detectable difference in reaction half-times in all-glass reactors or when sampling was being conducted.

Analyses.—Samples were analyzed by glpc and compared with known materials. The following liquid phases were used: adiponitrile on firebrick (1-pentene) and tetracyanoethylated pentaerythritol (TCEPA) on Chromosorb P (4-vinylcyclohexene, 2-methyl-1,5-hexadiene).

Registry No.—Sodium borohydride, 16940-66-2; nickel(II) acetate, 373-02-4; safrole, 14871-41-1; 1-octene, 111-66-0; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cyclooctene, 931-88-4.

Acknowledgments.—This study was assisted in part by a Research Award (585 C) from the American Chemical Society Petroleum Research Fund, a grant from Parke, Davis and Co., and a fellowship from the National Science Foundation.

Diastereomers of Quinic Acid. Chemical and Nuclear Magnetic Resonance Studies

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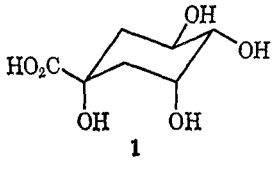
(±), (−), and (+)-*epi*-Quinides (γ-lactones of 34/15 and 45/13-tetrahydroxycyclohexanecarboxylic acids) have been prepared from their respective acetates. (+)-*epi*-Quinide triacetate separated by a spontaneous resolution in the crystallization of the optically impure (±) compound. *scyllo*-Quinic acid [*meso*-(4/135)-tetrahydroxycyclohexanecarboxylic acid] was also prepared from its acetate and its structure and conformation were determined. The 3.0- and 6.5-Hz splittings of the H-4 proton resonance in the 100-MHz nmr spectrum of the *epi*-quinic anion can most reasonably be assigned to *gauche* and *trans* splittings of a deformed chair (**9**), indicating that the H-4 and either H-3 or H-5 are axial. The magnitude of the *trans* coupling is considerably lower than that observed for other isomers. Ir and nmr (both ordinary and decoupled) spectra of *epi*-quinide triacetate verify a γ-lactone structure with the hydroxyls on C-4 and C-5 equatorial (**11**). Of particular interest in the nmr spectrum are the zero value of $J_{2(a),3(e)}$, the 1.0-Hz value for $J_{3(e),4(a)}$, and the 3.5-Hz long-range coupling between the equatorial methylene protons. The 9.0-Hz triplet splitting in H-4 in the nmr spectrum of *scyllo*-quinic acid clearly indicates that the three hydroxyls are equatorial (**13** or **14**). The formation of δ-lactone **16** on prolonged heating in acetic acid establishes that the carboxyl is *cis* to the 4-hydroxyl group and that *scyllo*-quinic acid has structure **14**.

(−)-Quinic acid, intimately involved in the "shikimic acid route" of the main pathway of aromatic biosynthesis, is one of eight diastereoisomeric 1,3,4,5-tetrahydroxycyclohexanecarboxylic acids. Of the eight such acids, only two, (−)-quinic acid (**1**) and its mirror image (**2**), (+)-quinic acid, are known.[1a] Gorin[2] isomerized (−)-quinic acid with acetic acid–sulfuric acid mixtures and obtained, after acetylation, three acetates. These were assigned the structure (−)-*epi*-



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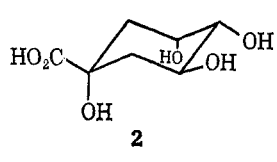

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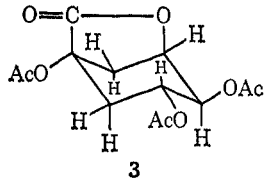
quinide triacetate (**3**), (±)-*epi*-quinide triacetate, and *scyllo*-quinic acid tetraacetate, derived from one of the four *meso* acids. The structural assignments were based on the positions of the acetoxy protons in their respective nmr spectra and a series of reactions of the carboxyl-reduced derivatives, quinicols. Gorin favored **4** [*meso*-(35/14)-tetraacetoxycyclohexane-1-carboxylic acid] over **5** [the (4/135) isomer] for the structure of *scyllo*-quinic acid tetraacetate, mainly on the basis of



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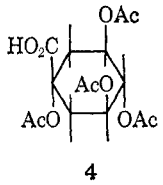

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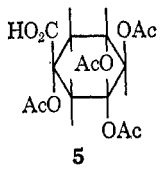

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extrapolated kinetic data. Since *epi*-quinic acid is the only isomer (pair) other than quinic acid which may be optically active, the structural recognition of *epi*-quinide triacetate was on a sound basis (although two of the *meso* acids can form optically active lactones).

The nomenclature of the quinic acids is in a state of uncertainty. The "Tentative Rules for Cyclitol Nomenclature" proposes that the quinic acids be named according to cyclitol rules. In our opinion such an action would be premature without radical changes being made to avoid grave errors. In this paper the system currently in general use will be followed: the carboxyl will be numbered 1 and will be drawn above the ring; the numbering will be clockwise as in the Maquenne system.[1b] Thus (−)-quinic acid is (−)-(3/145)-tetrahydroxycyclohexane-1-carboxylic acid, and (+)-quinic acid is the (+)-(5/134) isomer. We realize that it is not immediately apparent that these two are enantiomers, but to give them the same Maquenne fraction requires both clockwise and counterclockwise numbering. This leads to a remarkable confusion in describing the reactions discussed in this paper and in relating the acids of aromatic biosynthesis from 5-dehydroquinic acid. The comparable confusion possible in the carbohydrates and inositols has been sidestepped by using trivial names *solely* as a basis of nomenclature. Hence the trivial names (±)-*epi*-quinic and *scyllo*-quinic acids introduced by Gorin will be retained because of their convenience. The Sequence Rule[3,4] nomenclature, although awkward in use, is a definitive nomenclature: (−)-quinic acid is (1*R*:3*R*:4*S*:5*R*)-3/145-tetrahydroxycyclohexane-3-car-

(1) (a) T. Posternak, "The Cyclitols," Holden-Day, Inc., San Francisco, Calif., 1965, p 268 ff; (b) p 8 ff.

