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Aminocyclitols. XX. Bromination of DL-*epi*-Inositol

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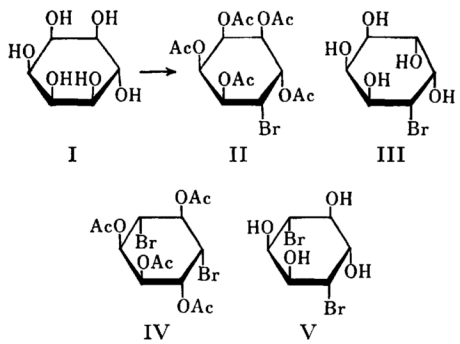
Bromination of DL-*epi*-inositol yielded two hitherto unknown dibromo-dideoxyinositols, along with two known bromo-deoxyinositols (DL-5-bromo-5-deoxy-*allo*-inositol and DL-1-bromo-1-deoxy-*neo*-inositol). The proton magnetic resonance spectroscopic studies of the dibromo-dideoxyinositols with the aid of spin decoupling technique established their configurations to be DL-2,4-dibromo-2,4-didoxy-*chiro*-inositol and DL-1,4-dibromo-1,4-dideoxy-*chiro*-inositol.

As a continuation of the previous paper of this series,[1] configurational studies of two hitherto unknown dibromo-dideoxyinositols which were obtained from DL-*epi*-inositol by a drastic bromination will be described in the present article.



Scheme 1

When DL-*epi*-inositol (I)[2] was heated in a mixture of acetyl bromide and acetic anhydride in a sealed tube at 130—140°C for 8 hr, two new dibromo-dideoxyinositols (IV and V) were obtained, along with two known bromo-deoxyinositols (II and III).[3-5] One of the two reported bromo-deoxyinositols was DL-1,2,3,4,6-penta-*O*-acetyl-5-bromo-5-deoxy-*allo*-inositol (II) which had been described by McCasland and his co-workers in this bromination.[3] Another bromo-deoxyinositol was found to be identical with DL-1-bromo-1-deoxy-*neo*-inositol (III), which had been prepared by McCasland *et al.*[4] and Nakajima and Kurihara[5] in other preparations.

From the bromination mixture of I, II was first isolated in a yield of 25.5%, as was described by McCasland *et al.*[3] Then the tetra-*O*-acetyl-dibromo-dideoxy-inositol of mp 180—182°C (IV) was obtained in a yield of 4.2% from the mother liquor of II after a long storage in a refrigerator,

1) T. Suami, S. Ogawa, Y. Nakashima and H. Sano, This Bulletin, **40**, 2958 (1967).

2) T. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).

3) G. E. McCasland and J. Reeves, *J. Am. Chem. Soc.*, **77**, 1812 (1955); G. E. McCasland, S. Furuta and V. Bartuska, *J. Org. Chem.*, **28**, 2096 (1963).

4) G. E. McCasland, S. Furuta, J. F. Johnson and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 2335 (1961).

5) M. Nakajima and N. Kurihara, *Chem. Ber.*, **94**, 515 (1961).

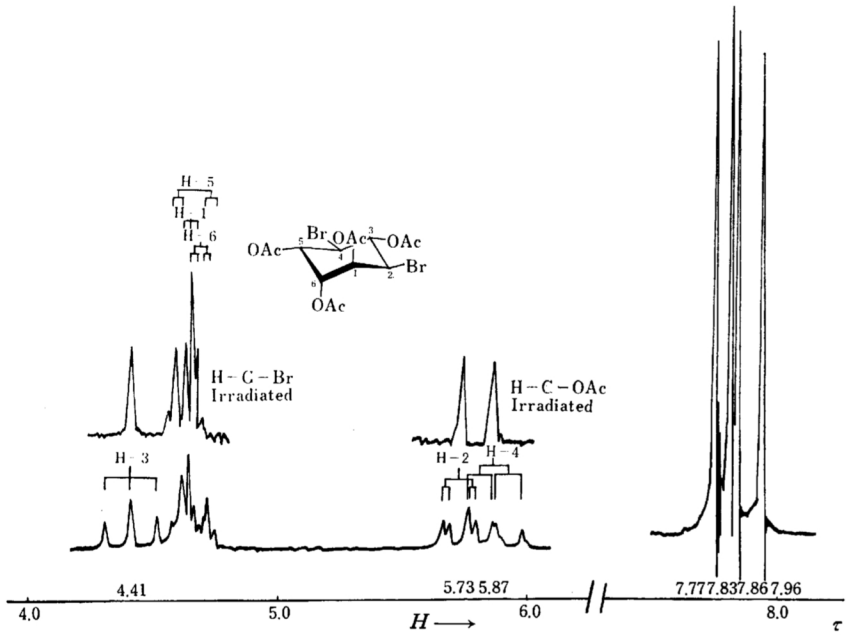
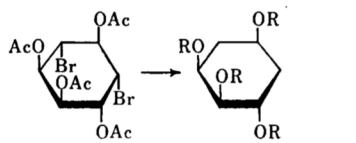


