Treatment of III with Sodium Hydroxide.—III (1.3 g.) was added to a stirred solution of 1 g. of sodium hydroxide in 25 ml. of water. The quinone dissolved immediately, and the resulting clear yellow solution was acidified with concentrated hydrochloric acid to give hydrogen cyanide (identified by benzidine acetate–copper acetate test paper) and a solid (0.39 g.). The solid was recrystallized from alcohol–water to yield 0.3 g. of IIa identified by infrared and analysis. The mother liquors were evaporated to dryness and the residue was extracted with 25 ml. of hot ethanol. The extract was evaporated to dryness and the residue (0.59 g.) was recrystallized from a mixture of ethanol and petroleum (b.p. 35–60°) to give 0.45 g. of 2-cyano-3-hydroxy-1,4-naphthoquinone (VII), m.p. 198–199°. The infrared spectrum showed strong absorption at 2.8 and 4.4 μ for the hydroxy and cyano groups, and at 5.9 and 6.0 μ for the carbonyl groups.

Anal. Calcd. for $C_{11}H_5NO_3$: C, 66.2; H, 2.5; N, 7.0. Found: C, 66.0; H, 2.5; N, 7.3.

Quantitative Studies in Stereoselective Addition Reactions by Isotope Dilution. Additions of Organometallic Reagents Leading to 2,3-Dicyclohexyl-2,3-butanediol. A Strong Halide Effect[1]

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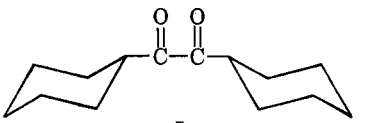
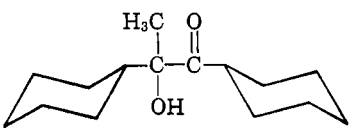
The addition of methyllithium, methylmagnesium chloride, methylmagnesium bromide, and methylmagnesium iodide to 1,2-dicyclohexylethanedione (I) and 1,2-dicyclohexylpropan-2-ol-1-one (II) has been studied by isotope-dilution techniques. The identity of the diastereoisomeric glycols formed was established by nuclear hydrogenation of the established *meso*- and *dl*-racemate phenyl analogs. The following ratios were observed for I and (II), the *meso* form predominating in all cases: methyllithium, 7:1 (8:1); methylmagnesium chloride, 9:1 (7:1); methylmagnesium bromide, 4.5:1 (4:1); and methylmagnesium iodide, 3:1 (3:1). While monoaddition to I appeared rapid, Grignard production of glycol was very slow, particularly in the case of the iodide. The results underscore the need to specify or choose the Grignard halogen in stereoselective synthesis. The addition of cyclohexylmagnesium chloride, cyclohexylmagnesium bromide, and cyclohexylmagnesium iodide to biacetyl produced less than 1.0% of either glycol.

Two general methods are presently used in predicting the course of the stereoselective production of a second, adjacent asymmetric carbon by various addition–reduction techniques. These methods involve conformational control,[2] or a more or less rigid cyclic intermediate.[3] It has recently been suggested[4] that a dipolar model, also involving conformation control, may be invoked usefully. The examination[3] of a "test case," where the first two models would predict opposite results (*i.e.*, the addition of appropriate organolithium reagents to benzil or biacetyl to produce, stereoselectively, the two diastereoisomers of 2,3-diphenyl-2,3-butanediol) gave results in accord with the semirigid model. A subsequent examination employing the related Grignard reagents[5] showed the situation to be considerably more complex. Although the addition of the various methyl organometallic reagents to benzil gave results in accord with the semirigid model, as did the addition of phenyllithium, phenylmagnesium iodide, and diphenylmagnesium to biacetyl, addition to the latter of the chloride or bromide Grignard reagent could best be explained by invoking one of the alternative models. Accordingly, it should be of value to have additional data describing this type of reaction involving other systems. Referring to the earlier work as involving a methyl–phenyl system, the present paper, to be the first of several, offers details of an investigation of the methyl–cyclohexyl system, selected for its freedom from aromatic influences. The correspondence of the methyl group in the two systems should permit some cross comparison of the relative effects of the cyclohexyl and phenyl substituents.