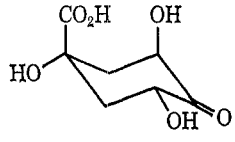
(2) P. A. J. Gorin, *Can. J. Chem.*, **41**, 2417 (1963).

(3) R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

(4) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

boxylic acid and (−)-*epi*-quinic acid is probably (1*R*:3*R*:4*S*:5*R*)-3,4/1,5-tetrahydroxycyclohexane-1-carboxylic acid (and not its mirror image).

A possible synthesis of *epi*-quinic acid would be by the reduction of 4-dehydroquinic acid (**6**). Haslam and Marriott[5] recently reported this reduction to give (−)-quinic acid and not *epi*-quinic acid under neutral conditions. It would be necessary to effect a conformational change in the 4-dehydroquinic acid to have any success with this approach, since carbonyl reduction usually produces an axial hydroxyl group. Such a conformational change does not appear feasible at the present time.



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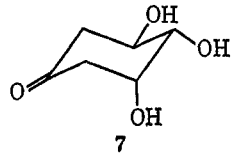

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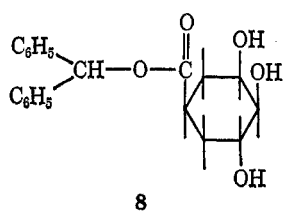
A second possible synthesis of *epi*-quinic acid would be the cyanohydrin reaction with a derivative of (3/45)-trihydroxycyclohexanone (**7**). (3/45)-Triacetoxycyclohexanone reacts to give only (−)-quinic acid.[6] We have used this reaction and the cyanohydrin reaction with the 4,5-isopropylidene derivative of (**7**) to prepare ^{14}COOH-labeled quinic acid.

Repetition of Gorin's isomerization and acetylation procedure led to a mixture of acetates which was fractionally crystallized as described, and the same three products were isolated: (−)-*epi*-quinide triacetate, mp 216–220°, $[\alpha]^{26}D$ −120° (lit. mp 209–210°, $[\alpha]^{25}D$ −119°);[2] (±)-*epi*-quinide triacetate, mp 186–188° (lit. mp 182–183°); and *scyllo*-quinic acid tetraacetate, mp 203–205° (lit. mp 198–200°). Spontaneous crystallization of (+)-*epi*-quinide triacetate occurred during a fractionation of racemic *epi*-quinide triacetate with chloroform, and it was possible to prepare it by seeding reasonable quantities of the (+) enantiomer, $[\alpha]^{27}D$ +120°, from the racemic form.

Saponification of either (−)- or (±)-*epi*-quinide triacetate by sodium hydroxide and removal of the sodium ions with a cation-exchange resin gave the corresponding *epi*-quinide on evaporation *in vacuo*. When *epi*-quinide was saponified with sodium hydroxide and again freed of sodium ions by passage through a cation-exchange resin column at 1°, the resulting solution reacted smoothly with diphenyldiazomethane to form the benzhydryl ester **8**. If the solutions of free



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epi-quinic acid were lyophilized at 0.01 mm, with a final overnight drying at room temperature, a mixture of lactone and acid was always formed. Pure *epi*-quinide could be readily obtained by trituration of the semicrystalline solid with absolute alcohol. This ease of lactonization of *epi*-quinic acid, compared with that

(5) E. Haslam and J. E. Marriott, *J. Chem. Soc.*, 5755 (1965).
(6) R. Grewe and E. Vangermain, *Chem. Ber.*, **98**, 104 (1965).

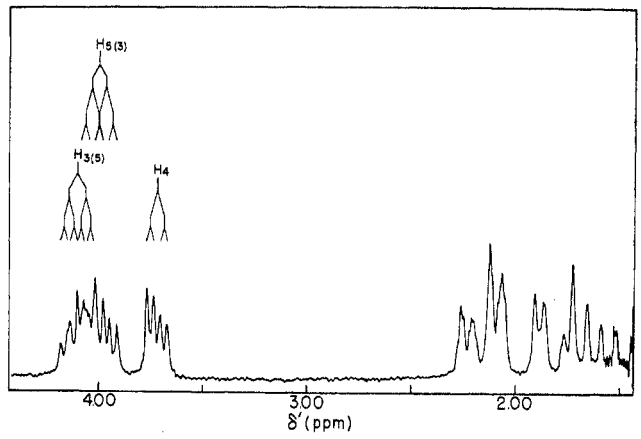
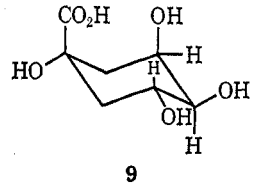


Figure 1.—100-MHz nmr spectrum of (−)-*epi*-quinic acid anion in 1 *N* NaOD in D_2O at 31°.

of quinic acid or *scyllo*-quinic acid, was completely unexpected. Quinic acid forms acetone quinide on treatment with acetone and a mineral acid.[7] Thermal lactonization of quinic acid is carried out by heating at 230° for a short time (yield not given).[8] Longer heating times cause racemization. 4-Dehydroquinic acid is reported to form the lactone diacetate on treatment with acetic anhydride.[5] 5-Dehydroquinic acid aromatizes under these conditions to form 4,5-diacetylprotocatechuic acid.[5] Lactone(s) of *scyllo*-quinic acid have not been prepared prior to this work, and its lactone acetates have not been isolated from the quinic acid isomerization process used here.

