chloroform yielded 2.54 g of an orange oil which was eluted through a short column of 25 g of alumina with 2 l. of benzene to yield 2.2 g of *p*-nitrobenzoate.

Two recrystallizations of material obtained in this manner (3.75 g) from acetone–petroleum ether yielded 1.93 g of pure 19-(*p*-nitrobenzoyloxy)androsta-3,5-dien-17-one (**5c**): mp 177–181°; $[\alpha]^{25}D$ −92°; $\tilde{\nu}_{max}$ 3020, 1720, 1648, 1604, 1524 cm^{-1}; λ_{max} 234 mμ (ε 23,500).

Anal. Calcd for $C_{26}H_{29}O_5N$: C, 71.71; H, 6.71; N, 3.22. Found: C, 71.76; H, 6.76; N, 3.16.

An additional 295 mg of **5c**, mp 180–183°, was obtained from the mother liquors by chromatography on alumina and crystallization.

A solution of 2.08 g of the *p*-nitrobenzoate **5c** in 140 ml of 5% methanolic potassium hydroxide solution was heated under reflux for 1 hr. Ether extraction followed by recrystallization from acetone–water solution yielded 1.05 g of 19-hydroxyandrosta-3,5-dien-17-one (**5a**): mp 120–125°; $[\alpha]^{25}D$ −92°; $\tilde{\nu}_{max}$ 3618, 3570, 3448, 3016, 1728, 1644 cm^{-1}; λ_{max} 234 mμ (ε 18,800); 100-MHz nmr, 5.5-6.1 (vinyl H's), 3.647, 3.680 ($C_{19}H_2$, d), 0.95 ($C_{18}H_3$, s).

A second crop of 120 mg of **5a**, mp 120–125°, was obtained from the mother liquors.

Preparation and Hydrolysis of 19-Methanesulfonoxyandrosta-3,5-dien-17-one (5b).—A solution of 1.06 g of 19-hydroxyandrosta-3,5-dien-17-one (**5a**) in 30 ml of pyridine was cooled in an ice bath and 1.3 ml of methanesulfonyl chloride was added with stirring. Stirring was continued with the reaction vessel in an ice bath for 30 min and the resulting solution was then allowed to stand at room temperature for 3 hr. The product was isolated by chloroform extraction including a washing with 5% sodium bicarbonate solution. The chloroform solution was dried ($MgSO_4$) and the solvent was evaporated leaving 1.40 g of a yellow glass. The ir and nmr spectra of the product were compatible with the structural assignment as 19-methanesulfonoxyandrosta-3,5-dien-17-one (**5b**) [$\tilde{\nu}_{max}$ 3020, 1729, 1648, 1350, 1168 cm^{-1}; 60-MHz nmr, 5.50–6.25 (vinyl H's), 4.050, 4.225, 4.272, 4.447 ($C_{19}H_2$, q), 2.97 ($-OSO_2CH_3$, s), 0.97 ($C_{18}H_3$, s)], and the crude product was used without further purification.

A solution of 1.34 g of **5b**, 1.21 g of potassium acetate, 35 ml of water, and 118 ml of acetone was heated under reflux for 26 hr. The resulting solution was diluted with 120 ml of water, and the major portion of the acetone was evaporated under reduced pressure. The aqueous suspension was extracted with ether, and the ether solution was washed with water, 5% sodium bicarbonate solution, and then to neutrality with water, and dried ($MgSO_4$). Evaporation of the ether left 1.04 g of a yellow oil. The 60-MHz nmr spectrum showed the absence of any methanesulfonate (no singlet at 2.97).

The product was heated under reflux for 1 hr in 100 ml of 2.5% methanolic potassium hydroxide solution. The product was isolated by ether extraction to yield 893 mg of an orange oil.

