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Aminocyclitols. XXVII. Preparation of Deoxyinosamines from *vibo*-Quercitol[1]

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On bromination with acetyl bromide and acetic anhydride at 130°C, *vibo*-quercitol (**1**) gave tetraacetyl 1-bromo-1-deoxy-*scyllo*-quercitol (**2**) in 23% yield. Treatment of **2** with sodium azide in an appropriate solvent afforded three azido compounds, from which, by hydrogenation, corresponding three deoxyinosamines were obtained: 1-deoxy-*scyllo*-2, 5-deoxy-*chiro*-1 and 1-deoxy-*myo*-2-inosamine. The latter two are new compounds and their structures were established by their proton magnetic resonance (PMR) spectra and the reaction sequences.

We previously described the synthesis of two deoxyinosamines from *vibo*-quercitol (**1**).[2] In the present paper, we wish to report an alternative synthetic route to deoxyinosamines using bromodeoxyquercitol.

When **1** was treated with acetyl bromide and acetic anhydride in a sealed tube at 125—130°C for 8 hr, and subsequently acetylated with acetic anhydride and conc. sulfuric acid, hitherto unknown tetraacetyl bromodeoxyquercitol (**2**), mp 148°C, was obtained as a sole crystalline product in 23% yield. Hydrolysis of **2** by refluxing in 3N hydrochloric acid gave bromodeoxy-

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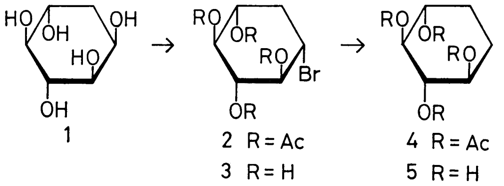
1) All the compounds described in this paper are racemic.

2) T. Suami and K. Yabe, This Bulletin, **39**, 1931 (1966).



quercitol (**3**). On catalytic hydrogenolysis in the presence of Raney nickel T-4[3] and Amberlite IR-4B (OH^-), **2** afforded tetraacetyl cyclohexanetetrol (**4**), which was converted into known cyclohexanetetrol (1, 3/2,4) (**5**).[4] Therefore, **2** should be either 1-bromo-1-deoxy-*scyllo*- or 1-bromo-1-deoxy-*vibo*-quercitol. This could be easily differenciated on the basis of its PMR spectrum in deuteriochloroform ($CDCl_3$) (Fig. 1). The ring proton attached to the carbon atom bearing bromine atom appeared at τ 5.97 as a septet (J=4.5, 9, and 13 Hz), which indicated that the bromine atom should be in equatorial position in the favored conformation and located adjacent to methylene protons. This was further supported by a decoupling experiment. The equatorial methylene proton showed a clearly resolved sextet (J=4.5, 4.5, and 13 Hz) at τ 7.24, which collapsed to a quartet when the septet at τ 5.97 was irradiated at this frequency. While the sextet was irradiated to collapse the septet into a wide triplet. Consequently, **2** was assigned to tetraacetyl 1-bromo-1-deoxy-*scyllo*-quercitol unambigously. The reaction mechanism of the bromination reaction was proposed by assuming an intermediary acetoxonium ion formation between the *cis* hydroxyl groups in *vibo*-quercitol, which was attacked by a bromide ion in a less sterically hindered direction.

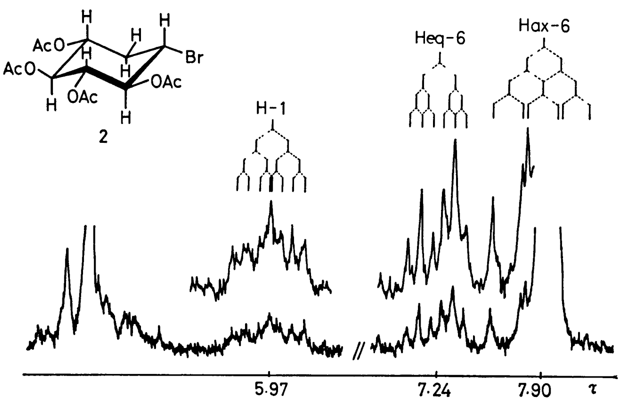
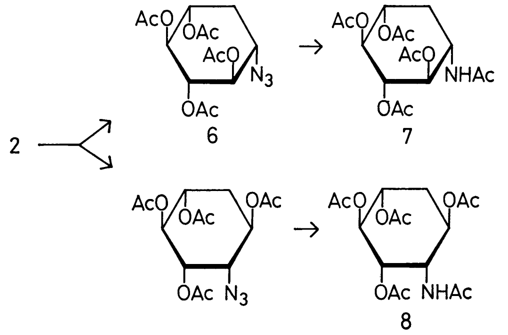
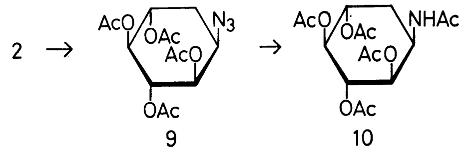