Fig. 1

and its structure was assigned to be DL-1,3,5,6-tetra-*O*-acetyl-2,4-dibromo-2,4-diedoxy-*chiro*-inositol by pmr spectroscopic studies, as will be described below.

Another dibromo-dideoxyinositol of mp 220—222°C (dec.) (V) was recovered in a 9.6% yield from the mother solution of IV after it had been hydrolyzed, and V was assigned to be DL-1,4-dibromo-1,4-dideoxy-*chiro*-inositol by pmr spectroscopic and chemical evidences.

Finally, III was obtained in a yield of 5.2% by adding ethanol to the mother liquor of V.



IV VII

R=CO·C$_6$H$_4$·NO$_2$

Scheme 2

In order to establish the configuration of IV, a catalytic debromination was carried out to give an oily product of tetra-*O*-acetyl-dideoxyinositol which failed to crystallize. Hydrolysis of this oily product afforded cyclohexanetetrol as a syrup, which was converted to a crystalline tetra-*O*-*p*-nitrobenzoyl-cyclohexane-tetrol (VII).

The proton magnetic resonance spectrum of IV was determined in deuteriochloroform at 100 Mc and was shown in Fig. 1 which enabled us to establish its conformation for the following reasons: 1) The four protons (H–C–OAc) showed a signal pattern at τ 4.31—4.75. In the lowest field, there was a triplet centered at τ 4.41 with a coupling constant of 10.5 Hz which revealed an axial-axial-axial arrangement of three neighboring protons. 2) The two protons (H–C–Br) exhibited the signal at τ 5.66—6.00. When these protons were irradiated, the above mentioned triplet collapsed to a singlet (Fig. 1). This fact proved that there were two bromo groups adjacent to the proton which had shown the triplet. 3) When the four protons (H–C–OAc) were irradiated simultaneously, the complex signals of the two protons (H–C–Br) collapsed to a doublet with an equal intensity (Fig. 1). This phenomenon showed that these two protons (H–C–Br) were geometrically not equivalent in their environments. Therefore, if an acetoxy group on C-1 was in an axial position, an acetoxy group on C-5 had to be in an equatorial position. 4) This arrangement of the protons was also confirmed by a coupling constant observed in the spectrum. That is, $J_{1-2}=3$ Hz, $J_{2-3}=10.5$ Hz, $J_{3-4}=10.5$ Hz and $J_{4-5}=12$ Hz, and the observed spectrum at τ 4.59—4.75 was the superposition of the three sets of a quartette. Now, the three of the four acetoxy groups occupied their proper positions, that is, there were two equatorial acetoxy groups and one axial acetoxy group. 5) The methyl protons of the four acetoxy groups showed four sharp signals at τ 7.77 (3H), 7.83 (3H), 7.86 (3H) and 7.96 (3H). The first two signals were attributed to two axial acetoxy groups and the fourth signal was ascribed to an equatorial acetoxy group.[6] Considering the fact that there was

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

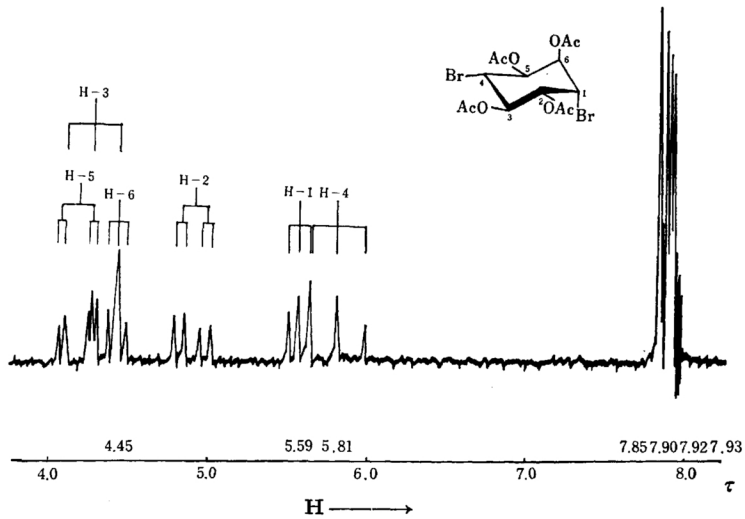
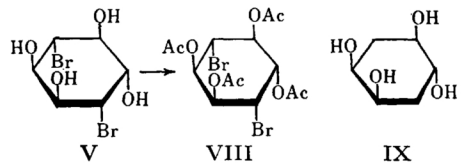


