Anal. Calcd. for $C_{19}H_{29}NO_2.C_4H_6O_6.1.5H_2O$: Mol. wt., 480. Found: Mol. wt., 480.

Ethyl α-hexylacrylate (I, R = C_6H_{13}). Ethyl hydrogen hexylmalonate (490 g.) by Mannich's procedure[13] was converted to ethyl α-hexylacrylate in 76% yield; b.p. 100–102°/15 mm.

Ethyl 2-hexyl-3-methylaminopropionate (II, R = C_6H_{13}). Ethyl α-hexylacrylate (316 g.) was added to a solution of 60 g. of methylamine in 250 ml. of ethyl alcohol and the solution heated at 100° for 4 hr. under 600 lbs. of nitrogen. The product distilled at 130–135°/15 mm.; yield 314 g.

Diethyl α-hexyl-β,β'-(methylimino)dipropionate (III, R = C_6H_{13}). Ethyl 2-hexyl-3-methylaminopropionate (315 g.) was added to 150 g. of ethyl acrylate and the solution heated for 4 hr. at 100° in an autoclave under 600 lbs. of nitrogen. The product distilled at 152–158°/1 mm.; yield 345 g. (77%).

Anal. Calcd. for $C_{17}H_{33}NO_4$: Mol. wt., 315. Found: Mol. wt., 316.

1-Methyl-3-hexyl-4-piperidone (IV, R = C_6H_{13}). The above diester (III, R = C_6H_{13}), 345 g. was cyclized in the usual way[14] to 1-methyl-3-hexyl-4-piperidone. The product distilled at 153–155°/25 mm.; yield 153 g. (71%).

1-Methyl-3-hexyl-4-phenyl-4-hydroxypiperidine (V, R = C_6H_{13}). In the usual manner, 40 g. of the ketone (IV, R = C_6H_{13}) was reacted with phenyllithium prepared from 43 g. of bromobenzene and 3.8 g. of lithium wire. The product (V, R = C_6H_{13}) distilled at 170–173°/2 mm.; yield 47 g. (86%). The product is mainly the α form contaminated perhaps with some of the β form.

Anal. Calcd. for $C_{18}H_{29}NO$: Mol. wt., 275. Found: Mol. wt., 275.

α-1-Methyl-3-hexyl-4-phenyl-4-propionoxypiperidine dl-malate (VI, R = C_6H_{13}). 1-Methyl-3-hexyl-4-phenyl-4-hydroxypiperidine was converted to the 4-propionoxy derivative in the usual way; b.p. 191–193°/4 mm. The *dl*-malate was prepared by adding 1.1 g. of the 1-methyl-3-hexyl-4-phenyl-4-propionoxypiperidine to a solution of 0.45 g. of *dl*-malic acid in 10 ml. of acetone. The solution was distilled to dryness and the residue crystallized from ethyl acetate, m.p. 98–100°.

Anal. Calcd. for $C_{21}H_{33}NO_2.C_4H_6O_5$: Mol. wt., 465. Found: Mol. wt., 463.

The citrate was prepared in a similar manner, m.p. 125–127°.

Ethyl α-benzylacrylate. By Mannich's procedure[13], ethyl hydrogen benzylmalonate was converted to ethyl α-benzylacrylate, b.p. 106–107°/3 mm.; yield 78%.

Ethyl 1-benzyl-2-methylaminopropionate (II, R = $CH_2C_6H_5$). Ethyl α-benzylacrylate (170 g.) was added to a solution of 30 g. of methylamine in 200 ml. of ethyl alcohol and the solution heated in an autoclave at 100° for 4 hr. under 600 lbs. of nitrogen. The product distilled at 115–117°/3 mm.; yield 158 g. (80%).

Diethyl α-benzyl-β,β'-(methylimino)dipropionate (III, R = $CH_2C_6H_5$). Ethyl acrylate (140 g.) was added to 158 g. of ethyl 1-benzyl-2-methylaminopropionate and the solution heated in an autoclave at 110° for 4 hr. The product distilled at 160–162°/1 mm.; yield 210 g. (92%).

1-Methyl-3-benzyl-4-piperidone (IV, R = $CH_2C_6H_5$). The diester (III, R = $CH_2C_6H_5$) 210 g. was cyclized in the usual manner[14] to yield the 1-methyl-3-benzyl-4-piperidone,[16] b.p. 142–143°/4 mm.; yield 97 g. (73%).