Fig. 1. Partial PMR spectrum of tetraacetyl 1-bromo-1-deoxy-*scyllo*-quercitol (**2**) in $CDCl_3$.

When **2** was treated with an excess amount of sodium azidē in boiling 90% aqueous 2-methoxyethanol for 40 hr, tetraacetyl 1-azido-1-deoxy-*scyllo*-quercitol (**6**)[2] was obtained in 22% yield. The crude oily product obtained by evaporation of the mother liquor of **6** was hydrogenated in the presence of Raney nickel T-4[3] and subsequently acetylated to afford unknown pentaacetyl deoxyinosamine (**8**) in 19% yield. While, **2** was treated with methanolic ammonia in a sealed tube at 120°C for 12 hr and subsequent acetylation gave pentaacetyl 1-deoxy-*scyllo*-inosamine-2 (**7**)[2] and **8** in 14 and 10% yield, respectively.



In the PMR spectrum of **8** in dimethylsulfoxide-d_6 (DMSO-d_6), the acetyl methyl protons revealed four signals at τ 8.14 (1), 8.08 (1), 8.02 (2), and 7.93 (1),[5] which were assigned to one axial acetamido, one equatorial acetoxy, two equatrial acetoxy and one axial acetoxy group, respectively.[6] On the other hand, in the spectrum in $CDCl_3$, four signals due to the acetyl methyl protons were appeared at τ 8.01 (1), 7.96 (1), 7.93 (2), and 7.91 (1), which could be assigned to one equatorial acetamido, one equatorial acetoxy, two axial acetoxy and one axial acetoxy group, respectively.[6] The sextet (J=3, 8, and 8 Hz) at τ 5.50 was attributed to the hydrogen atom attached to the carbon atom bearing the acetamido group, because an addition of deuterium oxide collapsed it into a quartet. Therefore, in $CDCl_3$, **8** seems to take a favored conformation having the acetamido group in an equatorial position. Consequently, according to a reaction sequence and its PMR spectra, **8** was assigned to pentaacetyl 5-deoxy-*chiro*-inosamine-1.



Treatment of **2** with sodium azide in boiling 90% aqueous dimethylformamide for 40 hr and subsequent acetylation gave another tetraacetyl azidodeoxyquercitol (**9**) in 60% yield. Hydrogenation of **9**, followed by acetylation, afforded the corresponding pentaacetyl deoxyinosamine (**10**) in 74% yield. The structures of **9** and **10** were established mainly by way of their PMR spectra. The PMR spectrum of **9** in $CDCl_3$ revealed a narrow quartet (J=3 Hz) at τ 5.83, which was assigned to the equatorial hydrogen atom attached to the carbon atom having azido group[7] and, then, the azido group was proved to be adjacent to the methylene protons. The acetyl methyl protons showed two peaks at

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[3] S. Nishimura, *ibid.*, **32**, 61 (1959).

[4] P. Bedos and A. Ruyer, *Compt. rend.*, **106**, 625 (1933); G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953).

[5] Values in parenthesis show number of acetoxy methyl groups.

[6] F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.*, **7**, 121 (1968).

[7] T. Suami, S. Ogawa, and M. Uchida, This Bulletin, **43**, 3577 (1970).

τ 8.01 (3) and 7.93 (1). The latter might be considered to be downshifted from the ordinary chemical shift[6] under the influence of the adjacent azido group.[7] While, the PMR spectrum of **10** in DMSO-d_6 indicated two signals at τ 8.11 (1) and 8.04 (4), which were assigned to one axial acetamido and four equatorial acetoxy groups, respectively. Consequently, **9** should be tetraacetyl 1-azido-1-deoxy-*vibo*-quercitol and the corresponding **10** was assignable to pentaacetyl 1-deoxy-*myo*-inosamine-2.

