Preparation and Characterization of Two 1,2:5,6-Di-*O*-bromoethylidene-D-mannitols[1]

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When bromoacetaldehyde diethyl acetal was treated with D-mannitol in 18 *N* H_2SO_4, a solid was isolated, mp 135–145°, and analyzed for a di-*O*-bromoethylidenehexitol. Concentration of the mother liquors gave a solid, mp 100–120°. After four to six recrystallizations, from 1% w/v water, compounds having mp 119–120° and 154–155° were isolated. Both isomers on catalytic hydrogenolysis, methylation, and hydrolysis gave 3,4-di-*O*-methyl-D-mannitol. Both isomers gave crystalline di-*O*-*p*-tolylsulfonyl and di-*O*-acetyl derivatives, which exhibited different melting points. Nmr spectroscopy was used to assign to the low-melting isomer the *cis*-1,2:*trans*-5,6-di-*O*-bromoethylidene-D-mannitol structure and to the high-melting isomer the *cis*-1,2:*cis*-5,6-di-*O*-bromoethylidene-D-mannitol structure.

In 1923, Hibbert and Hill[3] reported the isolation of a di-*O*-bromoethylidenehexitol, mp 137–141°, from the acid-catalyzed condensation of bromoacetaldehyde and D-mannitol. Application of the Hann–Hudson rules, as extended by Barker and Bourne,[4] leads to the assignment of a 1,3:4,6-diacetal structure for this compound.

Condensation of bromoacetaldehyde diethyl acetal with D-mannitol has been reexamined. Two diacetals are formed, neither of which has the structure predicted by the Hann–Hudson rules. This paper describes the preparation, separation, and characterization of these diacetals.

Results

When bromoacetaldehyde diethyl acetal was added to a solution of D-mannitol in 18 *N* sulfuric acid, a heterogenous mixture resulted which on stirring became homogenous. Over the course of 2 hr the mixture turned solid. After standing overnight, the solid was broken up, separated by filtration, washed with water, and recrystallized from water to yield a crystalline product, mp ~135–145°. The mother liquor on concentration gave a crystalline product, mp ~100–120°.

Examination of these two products by chemical analysis, tlc, and ir spectra did not reveal significant differences. When these products were recrystallized from water (1% w/v) four to six times, two different crystalline compounds resulted, mp 154–155° and mp 119–120°. When these purified compounds were examined by tlc and ir spectra, the differences between them was still very small, and both exhibited low optical rotations (Table I).

TABLE I
PHYSICAL VALUES FOR DERIVATIVES OF DI-*O*-BROMOETHYLIDENE-D-MANNITOL[a]

Di-*O*-bromoethylidene-D-mannitol	High melting		Low melting	
	Mp, °C	$[\alpha]^{25}D$	Mp, °C	$[\alpha]^{25}D$
Unsubstituted	154–155	+9	119–120	+7
Di-*O*-tosyl	136–138.5	+9	149–151	+19
Di-*O*-acetyl	100–103	+15	75–77	+21

[a] Rotations were taken in *p*-dioxane.

Both the high- and low-melting products were analyzed for $C_{10}H_{16}Br_2O_6$, a di-*O*-bromoethylidenehexitol. Further, they were shown not to be crystalline polymorphs by preparation of crystalline di-*O*-*p*-tolylsulfonyl (tosyl) and di-*O*-acetyl esters, which exhibited different melting points (Table I).

Catalytic hydrogenolysis of the high-melting bromoethylidene acetal in ethanolic potassium hydroxide over palladium–charcoal resulted in a di-*O*-ethylidenehexitol, mp 115–117°, $[\alpha]^{23}D$ +5.8°. Methylation of this di-*O*-ethylidenehexitol with sodium hydride and methyl sulfate followed by acid hydrolysis yielded 3,4-di-*O*-methyl-D-mannitol, mp 145–148°, $[\alpha]^{24}D$ +39°.

When the low-melting bromoethylidene acetal was hydrogenolyzed similarly, a di-*O*-ethylidene hexitol, mp 84–86°, $[\alpha]^{24}D$ +7.6°, resulted which, when methylated and hydrolyzed, also gave 3,4-di-*O*-methyl-D-mannitol.

Nmr spectroscopy on the high-melting bromoethylidene acetal, its di-*O*-acetyl ester, and the derived di-*O*-ethylidenehexitol revealed, respectively, a triplet centered at δ 5.06 ($CHCH_2Br$), a triplet centered at 4.98 ($CHCH_2Br$), and a quartet centered at 5.01 ($CHCH_3$). In addition, the bromo acetal and its di-*O*-acetyl ester had doublets centered at δ 3.48 and 3.40 ($CHCH_2Br$), whereas the di-*O*-ethylidenehexitol had a doublet centered at 1.36 ($CHCH_3$). Spin-decoupling experiments showed these multiplets near δ 5.0 to be coupled with the upfield doublets.