Preparation of the unlabeled I was carried out in 84% over-all yield by way of a standard acyloin-type condensation followed by oxidation with cupric acetate. Contrary to the usual very brief reaction time for the latter step, a reflux time of less than 1 hr. produced inseparable diketone–ketol mixtures. The ketol II was prepared by the inverse addition of limited amounts of methylmagnesium bromide to I.



I



II

The identities of the diastereoisomeric glycols were established conveniently by nuclear hydrogenation of the known phenyl analogs[3] using 5% rhodium-on-alumina catalyst.[6,7] The yields were excellent: 93% for the *meso* and 94% for the *dl* form. These phenyl analogs were available from the stereoselective addition of methyllithium to benzil (*meso*) and phenyllithium to biacetyl (*dl*).[5] This route also proved useful for the preparation of larger amounts of the glycols to be used in the dilution studies. Some of the *meso* form so used

(1) Presented before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) "Cram's Rule"; see D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5829 (1952).

(3) D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).

(4) D. J. Cram and D. R. Wilson, *ibid.*, **85**, 1245 (1963).

(5) J. H. Stocker, P. Sidisumthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).

(6) Engelhard Industries, Newark, N. J.

(7) A brief communication describing the use of this catalyst to minimize benzyl-type hydrogenolysis in nuclear hydrogenation and including these examples appeared earlier: J. H. Stocker, *J. Org. Chem.*, **27**, 2288 (1962).

TABLE I

DIASTEREOISOMERIC RATIOS OBSERVED UPON REACTION OF ORGANOMETALLIC REAGENTS WITH DIKETONES OR KETOLS LEADING TO 2,3-DICYCLOHEXYL-2,3-BUTANEDIOL[a]

Entry	Compd.[b]	Organometallic reagent	% yield *meso*	% yield *dl*	Reaction time, hr.	*meso*–*dl*
1	I	MeLi	73.6	10.6	4.5	6.9:1
2	I	MeLi	81.7	11.8	8.0	6.9:1
3	II	MeLi	88.2	11.2	8.5	8:1
4	I	MeMgCl	25.9	2.9	30.0	8.9:1
5	I	MeMgCl	32.7	3.7	72.0	8.8:1
6	II	MeMgCl	40.1	6.1	40.0	7:1
7	I	MeMgBr	4.4	1.0	24.0	4.4:1
8	II	MeMgBr	13.7	3.2	51.0	4:1
9	I	MeMgI	1.9	0.8	4.5	2.4:1
10	I	MeMgI	11.7	3.2	75.0	3.6:1
11	I	MeMgI	20.2	6.5	188.0	3.1:1
12	II	MeMgI	5.1	1.6	24.0	3:1
13	Biacetyl	$C_6H_{11}MgCl$	<1	<1	74.0	...
14	Biacetyl	$C_6H_{11}MgBr$	<1	<1	36.0	...
15	Biacetyl	$C_6H_{11}MgBr$	<1	<1	72.0	...
16	Biacetyl	$C_6H_{11}MgI$	<1	<1	72.0	...

[a] All reactions in ether, employing a 4–6:1 ratio of organometallic to diketone or ketol, excepting entry 11 (10:1). [b] Ketol II and biacetyl: unlabeled starting materials, labeled diluents. For reasons of the inherent lower accuracy of this procedure, all ratios have been rounded off to the nearest whole number.

was also prepared by the highly stereoselective addition of methyllithium to I.

Labeled I was conveniently prepared by the rhodium-catalyzed nuclear hydrogenation of labeled benzoic acid to cyclohexanecarboxylic acid in methanol; subsequent preparation of the methyl ester directly from the hydrogenation media after removal of the catalyst, without isolating the acid, under azeotropically forcing conditions, gave a two-step, over-all yield of 90%. The ester was treated subsequently as in the preparation of the unlabeled I.