The reaction mechanism was interpreted by a direct S_N2 attack of azide ion in a dipolar aprotic solvent.[7,8]

Experimental

Melting point were determined on a Mitamura Riken micro hot stage and are uncorrected. PMR spectra were measured on a Varian Associate A-60D (60 MHz) spectrometer at a concentration of *ca.* 10% deuteriochloroform or dimethylsulfoxide-d_6 with tetramethylsilane as in internal standard. All solutions were concentrated by a rotary evaporator at 40—50°C under reduced pressure. Whenever pyridine was employed in a reaction, the residual pyridine was removed by repeated codistillation with dry toluene.

*Tetraacetyl 1-Bromo-1-deoxy-*scyllo*-quercitol (2).* *vibo*-Quercitol (**1**)[2] (3.0 g) was heated in a sealed tube at 125—130°C for 8 hr with acetyl bromide (2.5 m*l*) and acetic anhydride (7.0 m*l*). The reaction mixture obtained from ten sealed tubes evaporated to dryness and the resulting oily product was treated with acetic anhydride (300 m*l*) and conc. sulfuric acid (15 m*l*) at room temperature overnight. Then the mixture was poured into ice and water (1 *l*) and allowed to stand at room temperature overnight. A thick oily product was extracted with chloroform (300 m*l*) and the extracts were washed with 10% aqueous sodium carbonate and water, successively. The solvent was removed by evaporation and the residue was crystallized from ethanol to yield colorless crystals (22.0 g, 23%) of **2**, mp 147—148°C. Recrystallization from ethanol gave an analytical sample, which showed the same melting point.

Found: C, 42.76; H, 5.08; Br, 20.48%. Calcd for $C_{14}H_{19}O_8Br$: C, 42.54; H, 4.85; Br, 20.22%.

*1-Bromo-1-deoxy-*scyllo*-quercitol (3).* A mixture of **2** (0.50 g) and ethanol (20 m*l*) containing conc. hydrochloric acid (5 m*l*) was refluxed for 90 min. The reaction mixture was evaporated to give a crystalline residue which was recrystallized from ethanol to afford crystals (0.18 g, 62%) of **3**, mp 178—182°C. An analytical sample was obtained by recrystallization from ethanol, mp 185—187°C.

Found: C, 32.28; H, 5.14; Br, 34.72%. Calcd for $C_6H_{11}O_4Br$: C, 31.73; H, 4.88; Br, 35.19%.

Tetraacetyl Cyclohexanetetrol (1,3/2,4) (4). A solution of **2** (0.39 g) in ethanol (20 m*l*) was hydrogenated in the presence of Raney nickel T-4 (one spatula) and Amberlite IR-4B (OH^-) (6 m*l*) in the hydrogen initial pressure of 3 atm for 20 hr. Filtering off the catalyst and resin, the filtrate was evaporated to give a crystalline residue, which was recrystallized from ethanol to afford colorless plates (0.21 g, 68%) of **4**, mp 138.5—139°C (after melting and resolidifying at 126—128°C). Recrystallization from ethanol gave an analytical sample, mp 125.5—127°C.

Found: C, 53.26; H, 6.40%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37%.

Cyclohexanetetrol (1,3/2,4) (5). A mixture of **4** (0.10 g) and 4N hydrochloric acid (6 m*l*) was heated at 90°C for 5 hr. Then the solution was evaporated to give an oily product, which crystallized upon addition of ethanol to afford colorless prisms (37 mg, 78%) of **5**, mp 184—186°C. Recrystallization from methanol gave a pure sample, whose melting point did not change (lit,[4] mp 187—188°C).

TABLE 1. PMR DATA[a]

Compd.	Solvent	Acetyl methyl protons	Ring protons
2	$CDCl_3$	7.91 (1) 7.95 (1) 7.99 (2)	
4	$CDCl_3$	7.98 (4)	
6	$CDCl_3$	7.90 (1) 7.96 (1) 7.99 (2)	6.30 (m, H-1)
7[2]	DMSO-d_6	8.02 (2) 8.06 (2) 8.22 (1)	
8	$CDCl_3$	7.91 (1) 7.93 (2) 7.96 (1) 8.01 (1)	5.50 (sextet, H-1, J=3, 8 and 8 Hz)
8	DMSO-d_6	7.93 (1) 8.02 (2) 8.08 (1) 8.14 (1)	
9	$CDCl_3$	7.93 (1) 8.01 (3)	4.52 (t, H-3, J=9.5 Hz) 5.83 (q, H-1, J=3 Hz)
10	DMSO-d_6	8.04 (1) 8.11 (4)	
Tetraacetyl 3-azido-3-deoxy-*proto*-quercitol[2]	$CDCl_3$	7.84 (1) 7.88 (2) 7.95 (1)	4.59 (t, H-2, J=10 Hz) 6.17 (q, H-3, J=3 and 10 Hz)

a) Chemical shifts are expressed in τ-values. Values in parenthesis show number of methyl groups. Abbreviations: t (triplet); q (quartet); m (complex multiplet). First-order coupling constants are expressed.

