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Epimerization of Aldoses Catalyzed by Dioxobis(2,4-pentanedionato-O,O')-molybdenum (VI). An Improved Procedure for C-2 Epimer Preparation

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Epimerization of aldo-hexoses and -pentoses to the corresponding C-2 epimers Proceeds more rapidly when catalyzed by dioxobis(2,4-pentanedionato-O,O')molybdenum (VI) in N,N-dimethylformamide than in the reported reaction with aqueous molybdic acid. Thus, on treatment at 50° for 5 hr, D-glucose or D-mannose gave an equilibrium mixture of D-glucose and D-mannose in a ratio of 55: 45.

Keywords——epimerization; epimer; D-glucose; D-mannose; L-arabinose; L-ribose; dioxobis-(2,4-pentanedionato-O,O')molybedenum (VI)

There have been extensive studies on the epimerization reactions of monosaccharides catalyzed by molybdic acid in aqueous media,[2] since such reactions have much synthetic potential for aldoses not easily accessible from readily available sugars. In the course of synthetic studies on oligosaccharides, we have observed that aldo-pentoses and -hexoses smoothly undergo rapid epimerization to provide an equiliblium mixture of C-2 epimeric aldoses when catalyzed by molybdenum (VI) reagents such as the 2,4-pentanedionato (=acetylacetonate: acac) complex under non-aqueous mild conditions. Thus, treatment of D-glucose in N,N-dimethylformamide (DMF) at 50° for 5 hr led to an equiliblium mixture with a ratio of glucose to mannose of 55: 45 without any detectable side reaction products (including fructose), and the mannose was isolated in 65% yield (based on unrecovered glucose) as the phenylhydrazone. This equiliblium ratio was also obtained on similar treatment of mannose and depended somewhat on the conditions employed (temperature and solvent) (Table I).

Table I. Epimerization of Aldoses by $MoO_2(acac)_2$ in DMF[a]

	Temp. (°C)	Time (hr)	C-2 epimer	Ratio[b] (%)
D-Glucose	50	5	D-Mannose	45
	50	5		(7)[c]
	95	1		34
	95	1		(25)[c]
D-Mannose	50	5	D-Glucose	55
	95	1		63
D-Galactose	50	5	D-Talose	32[d]
L-Rhamnose	50	5	L-Quinovose	55[d]
L-Arabinose	50	25	L-Ribose	36[d]

a) Performed at a 17: 1 molar ratio of aldose to $MoO_2(acac)_2$.
b) Determined by lc.
c) With H_2MoO_4 (0.1 eq. mol) in water.
d) Determined by glc as the O-perfluoroacetyl sugar alcohol.

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2) V. Bilik, *Chem. zvesti*, **29**, 114 (1975) and references cited therein [*C.A.*, **83**, 10621*f*].

On the other hand, epimerization of glucose with molybdic acid in water at 50° for 5 hr afforded an epimeric mixture containing only 6—8% mannose; higher temperature (at 95°) and/or prolonged reaction time, at which undesirable side reaction might be unavoidable, were required to attain equiliblium (glucose-to-mannose ratio of 75: 25), as reported previously.[3]

Among the molybdenum reagents examined so far, the MoO_2 $(acac)_2$–DMF system was the most efficient for the epimerization of glucose to mannose, though compounds such as molybdenum trioxide, molybdenum pentachloride-methanol and phosphomolybdic acid were also effective in aprotic solvents. Practically no epimerization occurred in the presence of vanadium pentoxide, tungsten trioxide or titanum tetra-O-isopropoxide.

When D-galactose and L-rhamnose were subjected to epimerization with $MoO_2(acac)_2$ in DMF at 50° (5 hr), the corresponding C-2 epimers, D-talose[4] and L-quinovose[5] were formed in 32% and 55% yields, respectively, based on glc analysis performed with the alditol trifluoroacetate.

L-Arabinose under similar conditions gave a C-2 epimeric mixture containing L-ribose (36%), which was isolated in 46% yield (based on unrecovered arabinose) as the anilide. The conditions employed were mild enough to give no significant amounts of side reaction products, in contrast to the reported method[6] which could lead to the formation of substantial amounts of isomeric aldopentoses.

This epimerization may proceed through a mechanism similar to that of the reported reaction catalyzed by aqueous molybdic acid, which involves the formation of complexes (I, II) with *quasi*-equatorial hydroxyl groups at C-1 and C-2, followed by intramolecular exchange of hydrogens at C-1 and C-2.[7] Similar interactions between molybdenum (VI) agents and aldoses may be anticipated under the present aprotic conditions.

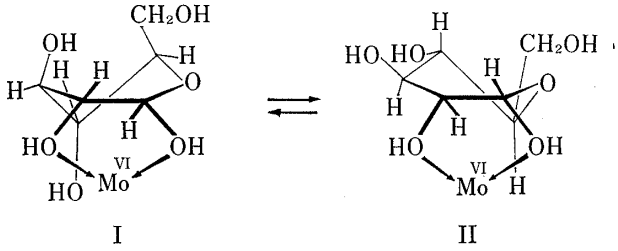

Fig. 1

Since the reaction takes place smoothly under mild and aprotic conditions, the present procedure should have wide applicability for preparative use, and may be applicable to oligosaccharades which are generally labile in the presence of acids.