The 100-MHz nmr spectrum of (−)-*epi*-quinic acid anion in 1 *N* NaOD referenced to DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) is shown in Figure 1. The spectrum is very similar to that of quinic acid in D_2O.[9] The protons on C-3, C-4, and C-5 give rise to the low-field multiplets at δ′ 3.72 and 4.04, while the four methylene protons are responsible for the complex group of overlapping multiplets in the vicinity δ′ 2. The δ 3.72 doublet-split doublet can be unambiguously assigned to H-4 because of the absence of a third coupling. Its two splittings of 3.0 and 6.5 Hz can be reasonably assigned to gauche and *trans* couplings, respectively. Thus H-4 would be axial together with either H-3 or H-5, indicating that *epi*-quinic acid has the conformation (a)-CO_2H (**9**) and not the (*e*)-CO_2H (**10**). Unfortunately, because of the low magnitude of



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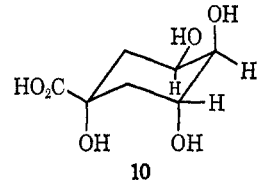

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the *trans* coupling there is some doubt about this assignment. For example, in quinic acid[9] and *scyllo*-quinic acid (*vide infra*), the 3–4 and/or 4–5 *trans* couplings are 9.0 Hz.

The overlapping multiplets for H-3 and H-5 cannot be adequately resolved by first-order methods. The

(7) H. O. L. Fischer, *Ber. Deut. Chem. Ges.*, **54**, 775 (1921).
(8) J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3596 (1964).
(9) J. Corse, R. E. Lundin, E. Sondheimer, and A. C. Waiss, Jr., *Phytochemistry*, **5**, 767 (1966).

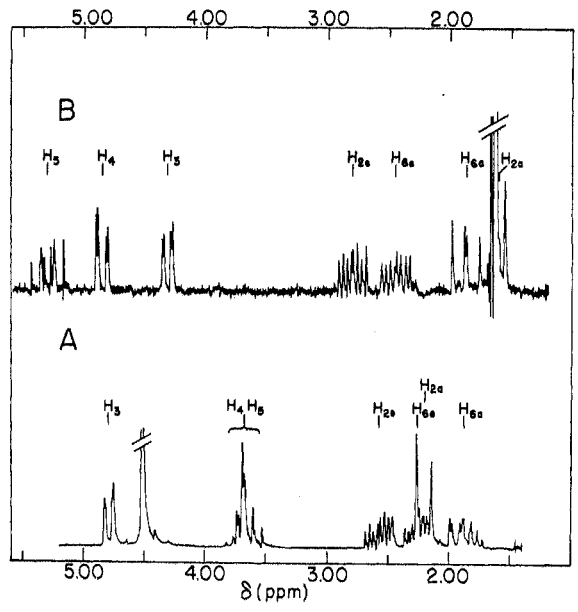


Figure 2.—(a) 100-MHz nmr spectrum of (−)-*epi*-quinide in D_2O at 60°; (b) 100-MHz nmr spectrum of (−)-*epi*-quinide triacetate in benzene-d_6 at 75°.

present data are insufficient for a computer analysis that would provide accurate values for the couplings of the four methylene protons with H-3 and H-5. Hence the splitting scheme in Figure 1 should be taken with some reservation. However, these values are at least partially confirmed by a first-order analysis of the 220-MHz spectrum of the anion. A value of 8 Hz for $J_{2(a),3(e)}$ is entirely too high for a *gauche* coupling. The alternate conformation, (e)-CO_2H, provides a more reasonable fit, as shown in Table I, but it must be

TABLE I

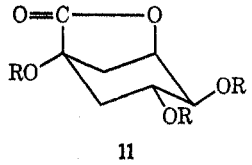
SPIN-SPIN COUPLING CONSTANTS OF *epi*-QUINIC ACID IN 1 *N* NaOD[a]

Interaction	Coupling constant,
$J_{2(e),3(a)}$	~5
$J_{2(a),3(a)}$	~8
$J_{3(a),4(e)}$	3.0
$J_{4(e),5(e)}$	6.5
$J_{5(e),6(e)}$	~4
$J_{5(e),6(a)}$	~6

[a] Based on conformation **10** with (e)-CO_2H.

emphasized that a first-order analysis is not fully justified. The coupling constants observed could result from a deformed or interconverting chair conformation. The low $\Delta G°$ of these conformations (*cf.* Table II) is indicative of the latter possibility.

