REPLACEMENT REACTIONS IN THE QUINIC ACID SERIES[1,2]

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ABSTRACT

The action on D-quinic acid of hot 95% acetic acid containing mineral acid gave, after complete acetylation, 1,4,5-tri-*O*-acetyl-epi-quinide consisting of approximately equal portions of the (−)- and (±)-isomers, and tetra-*O*-acetyl-scyllo-quinic acid. The stereochemistry of the products and their derived free polyols were determined by nuclear magnetic resonance (n.m.r.) spectroscopy and synthesis.

Elimination of the tosyloxy group in 5-tosyl-epi-quinicol was shown to take place readily in aqueous acetic acid with participation of the primary carbinol group to give an anhydro quinicol derivative and epi-quinicol.

It has been shown (1) that certain inositols can be converted to partly acetylated stereoisomers by refluxing with 95% acetic acid – mineral acid. Inversion takes place most readily when one hydroxyl group in a six-membered ring has an adjacent *cis*-hydroxyl on one side and a *trans*-hydroxyl on the other. Such an arrangement is common in the more readily available inositols, *O*-methylinositols, quercitols, and cyclohexanetetrols. Reactions involving these materials have been evaluated, both from a preparative point of view and as a means of calculating non-bonded interaction energies in six-membered rings (2).

D-Quinic acid, by virtue of the orientation of its hydroxyl groups, should also undergo modification to yield partly acetylated derivatives of its optically active stereoisomer. Accordingly, quinic acid was treated for several days in refluxing 95% acetic acid containing 1.5% sulphuric acid. Gas phase chromatographic examination of the product after complete acetylation followed by treatment with diazomethane indicated that at least five materials were present. The reaction when followed by this method showed that equilibrium was not reached in 93 hours at which time carbonization in the medium was considerable. Because of this consideration and the complexity of the mixture the system does not lend itself to the calculation of non-bonded interaction energies, but only to the preparation of new isomeric quinic acid derivatives.

The reaction product obtained after 100 hours was acetylated with acetic anhydride to give a mixture containing 45% lactone and 55% free acid. Two chemically distinguishable compounds were isolated by fractional crystallization. One of these, obtained in 5% yield, was an optically inactive stereoisomer of tetra-*O*-acetyl-D-quinic acid, indicating that the reaction was not as stereospecific as with hexasubstituted cyclitols. The other product was isolated in 17% yield and shown to be an optically active γ-lactone triacetate with an empirical formula of $C_{13}H_{16}O_8$ (I). On fractional crystallization this product ($[\alpha]_D$ −61°) gave two materials, chemically the same, as indicated by their identical n.m.r. spectra, but having different specific rotations (−119° and 0°). The rotation of the optically active substance differed markedly from the D-quinic acid analogue (3) and although there are several structures possible for the active lactone only one (I) arising by inversion of the substituent at C-4 is possible. All other active lactones would be racemized in the equilibrium mixture on re-formation from the corresponding acid.

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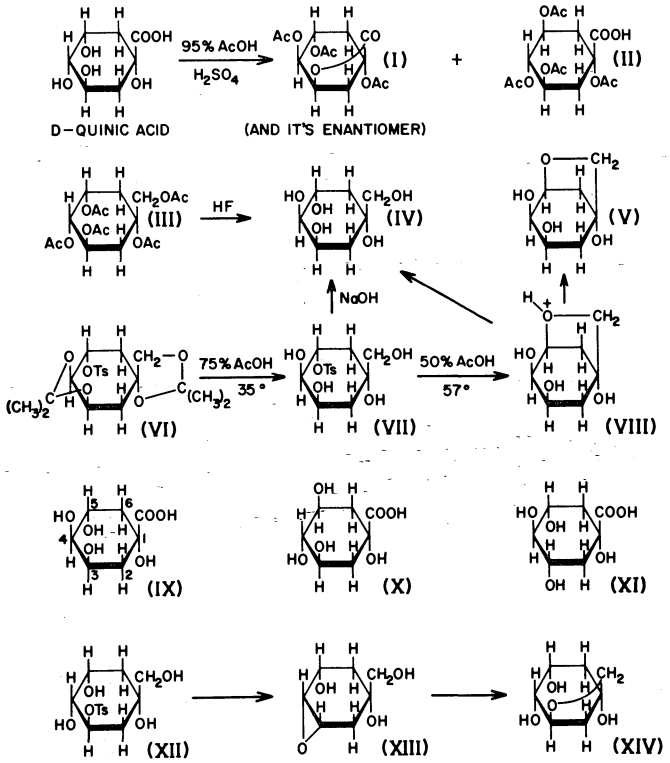
Fletcher and Hedgeley (4) have shown that an acetate group bounded by *cis*- and *trans*-acetoxy neighbors in inositols can be inverted, with concomitant deacetylation, by the action of liquid hydrogen fluoride. In the present investigation this reagent, however, did not yield the lactone triacetate (I) readily from quinic acid. Starting with tetra-*O*-acetyl-D-quinic acid, a mixture of γ-lactones was obtained. Acetylation of this with acetic anhydride in pyridine yielded the highly crystalline optically active lactone triacetate, but only in 1% yield.