This product (353 mg) was chromatographed on a Sephadex (LH-20) column (90 × 2.5 cm) in an ascending system with chloroform as the eluent to yield 189 mg (45% based on **5a**) of 6β-hydroxy-5β,19-cycloandrost-3-en-17-one (**39**), mp 117–124°. Recrystallization from acetone–petroleum ether gave the analytical sample: mp 127–128°; $[\alpha]D$ +27°; $\tilde{\nu}_{max}$ 3601, 3448, 3062, 3022, 1730, 1638 cm^{-1}; λ_{max} 205 mμ (ε 5600); 100-MHz nmr, 5.892, 5.924, 5.990, 6.012 (C_4H, q), 5.41 (C_3H, m), 4.277, 4.290, 4.325, 4.336 (C_6H, q), 0.89 ($C_{18}H_3$, s), 0.769, 0.816, 0.982, 1.030 ($C_{19}H_2$, q).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.86; H, 9.18.

Acid-Catalyzed Rearrangement of 6β-Hydroxy-5β,19-cycloandrostane-3,17-dione (15).—A solution prepared from 507 mg of **15**, 6 ml of 1.4 *N* sulfuric acid and 32 ml of acetone was heated under reflux for 2 hr. The product was isolated by ether extraction to yield 480 mg of a white crystalline solid, mp 122–165°, which was chromatographed on 45 g of alumina. Elution with 1:5 chloroform–benzene gave 109 mg of 5β,6β-methanoandrost-8(9 or 14)-ene-3,17-dione (**30** or **31**), mp 141–149°. Recrystallization from acetone–water gave 77 mg: mp 150–152°; $[\alpha]^{26}D$ −90°; $\tilde{\nu}_{max}$ 3061, 1725, 1704 cm^{-1}; λ_{max} 210 mμ (ε 7400); 100-MHz nmr, 2.48 (C_8H_2, s, $W_{1/2}$ = 2 Hz), 1.555, 1.826, 2.745, 2.914 (C_4H_2, q), 0.91 ($C_{18}H_3$, s), 0.40–0.80 (cyclopropyl protons, m); molecular ion peak at *m/e* 284.

Elution of the column with chloroform gave 298 mg of **15**, mp 170–192°. Recrystallization from acetone–petroleum ether gave 218 mg, mp 194–200°. Both ir and nmr spectra were identical with those of starting materials.

Registry No.—**4b**, 5295-60-3; **5a**, 21899-70-7; **5b**, 21899-71-8; **5c**, 21889-72-9; **7**, 6037-79-2; **9**, 4677-42-3; **12**, 2352-95-6; **15**, 21899-76-3; **16**, 21899-77-4; **18**, 21899-78-5; **39**, 21899-79-6.

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2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 4-N-Oxide. A Condensation Product of 2-Amino-2-deoxy-D-glucose Oxime and Glyoxal

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Received February 19, 1969

Condensation of 2-amino-2-deoxy-D-glucose oxime (**2**) or 2-amino-2-deoxy-D-mannose oxime (**6**) with glyoxal in water at room temperature gave 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-N-oxide (**3**). The carbohydrate side chain of this compound was identical with that of 2,5-bis(D-*arabino*-tetrahydroxybutyl)pyrazine (fructosazine) (**9**) and 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (**10**) according to nmr data.

In previous studies on heterocyclic compounds derived from carbohydrates, we have reported the formation of the "two-armed" pyrazines, 2,5-bis(D-*arabino*-tetrahydroxybutyl)pyrazine (fructosazine)[2a] (**9**) and 2,5-bis(D-*lyxo*-tetrahydroxybutyl)pyrazine (tagatosazine).[2b] As an extension of these studies, we report here the formation of one of the "one-armed" pyrazines. These pyrazines may have valuable medical applications, such as in chemotherapy of virus diseases, which we will report at a later date.