The structures of *epi*-quinide and its triacetate could reasonably be either γ- or δ-lactones (**11** or **12**), respectively. Gorin reported *epi*-quinide triacetate to have a



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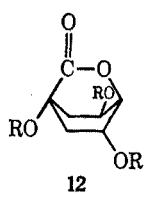

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carbonyl stretching frequency at 1795 cm^{-1}, which clearly indicates a γ-lactone.[10] (±)-*epi*-Quinide itself

TABLE II

PREDICTED CONFORMATIONAL PREFERENCES OF ISOMERIC QUINIC ACIDS FROM ENERGY TABLES[a]

Acid	Hydroxyl group configurations	Conformation[b] (e)-CO_2H	Conformation[b] (a)-CO_2H
(±)-Quinic	3/145, 5/134	1.74*	3.09
(±)-*epi*-Quinic	34/15, 45/13	2.61	2.22*
scyllo-Quinic (**14**)	*meso*-(4/135)	3.48	1.35*
Unknown *meso* (**13**)	*meso*-(35/14)	0.87*	3.96
Unknown *meso*	*meso*-(345/1)	1.74*	3.09
Unknown *meso*	*meso*-(0/1345)	2.61	2.22*
4-Dehydroquinic		1.74[c]	2.22
5-Dehydroquinic		0.87*[c]	2.09

[a] Values in kcal/mol ($-\Delta G°$) from D. L. Robinson and D. W. Theobald, *Quart. Rev.* (London), **21**, 314 (1967). [b] Preferred conformation is asterisked; values for hydroxyl groups are those in hydroxylic solvents. [c] See text.

shows a strong absorption at 1788 cm^{-1}, while our triacetate shows one at 1790 cm^{-1} in close agreement with Gorin's value. The lactone absorptions match bands in the quinic acid series [(−)-quinide, 1796 cm^{-1}; (−)-quinide triacetate, 1800 cm^{-1}] and leave no doubt of the γ-lactone structure **11** (R = H).

The 100-MHz nmr spectrum of (±)-*epi*-quinide in D_2O (referenced to DSS) is shown in Figure 2a. The resonances of the protons on carbons 3, 4, and 5 fall between δ′ 3.5 and 4.5, while the methylene protons on carbons 2 and 6 give rise to the bands at δ′ 1.7–2.7. The singlet at δ′ 4.50 is due to residual HDO. Because it was impossible to analyze the overlapping multiplets from two of the protons in the vicinity of δ′ 3.7 (these were subsequently assigned to H-4 and H-5 as shown on the basis of the triacetate assignment), the triacetate of *epi*-quinide **11** (R = Ac) was run in both chloroform-*d* and benzene-d_6. Its spectrum in the latter solvent is shown in Figure 2b. The differential shifts of the carbinol and axial methylene protons in this solvent make possible a straightforward analysis of the entire spectrum. The multiplet assignments are shown on the figure, and the apparent coupling constants based on a first-order analysis of the splitting patterns are given in Table III. It is obvious that the triacetate must have

TABLE III

COUPLING CONSTANTS[a] FOR SOME SUBSTITUTED QUINIDES

Coupling constant	(−)-*epi*-Quinide triacetate $CDCl_3$	(−)-*epi*-Quinide triacetate C_6D_6	(±)-*epi*-Quinide tribenzoate C_6D_6	(−)-Quinide tribenzoate C_6D_6
$J_{2(e),6(e)}$	3.5	3.6	3.6	2.0
$J_{2(e),2(a)}$	11.8	11.8	11.8	12
$J_{6(e),6(a)}$	12.0	11.9	11.9	
$J_{2(e),3(e)}$	7.0	6.8	6.8	5.2
$J_{2(a),3(e)}$	0.0	0.0	0.0	~0
$J_{3(e),4(e)}$				4.7–5.2
$J_{3(e),4(a)}$	1.0	1.2	1.2	
$J_{4(e),5(a)}$				4.7
$J_{4(a),5(a)}$	8.5	8.5	8.5	
$J_{5(a),6(e)}$	7.0	7.4	7.4	8.0
$J_{5(a),6(a)}$	10.1	10.8	10.8	10.4

[a] In hertz.

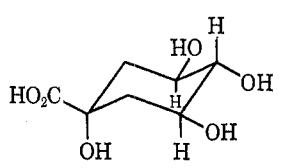
the γ-lactone structure **11** (R = Ac), in agreement with the ir data. Spin decoupling was used to identify H-4 both in benzene-d_6 and for the more complex spectrum obtained in chloroform-*d*, since it is the only HOCH

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1959, p 178.

proton *not* coupled to a methylene proton. Table III also gives the coupling constants obtained from a similar analysis of the spectra of the tribenzoates of *epi*-quinide and quinide, which was used as a model structure for checking the assignment of couplings. Because the multiplets from H-2 and H-6 overlap in the quinide tribenzoate spectrum, the values of the couplings to them are only approximate. Otherwise, the agreement in the values of the corresponding constants is most satisfactory.

Three couplings deserve special comment: the essentially zero coupling of the 2-axial proton with the 3-equatorial, the small coupling of this proton (H-3(e)) to the 4-axial, and the long-range coupling between the 2- and 6-equatorial protons. Dunkelblum and Klein[11] recently reported that the couplings of the equatorial proton on C-3 to vicinal axial protons were immeasurably small in 1–3 lactone-bridged cyclohexanes. They explain this result on the basis of a dihedral angle (roughly 90°) for these two couplings in the bridged-ring structure which approximates the zero coupling angle in the Karplus equation.[12] The small coupling observed in this study for $J_{3(e),4(a)}$ may result from the hydroxyl substituent on C-4. However, from the 60-MHz spectra reproduced in the earlier study[11] it is questionable whether a 1-Hz splitting would have been resolved. The rather large long-range coupling between the equatorial methylene protons is probably a consequence of the distorted chair conformation of the bridged γ-lactone cyclohexane structure.