Labeled biacetyl, of use in approaching the glycols under study by addition of cyclohexyl Grignard reagents, is difficult to prepare, volatile, and deteriorates on storage. Cyclohexyllithium decomposes ethyl ether sufficiently rapidly that its use was not considered. Accordingly, it was decided to make use of inverse dilution study techniques (dilution with labeled glycols instead of employing labeled starting materials) as was utilized successfully in the methyl–phenyl system studied earlier. To this end, labeled *meso* glycol was prepared from labeled benzil as described in the previous paragraph. Labeled *dl* glycol was prepared by the *poorly* stereoselective addition of methylmagnesium iodide to labeled benzil, "fished out" with added inactive material, and subsequently hydrogenated.

The results of the dilution studies are summarized in Table I. It will be noted that the *meso* form, predicted by the semirigid but not the other model, prevails in all cases in Table I for which ratios could be measured. Several items of considerable interest emerge from the data.

(a) The very large difference in diastereoisomeric ratios results solely from a change in the halogen of the methyl Grignard employed. In the corresponding methyl additions to benzil,[5] changing the Grignard halide from iodide to chloride resulted in a change in diastereoisomeric ratios of less than 50%.

(b) The very high stereoselectivity of the methylmagnesium chloride exceeds that even of the methyllithium. This may be contrasted with the corresponding ratios of less than 3:1 for the chloride and 8:1 for the lithium reagent when added to benzil.[5]

(c) The Grignard additions, particularly that of the iodide, were extremely slow. Since the characteristic yellow color of the diketone disappeared on contact with the Grignard reagent, it is reasonable to assume that monoaddition occurred rapidly. That the "slowness" of the reaction, assumed from the yield data, actually has a kinetic basis may be inferred from the lack of change of diastereoisomeric ratios with change of time as well as the general inner consistency of the data.

All attempts to obtain data from the addition of cyclohexyl Grignard reagents to biacetyl met with failure as indicated in Table I. Similar experiments on a macroscale gave low yields of monoaddition product and a complex mixture of materials as indicated by eight distinguishable peaks on the gas chromatograph. Use of the monoaddition product, also derived from the addition of cyclohexylmagnesium bromide to biacetyl monoxime followed by acid hydrolysis of the oxime group, was abandoned when the data in Table I became available.

That the low yields of product for the extended reaction times were not due to decay, selective or otherwise, in the reaction media was established by essentially quantitative recovery of labeled glycol (by dilution techniques) refluxed for 72 hr. in an ether media containing a 24:1 molar ratio of methylmagnesium iodide.

Speculation concerning the mechanism of stereoselectivity in these reactions is clearly premature; all models invoked thus far essentially neglect the halide except to suggest that it plays a part in the Schlenk equilibrium and thereby, unpredictably, determines, at least in part, the concentration of the various magnesium-containing species present.[4] Alternative speculations could include intimate halogen involvement in the intermediate with simple polarity considerations making the carbonyl carbon more attractive to attack in the case of the chloride (increased rate) and steric considerations (greater solvent involvement in the case of the chloride) accounting for the increased stereoselec-

tivity. Current interest in the structures of Grignard and organolithium reagents by a number of investigators may be expected to provide some useful data for resolving this matter.

It had been hypothesized that the acquisition of sufficient data from analogous systems might permit the compilation of a list of the "effective bulks" of the various substituents. Data from the methyl–phenyl[5] and methyl–cyclohexyl systems permit a test of this hypothesis. The fact that methyllithium adds to both benzil and I with roughly the same degree of stereoselectivity (8:1 *vs.* 7:1 *meso* to *dl*, respectively) would suggest that the addition of phenyllithium to I should occur with very little stereoselectivity. Preliminary experiments have shown that, from this reaction, greater than 60% of one diastereoisomer (tentatively assigned the racemate form) may be isolated with recovery of any of the other form very difficult. Clearly this reaction is therefore highly stereoselective and any cross comparisons must be made with caution.