2-Amino-2-deoxy-D-glucose (**1**) reacts with hydroxylamine in methanol to form 2-amino-2-deoxy-D-glucose

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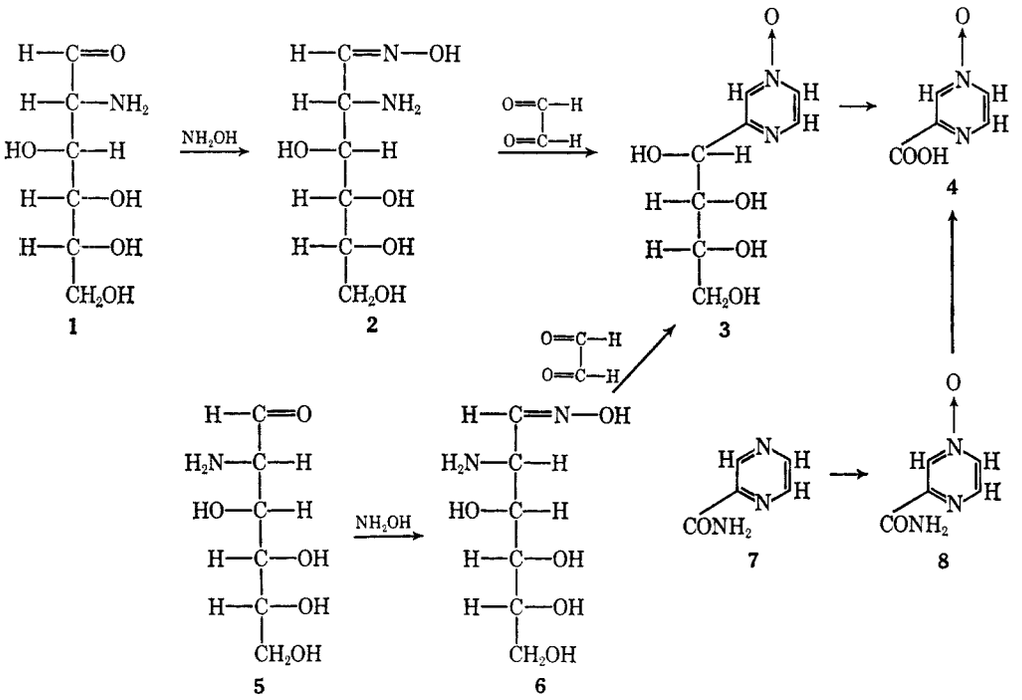
(2) (a) S. Fujii, R. Kikuchi, and H. Kushida, *J. Org. Chem.*, **31**, 2239 (1966); (b) S. Fujii and H. Kushida, *ibid.*, **31**, 2406 (1966).

SCHEME I



oxime[3-5] (2) in good yield. In water, the oxime reacts with glyoxal, yielding a crystalline product (3).

The product 3 with molecular formula $C_8H_{12}N_2O_5$ is oxidized to another crystalline product, $C_5H_4N_2O_3$, with potassium permanganate and potassium hydroxide in water; the latter substance was identical with pyrazine-2-carboxylic acid[6] 4-N-oxide (4), derived from pyrazinamide 7, according to infrared spectra, ultraviolet spectra, and paper chromatography. Thus the condensation product 3 has a pyrazine 4-N-oxide ring, and the carbohydrate side chain is situated at position 2 of the pyrazine ring. See Scheme I.

2-Amino-2-deoxy-D-mannose[7] (5) reacts with hydroxylamine to form 2-amino-2-deoxy-D-mannose oxime (6). This is an isomer of 2-amino-2-deoxy-D-glucose oxime (2), and its physical constants and infrared spectrum are quite different from those of 2-amino-2-deoxy-D-glucose oxime. However, when it reacts with glyoxal, the product is identical with the one derived from 2-amino-2-deoxy-D-glucose oxime, according to mixture melting point determination and ir spectra. The identity was also established by conversion of both products, according to the procedure of Taha,[8] into the same acetylated derivative, 2-tetraacetoxybutylpyrazine 4-N-oxide (3a).

The fact that the same glyoxal-condensation product (3) was obtained from 2-amino-2-deoxy-D-glucose oxime and from 2-amino-2-deoxy-D-mannose oxime suggest that the carbohydrate chain of 3 has the D-*arabino* configuration.