The 100-MHz nmr spectrum of *scyllo*-quinic acid in 1 *N* NaOD (referenced to DSS) is shown in Figure 3. Again, the proton resonances on carbons bearing hydroxyl groups in the vicinity of δ' 3.5 are shifted *ca.* 1.5 ppm downfield from the methylene protons whose multiplets at *ca.* δ' 2.0 are so completely overlapped that no analysis of these resonances was attempted. The triplet centered at δ' 3.28 can be immediately assigned to H-4 because of the absence of any indication of coupling to more than two protons. The 9.0-Hz splitting is consistent with either the *meso*-(35/14) structure in the (e)-CO_2H conformation **13**, or the *meso*-(4/135) structure in the (a)-CO_2H conformation



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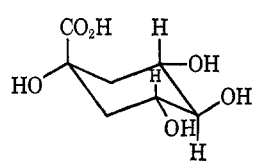

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14, wherein H-3, H-4, and H-5 are *all axial*, and it is not possible from the nmr spectrum to distinguish between the two possibilities. The complex multiplet centered at δ' 3.68 cannot be satisfactorily analyzed by first-order methods, and again the splittings shown on Figure 3 must be viewed with reservation. Table IV lists the approximate couplings, which are completely compatible with the two possible structures.

The large *gauche* couplings of the 2- and 6-equatorial protons to the 3- and 5-axial protons again confirm the finding of Williams and Bhacca[13] that an equatorial

(11) E. Dunkelblum and J. Klein, *Tetrahedron Lett.*, 55 (1968).
(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(13) D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964).

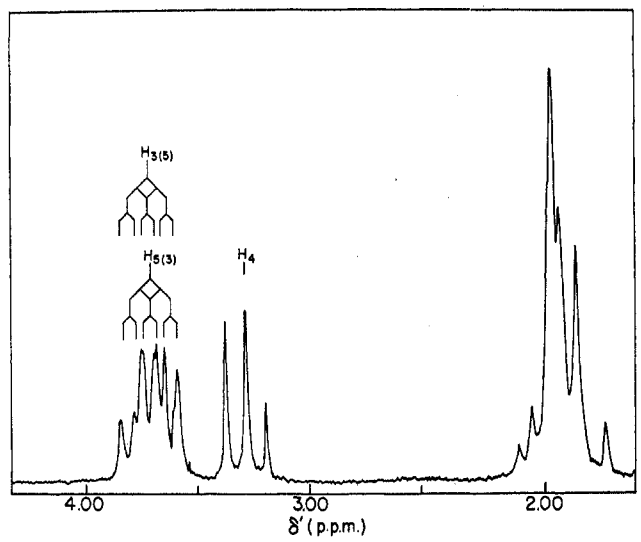


Figure 3.—100-MHz nmr spectrum of *scyllo*-quinic acid anion in 1 *N* NaOD in D_2O at 31°.

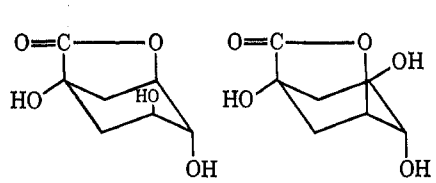
TABLE IV
SPIN-SPIN COUPLINGS IN *scyllo*-QUINIC ACID[a]

Interaction	Coupling constant, Hz
$J_{2(a),3(a)}$	~9
$J_{2(e),3(a)}$	~6
$J_{3(a),4(a)}$	9.0
$J_{4(a),5(a)}$	9.0
$J_{5(a),6(e)}$	~6
$J_{5(a),6(a)}$	~8

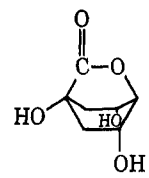
[a] In 1 *N* NaOD.

oxygen substituent apparently causes a *gauche* coupling to be unexpectedly large (4.5 ± 1 Hz), whereas with an axial substituent the coupling falls within the usual range (2.5–3.2 Hz). In an earlier paper[9] this dependence of *gauche* coupling on oxygen conformation was applied to a discussion of quinic acid and some of its derivatives.

Although nmr spectroscopy cannot distinguish between the *meso*-(35/14) (**13**) and *meso*-(4/135) (**14**) structures for *scyllo*-quinic acid, the position of the lactone carbonyl absorption band in the infrared spectrum of the corresponding lactone should clearly delineate the structure, similar to *epi*-quinide (*vide supra*). Structure (**13**) could be expected to form a racemic pair of γ-lactone isomers (**15**), and structure **14** would form a *meso* δ-lactone (**16**). On prolonged



15

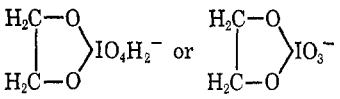


16

heating of an acetic acid suspension of *scyllo*-quinic acid, solution was effected with lactonization. The lactone showed a strong infrared absorption band at 1720 cm^{-1}, as is expected of **16**. This clearly indicates that the 4-hydroxy and the carboxy groups are *cis* to each other. It then follows that *scyllo*-quinic acid has configuration **14**, *meso*-(4/135)-tetrahydroxycyclohexane-1-carboxylic acid. The 100-MHz nmr spectrum of *scyllo*-quinide gave an overlapping group of multiplets

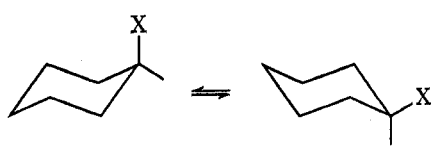
which could not be resolved. No increase in resolution occurred in acetylating or benzoylating the free hydroxy groups. The nmr spectrum did not resemble those of the several γ-lactones of the quinic and *epi*-quinic acid series.

