SOME RING-OPENING REACTIONS OF A DIEPOXIDE DERIVED FROM (−)-QUINIC ACID

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ABSTRACT

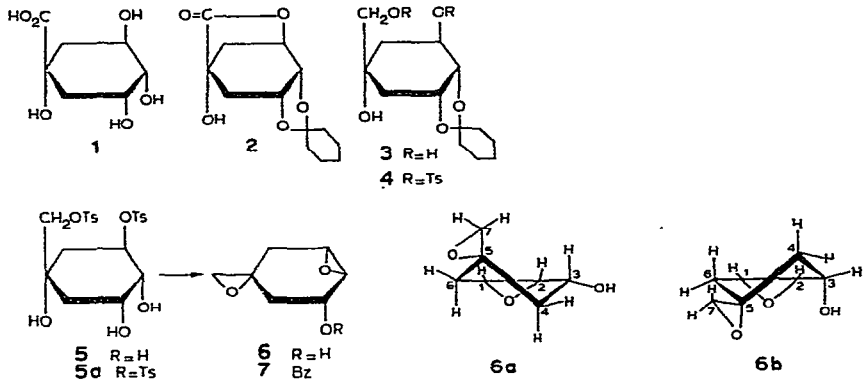
A useful preparative route to nitrogen-containing, carbocyclic derivatives is described from (−)-quinic acid. (−)-Quinic acid was converted via the 3,4-*O*-cyclohexylidene-lactone into 1-L-3-*O*-tosyl-5-*C*-tosyloxymethylcyclohexane-1,2,5/3-tetrol (**5**) by sequential reduction with sodium borohydride, toluene-*p*-sulphonylation, and acid hydrolysis. Reaction of the disulphonate **5** with methanolic sodium methoxide afforded 1-D-1,2:5,7-dianhydro-5-*C*-hydroxymethylcyclohexane-1,2,3,5/0-tetrol (**6**). The ring-opening reactions of the diepoxide **6** with azide ion furnished a mixture of two diazides **9** and **13** in the ratio 4 to 1. The structure and conformation of the derived dibenzoates **10** and **14** have been determined by n.m.r. spectroscopy.

INTRODUCTION

The opening of epoxide rings of steroids[1,2], nucleosides[3], and carbohydrates[4] with nucleophilic reagents has provided valuable substances for biochemical studies. We have explored the use of such procedures for the synthesis of carbocyclic analogues of hexopyranosides, and as part of a programme on the synthesis of analogues of aminoglycoside antibiotics, we now report the preparation of some carbocyclic analogues of dianhydro- and diamino-hexopyranosides. The IUPAC–IUB Tentative Rules for Cyclitol Nomenclature[6] have been used in this paper.

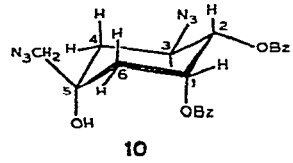
RESULTS

Treatment of the readily available (−)-quinic acid (**1**) with cyclohexanone in the presense of Amberlite IR-120 (H^+) resin, with azeotropic removal of water, yielded the 3,4-*O*-cyclohexylidene-lactone **2**. Reduction of **2**, using sodium borohydride in ethanol, afforded 1-L-1,2-*O*-cyclohexylidene-5-*C*-hydroxymethylcyclohexane-1,2,5/3-tetrol (**3**). Toluene-*p*-sulphonylation of **3**, followed by hydrolysis of the cyclohexylidene group from the product **4** using a mixture of methanol and 2M hydrochloric acid, gave the disulphonate **5**. When **5** was treated with methanolic sodium methoxide, 1-D-1,2:5,7-dianhydro-5-*C*-hydroxymethylcyclohexane-1,2,3,5/0-tetrol (**6**) was formed and subsequently characterized as its 3-benzoate **7**.



Treatment of the diepoxide **6**, with sodium azide in boiling 2-methoxyethanol containing ammonium chloride gave a mixture of two products, from which a syrupy, major product, 1-L-[1,2,5(OH)/3]-3-azido-5-*C*-azidomethylcyclohexane-1,2,5-triol (**9**), and a crystalline, minor component, *meso*-[1,3,5(OH)/2]-2-azido-5-*C*-azidomethyl-cyclohexane-1,3,5-triol (**13**), were isolated in the ratio 4 to 1 by chromatography on silica gel. Proof of structure of the azides was provided by n.m.r. analysis of the respective dibenzoates **10** and **14**.

In the n.m.r. spectrum of **10** (Fig. 1) a one-proton quartet (with components of equal intensities) centred at δ 5.18 ($J_{2,3}$ 10 Hz, $J_{1,2}$ 3 Hz) was assigned to H-2.



