, 7.49.

cis-3-Hydroxy-cis-4-methylcyclohexanecarboxylic acid. Using rhodium on alumina, 30 g. of 3-hydroxy-4-methylbenzoic acid was reduced at an initial pressure of three atmospheres. Hydrogen uptake was complete overnight. Following filtration to remove the catalyst, distillation afforded 13 g. (47%) of the impure lactone of *cis*-3-hydroxy-*cis*-4-methylcyclohexanecarboxylic acid, b.p. 102–105° (7 mm.), n_D^{25} 1.4665–1.4684. A small higher boiling fraction was obtained, b.p 110–115° (7 mm.). This material was identified, *via* the *p*-bromophenacyl ester, m.p. 110.5–111.4°,[27] as *cis*-4-methylcyclohexanecarboxylic acid.

Hydrolysis of the lactone was accomplished by warming with dilute sodium hydroxide and working up in the usual fashion; after several recrystallizations from methyl acetate, pure *cis*-3-hydroxy-*cis*-4-methylcyclohexanecarboxylic acid, m.p. 141.0–141.5°, was obtained.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92; neut. equiv. 158.2. Found: C, 60.67; H, 8.97; neut. equiv., 158.2.

A sample of the pure acid was converted to the *p*-bromophenacyl ester, which melts at 121.2–122.0° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{16}H_{19}O_4Br$: C, 54.09; H, 5.39; Br, 22.49. Found: C, 53.90; H, 5.46; Br, 22.51.

cis-3-Hydroxy-cis-4-isopropylcyclohexanecarboxylic acid. Hydrogenation of a slightly impure sample of 3-hydroxy-4-isopropylbenzoic acid using rhodium on alumina catalyst afforded the lactone of *cis*-3-hydroxy-4-isopropylcyclohexanecarboxylic acid, b.p. 122–125° (6 mm.), n_D^{25} 1.4736–1.4738. The index of refraction is indistinguishable from that of the pure lactone, *vide infra.*

Hydrolysis with dilute sodium hydroxide and workup in the usual fashion afforded *cis*-3-hydroxy-*cis*-4-isopropylcyclohexane carboxylic acid, m.p. 95–96°.

(b) Hydrogenation studies using Raney nickel. Ethyl 3-hydroxy-4-isopropylbenzoate (100 g.) was reduced at 2500 p.s.i. and 200° using W-2 Raney nickel catalyst. Workup in the usual fashion afforded several fractions, b.p. 90–135° (5 mm.).

The lowest boiling fractions contained an appreciable quantity of neutral, nonsaponifiable material of properties (infrared, b.p., index of refraction) concordant with mixed menthols. Five per cent of the total material was accounted for in this fashion.

The center fractions, b.p. 102–110°, were saponified, acidified, and extracted with sodium carbonate solution to afford an ether solution of a fraction, b.p. 96° (6 mm.) which was void of carbonyl absorption in the infrared. Preparation of the aryloxyacetic acid confirmed the identification of this material as thymol, m.p. and mixed m.p. 148–149°. The yield was 4% of the total amount of ethyl 3-hydroxy-4-isopropylbenzoate reduced.

The higher boiling fractions, b.p. 110–135° (5 mm.), were saponified, acidified, and continuously extracted with ether. Distillation afforded 15 g. of the mixed lactones of the 4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acids, b.p. 120–126° (6.5 mm.).

Saponification of this material afforded on working up in the usual fashion crude *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 90–92°.

trans-4-Isopropyl-cis-3-hydroxycyclohexanecarboxylic acid. Reduction of 3-hydroxy-4-isopropylbenzoic acid (9.1 g.) was carried out in 100 ml. of 0.5*N* sodium hydroxide using W-2 Raney nickel catalyst at an initial pressure of 3500 p.s.i. at 150°. After filtration to remove the catalyst, the solution was acidified and continuously extracted with ether. The ether was removed by distillation and the residue heated under reflux for 30 min. with 50 ml. of acetic anhydride. Fractionation afforded 4.1 g., b.p. 128–133° (7.5 mm.), of the lactones of 4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid. The center fraction solidified. Recrystallization of this fraction (1.5 g.) from pentane afforded the lactone of *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 55.5–56.5°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.38.