The nmr spectrum of the acetylated derivative of 3 agrees with its formulation as **3a**, containing an acyclic side chain in the "D-*arabino*" configuration, but not with the alternative bicyclic structures **3b** and **3c**. The spectrum in deuteriochloroform shows one low-field unit-intensity quartet at τ 1.60, which may be assigned to the H-5 or H-6 proton of the pyrazine system. Signals of two intensity units at τ *ca.* 1.90–2.05 may be assigned to H-3 and H-6 or H-5 of the pyrazine ring. No other signals are observed below τ 3.8. The presence of three low-field aromatic protons is in good agreement with the structure **3a**, but not with **3b**, which has one aromatic proton, nor with **3c**, which has two aromatic protons. The presence of four acetoxy singlets at τ 7.75–8.03 also agrees with formulation **3a** and excludes formulation **3b** and **3c**, from which three singlets would be expected. See Table I.

TABLE I

NMR SPECTRAL DATA ON 2-(D-*arabino*-TETRAACETOXYBUTYL)PYRAZINE 4-N-OXIDE (3a)

Protons	Chemical shift, τ	Integral protons	Multiplicity	Coupling constant, Hz
H-5 or -6	1.60	1	q	
H-3 and H-5 or -6	1.90–2.05	2	m	
H-1	3.89	1	d	$J_{1'2'} = 2.5$
H-2	4.30	1	q	$J_{1'2'} = 2.5$
				$J_{2'3'} = 9.0$
H-3	4.74	1	m	
H-4	5.74	2	m	$J_{4a'4b'} = 12.5$
				$J_{3'4a'} = 2.5$
				$J_{3'4b'} = 4.5$
AcO-1	7.78	3	s	
AcO-2	7.89	3	s	
AcO-3	7.94	3	s	
AcO-4	8.05	3	s	

In the carbohydrate side chain proton region, the H-1′ proton of the D-*arabino*-tetraacetoxybutyl group of **3a** appears at τ 3.89, as doublet through coupling with the H-2′ proton, $J_{1'2'} = 2.5$ Hz. A projected angle between the C–H bonds on H-1′ and H-2′ is approxi-

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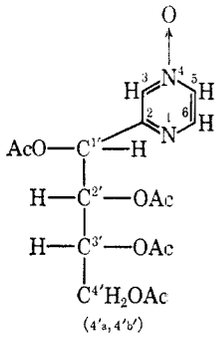
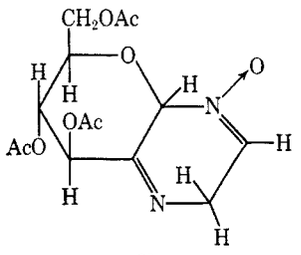
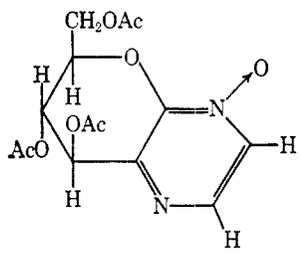


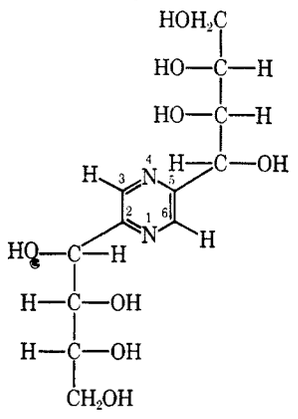
3a



3b



3c



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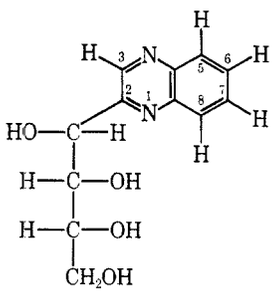

10

mately 60° as calculated by the Karplus equation. The H-2′ proton appears as a quartet at τ 4.30, $J_{2'1'} = 2.5$ and $J_{2'3'} = 9.0$ Hz. The $J_{2'3'}$ value indicates a projected angle of approximately 180° between the C–H bonds at H-2′ and H-3′. The H-3′ proton appears as a multiplet at τ 4.74 through coupling with the H-2′ proton and with the methylene group at H-4′. The two methylene protons at H-4′ give a multiplet, an AB part of an ABX system, centered at τ 5.74. These signals of **3a** are closely similar to the corresponding side-chain proton signals of the acetyl derivatives of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline[9] (**10**) and 2,5-bis(D-*arabino*-tetrahydroxybutyl)pyrazine[1] (**9**). The close similarity suggests that the conformation and hence the configurations of carbohydrate side chain in the three compounds are identical. The configurations of the side chain in the parent compounds **3**, **10**, and **9**, accordingly, should also be identical.