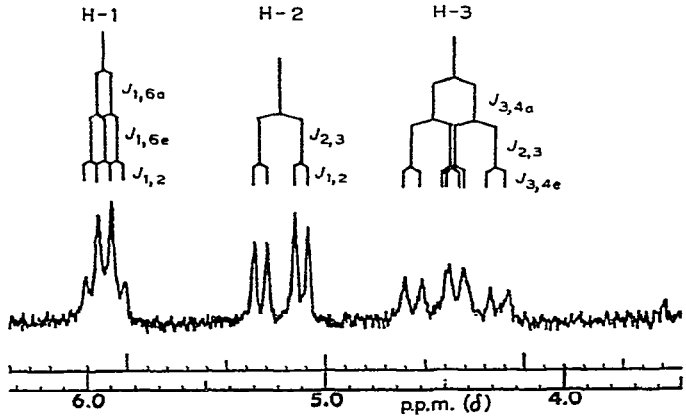


Fig. 1. Partial n.m.r. spectrum ($CDCl_3$) of **10** at 60 MHz.

The large coupling between H-2 and H-3 indicates that these hydrogen atoms are disposed diaxially. The small coupling between H-1 and H-2 is consistent with that expected for an equatorial H-1. The one-proton quartet centred at δ 5.92 was assigned to H-1, and the one-proton sextet centred at δ 4.44 to H-3. These data are entirely consistent with structure **10** for the diazide.

In the n.m.r. spectrum of **14** (Fig. 2), the one-proton triplet centred at δ 4.05 ($J_{1,2}$ 8.5 Hz, $J_{2,3}$ 8.5 Hz) was assigned to H-2. The large (diaxial) couplings for H-1 and H-2 and for H-2 and H-3 are consistent with the *meso* structure **14**; the signals centred at δ 5.07 can be assigned to H-1 and H-3. The zero optical rotation of **14** is also consistent with a *meso* structure.

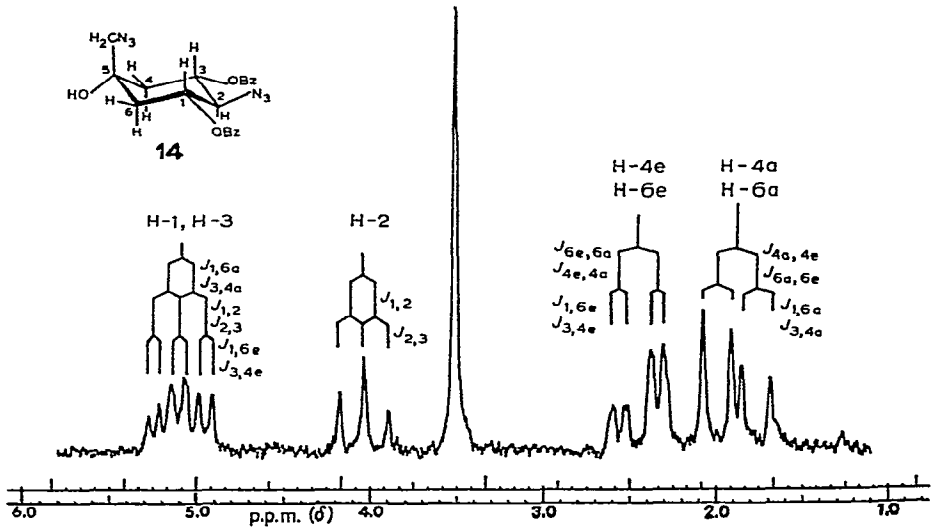
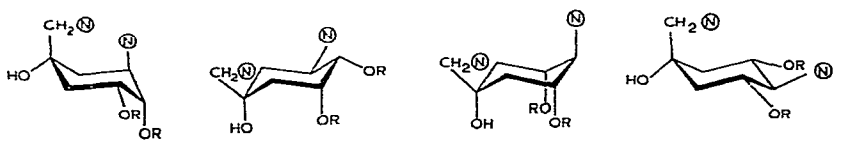


Fig. 2. Partial n.m.r. spectrum ($CDCl_3$–D_2O) of **14** at 60 MHz.