Saponification of the lactone with dilute alkali followed by isolation in the usual manner afforded *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 114–115° after crystallization from acetone-hexane.

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(27) Comparison was made with an authentic sample, kindly supplied by Mr. Laird Gale, *cf.* thesis, University of California, 1959.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.47; neut. equiv., 186.2. Found: C, 64.48; H, 9.62; neut. equiv., 186.

The *p*-bromophenacyl ester was prepared in the usual manner, and crystallized from benzene-hexane, m.p. 118.6–119.5°.

Anal. Calcd. for $C_{18}H_{23}O_4Br$: C, 56.40; H, 6.05; Br, 20.85. Found: C, 56.22; H, 6.30; Br, 20.65.

cis-4-Isopropyl-cis-3-hydroxycyclohexanecarboxylic acid. Crude *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid (4.8 g., m.p. 90–91°) was chromatographed on Florex. The early fractions, eluted with 30% ether-hexane, afforded 4.2 g. of *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid, and the late fraction, eluted with ether, afforded 0.22 g. of *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid.

Recrystallizations of the all-*cis* isomer from hexane afforded pure material, m.p. 98.0–98.4°, unchanged on further crystallization.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; neut. equiv., 186.2. Found: C, 64.54; H, 9.71; neut. equiv., 184.1.

It was observed that samples of the pure acid reverted to lactone upon standing. There was also considerable loss on crystallization because of lactone formation.

The *p*-bromophenacyl ester was prepared in the usual manner and crystallized from benzene-hexane, m.p. 114.9–115.1°.

Anal. Calcd. for $C_{18}H_{23}O_4Br$: C, 56.40; H, 6.05; Br, 20.85. Found: C, 56.48; H, 6.25; Br, 20.94.

When admixed with an equal amount of the *p*-bromophenacyl ester of *trans*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid, the melting point is depressed to 107–109°.

cis-4-Isopropyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. A sample of pure *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid was converted to the lactone by heating the acid at 160° for 10 min. and then distilling under reduced pressure, b.p. 124–125° (6 mm.), n_D^{25} 1.4738.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.27; H, 9.55.

cis-4-Ethyl-cis-3-hydroxycyclohexanecarboxylic acid. Reduction of ethyl 3-hydroxy-4-ethylbenzoate with hydrogen, using W-2 Raney nickel catalyst at 2000 p.s.i. and 220° gave a complex mixture of saturated hydroxy esters, lactones, and other reduction products. The lower boiling fractions showed the presence of phenolic material, and of neutral nonsaponifiable material, just as in the case of ethyl 3-hydroxy-4-isopropylbenzoate. The fraction, b.p. 110–140° (7 mm.) was saponified with dilute alcoholic sodium hydroxide. Following removal of neutral material by steam distillation, the alkaline solution was acidified and continuously extracted with ether. The ether was removed by distillation, and the residue was heated under reflux with acetic anhydride for 1 hr. At the end of this time the entire solution was distilled under reduced pressure to give a mixture of the stereoisomers of 4-ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone. This material was directly hydrolyzed to 4-ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid. Fractional crystallization from acetone-hexane afforded pure *cis*-4-ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 117.0–117.2° (over-all yield 8% from the aromatic ester).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36; neut. equiv., 172.2. Found: C, 62.77; H, 9.36; neut. equiv., 173.5.

A sample of the pure acid was converted to the *p*-phenylphenacyl ester, m.p. 122.9–124.0° after crystallization from ethanol.

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.27; H, 7.10.

cis-4-Ethyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. After heating a sample of the acid at 160° for 15 min., the lactone was distilled, b.p. 110–111° (6 mm.), n_D^{25} 1.4711.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.30.

cis-2-Methyl-cis-3-hydroxycyclohexanecarboxylic acid. 2-Methyl-3-hydroxybenzoic acid was prepared by the method of Fieser and Lothrup.[11] Purification of the acid was most easily accomplished by esterification, distillation, and saponification. It was found that the recovery of the acid was appreciably increased by using continuous extraction of the aqueous solutions. The yield of purified acid was 27%.

