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Inositol Derivatives. VI. Convenient Synthesis of DL-*proto*-Quercitol from *myo*-Inositol

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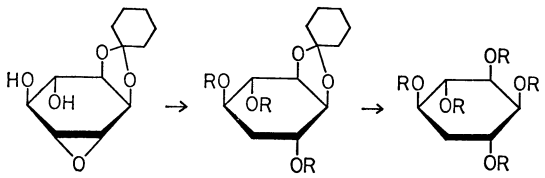
(+)-*proto*-Quercitol was discovered in acorns in 1849,[1] and its configuration was established in 1932,[2] whereas, levorotatory isomer remained unknown until 1961.[3] Plouvier[3] prepared a racemic form of *proto*-quercitol by mixing an equal weight of the two enantiomers, and it was shown to exist as a solid solution.

The total synthesis of (−)-*proto*-quercitol was first accomplished in 1966 by McCasland and his coworkers[4] starting from quebracitol or, somewhat less conveniently from (−)-*chiro*-inositol. Their identical procedure applied to (+)-*chiro*-inositol should lead to (+)-*proto*-quercitol, and, similarly, DL-*proto*-quercitol should be synthesized from DL-*chiro*-inositol.

Since we require large quantities of DL-*proto*-quercitol in order to synthesize deoxyinosadiamines and pseudo sugars of biological interest, we have been studying its alternative and facile preparation from *myo*-inositol. In the present paper, we wish to report the convenient synthesis of DL-*proto*-quercitol from readily avairable DL-1,2-anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol (**2**).[5]



2 **3a** R=H, **b** R=Ac **4a** R=H, **b** R=Ac

Treatment of DL-1,2-*O*-cyclohexylidene-3-*O*-*p*-tolylsulfonyl-*myo*-inositol (**1**)[6] in methanol with a slight excess of sodium methoxide gave **2** almost exclusively in 86% yield. Reduction of **2** with lithium aluminum hydride in tetrahydrofuran at refluxing temperature for 4 hr gave DL-1,2-*O*-cyclohexylidene-4-deoxy-*muco*-inositol (**3a**) predominantly in 87% yield, which was converted into the tri-*O*-acetyl derivative (**3b**) in the usual way. Hydrolysis of **3a** with boiling 6N hydrochloric acid gave crystals of DL-*proto*-quercitol (**4a**) in 80% yield. The crystalline pentaacetate (**4b**) was also prepared from **4a**.

Assuming that an epoxide-migration occurred under the reduction condition, two stereoisomers of deoxyinositols should be formed from **2**; namely, DL-*proto*- and DL-*vibo*-quercitols. In the proton magnetic resonance (PMR) spectrum of **4b** in deuteriochloroform ($CDCl_3$), the signals of five acetyl methyl protons appeared as three singlets at τ 7.86, 7.97, and 7.99 in the relative intensities of 2 : 2 : 1, which could be assigned to the signals of two axial, two equatorial and one equatorial acetoxy groups, respectively.[7] Therefore, the spectrum was not compatible with the *vibo*-configuration, since it has only one axial acetoxy group. Moreover, an authentic sample of the pentaacetate of DL-*vibo*-quercitol[8] was proved to be different from **4b** in all respect.

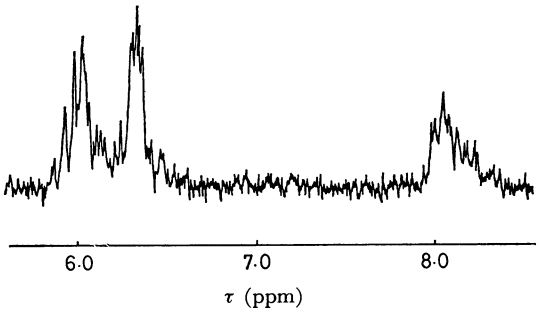


Fig. 1. PMR spectrum of DL-*proto*-quercitol (**4a**) in D_2O at 60 MHz,

The PMR spectrum of **4a** in deuterium oxide (D_2O) was shown to be identical with that of (−)-*proto*-quercitol reported by McCasland[9] (Fig. 1). Consequently, the structure of **4a** was established unequivocally, and it was found that the reduction of **2** with lithium aluminum hydride proceeded almost stereospecifically to afford **3a**. The overall yield of **4a** from **1** was 60%.