The lactone triacetate (I) prepared by the 95% acetic acid – sulphuric acid method could be reduced to a polyol using sodium borohydride. This polyol (IV) could be prepared definitively by treating the polyol pentaacetate (5) (III), derived from D-quinic acid, with liquid hydrogen fluoride. Chromatography yielded the required material which was characterized as its di-*O*-isopropylidene derivative. A similar type of reaction could be effected by treating the polyol with the 95% acetic acid reagent. However, the yield of desired product was poor probably due to simultaneous oxidation.



It should be noted that stereoisomers of quinic acid have not been previously obtained and named. Maquenne's nomenclature systems for cyclitols (6) is available and this can be modified in order to cover systematically the quinic acids and their derived alcohols. On the other hand, it is proposed that the three new quinic acids, described presently, be called epi-(−)-quinic acid (XI), epi-(±)-quinic acid, and scyllo-quinic acid (X). Although there are many types of compounds having somewhat similar names, it should not be confusing to call the corresponding alcohols epi-quinicol and scyllo-quinicol, respectively. The acids are numbered in the same way as in quinic acid (as depicted in IX) and the derived alcohols too, except that the hydroxymethyl carbon atom is called C-2′.

As mentioned previously one crystalline product obtained from quinic acid was an optically inactive isomer of tetra-*O*-acetyl-D-quinic acid which is believed to be tetra-*O*-acetyl-scyllo-quinic acid (II). This material, on examination by n.m.r. spectroscopy, gave two acetoxy proton signals, the greater at 2.06 p.p.m. and the other, one third in magnitude, at 2.22 p.p.m. Tetra-*O*-acetyl-D-quinic acid gave three signals at 2.07, 2.11, and 2.18 p.p.m. in the ratio of 2:1:1, respectively. The signal at 2.07 p.p.m. clearly corresponds to the equatorial acetoxy protons at C-4 and C-5 (7). It seems likely that the signal at 2.11 p.p.m. is from the C-3 acetoxy protons and the one at 2.18 p.p.m. arises from the C-1 acetoxy protons.* By analogy the signals in tetra-*O*-acetyl-scyllo-quinic acid would correspond to equatorial acetoxy protons at C-3, C-4, and C-5 (2.06 p.p.m.) and C-1 acetoxy protons (2.22 p.p.m.). Lithium aluminum hydride reduction of tetra-*O*-acetyl-scyllo-quinic acid methyl ester gave scyllo-quinicol and this was readily converted to its 2′,3,4,5-tetraacetate, the tertiary hydroxyl group remaining unacetylated. The n.m.r. spectrum of this material was in accord with that assigned to its acidic precursor since signals at 2.05 p.p.m. and 2.11 p.p.m. were obtained in the ratio 3:1. These should correspond to the protons of the equatorial 3-, 4-, and 5-acetoxyls and those of the primary acetoxyl respectively.

Synthesis of scyllo-quinicol was possible by two methods. It was isolated, in 3% yield, from the sodium borohydride reduction of crude quinide, that is, material obtained by lactonizing D-quinic acid at 210° C. These lactonizing conditions are milder than those of Hesse (8), who used 220–250° C and produced 'inactive quinide', as it was named by later workers. Evidently isomerization of the quinic acid or its derived lactone took place under these conditions and it would not be surprising if further examination of the crude mixture showed that other materials in the quinic series were present.