Reduction of 2-methyl-3-hydroxybenzoic acid using 5% rhodium on alumina afforded, upon distillation, 51% of the mixed lactones of 2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid, b.p. 90–116° (6 mm.), n_D^{25} 1.4636–1.4700. The lactone mixture was saponified by heating with dilute sodium hydroxide. The acid, isolated in the usual fashion, was fractionally crystallized from methyl acetate and from acetonitrile, m.p. 136.2–137.0°.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92; neut. equiv., 158.2. Found: C, 60.86; H, 8.92; neut. equiv., 159.4.

The *p*-bromophenacyl ester was prepared in the usual manner. It melts at 148.7–149.5° after five crystallizations from absolute ethanol.

Anal. Calcd. for $C_{16}H_{19}O_4Br$: C, 54.09; H, 5.39; Br, 22.49. Found: C, 54.01; H, 5.28; Br, 22.43.

cis-2-Methyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. A 1-g. sample of the pure acid was converted to the lactone by heating at 160°. The lactone boiled at 95–96° (6 mm.) and solidified immediately. After three crystallizations from pure pentane there was obtained 650 mg. of pure *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m.p. 39.6–40.2°, unchanged by further crystallization.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.60; H, 8.62.

Large scale equilibration of crude 2-methyl-3-hydroxycyclohexanecarboxylic acids. A total of 13.8 g. of the crude lactones obtained above was heated under reflux with 1 l. of water for 1 week. The aqueous solution was titrated to a phenolphthalein end point with 1*N* sodium hydroxide and continuously extracted with ether for 48 hr. The ether was flash distilled and the residue fractionated. There was obtained 4.8 g. of material, b.p. 95–105°/6 mm., collected in three fractions. The center fraction, b.p. 96–96.5° (6 mm.), solidified upon standing. The solid lactone thus obtained melts at 38–39°.

cis-2-Methyl-cis-3-hydroxycyclohexanecarboxylic acid. Fraction 3, 2 g. (0.014 mole), b.p. 95–105° (6 mm.), n_D^{25} 1.4690, obtained from the large scale equilibration, was saponified with 5 ml. of 5*N* sodium hydroxide and 5 ml. of water. Acidification in the cold precipitated the crude acid which was extracted into ethyl acetate. The ethyl acetate extracts were washed with water and evaporated under reduced pressure to yield the crude acid. After two crystallizations from methyl acetate, there was obtained 300 mg. of almost pure *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid m.p. 135–137°.

3-Keto-5-methylcyclohex-4-enecarboxylic acid. To 100 g. of polyphosphoric acid on the steam bath was added 15.4 g. of methallylsuccinic anhydride[8] in one portion with stirring. The solution turned pale green, then orange. Heating and stirring were continued for 30 min., after which the reaction mixture was cooled and 150 g. of ice added. The solution was diluted to 700 ml. and continuously extracted with ether for 18 hr. Evaporation of the ether afforded 14 g. (93%) of crude 3-keto-5-methylcyclohex-4-enecarboxylic acid which crystallized immediately. Recrystallization from chloroform-ligroin yielded 12.8 g. (85%) of almost pure acid, m.p. 91–92° (lit.[9] 92–94°).

cis-5-Methyl-cis-3-hydroxycyclohexanecarboxylic acid. 3-Keto-4-methylcyclohex-4-enecarboxylic acid was hydrogenated (1 mole) over 5% palladium on charcoal in methanol. After filtration to remove the catalyst the mixture was directly esterified by addition of sulfuric acid. Methyl 3-keto-5-methylcyclohexanecarboxylate was obtained in 80% yield, b.p. 110–115° (8 mm.), n_D^{25} 1.4596.

Aluminum isopropoxide reduction of methyl 3-keto-5-methylcyclohexanecarboxylate. A total of 110 g. (0.65 mole) of

methyl 3-keto-5-methylcyclohexanecarboxylate was heated under reflux with 100 g. (0.5 mole) of distilled aluminum isopropoxide and 700 ml. of dry isopropyl alcohol for 4 days. Isopropyl alcohol was distilled until no more acetone could be detected in the distillate. The usual workup and fractionation yielded 12.42 g. of forerun, b.p. 80–102° (8 mm.), n_D^{25} 1.4598–1.4735; 1.03 g. of material, b.p. 102–105° (8 mm.), n_D^{25} 1.4730, whose infrared spectrum showed carbonyl absorption at 1770 cm.$^{-1}$ characteristic of a γ-lactone; and 76.42 g. (*ca.* 60%) of material, b.p. 124–135° (8 mm.), which appeared to be a mixture of methyl and isopropyl 3-hydroxy-5-methylcyclohexanecarboxylate.