Experimental Section

Melting points are not corrected. Ultraviolet spectra were recorded on a Hitachi Perkin-Elmer 139 UV-VIS spectrophotometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform at 60 MHz with Varian Model A-60 spectrometer, and tetramethylsilane (τ 10.00) was used as the internal reference standard.

2-Amino-2-deoxy-D-glucose Oxime (**2**).—This compound was prepared by the method of Breuer,[5] using 2-amino-2-deoxy-D-glucose (**1**), which was derived from 2-amino-2-deoxy-D-glucose hydrochloride by the method of Inoue, *et al.*[10] Recrystallization was carried out from water and methanol: mp 127° dec (lit.[5] mp 127° dec); $[\alpha]^{25}D$ −10.9° (*c* 0.9, water); ir (Nujol) 1665 (=C=N—O—), 3300 cm^{-1} (OH).

Anal. Calcd for $C_6H_{14}N_2O_5$: C, 37.11; H, 7.27; N, 14.42. Found: C, 37.06; H, 7.33; N, 14.48.

2-Amino-2-deoxy-D-mannose Oxime (**6**).—The oxime was prepared from 2-amino-2-deoxy-D-mannose hydrochloride[7] by the same procedure as was used in the case of 2-amino-2-deoxy-D-glucose oxime (**2**). Reaction of 2-amino-2-deoxy-D-mannose hydrochloride 10.8 g (0.05 mol) and hydroxylamine hydrochloride 3.9 g (0.055 mol) yielded 9.1 g of crude material (93.8%). Recrystallisation from water and methanol gave white crystals, 7.8 g of **6**: mp 154° dec; $[\alpha]^{33}D$ 12.5 → 9.5° (after 24 hr) (*c* 1.0, water); ir (Nujol) 1670 (=C=N—O—), 3300 cm^{-1} (OH).

Anal. Calcd for $C_6H_{14}N_2O_5$: C, 37.11; H, 7.27; N, 14.42. Found: C, 36.84; H, 7.59; N, 14.43.

2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 4-N-Oxide (**3**). **A. From 2-Amino-2-deoxy-D-glucose Oxime** (**2**).—To a solution of 97 g (0.5 mol) of 2-amino-2-deoxy-D-glucose oxime in 200 ml of water was added with stirring 72 g (0.5 mol) of 40% aqueous solution of glyoxal. A few minutes later, white needles began to separate. After being kept in a refrigerator overnight, the separated crystalline substance was washed with cold water and methanol and dried. The yield was 34.9 g (32.5%), mp 217–220° dec. Condensation of the filtrate and the washing gave a further yield of 4 g. Two recrystallizations were carried out from hot water: mp 221°, mp 223° dec; $[\alpha]^{28}D$ −33.95° (after 24 hr) (*c* 1.0, water); ir (Nujol) 1600 (C=N), 3300 cm^{-1} (OH); uv max (water) 265 mμ (ϵ 12,000), 217 (11,000).

Anal. Calcd for $C_8H_{12}N_2O_5$: C, 44.44; H, 5.59; N, 12.96. Found: C, 44.51; H, 5.99; N, 13.09.

B. From 2-Amino-2-deoxy-D-mannose Oxime (**6**).—The preparation was carried out in the same way as mentioned above in A. From 7.8 g (0.04 mol) of 2-amino-2-deoxy-D-mannose oxime (**6**) and 5.8 g (0.04 mol) of 40% aqueous solution of glyoxal was obtained 2.1 g (30.1%) of **3**. Infrared spectrum and physical constants were identical in comparison with those of **3** derived from **2**, and no depression was observed in the mixture melting point.