Experimental

Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. PMR spectra were measured on a Varian Associates A-60D (60 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in τ-values. Thin layer chromatography (tlc) was done with silica gel (Wakogel B-10, Wako pure chemical industries Ltd.) and the compounds were detected by heating after spraying 50% sulfuric acid.

DL-*1,2-Anhydro-5,6-O-cyclohexylidene-chiro-inositol (2).* This compound was prepared from DL-1,2-*O*-cyclohexylidene-3-*O*-*p*-tolylsulfonyl-*myo*-inositol (**1**)[6] in 86% yield, following the procedure previously mentioned.[5]

1) H. Braconnot, *Ann. Chem. et Phys.*, **27**, 392 (1849).
2) T. Posternak, *Helv. Chim. Acta*, **15**, 948 (1932).
3) V. Plouvier, *C. R. Acad. Sci. Paris*, **253**, 3047 (1961).
4) G. E. McCasland, M. O. Naumann, and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967); *J. Org. Chem.*, **33**, 4220 (1968).
5) T. Suami, S. Ogawa, S. Oki, and K. Ohashi, This Bulletin, **45**, 2597 (1972).
6) T. Suami, S. Ogawa, T. Tanaka, and T. Otake, *ibid.*, **44**, 835 (1971).
7) F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7**, 121 (1968).
8) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953).
9) G. E. McCasland, "Deoxy Sugars," ed. by P. F. Gould, American Chemical Society (1968), p. 51.

DL-*1,2-O-Cyclohexylidene-4-deoxy*-muco-*inositol* (**3a**). To a solution of **2** (7.5 g) in dry tetrahydrofuran (350 m*l*) was added lithium aluminum hydride (5.0 g) in dry tetrahydrofuran (50 m*l*) and the mixture was refluxed for 4 hr. After cooling, water (30 m*l*) was added dropwise to destroy the excess of metal hydride. The solution was allowed to stand overnight at room temperature, and then the white precipitates were collected by filtration. The filtrate was evaporated to give a crystalline residue which was digested with ethanol and filtered to afford practically pure **3a** (5.2 g, 71%), mp 164—166°C. An additional crop (1.2 g, 87%) was recovered by extraction from dried white precipitates using Soxhlet extractor with tetrahydrofuran. An analytical sample was obtained by recrystallization from ethanol, mp 165—167°C. Tlc indicated a single spot (methyl ethyl ketone-toluene=1 : 1 volume).

Found: C, 58.97; H, 8.11%. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

The tri-*O*-acetyl derivative (**3b**) was prepared by treatment of **3a** with acetic anhydride and pyridine at room temperature in a quantitative yield. Recrystallization from ethanol gave a pure sample, mp 103—104°C. Tlc indicated a single spot (methyl ethyl ketone-toluene=1 : 10 volume). PMR ($CDCl_3$): τ 4.57 (1, quartet, H-3, J=3.0 Hz), 7.89, 7.92, 7.98 (3, singlet, OAc).

Found: C, 58.71; H, 7.03%. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08%.

DL-proto-*Quercitol* (**4a**). Compound **3a** (1.0 g) was treated with boiling 6N hydrochloric acid (20 m*l*) for 2 hr. Then the mixture was evaporated to dryness to give an oily product which was crystallized from ethanol-water to give crystals (540 mg, 80%) of **4a**, mp 208—215°C (decomp.). Recrystallization from the same solvent afforded an analytically pure sample, mp 236.5—238°C (lit,[4] mp 238—239°C). The PMR spectrum in D_2O was superimposable with that of an authentic sample of (−)-*proto*-quercitol reported by McCasland.[9]

Found: C, 44.01; H, 7.12%. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37%.

DL-proto-*Quercitol Pentaacetate* (**4b**). Compound **4a** (50 mg) was acetylated with acetic anhydride (5 m*l*) and pyridine (5 m*l*) overnight at room temperature. The mixture was evaporated to give an oily product which was crystallized from ethanol to give pure crystals (73 mg, 63%) of **4b**, mp 114—116.5°C. Tlc indicated a single spot (methyl ethyl ketone-toluene=1 : 10 volume).

Found: C, 51.63; H, 5.81%. Calcd for $C_{16}H_{22}O_{10}$: C, 51.33; H, 5.92%.

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