Nmr spectroscopy on the low-melting bromoethylidene acetal, its di-*O*-acetyl ester, and the derived di-*O*-ethylidenehexitol had, respectively, two triplets centered at δ 5.04 and 5.16 ($CHCH_2Br$), two triplets centered at 5.00 and 5.14 ($CHCH_2Br$), and two quartets centered at 5.04 and 5.16 ($CHCH_3$). In addition, the bromo acetal and its di-*O*-acetyl ester had two doublets centered at δ 3.34 and 3.38, and 3.47 and 3.49 ($CHCH_2Br$), whereas the di-*O*-ethylidenehexitol had two doublets centered at 1.36 and 1.37 ($CHCH_3$). Spin-decoupling experiments showed these multiplets near δ 5.0 to be coupled with the upfield doublets. The more downfield multiplet near δ 5.0 was coupled with the more upfield doublet; that is, in the bromo acetal, coupling involved the 5.04–3.38 and 5.16–3.34 resonances.

Discussion

Transformation of both the high- and low-melting di-*O*-bromoethylidene acetals from D-mannitol by a

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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.

(3) H. Hibbert and H. S. Hill, *J. Amer. Chem. Soc.*, **45**, 734 (1923).

(4) For a summary of these rules and the extensions, see S. A. Barker and E. J. Bourne, *Advan. Carbohyd. Chem.*, **7**, 137 (1952).

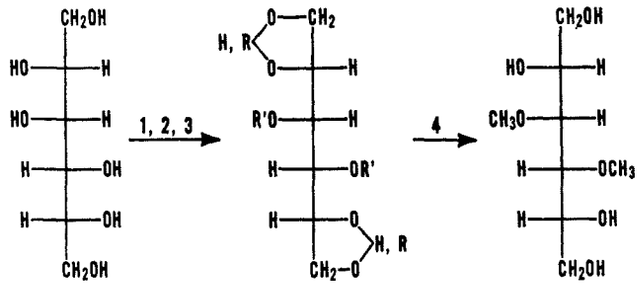


Figure 1.—Reaction sequence determining structure.

reaction sequence of catalytic hydrogenolysis, methylation, and hydrolysis into 3,4-di-*O*-methyl-D-mannitol established that the original acetals were both 1,2:5,6 di-*O*-acetals; the other two arrangements 1,6:2,5 and 1,5:2,6 were shown to be so far afield from past experience in polyol acetals[4] that they were not considered. These findings are summarized in Figure 1. Nmr spectroscopy confirmed that no rearrangement occurred during hydrogenolysis.

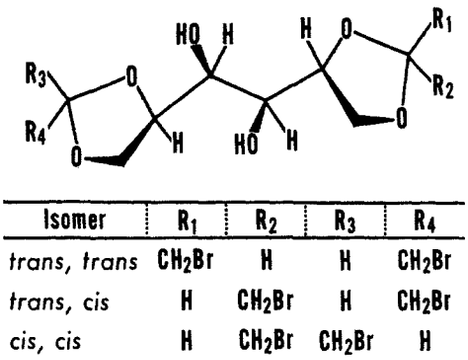
The low optical rotations noted in Table I are consistent with rotations reported for 1,2:5,6-di-*O*-isopropylidene-D-mannitol, $[\alpha]_D$ −0.5°,[5] its 3,4-di-*O*-acetate, $[\alpha]_D$ +26.7°,[6] and its 3,4-di-*O*-*p*-tolylsulfonate, $[\alpha]_D$ +9.3°.[7] Also, the low rotations for both 1,2:5,6-*O*-ethylidene-D-mannitols, $[\alpha]_D$ +5.8 and +7.6°, are consistent with the structural assignment and differ widely from that of 1,3:4,6-di-*O*-ethylidene-D-mannitol, $[\alpha]_D$ −71.7°.[8]

Since both isomers yielded different 3,4-di-*O*-*p*-tolylsulfonyl and 3,4-di-*O*-acetyl esters (Table I), when prepared by similar procedures and recrystallized from the same solvent, the bromoethylidene acetals were not crystalline polymorphs.

Since both isomers contained the same acetal arrangement, were not polymorphic, and were derived from D-mannitol, the difference must be located in the acetal portion. Three different stereoisomeric 1,2:5,6-di-*O*-bromoethylidene-D-mannitols can be constructed (Figure 2), the difference being the *cis,trans* relationship of the 2 and 4 substituents on the 1,3-dioxolane rings. This relationship can be obtained from the nmr data, but a brief background is needed.

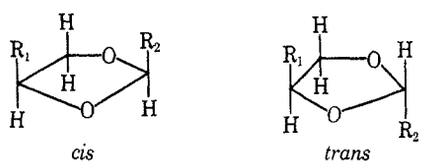
Observations by Baggett and coworkers[9] with polyol benzylidene acetals and by Forsèn, Lindberg, and Silvander[10] with trichloroethylidene derivatives of D-glucose (chloraloses) have shown in 2-substituted 1,3-dioxolanes that alkyl groups in the 4 and 5 positions which are *cis* to the 2 proton produce downfield shifts of approximately δ 0.12–0.14 per alkyl group.