At the suggestion of one of the referees, the reaction of *scyllo*-quinide with periodate was explored. Although the periodate oxidation method is of general application, the requirement of the formation of a cyclic periodate ester as the decomposing entity[14] could severely limit the use of this reaction in the rigid bicyclic quinic



acid series. This proved to be the case. (−)-Quinide and *cis*- and *trans*-1,2-cyclohexanediols reacted quickly with sodium metaperiodate solutions under the conditions of Aspinall and Ferrier.[15] However, no loss of periodate could be detected after 4 hr with (−)-*epi*-quinide nor after 65 hr with *scyllo*-quinide. The vicinal hydroxyl groups in *epi*-quinide are *trans* as they are in **15**, and the rigidity of these lactones prevents the five-membered periodate ring from forming.

The conformations of *scyllo*-quinic and *epi*-quinic acids in solution, wherein the carboxyl groups are axial, differ from quinic acid and all of its derivatives, which have the carboxyl group equatorial (except for the pertrimethylsilyl derivative of quinic acid).[16] These conformational preferences are in agreement with the predictions based on the standard free energy change ($-\Delta G_x°$) for the equilibrium[17,18] shown. The



values for the eight stereoisomeric quinic acids are summarized in Table II. The high difference in energies for the two conformers in *scyllo*-quinic acid may account in part for the difficulty in lactonization, since the groups on adjoining carbon atoms must eclipse each other in conformational changes. This may be made clear in a study of the 35/14 acid **13**, which, although it has two hydroxyls capable of forming lactones, has an even greater free-energy difference between the two conformers than *scyllo*-quinic acid.

The more nearly equal energies of the two conformers of *epi*-quinic acid may similarly account for the apparent deformed-chair conformation observed. The predictions of conformation preference for quinic acid and 5-dehydroquinic acid agree with observation.[9,16] However, the prediction for 4-dehydroquinic acid is at variance with the conformation suggested by Haslam and Marriott[5] on the basis of hydrogenation results. It should be noted that the values of $-\Delta G°$ have been derived from measurements on chair forms of cyclohexanes. The twist conformations frequently favored by cyclohexanones[19] may require $-\Delta G°$ values sufficiently different from the chair values to render use of the latter questionable.

The epimerization of the hydroxyl groups of quinic acid parallels those of tetra- and pentahydroxy cyclohexanes rather than those of the inositols. The methylene groups, as shown by Angyal, Gorin, and Pitman,[20] markedly affect the course of the reactions. The formation of (−)-*epi*-quinic acid may involve changes only in the 4-hydroxyl group, favorably flanked as it is by *cis* and *trans* adjacent hydroxyl (or acetoxy) groups. However, the formation of large amounts of (+)-*epi*-quinic acid and *scyllo*-quinic acids clearly results from displacements on the 3 and 5 carbon atoms.

Experimental Section

The melting points were taken on a Kofler hot stage and are corrected. Other physical measurements were made on the following instruments: nmr spectra, internally locked Varian HR-100;[21] infrared spectra, Cary Model 90; optical rotations, Bendix polarimeter type 143A; ORD, Cary Model 60; uv spectra Cary Model 15. The nmr spectra were run at concentrations of *ca.* 5% under the conditions noted with *t*-butyl alcohol-*d* as internal lock for aqueous solutions. The position of the lock resonance in respect to internal DSS was determined in a subsequent scan of the solvent at the same temperature.

Isomerization of Quinic Acid.[2]—A solution of 10 g of (−)-quinic acid in 500 ml of acetic acid to which 7.5 ml of sulfuric acid had been added was heated under reflux for 100 hr. The solution was then cooled, acetylated, and worked up as described. The fractionation of the mixed acetates proceeded by a series of recrystallizations from $CHCl_3$–ethyl acetate.

(−)-*epi*-**Quinide Triacetate** (**3**).—This compound was less soluble in $CHCl_3$ than the (±) modification or *scyllo*-quinic acid tetraacetate: yield 2.35 g; mp 216–220°; $[\alpha]^{24}D$ −120°, −118° (*c* 0.5, $CHCl_3$) (lit.[2] mp 209–210°, $[\alpha]^{24}D$ −119°).

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.0; H, 5.27.

(±)-*epi*-**Quinide Triacetate.**—This compound was recrystallized from ethyl acetate–$CHCl_3$–ether: yield 0.79 g; mp 186–188°; $[\alpha]^{24}D$ 0° (*c* 1, $CHCl_3$); ir carbonyl stretching 1790, 1838, and 1752 cm^{-1} (KBr pellet) [lit.[2] mp 182–183°; ir carbonyl stretching on mixture of (−) and (±) acetates 1795 and 1750 cm^{-1}]. The 100-MHz nmr and ir spectra of the (±) isomer and (−) isomers were superimposable.