*Tetraacetyl 1-Azido-1-deoxy-*scyllo*-quercitol (6).* A mixture of **2** (1.8 g), sodium azide (1.5 g), and 90% aqueous 2-methoxyethanol (60 m*l*) was refluxed for 40 hr. The reaction mixture was evaporated to dryness and the residue was treated with acetic anhydride (15 m*l*) and pyridine (15 m*l*) at room temperature overnight. An insoluble material was removed by filtration and the filtrate was evaporated to give an oily product, which crystallized upon addition of ethanol. The crude crystals were recrystallized from ethanol to afford colorless needles (0.35 g, 22%) of **6**, mp 136—138°C. This compound was identified with an authentic sample[2] by a mixed melting point determination and a comparison of infrared spectra.

From the mother liquor of **6**, a small amount of crystals was isolated after long storage in a refrigerator, mp 128—130°C. The infrared spectrum was different from that of **6**, so that this compound might be proposed to be tetraacetyl 4-azide-4-deoxy-*proto*-quercitol.

Found: C, 46.64; H, 5.10; N, 11.39%. Calcd for $C_{14}H_{19}N_3O_8$: C, 47.06; H, 5.36; N, 11.76%.

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[8] T. Suami, F. W. Lichtenthaler, and S. Ogawa, This Bulletin **38**, 754 (1965).

*Pentaacetyl 5-Deoxy-*chiro*-inosamine-1 (8).* The mother liquor of **6** was hydrogenated in the presence of Adams' platinum oxide (20 mg) in the initial hydrogen pressure of 3 atm for 12 hr. The hydrogenated product was acetylated with acetic anhydride and pyridine and crystallized from ethanol to give crystals (0.37 g, 22%) of **8**, mp 187—188°C. Recrystallization from ethanol gave an analytically pure sample, which showed the same melting point.

Found: C, 51.56; H, 6.14; N, 3.90%. Calcd for $C_{16}H_{23}NO_9$: C, 51.47; H, 6.21; N, 3.75%.

Ammonolysis of 2 using Methanolic Ammonia. Compound **2** (1.5 g) was heated with methanol (100 m*l*) saturated with ammonia at 0—5°C in an autoclave at 120°C for 12 hr. The reaction mixture was evaporated to dryness and treated with acetic anhydride and pyridine at room temperature overnight. Evaporation of the excess reagent gave a crude mixture, which was fractionally crystallized from ethanol and ether to afford pentaacetyl 1-deoxy-*scyllo*-inosamine-2 (**7**) (0.19 g, 13%), mp 224—226°C, and **8** (0.15 g, 10%), mp 187—188°C.

*Tetraacetyl 1-Azido-1-deoxy-*vibo*-quercitol (9).* A mixture of **2** (1.5 g), sodium azide (1.0 g) and 90% aqueous dimethylformamide (50 m*l*) was refluxed for 40 hr. The reaction mixture was processed similarly as described in the preparation of **6**. The crude product was crystallized from ethanol to give crystals (0.81 g, 60%) of **9**, mp 142—145°C. Recrystallization from ethanol afforded an analytical sample, mp 143.5—144.5°C.

Found: C, 46.82; H, 5.40; N, 11.79%. Calcd for $C_{14}H_{19}N_3O_8$: C, 47.06; H, 5.36; N, 11.76%.

*Pentaacetyl 1-Deoxy-*myo*-inosamine-2 (10).* A solution of **9** (0.35 g) in ethanol (50 m*l*) was hydrogenated similarly as described in the preparation of **8**. The crude product was acetylated with acetic anhydride and pyridine and crystallized from ethanol to give colorless crystals (0.27 g, 74%) of **10**, mp 224—225°C. Recrystallization from ethanol afforded an analytical sample, which showed the same melting point.

Found: C, 51.73; H, 6.46; N, 3.77%. Calcd for $C_{16}H_{23}NO_9$: C, 51.47; H, 6.21; N, 3.75%.

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