Here the terminal position further restricted the choice in the 1,3-dioxolane ring to two isomers; *i.e.*



Isomer	R_1	R_2	R_3	R_4
trans, trans	CH_2Br	H	H	CH_2Br
trans, cis	H	CH_2Br	H	CH_2Br
cis, cis	H	CH_2Br	CH_2Br	H

Figure 2.—The stereoisomers of 1,2:5,6-di-*O*-bromoethylidene-D-mannitol.



In addition, the *cis,cis*- and *trans,trans*-1,2:5,6 diacetal structures reveal an end to end symmetry and would be expected to show only one type of acetal proton, an upfield *cis* proton or a downfield *trans* proton. Whereas the *cis,trans*-1,2:5,6 diacetal structure would be expected to show both an upfield and a downfield proton.

By comparing the acetal proton position in the low-melting series, where two proton types were found, with the position in the high-melting series, where one proton type was found, the conclusion was drawn from Table II that in the low-melting series the upfield acetal proton (δ_2) resided on a *cis*-1,3-dioxolane and the downfield acetal proton (δ_1) resided on a *trans*-1,3-dioxolane; the δ_1–δ_2 values (Table II) correspond

TABLE II

δ VALUE FOR ACETAL PROTON

Compd	δ_1[a]	δ_1–δ_2	δ_2[a]	Solvent
	Low-Melting Series			
II	5.16	0.12	5.04	Dioxane-d_8
II diacetate	5.14	0.14	5.00	Dioxane-d_8
III	5.19	0.09	5.10	D_2O
	5.16	0.12	5.04	$CDCl_3$
	High-Melting Series			
II			5.06	Dioxane-d_8
II diacetate			4.98	Dioxane-d_8
III			5.11	D_2O
			5.01	$CDCl_3$

[a] δ values refer to internal TMS or Tier's salt and are reported as the center value of multiplets.

closely to the difference found by Baggett and coworkers[9] and Forsèn, Lindberg, and Silvander.[10] For the high-melting series Table II shows only one type of acetal proton that corresponds to the upfield acetal proton from the low-melting series. From these, data structures were assigned such that the low-melting series possessed a *cis*-1,2:*trans*-5,6 arrangement (Figure 2) and the high-melting series possessed a *cis*-1,2:*cis*-5,6 arrangement (Figure 2).

Mills[11] has pointed out that formation of many acetals from polyols and aldehydes can be explained by

(5) E. Fischer and C. Rund, *Ber.*, **49**, 88 (1916).
(6) L. V. Vargha, *ibid.*, **66**, 1394 (1933).
(7) P. Brigl and H. Gruner, *ibid.*, **67**, 1969 (1934).
(8) E. J. Bourne, G. T. Bruce, and L. F. Wiggins, *J. Chem. Soc.*, 2708 (1951).
(9) N. Baggett, K. W. Buck, A. B. Foster, M. H. Randall, and J. M. Webber, *Proc. Chem. Soc.*, 118 (1964); *J. Chem. Soc.*, 3394 (1965).
(10) S. Forsèn, B. Lindberg, and B-G. Silvander, *Acta Chem. Scand.*, **19**, 359 (1965).
(11) J. A. Mills, *Advan. Carbohyd. Chem.*, **10**, 1 (1955).

considering them as arising from acid-catalyzed equilibration. This idea, plus the additional observation that with aldehydes 1,3-dioxanes are usually preferred over 1,3-dioxolanes, constitutes the basis of the Hann–Hudson rules. A risk was recognized when applying these rules: if an equilibrium was not attained, the end products may not be the predicted ones. If the reaction pathway was irreversible, the end products would be determined by the stereochemistry of the transition state and the relative rate of formation.[11]

In many examples, the processing of reaction mixtures was incomplete, and in preparing crystalline compounds the recovery for many was low; consequently, other acetals only stereochemically different might have been present in the unexamined or discarded portions.[11] Many reports of isolation of two stereochemically different acetals can be found in carbohydrate chemistry. For example, chloral hydrate and D-glucose give two 1,2 mono-*O*-acetals and four 1,2:5,6 di-*O*-acetals;[10] 1,1,1-trifluoroacetone and D-mannitol give a mixture of di- and tri-*O*-acetals from which two 1,2:5,6 di-*O*-acetals were separated;[12] benzaldehyde and several polyols yield identifiable diastereomers.[13]

Nmr spectroscopy has shown that with acid-catalyzed benzylidation, the rapid appearance of an upfield (*cis*) acetal proton in 1,4-anhydroerythritol[14] and cyclohexane-*cis*-1,2-diol[14] is followed by a reduction in this proton's intensity and by the simultaneous appearance of a downfield (*trans*) acetal proton. Observations on the migration of 1,4-anhydro-3,5-*O*-benzylidene-D-mannitol[14] to the 2,3-*O*-benzylidene acetal and 2,4-*O*-benzylidene-D-erythrose[15] to the 2,3-*O*-benzylidene acetal also supported the initial *cis* isomer formation followed by an equilibration phase. However, on benzylidation of terminal vicinal diols the *cis* isomer was not preferentially formed; instead both diastereomers were formed at about the same rate.[14]