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.1; H, 5.34.

(+)-*epi*-**Quinide Triacetate.**—A sample of 17.6 g of *epi*-quinide triacetate, $[\alpha]^{26}D$ −19°, was dissolved in the minimum amount of boiling $CHCl_3$ and the solution was placed in the refrigerator. After standing for 2 days, 4.2 g of crystals (dry weight) had separated and were collected, $[\alpha]^{25}D$ +92°. These were again recrystallized from $CHCl_3$: yield 0.92 g; mp 216°; $[\alpha]^{27}D$ +120° (*c* 0.5, $CHCl_3$). The 100-MHz nmr spectrum was superimposable on the spectra of the (−) enantiomer or the (±) compound.

Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 52.1; H, 5.41.

scyllo-**Quinic Acid Tetraacetate** (**4**).—This acid was purified by treating crude lactone fractions [containing (±)-*epi*-quinide triacetate] with dilute $KHCO_3$ solution, filtering, and carefully acidifying the filtrate recrystallized from ether–petroleum ether: yield 3.50 g; mp 203–205° (lit.[2] mp 198–200°); $[\alpha]^{24}D$ 0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{15}H_{20}O_{10}$: C, 50.00; H, 5.60. Found: C, 50.1; H, 5.53.

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(21) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

scyllo-**Quinic Acid** (**14**).—A solution of 1 g of *scyllo*-quinic acid tetraacetate (**4**) in 13 ml of 2 *N* NaOH was allowed to stand for 4 hr at room temperature. The reaction mixture was freed of sodium ions by passing through a Dowex AG-50W-X2, 100–200 mesh, acid-form column (12 mm × 40 cm) and eluting with water until the eluate was neutral. The eluate was evaporated to dryness *in vacuo* and the crystalline acid was recrystallized from acetone–petroleum ether, yield 0.47 g mp 228–230°.

Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.6; H, 6.25.

scyllo-**Quinide**.—A suspension of 0.5 g of *scyllo*-quinic acid in 15 ml of acetic acid was heated on a steam bath for 1 week with occasional shaking. The resulting solution was filtered and the filtrate was evaporated to dryness in a N_2 stream. The product, a hygroscopic glass, was dried at 100° (0.2 mm). A Nujol mull showed a carbonyl absorption band at 1720 cm^{-1}.

Anal. Calcd for $C_7H_{10}O_6$: C, 48.27; H, 5.79. Found: C, 48.3; H, 5.92.

Saponification of a sample of *scyllo*-quinide and recovery of the free acid in a manner similar to the hydrolysis of the tetraacetate gave an essentially quantitative recovery of acid.

Equal volumes of 0.03 *M* sodium *m*-periodate and 0.015 *M* *scyllo*-quinide were mixed at room temperature. Aliquots of 1 ml were taken at intervals and diluted to 250 ml, and the absorbance of the diluted solution was measured at 223 mμ.[15] There was no observable reduction of periodate over a period of 65 hr. Under the same conditions, (−)-quinide reacted with 1 mol of periodate in 10 min and *cis*- and *trans*-1,2-cyclohexanediols each reacted with 1 mol of periodate in less than 2 min. (−)-*epi*-Quinide showed no reaction in 4 hr.

Benzhydryl *scyllo*-**Quinate**.—A solution of 1 g of *scyllo*-quinic acid in 25 ml of ethyl acetate was treated with diphenyldiazomethane until the pink color just persisted. The solvent was removed *in vacuo*, and the residue was washed with petroleum ether and then recrystallized from ethyl acetate–petroleum ether, mp 84–87°.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.0; H, 6.23.

(±)-*epi*-**Quinide**.—A solution of 1 g of (±)-*epi*-quinide triacetate in 13 ml of 2 *N* NaOH was allowed to stand overnight at room temperature. The sodium ions were removed by passing the saponified ester through a Dowex AG-50X2 column (12 mm × 40 cm) and eluting with water until all the acids were off the column. The eluate was evaporated to dryness *in vacuo* and the last traces of acetic acid were blown off in a N_2 stream. The semisolid material was triturated with absolute EtOH and chilled. The resulting crystals were collected and recrystallized from EtOH, yield 0.3 g, mp 202–204°.

Anal. Calcd for $C_7H_{10}O_6$: C, 48.27; H, 5.79. Found: C, 48.5; H, 5.80.

Benzhydryl (±)-*epi*-**Quinate**.—A solution of 1 g of (±)-*epi*-quinide, after standing for 1 hr in 10 ml of *N* NaOH at room temperature, was passed through a Dowex AG-50X2 column as before. The eluate was concentrated to about 5 ml by evaporation at 35° *in vacuo* and treated with a slight excess of diphenyldiazomethane. The reaction product was evaporated to dryness washed with petroleum ether, and recrystallized from ethyl acetate–petroleum ether, mp 122–124°. The product was analyzed after drying at 100° *in vacuo*.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.5; H, 6.13.

The product was also analyzed after drying at room temperature.

Anal. Calcd for $C_{20}H_{22}O_6 \cdot H_2O$: C, 63.82; H, 6.43. Found: C, 63.5; H, 6.25.