The opening of epoxides attached to cyclohexane or pyranoside rings occurs, in the great majority of cases, according to the Fürst–Plattner[5] rule. The distribution of products from the ring opening of the diepoxide **6** should be largely dependent upon the equilibrium mixture of the two half-chair conformations **6a** and **6b** and the developing non-bonded interactions in the transition state. It is anticipated that the



8 Ⓝ = N_3; R = H

9 Ⓝ = N_3; R = H
10 Ⓝ = N_3; R = Bz
11 Ⓝ = NHBz; R' = Bz

12 Ⓝ = N_3; R = H

13 Ⓝ = N_3; R = H
14 Ⓝ = N_3; R = Bz
15 Ⓝ = NH_3Cl; R = H
16 Ⓝ = NH_2; R = H

transition state will be much more product-like than reactant-like. Thus, the formation of the major product **9**, can be explained by initial diaxial openings at C-1 and C-7 in the more-stable, half-chair conformation **6a** to give diazide **8**, which then undergoes chair inversion into conformation **9**. The minor component **13** arises via the diaxial openings at C-2 and C-7 of the other half-chair conformation (**6b**) to furnish the diazide **12**. Conformation **12** contains several 1,3-diaxial substituents and so rearranges into the more-stable, chair conformation **13**. The greater stability of **6a** over **9b** is presumably due to the 1,3 interaction between the hydroxyl group and the *spiro*-epoxide ring.

Catalytic reduction of diazides **9** and **13** afforded the corresponding, syrupy diamines. That derived from **9** was characterized as 1-L-[1,2,5(OH)/3]-3-benzamido-5-*C*-benzamidomethyl-1,2-di-*O*-benzoylcyclohexane-1,2,5-triol (**11**) and that from **13** as the dihydrochloride **15** of *meso*-[1,3,5(OH)/2]-2-amino-5-*C*-aminomethylcyclohexane-1,3,5-triol (**16**).

EXPERIMENTAL

Rotations were measured for solutions in chloroform. T.l.c. and preparative layer chromatography (p.l.c.) were carried out with silica gel; compounds were detected by charring with sulphuric acid. Evaporations were carried out at 40°, *in vacuo*. All melting points are corrected. New compounds had i.r., n.m.r., and mass spectra consistent with the assigned structures.

4,5-O-Cyclohexylidene derivative (**2**) *of the lactone of quinic acid.* — Quinic acid **1** (50 g), cyclohexanone (180 ml), benzene (200 ml), and *N,N*-dimethylformamide (210 ml) were refluxed, with azeotropic distillation and vigorous stirring in a Dean–Stark apparatus, until no more water separated. The apparatus was cooled slightly, Amberlite IR-120(H^+) resin (70 g) was added, and heating was continued with vigorous stirring for 4 h. The cooled mixture was filtered, and the filtrate was washed with cold, aqueous 5% sodium hydrogen carbonate and water. Evaporation of the dried (Na_2SO_4) solution gave a colourless residue which was crystallized from ethanol–light petroleum to give the lactone **2** (57 g, 86%), m.p. 139–141°, $[\alpha]_D^{25}$ −33° (*c* 1.05) (Found: C, 61.2; H, 7.3. $C_{13}H_{18}O_5$ calc.: C, 61.4; H, 7.15%).

1-L-1,2-O-Cyclohexylidene-5-C-hydroxymethylcyclohexane-1,2,5/3-tetrol (**3**). — A solution of lactone **2** (35 g) in ethanol (650 ml) was stirred at room temperature with sodium borohydride (35 g) for 24 h. Cold, saturated, aqueous sodium chloride was then added, and the mixture was stirred for an additional 10 h and then extracted with chloroform (5 × 150 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give a white residue which, on recrystallization from ethyl acetate–light petroleum, gave compound **3** (25 g, 70%), m.p. 90–91° $[\alpha]_D^{24}$ −64° (*c* 1.6) (Found: C, 60.6; H, 8,35. $C_{13}H_{22}O_5$ calc.: C, 60.6; H, 8.6%).

1-L-1,2-O-Cyclohexylidene-3-O-tosyl-5-C-tosyloxymethylcyclohexane-1,2,5/3-tetrol (**4**). — A solution of **3** (23.5 g) in pyridine (120 ml) was treated with toluene-*p*-

sulphonyl chloride (54 g) for 16 h and then poured into ice–water containing sodium hydrogen carbonate. The mixture was extracted with chloroform (4 × 200 ml) and the extracts were washed with water, dried (Na_2SO_4), and evaporated. The pale-yellow, oily residue crystallised from ethanol to give the disulphonate **4** (44.5 g, 89%), m.p. 123–125°, $[\alpha]_D^{22}$ −75° (*c* 2) (Found: C, 56.9; H, 6.1; S, 11.2 $C_{27}H_{34}O_9S_2$ calc.: C, 57.2; H, 6.05, S, 11.25%).

1-L-3-O-Tosyl-5-C-tosyloxymethylcyclohexane-1,2,5/3-tetrol (**5**). — A mixture of **4** (21 g) and 0.6M methanolic hydrochloric acid (200 ml) was heated under reflux for 21 h. The solution was evaporated, the residue was redissolved in water and methanol, and the solution again evaporated. A solution of the residue in aqueous methanol deposited amorphous **5** (17 g, 98%), m.p. 134–136°, which was readily converted into the tetra-sulphonate **5a**, m.p. 91–93°, $[\alpha]_D$ −11° (*c* 1) (Found: C, 52.55; H, 4,6; S, 15.85. $C_{35}H_{38}O_{13}S_4$ calc.: C, 52.85; H, 4.8; S, 16.1%).