The condensation of bromoacetaldehyde diethyl acetal with D-mannitol followed a pattern similar to ketones; *e.g.*, acetone[4] and 1,1,1-trifluoroacetone,[12] 1,2 → 1,2:5,6 → 1,2:3,4:5,6. From the large proportion of *cis*-1,3-dioxolane rings found, the results suggested that under the reaction conditions the interconversion of the many positional and stereochemical isomers did not occur. The products appeared to be determined by kinetic factors, but, since both dioxolane rings involved a terminal vicinal diol where a kinetic preference was unexpected,[14] the results were puzzling. A possible explanation for this preference might be that the first ring closure exhibits no kinetic preference, but in some manner the monoacetal exhibits a long-range directive effect on the second ring closure, even though it involves a terminal vicinal diol. Experiments are in progress to see if a directive effect can be confirmed.

(12) E. J. Bourne, A. J. Huggard, and M. Stacey, *J. Chem. Soc.*, 2716 (1960).

(13) (a) A. B. Foster, M. H. Randall, and J. M. Webber, *ibid.*, 3388 (1965); (b) B. Dobinson, A. B. Foster, and M. Stacey, *Tetrahedron Lett.*, No. 1, 1 (1959).

(14) (a) F. S. Al-Jeboury, N. Baggett, A. B. Foster, and J. M. Webber, *Chem. Commun.*, 222 (1965); (b) N. Baggett, A. B. Foster, J. M. Webber, D. Lipkin, and B. S. Phillips, *Chem. Ind.* (London), 136 (1965).

(15) N. Baggett, K. W. Buck, A. B. Foster, B. H. Rees, and J. M. Webber, *J. Chem. Soc.* (C), 212 (1966).

Experimental Section

Tlc was carried out on silica gel G[16] with air-equilibrated plates of 0.25-mm thickness and the solvent systems as specified. The spots were detected by spraying with 5% ethanolic sulfuric acid and heating until charred. Linear horizontal paper chromatography was carried out on Schleicher and Schull 2043b with a solvent system *n*-BuOH–*i*-PrOH–H_2O 3:1:1 (v/v). The spots were detected by either the periodate–permanganate spray of Lemieux and Bauer[17] or the $AgNO_3$–NaOH dipping reagent of Smith.[18] Tlc values are reported as R_F and paper chromatographic values as R_f. Uv spectra were measured with a Cary Model 14 spectrophotometer. Ir spectra of samples either in solution or KBr pellets as specified were determined with a Perkin-Elmer Model 621 spectrophotometer. Nmr spectra were obtained with a Varian Model A-60 or Model HA-100 spectrometer. The chemical shifts were compared against internal tetramethylsilane or sodium 3-(trimethylsilyl)-1-propanesulfonate (δ 0.00 ppm). Melting points of samples in capillary tubes were measured on a Mel-Temp apparatus. All analytical samples were dried over $NaOH/H_2SO_4$ at room temperature and 1–10-mm vacuum for 24–48 hr.

***cis*-1,2:*cis*-5,6- and *cis*-1,2:*trans*-5,6-Di-*O*-bromoethylidene-D-mannitol (II). Preparation and Separation.**—D-Mannitol (40 g) was added to a mixture of 40 ml of water and 40 ml of concentrated sulfuric acid and stirred until it dissolved (*ca.* 20 min); then bromoacetaldehyde diethyl acetal (90 g) was added in one portion. A heterogeneous mixture resulted. On continued stirring the reaction mixture turned homogenous and over a 2–4-hr period became solid. After standing for 16–18 hr at room temperature, the solid was broken up, placed in a Waring Blendor, and washed free of acid by successive filtration and blender treatment; usually three 250-ml portions of water were used. The damp solid (~100–120 g) was dissolved in 3 l. of boiling water [continually testing the pH (paper) to maintain pH 7–8] and allowed to cool to room temperature overnight. The crystals were separated by filtration, sucked dry on a funnel, and finally dried in a vacuum desiccator over sodium hydroxide pellets to yield 35.8 g (41.6%), mp ~135–145° (fraction A). Concentrating the mother liquor from fraction A (Table III) to dryness yielded 16.7 g (19.4%), mp ~100–120°, which was partitioned between 500 ml of chloroform and 300 ml of water. After drying and concentrating the chloroform, the solid (14 g) was recrystallized from 1400 ml of water to yield after drying 7.44 g, mp 116–120°, solid (fraction B, Table IV); concentrating the