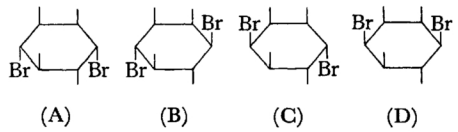
Fig. 2

one equatorial acetoxy group between two bromo groups, a signal of this type of an acetoxy group was shifted to a considerably lower field by a deshielding effect of the neighboring bromo groups. An analogous phenomenon had been observed in the pmr spectrum of DL-3-*N*-acetyl-1,5,6-tri-*O*-acetyl-2,4-dibromo-2,4-dideoxy-*chiro*-inosamine-3,[1] where a signal of an equatorial acetamido group on C-3 was shifted to a lower field by an influence of vicinal bromo groups. Therefore, the third signal (τ 7.86) was ascribed to an equatorial acetoxy group located between two bromo groups. Now, the whole conformation of IV was established to be DL-1,3,5,6-tetra-*O*-acetyl-2,4-dibromo-2,4-dideoxy-*chiro*-inositol.

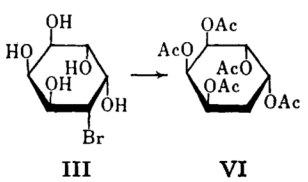


Scheme 3

The configuration of another dibromide (V) of mp 220—222°C (dec.), was studied by a catalytic hydrogenolysis and determination of pmr spectrum. A catalytic hydrogenolysis of V with Raney nickel in the presence of Amberlite IR-4B afforded cyclohexanetetrol of mp 206—208°C (IX). As judged by the melting points of its acyl derivatives, this cyclohexanetetrol was *para*-cyclohexanetetrol of (124/5).[7] Therefore, the possible configuration of V was limited to the following four structures.

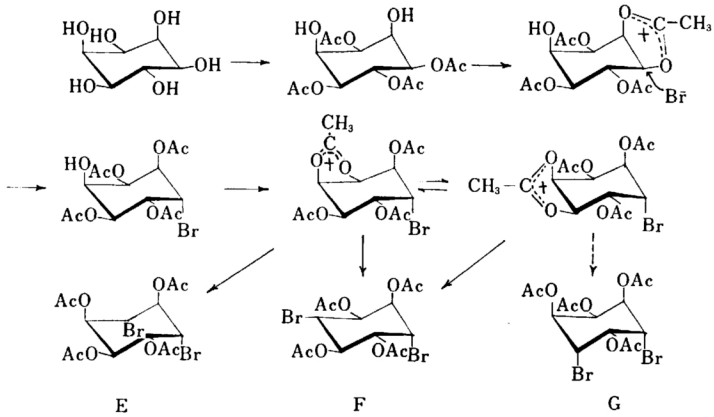


The pmr spectrum of tetra-*O*-acetyl derivative of V (VIII) in deuteriochloroform (Fig. 2) revealed four sharp signals at τ 7.85, 7.90, 7.92 and 7.93 which were attributed to the four acetoxy groups. The signals of the two protons (H–C–Br) produced a quintet (τ 5.50—6.00) which consisted of two triplets. The coupling constant of the triplet centered at τ 5.81 was 10 Hz, suggesting the existence of an axial-axial-axial arrangement of three neighboring protons. Another triplet centered at τ 5.59 had a coupling constant of 3.5 Hz, which revealed equatorial-equatorial-equatorial, an axial-equatorial-axial, an axial-equatorial-equatorial, an equatorial-axial-equatorial or an equatorial-equatorial-axial arrangement of three neighboring protons. These facts were compatible only with the structure of A and all other structures could not produce the above mentioned triplets. Also the complex pattern of the signals produced by the remaining four protons (H–C–OAc) helped to confirm the configuration. Hence VIII was reasonably assigned to be DL-2,3,5,6-tetra-*O*-acetyl-1,4-dibromo-1,4-dideoxy-*chiro*-inositol.