Attempts to improve the low yield were made by hydrogenolyzing D-quinicol at 165° C with copper chromite. This procedure, which can cause isomerization (9, 10) to yield all-*trans* methyl β-glucopyranoside starting from isomeric methyl β-hexopyranosides (11), gave scyllo-quinicol in only 2% yield. Increasing the temperature to 180° C gave mainly tetrols instead of quinicols and from the mixture one unidentified tetrol was isolated in a crystalline state.

Since a more definitive synthesis of scyllo-quinicol was required an alternative route was attempted. Reduction of crude 1,4,5-tri-*O*-acetyl-epi-quinide ($[\alpha]_D$ −61°) with sodium borohydride yielded epi-quinicol (IV), which was converted to its di-*O*-isopropylidene derivative with acetone – sulphuric acid. Tosylation gave 5-tosyl-2′,1:3,4-di-*O*-isopropylidene-epi-quinicol (VI) which proved to be racemic, and could be hydrolyzed to 5-tosyl-epi-quinicol (VII) with 75% acetic acid at 35° C. However, treatment of this substance with hot aqueous alkali gave mainly epi-quinicol (IV) and only a trace of material corresponding with scyllo-quinicol on a paper chromatogram.

The above n.m.r. and synthetic data therefore suggest that scyllo-quinic acid has either structure X or XI, with a preference for the former. Although the action of 95% acetic acid – mineral acid on D-quinic acid does not bring about equilibrium, the kinetic data obtained shows that, on extrapolation, it is unlikely that partly acetylated D-quinic acid or its racemate would ever predominate over the scyllo isomer. The formation of XI rather than X in such proportions would therefore not be likely in view of the higher free energy of the former.

At 57° C in 50% acetic acid further reaction of 5-tosyl-epi-quinicol took place, the

**Examination of tetra-O-acetyl-epi-quinic acid gave one signal only at 2.17 p.p.m., presumably due to time averaging.*

tosyloxy group being eliminated by rearward attack of the C-2′-hydroxymethyl group to yield a 2′,5-anhydro quinicol (V). From this a monoisopropylidene derivative and a triacetate could be prepared. The remainder of the product consisted of epi-quinicol (IV). This reaction appears to involve an oxonium ion intermediate (VIII) which can decompose via two separate routes. The participation of a hydroxyl group is rare, one of the very few unequivocal examples being the ring closure of tetramethylene chlorhydrin to yield tetrahydrofuran in water at 70° C (12).

The participation of the primary hydroxyl group of compounds in this series in alkaline elimination reactions can also be demonstrated. Treatment of 3-tosyl-D-quinicol (XII) with sodium methoxide and following of the reaction chromatographically showed the presence of an intermediate 1,2-epoxide (XIII) which rearranged to give 2′,3-anhydro-D-quinicol (XIV), a more rapid conversion occurring when aqueous alkali was used. These reactions bear a resemblance to the conversion of 4,1′6′-tri-*O*-tosylsucrose pentaacetate to 3,6-anhydro-α-D-galactopyranosyl-1,4:3,6-dianhydro-β-D-fructose using sodium ethoxide (13). In this case, an epoxide migration took place prior to formation of the 3,6-anhydro ring in the pyranose moiety.

EXPERIMENTAL

Solutions were evaporated under reduced pressure and specific rotations measured at 25° C.

Reaction of D-Quinic Acid with 95% Acetic Acid – Sulphuric Acid

A 1% solution of quinic acid in 95% acetic acid containing sulphuric acid (1.5% by volume) was refluxed. At appropriate intervals aliquots were withdrawn and added to excess pyridine – acetic anhydride (1:1). After a day at 40° C the solutions were added to excess dilute sulphuric acid and left until destruction of acetic anhydride was complete. Extraction with chloroform followed by evaporation yielded the acetate mixtures, which were treated in methanol with ethereal diazomethane. Gas chromatographic examination was carried out at 210° C on a 4-ft column of 2% LAC-IR-296 on Chromosorb W 80/100 mesh (14) using helium as carrier gas. The results (in %) are listed below:

Emergence order of acetates	Time (hr)					
	1	2.25	10.25	30	60	93
1 (Unknown)			2	4	8	14
2 (Tetra-*O*-acetyl-scyllo-quinic acid methyl ester)	6	10	17	31	32	25
3 (1,4,5-Tri-*O*-acetyl-D-quinide and tetra-*O*-acetyl-epi-quinic acid methyl ester)	16	25	34	20	16	16
4 (Tetra-*O*-acetyl-D-quinic acid methyl ester)	68	50	23	19	16	15
5 (1,4,5-Tri-*O*-acetyl-epi-quinide)	12	16	22	25	28	29