1-D-1,2:5,7-Dianhydro-5-C-hydroxymethylcyclohexane-1,2,3,5/0-tetrol (**6**). — A solution of the disulphonate **5** (5 g) in dry methanol (5 ml) was stirred with methanolic sodium methoxide (2.2 molar equivalents) at room temperature for 1 h; during the course of the reaction, a precipitate formed. Solid carbon dioxide was then added, the mixture was stirred for 1 h, and the filtered solution was evaporated. The residue was then dissolved in dry chloroform, and the solution filtered again and evaporated. The resulting, syrupy residue was distilled to give the diepoxide **6**(1.29 g, 88%), b.p. 115–120°/0.05 mmHg, m.p. 57–58°, $[\alpha]_D^{22}$ +26.6° (*c* 1.17) (Found: C, 59.3; H, 7.1; O, 33.8. $C_7H_{10}O_3$ calc.: C, 59.15; H, 7.1; O, 33.75%).

The 3-benzoate **7** had m.p. 123–124°, $[\alpha]_D^{23}$ +87.5° (*c* 2) (Found: C, 68.25; H, 5.75; O, 26.0. $C_{14}H_{14}O_4$ calc.: C, 68.3; H, 5.7; O, 26.0%).

Reaction of azide ion with the diepoxide **6**. — A solution of the diepoxide **6** (1.4 g), sodium azide (2.8 g), and ammonium chloride (2.8 g) in 2-methoxyethanol (28 ml) and water (2.8 ml) was boiled under reflux for 2 h, and was then cooled and poured into ice–water. The mixture was extracted with chloroform, and the extract was dried (Na_2SO_4) and evaporated. The syrupy residue was found to be a mixture of two components (t.l.c., ethyl acetate–light petroleum, 2:1). Column chromatography on silica gel (50 g) with ethyl acetate–light petroleum (2:1) afforded first a syrupy diazide **9** (0.89 g, 40%) characterized as 1-L-[1,2,5(OH)/3]-3-azido-5-*C*-azidomethyl-1,2-di-*O*-benzoylcyclohexane 1,2,5-triol (**10**), m.p. 89–91°, $[\alpha]_D^{24}$ −164° (*c* 2.24) (Found: C, 57.95; H, 4.7; N, 19.1. $C_{21}H_{20}N_6O_5$ calc.: C, 57.8; H, 4.6; N, 19.25%).

Eluted second was *meso*-[1,3,5(OH)/2]-2-azido-5-*C*-azidomethylcyclohexane-1,3,5-triol (**13**) (0.22 g, 9.8%), m.p. 131–132°, $[\alpha]_D$ 0° (Found: C, 37.05; H, 5.15. $C_7H_{12}N_6O_3$ calc.: C, 36.85; H, 5.3%), characterized as its 1,3-dibenzoate **14**, m.p. 107–108°, $[\alpha]_D$ 0° (Found: C, 58.1; H, 4.65, N, 19.15: $C_{21}H_{20}N_6O_5$ calc.: C, 57.8; H, 4.6; N, 19.25%).

Catalytic reduction of diazides **9** *and* **13**. — (*a*) A solution of the diazide **9** (0.14 g) in methanol (7 ml) was hydrogenated for 2 h over platinum dioxide (40 mg). The catalyst was removed, and the filtrate was concentrated to give a syrup. Benzoylation by the conventional method furnished, 1-L-[1,2,5(OH)/3]-3-benzamidomethyl-

1,2-di-*O*-benzoylcyclohexane-1,2,5-triol (**11**) m.p. 286–288° $[\alpha]_D$ −78.2° (*c* 1.56) (Found: C, 71.2; H, 5.4; N, 4.6. $C_{35}H_{32}N_2O_7$ calc.: C, 70.9; H, 5.4; N, 4.7%).

(*b*) Diazide **13** (0.14 g) was hydrogenated as described in (*a*). The resulting, syrupy *meso*-[1,3,5(OH)/2]-2-amino-5-*C*-aminomethylcyclohexane-1,3,5-triol (**16**) was characterized as its dihydrochloride **15**, m.p. 251–252° (dec.), $[\alpha]_D$ 0° (Found C, 33.65; H, 7.55; Cl, 28.55; N, 11.05. $C_7H_{18}Cl_2N_2O_3$ calc.: 33.7; H, 7.3; Cl, 28.5; N, 11.2%).

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