Scheme 4

7) G. E. McCasland, Stanly Furuta, L. F. Johnson and S. N. Shoolery, *J. Org. Chem.*, **28**, 894 (1963); This system for the naming of stereoisomers was proposed by G. E. McCasland: G. E. McCasland, "Advances in Carbohydrate Chemistry," Vol. 20, Academic Press Inc., London (1965), p. 13.



Scheme 5

The configuration of monobromide, III, was assigned to be DL-1-bromo-1-deoxy-*neo*-inositol by the following evidence. The pmr spectrum of III (mp 222—223°C) determined in deuterium oxide at 60 and 100 Mc were identical with the optically active L-1-bromo-1-deoxy-*neo*-inositol prepared by McCasland *et al.*[8] The melting point of this bromide was different from that of bromoquercitol prepared by McCasland *et al.*[8] from 1,2-anhydro-*allo*-inositol. But this could be accounted for by the fact that the present compound was racemic and McCasland's compound was levo-rotatory.

The catalytic hydrogenolysis of III yielded the previously known DL-*talo*-quercitol derivative (VI)[8] and this fact supported the above mentioned configuration of III.

The mechanism of the bromination reaction giving the dibromo-dideoxyinositols (IV and V) is proposed as follows. The monobromination of DL-*epi*-inositol occurs *via* a formation of an intermediary acetoxonium ion[9] which is then opened by a bromide ion in a manner of trans diaxial opening to give II. The second step of the bromination is likely to be a formation of another acetoxonium ion which gives E, F and G by an attack of a bromide ion. E and F are IV and V respectively, which were actually obtained in the present experiment, but G was not obtainable in this work.

Experimental

The melting points reported were determined in a liquid bath and uncorrected. The pmr spectra of the samples were recorded on Varian Associates A-60D and HA-100 spectrometers at the frequency of 60 and 100 Mc in deuteriochloroform, deuteriodimethylsulfoxide or deuterium oxide with tetramethylsilane or sodium trimethylsilylpropanesulfonate as an internal standard. The peak positions are given in τ-values.

DL-1,2,3,4,6-Penta-*O*-acetyl-5-bromo-5-deoxy-*allo*-inositol (II). Ten sealed tubes, containing a mixture of DL-*epi*-inostitol (I) (3.0 g), acetyl bromide (5.0 m*l*) and acetic anhydride (5.0 m*l*), were heated at 135—140°C for 6 hr. Then the mixture was evaporated under reduced pressure. The residue was acetylated with acetyl bromide. The reaction mixture was evaporated under reduced pressure. The oily residue was dissolved in 100 m*l* of ethanol, decolorized with active charcoal and left to settle. The crystals were collected by filtration to give 21.6 g of a crude product of mp 145—149°C. Recrystallization from ethanol afforded 17.9 g of II (25.5% yield), mp 152—153°C. (lit.[3] mp 153°C). (Found: C, 42.37; H, 4.67; Br, 17.63%).

DL-1,3,5,6-Tetra-*O*-acetyl-2,4-dibromo-2,4-dideoxy-*chiro*-inositol (IV). The mother liquor of II was left to settle in a refrigerator for a long period (two months) to give 3.4 g of a crystalline product of mp 176—180°C. The product was recrystallized from ethanol to give 3.0 g (4.2% yield) of an analytically pure sample of IV, mp 180—182°C.

Found: C, 35.79; H, 4.00; Br, 34.06%. Calcd for $C_{14}H_{18}Br_2O_8$: C, 35.44; H, 3.78; Br, 33.75%.

DL-Tetra-*O*-*p*-nitrobenzoyl-cyclohexane-1,2,3,5-tetrol (125/3) (VII). A 560 mg portion of IV was hydrogenated in 50% aqueous ethanol (20 m*l*) with Raney nickel and Amberlite IR-4B under 3.4 kg/cm^2 of hydrogen pressure for 20 hr. After the catalyst and the ion exchange resin were removed by filtration, the filtrate was evaporated giving an oily residue. The residue was heated in a mixture of 2N hydrochloric acid (15 m*l*) and ethanol (15 m*l*) for 20 hr under reflux. The hydrolyzate was evaporated *in vacuo* and an oily residue was acylated with *p*-nitrobenzoyl chloride (30 mg) in pyridine (15 m*l*). After an excess acylating reagent was removed by evaporation, the residue was crystallized from a mixture of acetone and ether to give 33 mg (3.8% yield) of needles melting at 221—223°C.