(−)-*epi*-**Quinide**.—A solution of 1 g of (−)-*epi*-quinide triacetate was saponified and worked up exactly as described for (±)-*epi*-quinide, mp 196–197°, $[\alpha]_D^{23}$ −127° (*c* 0.5, H_2O). The rotation of (−)-*epi*-quinide, $[\alpha]_D^{23}$ −127°, shows a negative Δ value in relation to (−)-*epi*-quinic acid, in accord with Klyne's modification[22] of Hudson's lactone rule.

Anal. Calcd for $C_7H_{10}O_5$: C, 48.27; H, 5.79. Found: C, 48.4; H, 5.75.

In an attempt to prepare free (−)-*epi*-quinic acid, the saponification mixture was cooled to 0° and the ion-exchange column was used in a cold room at 1°. The eluates were frozen and lyophilized at 0.005 mm. As soon as the ice film on the outside of the lyophilization flask melted, the flask was removed from the lyophilization apparatus and placed in a vacuum desiccator over P_2O_5 and it was evacuated to 0.01 mm. The sample of *epi*-quinic acid was analyzed the next morning.

Anal. Calcd for $C_7H_{12}O_6$ (acid): C, 43.75; H, 6.29. Found: C, 45.0; H, 6.15. Calcd for $C_7H_{10}O_6$ (lactone): C, 48.27; H, 5.79.

The optical rotation of (−)-*epi*-quinic acid was taken by dissolving (−)-*epi*-quinide in sodium hydroxide, $[\alpha]^{24}D$ −22° (*c* 1). The nmr spectrum was taken by dissolving *epi*-quinide in D_2O and adding an excess of NaOD.

The ORD of (−)-*epi*-quinic acid shows a strong negative Cotton effect, in contrast to (−)-quinic acid, which gave a low-wavelength positive Cotton effect.

Benzhydryl (−)-*epi*-**Quinate**.—This substance was prepared from (−)-*epi*-quinide in the same manner as the (±) isomer, mp 127–128°, $[\alpha]^{24}D$ −34°. The elementary analyses were very dependent on drying conditions. Drying *in vacuo* over P_2O_5 at room temperature gave the hemihydrate.

Anal. Calcd for $C_{20}H_{22}O_6 \cdot {}^1/_2H_2O$: C, 65.38; H, 6.31. Found: C, 65.6; H, 6.25.

This water of crystallization was apparent in the nmr spectrum (run in dimethyl sulfoxide-d_6). Drying overnight at 80° *in vacuo* caused the crystalline sample to become a gum; water elimination in the ring evidently occurred. This phenomenon did not take place with the other benzhydryl esters described here.

Anal. Found: C, 69.0; H, 5.97.

Benzhydryl (−)-**Quinate**.—A suspension of 2 g of (−)-quinic acid in 25 ml of ethyl acetate was warmed and treated with diphenyldiazomethane until reaction ceased. Addition of petroleum ether caused the separation of the crystalline ester in near quantitative yield. It was recrystallized from ethyl acetate–petroleum ether, mp 85–87°, $[\alpha]D$ −21° (*c* 1, EtOH).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.0; H, 6.16.

(±)-*epi*-**Quinide Tribenzoate**.—A solution of 0.28 g of (±)-*epi*-quinide in 3 ml of pyridine was warmed on the steam bath with 0.65 ml of benzoyl chloride for 0.5 hr and allowed to stand at room temperature for 2 hr. The reaction mixture was stirred with 50 ml of ethyl acetate and 200 ml of water. After separation, the ethyl acetate layer was successively washed with cold, dilute HCl, cold dilute NaOH, and cold water. After drying ($MgSO_4$), the solution was concentrated by warming in a N_2 stream. Addition of light petroleum and chilling yielded 0.53 g of tribenzoate, mp 183–184°.

Anal. Calcd for $C_{28}H_{22}O_8$: C, 69.13; H, 4.56. Found: C, 69.1; H, 4.55.

(−)-**Quinide Tribenzoate**.—This compound was prepared from quinide analogously to the *epi* isomer in near quantitative yield, mp 154–155° (lit. mp 148°).[23]

Anal. Calcd for $C_{28}H_{22}O_8$: C, 69.13; H, 4.56. Found: C, 69.3; H, 4.59.

Registry No.—(±)-*epi*-Quinide triacetate, 23804-26-4; (+)-*epi*-quinide triacetate, 23804-27-5; *scyllo*-quinic acid tetraacetate, 23804-28-6; benzhydryl *scyllo*-quinate, 23804-30-0; (±)-*epi*-quinide, 23804-31-1; benzylhydryl (±)-*epi*-quinate, 23804-32-2; (−)-*epi*-quinide, 23804-33-3; (−)-*epi*-quinic acid, 23804-34-4; benzhydryl (−)-quinate, 23804-35-5; (±)-*epi*-quinide tribenzoate, 23804-36-6; benzhydryl (−)-*epi*-quinate, 23804-37-7; *epi*-quinic acid, 23804-38-8; (−)-quinide tribenzoate, 23804-39-9; (±)-quinic acid, 23804-40-2; (±)-*epi*-quinic acid, 23804-41-3; 4-dehydroquinic acid, 18543-47-0; 5-dehydroquinic acid, 10236-66-5; **3**, 23804-25-3; **13**, 23804-44-6; **14**, 23804-29-7.

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