TABLE III

PURIFICATION OF *cis*-1,2:*cis*-5,6-DI-*O*-BROMOETHYLIDENE-D-MANNITOL. FRACTION A

Recrystn no.	Starting wt, g	Recovered crystals—Wt, g	Recovered crystals—Mp, °C	Recovery, %
1	10.000	6.919	143–144	69.2
2	6.919	5.284	147–152	76.3
3	5.284	4.365	150–155	82.6
4	4.365	3.828	152–156	87.6
5	3.828	3.424	152–156	89.4
6	3.424	3.050	154.2–155.2	89.0

TABLE IV

PURIFICATION OF *cis*-1,2:*trans*-5,6-DI-*O*-BROMOETHYLIDENE-D-MANNITOL. FRACTION B

Recrystn no.	Starting wt, g	Recovered crystals—Wt, g	Recovered crystals—Mp, °C	Recovery, %
1	7.438	4.955	118.2–121	66.6
2	4.955	4.168	120–121.6	84.1
3	4.168[a]	3.549	120–122	85.1
4	3.549	3.003	119.5–122	84.6

[a] Some solution spilled.

(16) The mention of firm names or trade products does not imply that they are endorsed by the U. S. Department of Agriculture over similar or unmentioned products.

(17) R. U. Lemieux and H. F. Bauer, *Anal. Chem.*, **26**, 920 (1954).

(18) I. Smith, "Chromatographic Techniques," Interscience Publishers, Inc., New York. N. Y., 1958, p 169.

mother liquor from fraction B yielded 4.75 g, mp 98–111°, solid (fraction C).

Fraction A was recrystallized successively from 1% w/v water, with each recrystallization being allowed to equilibrate at 25 ± 0.01° for at least 6 hr. Crystals were separated, briefly air dried, and then dried in a vacuum desiccator over sodium hydroxide pellets. The following data was obtained from recrystallization no. 6: λ_{max}^{KBr} 3320, 3380 (OH); 1150, 1100, 1050 (acetal), 550 cm^{-1} (C–Br?); R_F 0.38 (20:1 v/v chloroform–isopropyl alcohol); $[\alpha]^{23}D$ +9.2° (*c* 1.079, *p*-dioxane); nmr data in text. *Anal.* Calcd for $C_{10}H_{16}Br_2O_6$: C, 30.63; H, 4.11; Br, 40.76. Found: C, 30.64; H, 4.16; Br, 41.19.

Fraction B was recrystallized as fraction A (described above). The following data was obtained from recrystallization no. 4: λ_{max}^{KBr} 3420, 3200 (OH); 1150, 1105, 1040 (split) (acetal), 550 cm^{-1} (C–Br?); R_F 0.55 (15:1 v/v chloroform–isopropyl alcohol); $[\alpha]^{23}D$ +7° (*c* 0.807, *p*-dioxane); nmr data in text. *Anal.* Calcd for $C_{10}H_{16}Br_2O_6$: C, 30.63; H, 4.11; Br, 40.76. Found: C, 30.61; H, 4.12; Br, 41.00.

Fraction C when recrystallized from 1% w/v water yielded only the low-melting isomer from fraction B. Reworking the mother liquors gave only fractions with very broad melting ranges; the fractions were not further examined.

***cis*-1,2:*cis*-5,6-Di-*O*-bromoethylidene-3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (II, R = Ts).**—*cis*-1,2:*cis*-5,6-Di-*O*-bromoethylidene-D-mannitol (1.002 g), mp 152–154°, was dissolved in 5 ml of anhydrous pyridine and cooled in a Dry Ice–acetone bath until solid when *p*-toluenesulfonyl chloride (1.985 g) was added in one portion. The reaction mixture was allowed to warm until the solution was homogenous and then stored at 0–5° for 90 hr. Water (2 ml) was added 4–5 drops every 5 min with stirring and ice-bath cooling (pyridine hydrochloride dissolves and product deposits); finally, 50 ml of ice water was added; and the mixture was stored for 16–18 hr at 0–5°. The solid was separated by filtration, washed (on the funnel) with 10 ml of ice water, sucked dry, and then dried in a vacuum desiccator over sodium hydroxide pellets to yield 1.745 g (97%), mp 134–137°. An analytical sample was prepared by recrystallizing 1.62 g from 100 ml of ethanol and 50 ml of water: recovery was 1.11 g; mp 137–139°; λ_{max}^{KBr} 1350, 1330, 1170, 1155 (sulfonate); 1130, 1050, 1030 (acetal), 550 cm^{-1} (C–Br?); λ_{max} in 95% ethanol 263 nm (ϵ 1350), 274 (1053); R_F 0.55 (10:1 v/v carbon tetrachloride–ethyl acetate); $[\alpha]^{23}D$ +9.7° (*c* 1.281, *p*-dioxane). *Anal.* Calcd for $C_{24}H_{28}Br_2O_{10}S_2$: C, 41.16; H, 4.03; Br, 22.82; S, 9.16. Found: C, 41.31; H, 4.13; Br, 23.05; S, 9.33.