Preparation of Isomeric Quinic Acid Derivatives

In a typical run, D-quinic acid (10 g) was refluxed in 95% acetic acid (500 ml) containing sulphuric acid (7.5 ml) for 100 hours. After the mixture was cooled, acetic anhydride (500 ml) was added, the temperature not being allowed to rise above 50° C, and after 18 hours the acetylation mixture was added to excess ice water. The mixture was extracted twice with chloroform, washed once with water, dried ($MgSO_4$), filtered, and evaporated to a syrup which crystallized.

Crystallization was completed by addition of a little ether to yield a substance which was recrystallized twice from ethyl acetate – ether. It (2.72 g) had m.p. 176–178° C and $[\alpha]_D$ −61° (*c*, 2,2, $CHCl_3$). In the infrared there were two absorption bands at 1750 cm^{-1} corresponding to acetate carbonyls and a single peak at 1795 cm^{-1} due to a γ-lactone carbonyl of a quinic acid isomer (1,4,5-tri-*O*-acetyl-epi-quinide (I)). Calculated for $C_{13}H_{16}O_8$: C, 52.0%; H, 5.3%. Found: C, 51.65%; H, 5.0%.

Fractional crystallizations from chloroform – ethyl acetate yielded the (−)-isomer with m.p. 209–210° C and $[\alpha]_D$ −119° (*c*, 1.0, $CHCl_3$). The mother liquors contained the racemic isomer with m.p. 182–183° C. The n.m.r. spectra of these substances were identical.

After removal of the above lactone derivatives the mother liquors yielded more crystals from ether. Two further recrystallizations from ether yielded optically inactive tetra-*O*-acetyl-scyllo-quinic acid (II)

(0.92 g) with m.p. 198–200° C. It absorbed in the infrared at 1750 cm^{-1} (acetate carbonyl) and 1720 cm^{-1} (carboxyl carbonyl). Nuclear magnetic resonance spectroscopy in chloroform showed two proton signals, one at 2.22 p.p.m. corresponding to one acetate and the other at 2.06 p.p.m. to three acetate groups. Calculated for $C_{15}H_{20}O_{10}$: C, 50.0%; H, 5.6%. Found: C, 50.0%; H, 5.6%. Authentic tetra-*O*-acetyl-D-quinic acid gave three signals at 2.07, 2.11, and 2.18 p.p.m. in the ratio 2:1:1 respectively.

The crude mixture obtained above from D-quinic acid was fractionated on a silicic acid column. Lactones were eluted with chloroform and free acids with acetone. By a gravimetric estimation the mixture consisted of 45% lactone triacetates and 55% acid tetraacetates.

1,4,5-Tri-O-acetyl-epi-(−)-quinide (I) from Tetra-O-acetyl-D-quinic Acid using Hydrogen Fluoride

Liquid hydrogen fluoride (20 ml) was added to an ice-cooled polythene vessel containing tetra-*O*-acetyl-D-quinic acid (7.5 g). After the mixture had been left at 25° C overnight it was added to pyridine (100 ml) containing acetic anhydride (50 ml) and kept at 50° C for 6 hours. The acetylated products were isolated by addition to ice-cold 5% sulphuric acid (2 liters) and extraction with chloroform. The acetates, consisting entirely of γ-lactones with infrared absorption at 1800 cm^{-1}, were dissolved in ether (50 ml) and kept in the refrigerator for a week. The crystals which formed were recrystallized from ethyl acetate. The triacetyl-epi-quinide (80 mg) had m.p. and mixed m.p. 208° C and $[\alpha]_D$ −112° (*c*, 1.0, $CHCl_3$). Calculated for $C_{13}H_{16}O_8$: C, 52.0%; H, 5.3%. Found: C, 52.1%; H, 5.3%.

epi-(−)-Quinicol (IV) from Penta-O-acetyl-D-quinicol (III) using Hydrogen Fluoride