Experimental[8]

Freshly opened cans of Mallinkrodt anhydrous ether were used without further purification. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride through 24 in. of glass helices and used immediately. Methyl acetate was dried over magnesium sulfate and distilled through 24 in. of glass helices, only the fraction boiling at 57.0° being used. Dry nitrogen was employed in all synthetic procedures involving organometallic reagents. Lithium was used as 1/8-in. wire, packed in grease, available from A. D. Mackay, Inc., New York, 38, N. Y. All other materials were of standard research grades, used as received.

1,2-Dicyclohexylethan-2-ol-1-one.—The procedure was adapted from that described for butyroin.[9] From 105 g. (4.5 g.-atoms) of sodium and 274 g. (2.0 moles) of methyl cyclohexanecarboxylate [81% from the equilibrium combination of acid and alcohol; b.p. 85–86° (25 mm.), $n^{27}D$ 1.4406] was derived 216 g. (100%) of undistilled crude product. Fractionation of the material from a smaller run (0.135 mole of ester) gave 63% of yellowish product, b.p. 115–118° (0.18 mm.) [lit.[10] b.p. 140–141.5° (3 mm.)]. An orange 2,4-dinitrophenylhydrazone of this material, prepared in standard fashion, melted at 223°.

Anal. Calcd. for $C_{20}H_{28}N_4O_5$: C, 59.4; H, 7.0; N, 13.9. Found: C, 59.2; H, 6.9; N, 14.1.

1,2-Dicyclohexylethanedione (I).—The procedure was adapted from that described for Sebacil.[11] A solution of the crude ketol (216 g.), 780 ml. of 90% acetic acid, 78 ml. of methanol, and 390 g. of copper acetate was refluxed for 3 hr. with occasional stirring and allowed to stand overnight. The mixture was filtered by suction through a Filter-cel mat, 1 l. of saturated salt solution was added to the filtrate, and the layers were separated. Three 300-ml. ether extractions of the aqueous layer were added to the organic layer. Solid sodium carbonate was added to the latter until effervescence ceased and the resultant aqueous layer was removed. The ether layer was washed with saturated salt solution and dried over magnesium sulfate, the ether was removed, and the remainder was fractionated *in vacuo* to yield 180 g. (84% yield based on starting ester) of I, b.p. 91–98° (0.14 mm.). This material solidified essentially completely on standing, m.p. 28–32°. Recrystallization from methanol gave a product with m.p. 34° [lit.[10] b.p. 168–169° (12 mm.)]. A yellow 2,4-dinitrophenylhydrazone of this material, prepared in standard fashion, melted at 133°.[12]

Anal. Calcd. for $C_{20}H_{26}N_4O_5$: C, 59.7; H, 6.5; N, 13.9. Found: C, 59.8; H, 6.6; N, 13.9.

***meso*-2,3-Dicyclohexyl-2,3-butanediol.**—A solution containing 14.3 g. of *meso*-2,3-diphenyl-2,3-butanediol,[3,5] 20 ml. of absolute methanol, 7.0 g. of 5% rhodium on alumina, and 0.5 ml. of glacial acetic acid was hydrogenated on the low-pressure Parr apparatus at room temperature and 60 p.s.i. Theoretical absorption of hydrogen for six double bonds occurred in approximately 24 hr. The reaction mixture was filtered through a Celite mat, the catalyst was washed well with methanol, and the filtrate was concentrated to dryness in an air stream on a steam bath. Recrystallization of the diol from hexane gave 14.0 g. (93%), m.p. 126–127°.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8. Found: C, 75.9; H, 11.8.