Found: C, 54.43; H, 3.61; N, 7.09%. Calcd for $C_{32}H_{24}N_4O_{16}$: C, 54.85; H, 3.25; N, 7.52%.

8) G. E. McCasland, S. Furuta, L. F. Johnson and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 2335 (1961); G. E. McCasland, S. Furuta and V. Bartuska, *J. Org. Chem.*, **28**, 2096 (1963); The pmr spectrum of III was determined and compared with that of authentic sample of L-1-bromo-1-deoxy-*neo*-inositol by Professor G. E. McCasland.

9) R. Boshan and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4921 (1956).

DL-1,4-Dibromo-1,4-dideoxy-*chiro*-inositol (V). The mother liquor of IV was mixed with 25 m*l* of 2N hydrochloric acid. The mixture was heated under reflux for 20 hr and then evaporated under reduced pressure. The residue was dissolved in 15 m*l* of water and decolorized with active charcoal. The solution was again evaporated to 5 m*l* and left to settle in a refrigerator. Then a crude products (5.1 g) of mp 202—212°C (dec.) was collected by filtration and recrystallized from 10 ml of boiling water to give 4.9 g (9.6% yield) of V, mp 220—222°C (dec.).

Found: C, 24.01; H, 3.33; Br, 58.53%. Calcd for $C_6H_{10}O_4Br_2$: C, 23.53; H, 3.27; Br, 59.29%.

DL-2,3,5,6-Tetra-*O*-acetyl-1,4-dibromo-1,4-dideoxy-*chiro*-inositol (VIII). A 535 mg portion of V was acetylated overnight with acetic anhydride (5 m*l*) in pyridine (5 m*l*) at room temperature. After an excess reagent was removed under reduced pressure, the oily product was dissolved in chloroform. The chloroform solution was washed with cold water, dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from ethanol to give 325 mg of the product. The product was recrystallized from the same solvent giving 303 mg (36.8% yield) of fine crystals, mp 120—123°C.

Found: C, 35.69; H, 3.99; Br, 33.83%. Calcd for $C_{14}H_{18}Br_2O_8$: C, 35.44; H, 4.09; Br, 33.75%.

DL-Cyclohexane-1,2,4,5-tetrol (124/5) (IX). A 2.23 g portion of V was hydrogenated in 50% aqueous ethanol (30 m*l*) with Raney nickel and Amberlite IR-4B under 3.4 kg/cm² of hydrogen pressure for 20 hr. After the catalyst and the ion exchange resin were removed by filtration, the filtrate was evaporated under reduced pressure. The oily residue was crystallized from ethanol to give a crude product (203.5 mg) of mp 202—205°C. The product was recrystallized from ethanol to give 154.1 mg (14.24% yield) of an analytically pure sample, mp 206—208°C (lit.[7] mp 208—209°C). (Found: C, 48.64; H, 8.16%.).

The product was acylated with acetic anhydride in pyridine giving the tetra-*O*-acetyl derivative of mp 89—91°C (lit.[7] mp 91—93°C), and with benzoyl chloride in pyridine to yield the tetra-*O*-benzoyl derivative of mp 169—171°C (lit.[7] mp 172—173°C).

DL-1-Bromo-1-deoxy-*neo*-inositol (III). Ethanol was added to the mother liquor of V until the solution was turbid. Then the solution was left to settle in a refrigerator to give 4.2 g of a crystalline product. The crude product was collected by filtration and recrystallized from 90% ethanol to give 3.1 g (5.2% yield) of III, mp 210—213°C dec. (lit.[5] 214°C dec.). (Found: C, 29.43; H, 4.44; Br, 33.01 %).

DL-Penta-*O*-acetyl-*talo*-quercitol (VI). A 1.0 g portion of III was dissolved in 15 m*l* of water and hydrogenated in 3.4 kg/cm² of hydrogen pressure in the presence of Raney nickel catalyst (2 spatulas) and Amberlite IR-4B for 20 hr. Then the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was acetylated by the usual procedure, and the product was recrystallized from ethanol to give 109 mg (7.1% yield) of fine crystals, mp 170—171°C (lit.[5] mp 170°C). (Found: C, 51.08; H, 6.01%).

VI was hydrolyzed in 2N hydrochloric acid and the hydrolyzate was evaporated *in vacuo*. The residue was recrystallized from aqueous ethanol to give DL-*talo*-quercitol, mp 222—225°C (dec.) (lit.[5] mp 225°C dec.). (Found: C, 44.08; H, 7.44%).

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