By a procedure similar to that described above, penta-*O*-acetyl-D-quinicol (2.00 g) was converted with hydrogen fluoride to a mixture of isomeric quinicol acetates (1.80 g). These were deacetylated in 0.1 *N* sodium methoxide (25 ml) and the resulting mixture of polyols was partially resolved by cellulose column chromatography using *n*-butanol one quarter saturated with water as solvent. The first compound eluted was epi-(−)-quinicol (211 mg) with $[\alpha]_D$ −3° (*c*, 4.1, MeOH). It was characterized by refluxing a 100-mg sample in acetone (15 ml) containing sulphuric acid (0.1 ml) for 3 hours. After neutralization (Na_2CO_3), filtration, and evaporation 2′,1:3,4-di-*O*-isopropylidene-epi-(−)-quinicol was obtained and recrystallized twice from hexane. It (37 mg) had m.p. and mixed m.p. 119–120° C and was identical with authentic material obtained from 1,4,5-tri-*O*-acetyl-epi-(−)-quinide by the method described later in this section. Calculated for $C_{13}H_{22}O_5$: C, 60.4%; H, 8.6%. Found: C, 60.3%; H, 8.5%.

scyllo-Quinicol and Derivatives from Tetra-O-acetyl-scyllo-quinic Acid (II)

Tetra-*O*-acetyl-scyllo-quinic acid was treated in methanol with an excess of ethereal diazomethane. On evaporation the methyl ester crystallized and after two recrystallizations from methanol had m.p. 145–148° C. Calculated for $C_{16}H_{22}O_{10}$: C, 51.3%; H, 5.9%. Found: C, 51.2%; H, 5.9%.

Crude methyl ester obtained from the free acid (1.3 g) was added in ether (25 ml) to refluxing ether (50 mg) which contained lithium aluminum hydride (1.5 g). After 1 hour ethyl acetate was added, followed by acetic acid, and the solution evaporated to dryness. Aqueous sodium hydroxide was added and the mixture heated at 100° C for 1 hour and the resulting suspension was treated with mixed-bed resin and filtered. Evaporation yielded a syrup (0.72 g), from which scyllo-quinicol could be isolated by crystallization. Two recrystallizations from methanol–ethanol gave 176 mg with m.p. 184–186° C. Calculated for $C_7H_{14}O_5$: C, 47.2%; H, 7.9%. Found: C, 47.0%; H, 7.8%.

The polyol (50 mg) was added to acetic anhydride – pyridine (1 ml:1 ml) which was heated at 100° C for 1 hour and the solvent then evaporated. Two recrystallizations from ether–hexane gave 2′,3,4,5-tetra-*O*-acetyl-scyllo-quinicol with m.p. 113–114° C. Calculated for $C_{15}H_{22}O_9$: C, 52.2%; H, 6.4%. Found: C, 52.0%; H, 6.3%. Examination of the acetate protons by n.m.r. spectroscopy in chloroform showed three protons at 2.11 p.p.m. and nine protons at 2.05 p.p.m.

Isolation of scyllo-Quinicol by Reduction of Crude D-Quinide

In a separate experiment quinic acid (10 g) was converted to a mixture containing mainly D-quinicol by the method used for the preparation of 3-tosyl-D-quinicol which is described later. Fractionation of the polyols on a cellulose column using *n*-butanol one quarter saturated with water as solvent gave D-quinicol (4.22 g) and scyllo-quinicol (0.31 g). The latter was recrystallized twice from ethanol to give a product with m.p. and mixed m.p. 185–186° C. Calculated for $C_7H_{14}O_5$: C, 47.2%; H, 7.9%. Found: C, 47.6%; H, 7.9%.

scyllo-Quinicol Formed by Hydrogenolysis of D-Quinicol

D-Quinicol (0.95 g) was dissolved in dioxane (50 ml) containing copper chromite (0.47 g) and hydrogenated for 6 hours at 165° C under 1000 p.s.i. of hydrogen. After filtration and evaporation a portion of the product was fractionated on a cellulose column as above to yield D-quinicol (437 mg) and scyllo-quinicol (45 mg). Two crystallizations of the latter from ethanol gave material with m.p. and mixed m.p. 184–185° C. Calculated for $C_7H_{14}O_5$: C, 47.2%; H, 7.9%. Found: C, 47.2%; H, 7.95%.