***cis*-1,2:*cis*-5,6-Di-*O*-bromoethylidene-3,4-di-*O*-acetyl-D-mannitol (II, R = Ac).**—In 5 ml of anhydrous pyridine 0.996 g of *cis*-1,2:*cis*-5,6-di-*O*-bromoethylidene-D-mannitol, mp 154–155°, was dissolved, and the mixture was cooled to near −20° when 4 ml of acetic anhydride was added. After the mixture was left for 48 hr at 0–5°, water (50 ml) was added, and the solution was stirred for 18 hr at 0–5°, during which time a fine granular solid separated. This solid was separated by filtration and air dried to yield 1.124 g (93%), mp 100–103°. An analytical sample was prepared by recrystallizing 107 mg from 2 ml of ethanol containing 1 ml of water; recovery was 76 mg: mp 101–102.8°; λ_{max}^{KBr} 1740 (C=O), 1200 (C—O ester), 1140, 1095, 1030 cm^{-1} (acetal); nmr data in text; R_F 0.42 (40:1 v/v benzene–isopropyl alcohol); $[\alpha]^{23}D$ +15° (*c* 0.610, *p*-dioxane). *Anal.* Calcd for $C_{14}H_{20}Br_2O_8$: C, 35.31; H, 4.23; Br, 33.56. Found: C, 35.36; H, 4.45; Br, 33.46.

***cis*-1,2:*cis*-5,6-Di-*O*-ethylidene-D-mannitol (III).**—*cis*-1,2:*cis*-5,6-Di-*O*-bromoethylidene-D-mannitol (10 g) was placed in 200 ml of 95% ethanol containing 3.2 g of potassium hydroxide (85% reagent grade) and 4 g of 5% Pd/C. The mixture was transferred to a hydrogenation bottle containing about 20 ml of 95% ethanol. Hydrogen was introduced at room temperature to 53.0 psi and the hydrogen uptake began immediately on shaking; the pressure dropped 4.5 psi in 15 min (theory 4.3 psi) and remained at this value for 45 min when the hydrogenolysis was terminated. After diluting the mixture with 500 ml of water, the catalyst was separated by filtration through a small bed of Celite 535, which was washed with two 25-ml portions of boiling ethanol. The combined filtrate and washings were adjusted to pH 7.0 ± 0.1 with 0.1 *N* hydrochloric acid. After concentration to 400 ml, the solution was transferred to a continuous ether extractor and extracted for 4 days. Removal of the ether left a solid (5.208 g), mp 103–114°, which tlc (2:1 v/v ethyl acetate–benzene) revealed as one major spot, R_F 0.40, and a trace spot, R_F 0.10. An analytical sample was prepared by dissolving 414 mg in 20 ml of chloroform and adding 100 ml of warm hexane which, after standing overnight, deposited a gellike solid and dried to a granular white powder: recovery was 254 mg; mp 115–117°; periodate oxidation[19] consumed 1.03 molar equiv in 15 min with no additional consumption over 22 hr; λ_{max}^{KBr} 1430 (CH_3), 1135, 1105, 1050 cm^{-1} (acetal); R_F 0.40 (2:1 v/v ethyl acetate–benzene); $[\alpha]^{23}D$ +5.8° (*c* 0.692, water). *Anal.* Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.45; H, 7.88.

***cis*-1,2:*trans*-5,6-Di-*O*-bromoethylidene-3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (II, R = Ts).**—In a similar manner 1.006 g of *cis*-1,2:*trans*-5,6-di-*O*-bromoethylidene-D-mannitol, mp 118–121°, was prepared as the *cis,cis* isomer with 1.027 g of *p*-toluenesulfonyl chloride in 5 ml of anhydrous pyridine. The work-up gave 1.672 g (93%), mp 142–147°. An analytical sample was made by recrystallizing 1.296 g from 30 ml of ethyl acetate: recovery was 0.935 g; mp 149–151.5°; λ_{max}^{KBr} 1360, 1340, 1185, 1170 (sulfonate), 1135, 1110, 1085, 1035 cm^{-1} (acetal); λ_{max} in 95% ethanol 263 nm (ϵ 1307), 274 (1094); R_F 0.44 (30:1 v/v benzene–ethyl ether); $[\alpha]^{23}D$ +19° (*c* 0.485, *p*-dioxane). *Anal.* Calcd for $C_{24}H_{28}Br_2O_{10}S_2$: C, 41.16; H, 4.03; Br, 22.82; S, 9.16. Found: C, 40.96; H, 4.20; Br, 22.60; S, 9.26.