Pyrazine-2-carboxylic Acid 4-N-Oxide (**4**). **A. Oxidation of 2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 4-N-Oxide** (**3**).—The oxidation was carried out according to the procedure of Mager and Berends.[11] Addition of potassium permanganate in small portion of a solution of 11 g (0.05 mol) of 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-N-oxide and 5.5 g of potassium hydroxide in 1100 ml of water was followed by stirring on a boiling-water bath for 1.5 hr. It needed about 63 g of potassium permanganate. After oxidation, a small excess of potassium permanganate was digested with addition of methanol. Precipitated manganese dioxide was filtered off and washed with hot water (five 100-ml washings). The combined filtrates and washings were acidified with Amberlite IR-120 (H^+) to pH 1.4. After removal of the resin by filtration, concentration of the filtrate *in vacuo* afforded 3 g of **4** (42%). Recrystallization from minimum hot water gave 2.1 g of **4**: mp 202° (lit.[6] 212–213°); ir (Nujol) 1590 (C=N), 1730 (C=O), 1300 cm^{-1} (N→O); uv max (water) 222, 266 mμ.

Anal. Calcd for $C_5H_4N_2O_3$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.91; H, 2.61; N, 20.07.

B. Preparation from Pyrazinamide (**7**).—For comparison, this carboxylic acid was also prepared *via* pyrazinamide 4-N-oxide (**8**) by oxidation of pyrazinamide (**7**) and by treatment of **8** with sodium hydroxide according to the procedure of Foks and Sawlewicz.[6] The infrared spectrum and ultraviolet spectrum of **4** prepared from pyrazinamide (**7**) were shown to be identical with those of **4** prepared by oxidation of 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-N-oxide (**3**) as described above A. In descending paper chromatography, both pyrazine-2-carboxylic

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acid 4-N-oxide samples showed the identical R_f values[12] and developed color by ferrosulfate.[13]

2-(D-*arabino*-Tetraacetoxybutyl)pyrazine 4-N-Oxide (3a).—A mixture of 5.0 g of **3** prepared from **2**, 100 ml of dry pyridine and 100 ml of acetic anhydride was warmed at about 50° to a solution with stirring. After keeping it at room temperature overnight, the solution was poured into 1000 ml of ice water. The aqueous mixture was extracted three times with 100 ml of chloroform, and the chloroform layer was washed twice with 100 ml of 2 *N* hydrochloric acid, twice with a 100 ml of saturated aqueous sodium hydrogen carbonate, and twice with a 100 ml of water. The solution was dried with anhydrous magnesium sulfate and concentrated *in vacuo*, giving 7.6 g (85.5%) of white needles by adding a little ether. Washing these with ethanol and ether and recrystallization from methanol and ethanol gave mp 142°; $[\alpha]^{28}D$ −6.82 → −2.79° (after 24 hr) (*c* 1.0 CHCl); ir (Nujor) 1050, 1270 (N→O), 1230 (C—O), 1600 (C=N), 1750 cm^{-1} (C=O); uv max (MeOH) 268 mμ; for nmr data, see Table I.

Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.52; N, 7.29. Found: C, 50.06; H, 5.72; N, 7.48.

According to the procedures described above, 2.0 g of 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-N-oxide (**3**) prepared from 2-amino-2-deoxy-D-mannose oxime (**6**) was acetylated to yield 2.2 g (61.8%) of tetraacetate. Analyses, infrared spectra, and mixture melting points showed that this acetate was identical with the acetylated compound **3a** prepared from 2-amino-2-deoxy-D-glucose oxime (**2**).

Registry No.—Glyoxal, 107-22-2; **2**, 21537-55-3; **3**, 21537-56-4; **3a**, 21537-57-5; ; **4**, 874-54-4; **6**, 21537-58-6.