Experimental

General Procedure for Epimerization——A solution of aldose (5 mmol) and dioxobis(2,4-pentanedionato-O,O′)molybdenum (VI) ($MoO_2(acac)_2$) (0.3 mmol) in DMF (10 ml) was stirred at 50° for 5 hr. Water (20 ml) was then added under cooling and the mixture was extracted with CH_2Cl_2 (20 ml) twice. The aqueous layer was deionized with ion exchange resin (Dowex 1×4, HCO_3^- from) and then lyophilized to leave an epimeric mixture as a syrup. The epimer ratio was determined by liquid chromatorgaphy[8] and/or glc as the perfluoroacetates after borohydride reduction to the sugar alcohols.[9]

3) V. Bilik, *Chem. zvesti*, **26**, 183 (1972)[*C.A.*, **77**, 62258*p*]; *ibid.*, **26**, 187 (1972) [*C.A.*, **77**, 62259*q*].
4) V. Bilik, W. Voelter and E. Bayer, *Ann.*, **1974**, 1162.
5) V. Bilik, W. Voelter and E. Bayer, *Ann.*, **759**, 189 (1972).
6) V. Bilik and J. Caplovic, *Chem. zvesti*, **26**, 372 (1972) [*C.A.*, **77**, 126942*s*]; *ibid.*, **27**, 547 (1973) [*C.A.*, **80**, 83428*w*].
7) V. Bilik, L. Petrus and V. Farkus, *Chem. zvesti*, **29**, 690 (1975) [*C.A.*, **84**, 150857*h*].
8) Sugar analyses were performed with a JEOL liquid chromatographic autoanalyzer (JLC-6AH) using a column of JEOL resin (LC-R3) transformed into the borate form. Sugar components were eluted successively with borate buffers adjusted at pH 7.5, 9.0 and 9.6, and detected by the orcinol-sulfuric acid method. *cf.*) H, Takahata, T. Kunieda and T, Takizawa, *Chem. Pharm. Bull.*, **23**, 3017 (1975).
9) Quantitative glc analyses were performed by the internal standard method on a Yanaco G-80 instrument utilizing a 1% XF-1105 column (2 m) at 140° with helium as a carrier gas. *cf*) T. Imanari, Y. Arakawa and Z. Tamura, *Chem. Pharm. Bull.*, **17**, 1967 (1968).

Preparation of D-Mannose from D-Glucose——D-Glucose (1.8 g) was treated with $MoO_2(acac)_2$ (0.2 g) in DMF (20 ml) at 50° for 5 hr. Water (40 ml) and CH_2Cl_2 (40 ml) were added to the mixture and the aqueous layer was deionized with Dowex 1×4 (HCO_3^-) and Amberlite IR-120 (H^+). Lyophilization gave a syrup (2.1 g) consisting of a mixture of glucose and mannose in a ratio of 55:45 as determined by lc analysis[8] usig an internal standard. The residue was dissolved in ethanol (10 ml) and kept at room temperature for 3 days. Crystalline D-glucose (0.9 g) that deposited was filtered off and the filtrate was evaporated to a syrup *in vacuo*. This syrup was dissolved in water (2 ml), followed by the addition of phenylhydrazine (0.48 g) in acetic acid (2 ml). This mixture was allowed to stand at room temperature overnight to give colorless crystals (0.88 g) of D-mannose phenylhydrazone. Recrystallization from aqueous ethanol gave colorless prisms, mp 183—185°, $[\alpha]_D^{20}$ +26.5° (c=0.3, pyridine) (lit.[10], mp 199—200°, $[\alpha]_D^{20}$ +26° (pyridine)). *Anal.* Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.67; N, 10.37. Found: C, 53.19; H, 6.79; N, 10.24. The IR spectrum (KBr) was identical with that of an authentic specimen.[10]

Similar treatment of D-glucose (0.9 g) with molybdic acid (0.1 g) in water (10 ml) gave, after similar work-up, a mixture of glucose and mannose in a ratio of 93:7, as determined by glc analysis.[9]

Preparation of L-Ribose from L-Arabinose——A solution of L-arabinose (1.8 g) and $MoO_2(acac)_2$ (0.2 g) in DMF (20 ml) was stirred at 50° for 25 hr and subsequent treatment as above gave a syrup (1.7 g) consisting of an epimeric mixture of arabinose and ribose in a ratio of 64:36 in addition to negligible amounts (less than 1%) of xylose and lyxose, based on glc analysis.[9] The syrup thus obtained was dissolved in methanol (4 ml) and kept in a refrigerator for 2 days. The resulting crystalline L-arabinose (0.95 g) was filtered off and the filtrate was concentrated *in vacuo*. The resulting syrup was treated wuth aniline (0.45 g) in ethanol and kept in a refrigerator for 2 days to give L-ribose anilide (0.58 g) as colorless crystals. Recrystallization from ethanol gave colorless needles, mp 105—108°, $[\alpha]_D^{20}$ −58.4° (c=1.0, pyridine). *Anal.* Calcd for $C_{11}H_{15}NO_4\cdot1/2H_2O$: C, 56.41; H, 6.84; N, 5.98. Found: C, 56.18; H, 6.91; N, 5.89. The IR spectrum (KBr) was identical with that of D-ribose anilide (mp 108—110°, $[\alpha]_D^{20}$ +61.7° (c=1.0, pyridine))[11] prepared separately.

10) H.S. Isbell and H.L. Frush, "Methods in Carbohydrate Chemistry," Vol-I, Academic Press, N.Y., 1962, p. 145.
11) G.P. Ellis and J. Honeyman, *J. Chem. Soc.*, **1952**, 1490.