3,4-Di-*O*-methyl-D-mannitol (V) from *cis*-1,2:*cis*-5,6-Di-*O*-ethylidene-D-mannitol (III).—Sodium hydride, 0.439 g in a 55% oil dispersion, was washed with three 20-ml portions of anhydrous ethyl ether; finally, the gray powder was covered with 20 ml of ether. *cis,cis* III (0.500 g) was added to the hydride slurry and stirred for about 1 hr; then 2 drops of anhydrous isopropyl alcohol was added. Four 0.2-ml portions of methyl sulfate were added 30 min apart, and the mixture was stirred for 24 hr at room temperature; tlc (2:1 v/v benzene–ethyl acetate) monitoring revealed the methylation to be complete. Ethanol (2 ml) was added dropwise to destroy excess hydride and then water (10 ml), to dissolve the solids. The mixture was transferred to a continuous ether extractor and extracted for 20 hr. Removal of the ether gave a waxy solid, 0.491 g. After dissolving 0.283 g of this waxy solid in methanol and adding 3 drops of concentrated hydrochloric acid, the solution was left for 18 hr at room temperature. Water (10 ml) was then added, and the solution was neutralized with 0.01 *N* sodium hydroxide to pH 7.0 ± 0.1, treated with decolorizing charcoal, filtered, and concentrated to dryness to yield a granular solid, 0.315 g. This granular solid was triturated with five 40-ml portions of boiling ethyl acetate. When concentrated the ethyl acetate gave a crystalline solid (0.189 g), mp 141–144°. An analytical sample was prepared by recrystallizing 0.238 g from 5 ml of ethanol and 15 ml of ethyl acetate: recovery was 0.230 g; mp 145–148°; λ_{max}^{KBr} 3400 (OH), 2865, 2830 cm^{-1} (CH_3O);[20] R_f 0.43 (D-mannitol R_f 0.16); $[\alpha]^{23}D$ +39° (*c* 0.191, water) [lit.[21] mp 144–146°; $[\alpha]^{25}D$ +40.8° (*c* 1, water)]. The melting point of a mixture of this compound V and 3,4-di-*O*-methyl-D-mannitol[21] was undepressed. *Anal.* Calc for $C_8H_{18}O_6$: C, 45.70; H, 8.63. Found: C, 45.95; H, 8.75.

***cis*-1,2:*trans*-5,6-Di-*O*-bromoethylidene-3,4-di-*O*-acetyl-D-mannitol (II, R = Ac).**—The titled compound was prepared in a similar manner as the *cis,cis* isomer from 0.996 g of *cis*-1,2:*trans*-5,6-di-*O*-bromoethylidene-D-mannitol and 1 ml of acetic anhydride in 5 ml of anhydrous pyridine. The work-up yielded 1.44 g, mp 75–77°. An analytical sample was prepared by recrystallizing 1.14 g twice from 100 ml of 95% ethanol: recovery was 0.83 g; mp 75–76.5°; λ_{max}^{KBr} 1745 (C=O), 1210 (C—O ester), 1140, 1100, 1030 cm^{-1} (acetal); R_F 0.38 (40:1 v/v benzene–isopropyl alcohol); $[\alpha]^{23}D$ +21° (*c* 0.678, *p*-dioxane). *Anal.* Calcd for $C_{14}H_{20}Br_2O_8$: C, 35.32; H, 4.23; Br, 33.57. Found: C, 35, 25, 35.70; H, 4.22, 4.46; Br, 33.92, 34.06.

***cis*-1,2:*trans*-5,6-Di-*O*-ethylidene-D-mannitol (III).**—Catalytic hydrogenolysis of *cis,trans* III (9.858 g) was carried out as reported for *cis,cis* III, with a pressure drop of 4.2 psi (theory 4.3 psi). Removal of the ether gave 4.908 g, mp 80–85°, which tlc (2:1 v/v ethyl acetate–benzene) revealed as one spot, R_F 0.41. An analytical sample was prepared by recrystallizing 1.126 g from 20 ml of chloroform and 200 ml of hexane. A gellike material separated but dried to a powder: recovery was 0.700 g; mp 84–86°; λ_{max}^{KBr} 1470 (CH_3), 1210, 1170, 1110 cm^{-1} (acetal);

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R_F 0.42 (2:1 v/v ethyl acetate–benzene); $[\alpha]^{24}D$ +7.6° (*c* 0.559, water). *Anal.* Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.39; H, 7.95.

3,4-Di-*O*-methyl-D-mannitol (V) from *cis*-1,2:*trans*-5,6-Di-*O*-ethylidene-D-mannitol (III).—Sodium hydride, 0.928 g in a 55% oil dispersion, was washed with two 50-ml portions of anhydrous ethyl ether; finally, the gray powder was covered with 50 ml of ether. *cis,trans* III (0.385 g) was added, and the reaction mixture was stirred for 30 min, when methyl sulfate (1.2 ml) was added in one portion. After the mixture was stirred at room temperature for 20 hr, tlc revealed the methylation to be complete. The reaction was worked up as reported for the *cis,cis* III to give, after removal of the ether, a syrup (0.241 g). This syrup was dissolved in 10 ml of methanol, and 5 drops of concentrated hydrochloric acid was added. After 20 hr at room temperature the methanolic solution was diluted with 20–30 ml of water, neutralized to pH 7.0 ± 0.1 with 0.01 *N* sodium hydroxide, and concentrated to dryness to a granularlike solid. Trituration of this solid with three 30-ml portions of ethyl acetate–isopropyl alcohol (1:1 v/v) gave on concentration 0.172 g, mp 143–148°, of crude 3,4-di-*O*-methyl-D-mannitol. Recrystallization from a mixture of 5 ml of ethanol and 10 ml of ethyl acetate gave 96 mg, mp 145–148° (concentrating mother liquor gave 72 mg of an impure sample). The melting point of a mixture of compound V from the *cis,cis* isomer and *cis,trans* isomer was undepressed. *Anal.* Calcd for $C_8H_{18}O_6$: C, 45.70; H, 8.63. Found: C, 45.73; H, 8.63.