***dl*-2,3-Dicyclohexyl-2,3-butanediol.**—The procedure described above for the diastereoisomer was employed with 12.1 g. (0.05 mole) of *dl*-2,3-diphenyl-2,3-butanediol[5] to yield 11.9 g. (94%) of silky, white needles. This product showed dimorphism, melting first at approximately 98°, and resolidifying to melt sharply at 107°. The needles sublimed to chunky, white crystals at reduced pressure and steam-bath temperature; these crystals melted sharply at 107° without displaying dimorphism. They may be recrystallized from petroleum ether (b.p. 30–60°) to reproduce the needle form. The infrared spectra of both forms in chloroform were superimposable.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.6; H, 11.8. Found: C, 75.5; H, 11.7.

1,2-Dicyclohexylpropan-2-ol-1-one (II).—A solution of 24 ml. of 3 *M* methylmagnesium bromide[13] diluted with 50 ml. of anhydrous ether was added over a 30-min. period to 13.2 g. (0.06 mole) of I under Grignard reaction conditions. After 1 hr. of reflux, customary work-up, and removal of solvent, the resultant oil was distilled *in vacuo* to give 6.50 g. (46%) of a colorless viscous oil, b.p. 106–107° (0.15 mm.).

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.6; H, 11.0. Found: C, 75.4; H, 10.8.

2-Cyclohexylbutan-2-ol-3-one.—To a Grignard reagent prepared from 24.3 g. of magnesium and 163 g. of bromocyclohexane in absolute THF was added 21.5 g. of freshly distilled biacetyl over a period of 30 min. The mixture was refluxed for 42 hr. Following a customary work-up and removal of solvent, the remaining yellow oil was fractionated through 150 mm. of glass helices to yield material on a more or less steady rise from 30–100° at 0.2 mm. The distillate was collected in arbitrary fractions; subjecting these to gas chromatography indicated that at least eight different components were present. The material collected from 60–65° (2.5 g.) was essentially pure ketol, as indicated by its infrared spectrum and gas chromatography.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.7. Found: C, 70.8; H, 10.6.

2-Cyclohexylbutan-2-ol-3-one Oxime.—To the Grignard reagent prepared from 7.8 g. of magnesium and 52 g. of bromocyclohexane in absolute ether was added a solution 8.1 g. of biacetyl monoxime (from ether) in 10 ml. of ether and the mixture was refluxed for 21 hr. Following a customary work-up and removal of solvent, the remaining brown, gummy solid was dissolved in a benzene–hexane solvent, chromatographed on Florisil, and eluted with hexane followed by benzene. The hexane fractions were discarded on the basis of their infrared analyses; the benzene fractions deposited an orange solid on evaporation to dryness. Recrystallization of this solid from benzene (Norit) gave the pure oxime, m.p. 104–105°, 1.48 g. (10% yield).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 17.6. Found: C, 64.6; H, 10.2; N, 17.6.

Cyclohexanecarboxylic Acid-7-C^{14}.—A solution of benzoic acid-7-C^{14} (24.4 g., specific activity approximately 4 mc./mole), 110 ml. of absolute methanol, 1.0 ml. of glacial acetic acid, and 3.0 g. of 5% rhodium on alumina was hydrogenated in a Parr low-pressure apparatus at 40–60 p.s.i.; absorption of the theoretical amount of hydrogen was complete in 1.5 hr. The reaction mixture was filtered with suction through a Celite mat and the filtrate was used directly for preparation of the ester below.

(8) Melting points and boiling points are uncorrected. Analyses were carried out by A. Bernhardt, Muhlheim, West Germany. The Dynacon Model vibrating-reed electrometer (Nuclear-Chicago Corp.) and the Tri-Carb scintillation counter (Packard Instrument Co., Inc.) were used for measuring activities.

(9) J. M. Snell and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 114.

(10) S. Danilov and E. Venus-Danilov, *Chem. Ber.*, **62**, 2653 (1929).

(11) A. T. Blomquist and A. Goldstein, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 838.

(12) P. S. Pinckney, G. A. Nesty, R. H. Wiley, and C. S. Marvel [*J. Am. Chem. Soc.*, **58**, 972 (1936)] have reported a mono-3,4-dinitrophenylhydrazone of this diketone, m.p. 120–121°.

(13) Arapahoe Chemicals, Boulder, Colo.