Crude cis-5-methyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. A total of 47.5 g. of mixed methyl and isopropyl 5-methyl-3-hydroxycyclohexanecarboxylate, b.p. 124–135° (6 mm.), was saponified with 30 g. (0.75 mole) of sodium hydroxide, 100 ml of ethanol, and 200 ml. of water. The saponification mixture was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and flash distilled. Distillation of the residue yielded 4.1 g. (12%) of crude *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, b.p. 100–100° (6 mm.), n_D^{25} 1.4756.

cis-5-Methyl-cis-3-hydroxycyclohexanecarboxylic acid. The 4.1 g. (0.292 mole) of crude *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone was saponified with aqueous sodium hydroxide and worked up in the usual fashion. The crude acid was dissolved in a small amount of ethyl acetate and chromatographed on 250 g. of commercial Florex. There was obtained 3.29 g. (71%) of almost pure *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid eluted with 3 l. of 10% ether-benzene. The material melts at 134–135.6° after crystallization from methyl acetate-hexane (lit.[15] m.p. 138–139°).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92; neut. equiv., 158.2. Found: C, 60.66; H, 8.82; neut. equiv., 157.6.

The *p*-phenylphenacyl ester melts at 140–141° after three crystallizations from absolute ethanol.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 74.78; H, 6.91.

cis-5-Methyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. A 3-g. sample of *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid was distilled at 180° (6 mm.) to yield 300 mg. of the semicrystalline lactone which was taken up in ether, washed with sodium carbonate solution, and sublimed to yield 200 mg. of almost pure *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m.p. 36–42° (lit.[15] b.p. 130–132°/13 mm.).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.73; H, 8.72.

The residue from the lactonization was distilled at atmospheric pressure through a short column with the aid of a Bunsen burner. The distillate was taken up in ether and washed with sodium carbonate and water. The ether was evaporated and the residue was sublimed to yield another 1.7 g. of *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone for a total yield of 75%.

Hydrogenation of 3-keto-5-methylcyclohex-4-enecarboxylic acid over rhodium on alumina. A total of 79 g. (0.51 mole) of the keto acid was hydrogenated in 20-g. portions dissolved in 150 ml. of warm water in the presence of 3 g. of 5% rhodium on alumina catalyst at an initial pressure of three atmospheres. The theoretical amount of hydrogen was absorbed in about 9 hr. The catalyst was filtered and the aqueous solution was continuously extracted with ether for 48 hr. The ether was flash distilled and the residue distilled under reduced pressure to yield 15 g. (20%) of crude *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, b.p. 95–102° (6 mm.), collected in two fractions. Fraction 1, 4.6 g., b.p. 95–102° (6 mm.), crystallized upon standing. Fraction 2 was washed successively with sodium carbonate solution and water and redistilled to yield 9.5 g. of the impure lactone, b.p. 103–106° (6 mm.), n_D^{25} 1.4705.

trans-5-Methyl-cis-3-hydroxycyclohexanecarboxylic acid lactone. A total of 5.88 g. of almost pure *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m.p. 38–40°, was crystallized seven times from hexane to yield 2.90 g. pure *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m.p. 40–41° (very slow heating).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.34; H, 8.52.

trans-5-Methyl-cis-3-hydroxycyclohexanecarboxylic acid. A 1.95-g. (0.0139 mole) sample of pure *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone was saponified with 7 ml. of 3*N* aqueous sodium hydroxide (0.021 mole) and 7 ml. of water. The crude hydroxy acid was isolated in the usual manner and crystallized twice from water and twice from ethyl acetatecyclohexane to yield 0.95 g. (42%) of pure *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid, m.p. 142–143°, unchanged by further crystallization.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.02; H, 9.02.

The *p*-phenylphenacyl ester of *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid was prepared in the usual manner. The ester melts at 95.5–97° after five crystallizations from 95% ethanol and sublimation at 105–110° (10^{-4} mm.).

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 74.71; H, 7.12.

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