Registry No.—II (*cis*-1,2:*cis*-5,6-), 17288-91-4; II (*cis*-1,2:*trans*-5,6-), 17288-92-5; II (R′ = Ts; *cis*-1,2:-*cis*-5,6-), 17326-49-7; II (R = Ac; *cis*-1,2:*cis*-5,6-), 17288-93-6; II (R = Ts; *cis*-1,2:*trans*-5,6-), 17288-94-7; II (R = Ac; *cis*-1,2:*trans*-5,6-), 17288-95-8; III (*cis*-1,2:*cis*-5,6-), 17288-96-9; III (*cis*-1,2:*trans*-5,6-), 17288-97-0; V, 17288-98-1.

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Novel Ring Openings in Methyl Levopimarate[1a]

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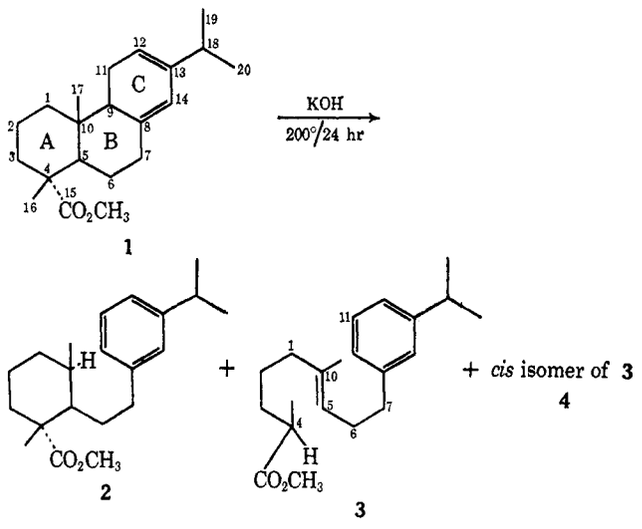
Methyl levopimarate (1) in the presence of a catalytic amount of potassium hydroxide at 200° rearranges to give four new compounds isomeric to 1, in about 57% yield. Three of these compounds (2, 3, and 4) have been isolated and their structures have been postulated. The reaction involves the opening of ring B in the formation of 2, and that of rings A and B in the formation of 3 and 4. In all three compounds ring C is aromatized. Treatment with iodine converts the *cis* isomer 4 into the *trans* isomer 3 and also closes ring A to form 2.

During the course of a systematic investigation[2-4] of the effect of heat and of heat and alkali upon the four conjugated dienoic resin acids (and their esters) found in pine gum, we have recently discovered two new ring-cleavage reactions to occur in the case of levopimaric acid methyl ester. Methyl levopimarate, in the presence of 5 mol % of potassium hydroxide at 200° for 24 hr under nitrogen was found to give a mixture of 6.2% **4**, 30% **3**, 14.6% an unknown peak, 22.9% **2**, 9.6% palustrate, 2.4% levopimarate, 2% dihydroabietate (?), 4.6% dehydroabietate, and 7.7% abietate.

The crude mixture was analyzed by means of glpc on a Versamid column.[2] Compounds **2**, **3**, and **4** were collected on a preparative glpc Versamid column and compounds **2** and **3** were rechromatographed on a SE-30 glpc column and collected.

The mass spectra confirmed the fact that **2**, **3**, and **4** were isomeric to **1** since all showed a molecular ion *m/e* 316. This was considered unusual in view of the fact that the compounds all came off the glpc columns much earlier than any of the resin acid esters. The infrared (ir) spectra indicated the presence of the ester group and of a *meta*-disubstituted aromatic ring in all cases. Similarly, all three compounds exhibited maxima in the ultraviolet (uv) absorption region of 263 mμ,

SCHEME I



typical of *meta*-disubstituted aromatic compounds.[5] The nuclear magnetic resonance (nmr) spectra of all three compounds showed multiplet peaks in the aromatic region (peaks from δ 6.85 to 7.25 ppm) equivalent on integration to four protons. The position and shape of these peaks resembled those exhibited by *m*-xylene.[6] These data would suggest that ring opening(s) had occurred in the three compounds in question.

Biemann[7] has postulated, based on mass spec-

(1) (a) Presented to the American Chemical Society, First Central Regional Meeting, Akron, Ohio, May 1968. (b) National Academy of Sciences, National Research Council postdoctoral fellow. (c) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

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