Repetition of the hydrogenolysis at 180° C with 2.0 g of D-quinicol gave a complex mixture, consisting mainly of tetrols. Only one of these was isolated crystalline by cellulose chromatography using benzene–ethanol–water (200:50:1) as solvent. Two recrystallizations from ethanol gave 55 mg of material with m.p. 151–152° C. Calculated for $C_7H_{14}O_4$: C, 51.8%; H, 8.7%. Found: C, 52.0%; H, 8.7%. No further characterization studies were carried out.

epi-Quinicol (IV) and its Di-O-isopropylidene Derivative from 1,4,5-Tri-O-acetyl-epi-quinide (I)

Crude 1,4,5-tri-*O*-acetyl-epi-quinide (8.0 g) consisting of a mixture of (−)- and (±)-isomers, was de-acetylated by addition of 0.1 equivalent of 0.1 *N* sodium methoxide in methanol and the solution evaporated to dryness.

The de-esterified product was dissolved in methanol (100 ml) at 0° C, sodium borohydride (3.0 g) added and the solution left in the refrigerator overnight. The polyol was isolated by the procedure described previously for the preparation of D-quinicol.

The di-*O*-isopropylidene derivative was obtained by heating the polyol under reflux for 10 minutes in acetone (50 ml) containing sulphuric acid (0.5 ml). The solution was neutralized (Na_2CO_3) and then added to a chloroform–water mixture. After shaking the mixture, the chloroform layer was washed once with water and evaporated to a syrup. This crystallized and one crystallization from *n*-hexane yielded 2′,1:3,4-di-*O*-isopropylidene-epi-quinicol (3.0 g). A further crystallization gave material with m.p. 121–122° C and $[\alpha]_D$ 0° (*c*, 1.0, $CHCl_3$). Calculated for $C_{13}H_{22}O_5$: C, 60.4%; H, 8.6%. Found: C, 60.3%; H, 8.6%.

2′,1:3,4-Di-O-isopropylidene-5-tosyl-epi-(±)-quinicol (V)

The diacetone polyol (2.01 g) was treated overnight in pyridine (4 ml) containing tosyl chloride (2.0 g). After work-up of the product the tosylate was crystallized twice from ether and had m.p. 115–116° C and $[\alpha]_D$ 0° (*c*, 2.0, $CHCl_3$). Yield, 2.74 g. Calculated for $C_{20}H_{28}O_7S$: C, 58.6%; H, 7.1%. Found: C, 58.2%; H, 6.8%.

Alkaline Hydrolysis of 5-Tosyl-epi-quinicol (VII)

The tosyl derivative (0.10 g) was dissolved in 75% acetic acid (2 ml) and the solution kept at 35° C for 3 hours. Evaporation yielded a syrup which was dissolved in 0.1 *N* sodium hydroxide (10 ml) and then heated on a steam bath for 2 hours. Deionization of the solution and evaporation gave a product which contained mainly epi-quinicol and only a trace of a substance corresponding to scyllo-quinicol on a paper chromatogram (solvent: *n*-butanol–ethanol–water, 40:11:19; spray: ammoniacal silver nitrate (15)).

Elimination of Tosyloxy Group of 5-Tosyl-epi-quinicol in 50% Acetic Acid

The tosylate (2.7 g) was heated at 57° C in 50% acetic acid (250 ml) for 6 hours. Liberated toluenesulphonic acid was removed by addition of Dowex-1, and the solution evaporated to a syrup. A portion was acetylated and examined by gas phase chromatography using 1½% LAC-IR-296 on a celite column. Peaks corresponding to epi-quinicol (18%) and anhydro quinicol (87%) derivatives were detected. Fractionation on a cellulose column using *n*-butanol one half saturated with water as solvent gave the anhydro quinicol (1.09 g) and a little epi-quinicol (0.14 g; characterized as its di-*O*-isopropylidene derivative).

The anhydro fraction gave 520 mg of crystals (V) with an indeterminate melting point greater than 165° C after two crystallizations from ethanol and $[\alpha]_D$ 0° (*c*, 1.0, H_2O). Calculated for $C_7H_{12}O_4$: C, 52.5%; H, 7.55%. Found: C, 52.2%; H, 7.45%. It was converted to its triacetate by being heated in pyridine–acetic anhydride at 100° C for an hour. The product was crystallized twice from ether–hexane and had m.p. 151–153° C. Calculated for $C_{13}H_{18}O_7$: C, 54.5%; H, 6.3%. Found: C, 54.7%; H, 6.2%.