Methyl Cyclohexanecarboxylate-7-C^{14}.—Following the addition of 100 ml. of methyl acetate and 3 ml. of concentrated sulfuric acid to the methanolic solution of cyclohexanecarboxylic acid-C^{14} above, the water–ester azeotrope was slowly removed through 24 in. of glass helices over a period of 4.5 hr. A total of 125 ml. of distillate was collected. The cooled reaction mixture was poured into 250 ml. of ice–water containing 10 g. of sodium carbonate. Chloroform (100 ml.) was added, the layers were separated, the aqueous layer was extracted twice (50 ml. and 25 ml.) with chloroform, and the combined chloroform solutions were washed with 10% sodium carbonate and water, and dried over magnesium sulfate. Removal of solvent followed by vacuum distillation through 10 in. of glass helices gave 25.5 g. of ester, b.p. 73–76° (13 mm.), 90% yield based on starting benzoic acid. Toward the end of the distillation 2 g. of unlabeled ester was added to reduce holdup of labeled material; the yield has been corrected for it.

1,2-Dicyclohexylethanedione-1,2-C^{14}.—The product was prepared as reported earlier for the unlabeled material. Reaction times and amounts were 9.65 g. of sodium (10% excess), 27.5 g. of methyl cyclohexanecarboxylate-7-C^{14}, and 22-hr. reaction time for preparation of the ketol (not isolated); for the oxidation, 80 ml. of glacial acetic acid, 8 ml. of anhydrous methanol, 40 g. of copper acetate monohydrate, and a reflux period of 4 hr. were employed. Final distillate was collected in several fractions: b.p. 103–110° at 0.45 mm., total 16.5 g. (corrected for 1 g. of unlabeled material added near the end of the distillation), 78% yield based on ester. Analysis of this material by the dry combustion technique[5] indicated it had a specific activity of 2.748 ± 0.0011 mc./mole. A fraction of it was diluted with unlabeled diketone to give material of a specific activity of 0.4639 ± 0.0074 mc./mole, measured by scintillation techniques, after correction for considerable quenching.

meso- **and *dl*-2,3-Dicyclohexyl-2,3-butanediol-2,3-C^{14}.** *meso-*.—Benzil-C^{14} [5] (0.630 g., 3 mmoles) in ether was added to an ether solution of 12 mmoles of methyllithium and refluxed overnight. Following a customary work-up and removal of solvent, the residue was treated with 5 g. of unlabeled *meso* glycol[5] and the mixture was crystallized from hexane–benzene to yield 3.9 g. of fine, white crystals of *meso*-2,3-diphenyl-2,3-butanediol-2,3-C^{14}. The filtrate was treated two additional times with 5 g. of unlabeled glycol to produce 4.1 and 6.4 g. of product, total 14.4 g. This material was hydrogenated as described above.

dl-.—Labeled benzil-C^{14} (0.630 g.) was treated similarly with 12 mmoles of methylmagnesium iodide. Utilization of 10 g. of unlabeled racemate[5] in three portions gave 9.9 g. of white needles, m.p. 124°. The hydrogenation of this material has been described above.

Dilution Studies.—The technique has been described in a previous paper.[5] Approximately 4 mmoles of diketone or ketol were added to an ether solution of organometallic reagent (4–6:1 with respect to diketone or ketol), prepared under argon, at reflux temperature. Following a standard but quantitative work-up of the reaction mixture after suitable reflux, the ether solution was concentrated to dryness, the residue was taken up in methanol, and known aliquots were added to the weighed amounts of dilution materials. Subsequent concentration to dryness followed by three to five recrystallizations from hexane gave pure materials. The results have been compiled in Table I. Assay was by either the vibrating-reed electrometer (entries 1 and 9) or the Tri-Carb scintillometer (all other entries).