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Di-*O*-bromoethylidene-D-mannitol Formation[1]

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The stereochemistry and structure of 1,2-*O*-bromoethylidene-D-mannitol and its role in the reaction pathway leading to 1,2:5,6-di-*O*-bromoethylidene-D-mannitol were studied. Nmr spectroscopy established that monoacetal formation was from the outset an equilibrium-controlled reaction, giving a 65:35 *cis/trans* ratio. Previously reported work pointed out the high proportion of *cis* rings in the diacetal formation, *ca.* 67:33 *cis,cis/cis,trans*. When the latest results are coupled with earlier data, the reaction pathway can be explained. Monoacetal formation is equilibrium controlled and the subsequent diacetal formation is kinetically controlled and irreversible because of insolubility. Examination of molecular models suggested that the *cis* preference in the second ring closure may be accounted for by a long-range directional effect transmitted through hydrogen bonding. The unreported 3,4,5,6-tetra-*O*-methyl-D-mannitol was prepared as its crystalline 1,2-di-*O*-*p*-tolylsulfonyl ester.

From the acid-catalyzed condensation of bromoacetaldehyde diethyl acetal and D-mannitol two diacetals[3] were isolated. These diacetals were shown to be *cis*-1,2:*cis*-5,6-di-*O*-bromoethylidene-D-mannitol and the related *cis*-1,2:*trans*-5,6 isomer; no *trans,trans* isomer was found. The *cis,cis* isomer constituted approximately twice the amount of the *cis,trans* isomer. In the 1,3-dioxolane ring the greater stability of the *cis* over the *trans* isomer has been demonstrated for 2,4-dimethyl-1,3-dioxolane[4,5] and 4-benzyloxymethyl-2- bromomethyl-1,3-dioxolane.[5] 1,3-Dioxolane formation proceeds through an initial kinetic phase where *cis* stereochemistry predominates, and a subsequent equilibrium phase where the *cis/trans* ratio resides around 60:40.[4,6] However, with terminal diols no significant kinetic phase was noted.[6] If the diacetal pathway were equilibrium controlled and assuming a 60:40 *cis/trans* ratio, the predicted ratios would be *cis,cis/cis,trans/trans,trans* 36:48:16, which are very much at variance with the results. This variance suggested that somewhere along the mannitol → monoacetal → diacetal pathway a kinetically controlled step was operating, yielding preferentially a *cis*-1,3-dioxolane. Since both ring closures would involve terminal hydroxyl groups, no kinetic preference was expected. Accordingly, the preparation of the monoacetal was carried out and its function in the pathway was investigated to clarify this question of a kinetic preference of terminal hydroxyl groups.

Results

On dissolving D-mannitol and bromoacetaldehyde diethyl acetal (BEA) in 3–12 *N* hydrochloric (or sulfuric) acid, exploratory investigations established that a mono-*O*-bromoethylidene-D-mannitol formed rapidly. With a molar ratio of 1:1 mannitol–BEA, a moderate amount of di-*O*-bromoethylidene-D-mannitols[3] precipitated from solution. By altering the ratio to 10:1 mannitol–BEA, diacetal precipitation was avoided, but, since separating the excess mannitol proved time consuming, a compromise ratio of 2–4:1 mannitol–BEA was commonly used. After the reaction mixture was worked up and the solid was recrystallized to constant melting range, 1,2-*O*-bromoethylidene-D-mannitol (**1**), mp 151–153°, was isolated which, on reaction with acetic anhydride in pyridine, gave a crystalline tetra-*O*-acetyl ester, **1**-Ac_4, mp 76–78° (Figure 1). Both *p*-toluenesulfonyl chloride and methanesulfonyl chloride in pyridine gave products that were crystalline at ice-bath temperature, but, since they liquefied on warming to room temperature, they were not investigated further. Periodate oxidation (3.1–3.4 equiv) confirmed the structural assignment of the acetal bonds in **1**.

Chromatographic techniques—paper, tlc, gas, ion exchange (borate)—failed to separate **1**. Multiple ascent

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(2) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

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