The anhydro compound (40 mg) was dissolved in acetone (20 ml) containing 2 drops of sulphuric acid and Drierite (5 g). After 3 hours the product was isolated after neutralization with sodium carbonate and extraction with chloroform from water. Crystallization from ether–hexane gave the isopropylidene compound with m.p. 98–99° C. Calculated for $C_{10}H_{16}O_4$: C, 60.0%; H, 8.05%. Found: C, 60.1%; H, 8.2%.

Starting from 1,4,5-tri-*O*-acetyl-epi-(−)-quinide the following derivatives were prepared and their specific rotations recorded: sodium epi-(−)-quinate, $[\alpha]_D$ −27° (*c*, 1.1, dil. NaOH); epi-(−)-quinic acid, $[\alpha]_D$ −18° (*c*, 1.0, H_2O); epi-(−)-quinicol, $[\alpha]_D$ −10° (*c*, 6.6, H_2O); 2′,1:3,4-di-*O*-isopropylidene-epi(−)-quinicol, $[\alpha]_D$ −9° (*c*, 10.0, $CHCl_3$), its 5-tosyl derivative, $[\alpha]_D$ −90° (*c*, 10.0, $CHCl_3$); and the derived anhydro compound, $[\alpha]_D$ −41° (*c*, 0.8, H_2O).

2′,1:4,5-Di-O-isopropylidene-3-tosyl-D-quinicol

The product obtained by heating D-quinic acid (10 g) at 210° C for 3 hours was dissolved in methanol (100 ml) which was made alkaline with sodium methoxide, and sodium borohydride (3.0 g) added. After 18 hours the solution was acidified with acetic acid and evaporated to dryness, the residue dissolved in water and treated with Amberlite-IR 120. Boric acid was removed by repeated evaporations in methanol. The product was refluxed for 10 hours in acetone (500 ml) containing sulphuric acid (2 ml). Excess sodium carbonate was added and when neutral the solution was evaporated to a solid which was partitioned between chloroform and water. The diisopropylidene polyol obtained by evaporation of the chloroform layer gave only gummy crystals and was therefore converted directly to its more crystalline tosyl derivative.

The syrup was dissolved in pyridine (20 ml) and tosyl chloride (5.0 g) added. After 18 hours the solution was cooled and excess reagent destroyed with a little water. Addition of excess water precipitated the tosylate, which was recrystallized from ethanol and had $[\alpha]_D$ −63° (*c*, 1.0, $CHCl_3$) and m.p. 149–152° C. Calculated for $C_{20}H_{28}O_7S$: C, 58.2%; H, 6.9%. Found: C, 58.3%; H, 6.8%.

3-Tosyl-D-quinicol (XII)

The di-*O*-isopropylidene tosyl quinicol (1.63 g) was hydrolyzed by being warmed for 6 hours at 60° C in 50% acetic acid (80 ml). The solution was evaporated and two recrystallizations of the residue from ethanol

gave 3-tosyl-D-quinicol (0.81 g) with m.p. 136–138° C and $[\alpha]_D$ −51° (*c*, 1.6, MeOH). Calculated for $C_{14}H_{20}O_7S$: C, 50.6%; H, 6.1%. Found: C, 50.9%, 50.9%; H, 6.1%, 6.2%.

2′,3-Anhydro-D-quinicol (XIV) from Alkaline Elimination of 3-Tosyl-D-quinicol

3-Tosyl-D-quinicol (200 mg) was dissolved in methanol (3 ml) containing sodium (16 mg). After 3 hours at 5° C all starting material had disappeared and two new spots appeared on a paper chromatogram. On leaving the mixture overnight at room temperature the slower moving material disappeared and the solution was evaporated and deionized with mixed-bed resin. Filtration and evaporation yielded crystals which were recrystallized twice from ether containing a trace of ethanol. The 2′,3-anhydro-D-quinicol had a vague melting point greater than 160° C and $[\alpha]_D$ −20° (*c*, 1.0, H_2O). Calculated for $C_7H_{12}O_4$: C, 52.5%; H, 7.55%. Found: C, 52.5%; H, 7.6%. The above reaction was observed to take place more readily with aqueous sodium hydroxide.

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