Control Study.—To eliminate any possibility of either glycol interconversion or selective decay during some of the extended reaction periods, the following experiment was carried out under conditions employed in the dilution studies. *meso*-2,3-Dicyclohexyl-2,3-butanediol-2,3-C^{14} (0.2020 g., specific activity 0.2456 mc./mole) and the *dl* diastereoisomer (0.2003 g., specific activity 0.08538 mc./mole) were refluxed together with a 24:1 molar ratio of methylmagnesium iodide for 72 hr. Reisolation by dilution techniques showed activities of 0.2441 and 0.08481 mc./mole for the *meso* and *dl* forms, respectively, indicating essentially quantitative recovery.

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A Stereospecific Synthesis of (±)-Quinic Acid

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A stereospecific synthesis of (±)-quinic acid is described. Methyl α-acetoxyacrylate is condensed with 1,3-butadiene and the resulting adduct is hydrolyzed to 1-hydroxy-3-cyclohexene-1-carboxylic acid. Bromo lactonization and dehydrobromination produces 1-hydroxy-Δ^{5}-3-oxabicyclo[3.2.1]octen-2-one which is converted with osmium tetroxide into (±)-quinide. Hydrolysis of (±)-quinide affords (±)-quinic acid.

(−)-Quinic acid, 1,3,4,5-tetrahydroxy-1-cyclohexanecarboxylic acid (I), has been known since 1790[2] and occurs widely in the plant kingdom.[3] Large quantities have been found in apple,[4] peach,[5] and rose[6] tissue. Derivatives of quinic acid, *i.e.*, chlorogenic acid,[7] isochlorogenic acid,[8] *p*-coumaryl quinate,[9] etc.,[10] are also common in plants.

Quinic acid has been considered as a possible intermediate in aromatic biosynthesis for nearly one-half

(1) This paper was taken from a portion of a thesis submitted by R. N. in partial fulfillment of the requirements for the M.S. degree from Purdue University, Jan., 1964.

(2) Hofmann, *Crells Ann.*, **II**, 314 (1790).

(3) H. Rentschler and H. Tanner, *Chem. Abstr.*, **48**, 9578 (1954); **49**, 1236 (1955); R. Ulrich and O. Thaler, *Compt. rend.*, **240**, 1625 (1955); D. E. Hathway, *Biochem. J.*, **63**, 380 (1956); J. K. Palmer, *Science*, **126**, 504 (1957); J. Carles, *Bull. soc. chim. Biol.*, **39**, 1177 (1957); A. Schneider, *Compt. rend.*, **246**, 2029 (1958); S. V. Ting and E. J. Deszyck, *Nature*, **183**, 1404 (1959); V. Plouvier, *Bull. soc. franc. physiol. vegetale*, **7**, 44, (1961); S. M. Manskaya and L. A. Kodina, *Chem. Abstr.*, **55**, 3055 (1961).

(4) A. C. Hulme, *J. Exptl. Botany*, **2**, 298 (1957).

(5) E. Anet and T. M. Reynolds, *Nature*, **172**, 1188 (1953).

(6) L. Weinstein, W. Smith, and H. Laurencot, *Contrib. Boyce Thompson Inst.*, **19**, 341 (1958).

(7) K. Gorter, *Ann.*, **358**, 327 (1907); G. C. Whiting and J. G. Carr, *Nature*, **180**, 1479 (1957).

(8) L. A. Griffiths, *Biochem. J.*, **70**, 120 (1958);

(9) A. H. Williams, *Chem. Ind.* (London), 1200 (1958); A. Pollard, M. E. Kieser, and D. J. Sissons, *ibid.*, 952 (1958); H. R. Schutte, and W. Langenbeck, *Naturwiss.*, **44**, 63 (1957); E. Haslam, R. D. Haworth, and G. K. Makinson, *J. Chem. Soc.*, 5153 (1961).

(10) C. C. Levy and M. Zucker, *J. Biol. Chem.*, **235**, 2418 (1960); D. F. Horler and H. E. Nursten, *J. Chem. Soc.*, 3786 (1961); E. Haslam, R. D. Haworth, and D. A. Lawton, *ibid.*, 2173 (1963).