Anal. Calcd. for $C_{13}H_{17}NO$: Mol. wt., 203. Found: Mol. wt., 203.

1-Methyl-3-benzyl-4-phenyl-4-hydroxypiperidine (V, R = $CH_2C_6H_5$). In the usual way, 1-methyl-3-benzyl-4-piperidone (40.6 g.) was reacted with phenyllithium prepared from 47.1 g. of bromobenzene and 4.2 g. of lithium in ether. Water (100 ml.) was added to decompose the complex, the ether separated and dried over anhydrous potassium carbonate. The ether was distilled off and the α-1-methyl-3-benzyl-4-phenyl-4-hydroxypiperidine crystallized from Skellysolve B, m.p. 126–127°; yield 38 g. The filtrate was examined for the presence of the β form but none could be isolated.

α-1-Methyl-3-benzyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R = $CH_2C_6H_5$). Five g. of V, (R = $CH_2C_6H_5$) was added to 15 ml. of propionic anhydride and the solution heated for 4 hr. on a steam bath. The excess propionic anhydride was distilled off in vacuum and the residue made alkaline with 10% sodium carbonate solution. The oil was extracted with ether and the solution dried, filtered and treated with hydrogen chloride gas. The salt formed was filtered off and crystallized from ethyl acetate–methanol, m.p. 207–208°; yield 4 g.

Anal. Calcd. for $C_{22}H_{27}NO_2.HCl$: Mol. wt., 373.5. Found: Mol. wt., 368.

For pharmacological testing, the free base was converted to the *dl*-malate (light yellow sirup) which is more soluble in water than the hydrochloride.

Acknowledgments. We wish to thank Dr. A. Steyermark and his associates for microchemical analyses, Mr. W. Oberhänsli for the skilled paper chromatographic work, and Mr. S. Traiman for the infrared spectra.

NUTLEY, N. J.

(16) S. M. McElvain and Gilbert Stork, *J. Am. Chem. Soc.*, **68**, 1049 (1946).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, UNITED STATES DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

The Structure of Tri-*O*-methylenevolemitol*

EMMANUEL ZISSIS AND NELSON K. RICHTMYER

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From the condensation of volemitol with formaldehyde we have obtained a 43% yield of a crystalline tri-*O*-methylene derivative that was converted by acetolysis to a di-*O*-methylene derivative. By combining with our experimental results the well-established empirical rule that in the methylenation of polyhydric alcohols the first preference is for a βC-ring we have established that the tri-*O*-methylenevolemitol is 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol. Some conformational aspects of this acetal and of the alternative 1,3:4,6:5,7-triacetal are discussed.

In a series of papers from this laboratory, Dr. Raymond M. Hann and Dr. C. S. Hudson, with their collaborators, attempted to correlate the configurations of certain polyhydric alcohols (alditols) with the structures of the cyclic methylene acetals derived from them. They were successful in

* To Lyndon F. Small, colleague and friend for thirty-five years. N.K.R.

devising a set of empirical rules[1] that permitted them to account for all the known cyclic methylene acetals and to predict the probable structures of other cyclic methylene acetals that they were able to prepare later. As additional information on the various cyclic acetals of the polyhydric alcohols became available, Barker and Bourne[2] published an extended statement of the original Hann-Hudson rules.[3] At about the same time Barker, Bourne, and Whiffen[4] suggested that the marked tendency for a carbon chain to adopt the planar zigzag form is sufficient to explain the main features of these empirical rules, since it appears that the most-favored rings involve the least energy for distortion of the planar chain.

Mills,[5] two years later, felt that a study of the end-products of reaction was a safer approach to the problem of acetal formation. He examined the structures of the acetals themselves and found that nearly all known stable cyclic acetals of sugars and sugar alcohols conformed to patterns predictable by methods of conformational analysis already familiar in the alicyclic field. His conformational analyses were of particular interest to us for through them he was able to predict that methylenation of D-arabinitol would afford 1,3:2,4-di-*O*-methylene-D-arabinitol whereas the empirical rules permitted no decision among the four possible di-*O*-methylene derivatives of D-arabinitol.[6] Our experimental results were disclosed almost simultaneously[7] with his prediction and verified it completely.

Mills stated also[5a] that, on the basis of conformational analyses, methylenation of volemitol (I) would probably afford 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV), which is analogous to the known 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol.[1b] Subsequently, however, he wrote[5b,8] that the alternative 1,3:4,6:5,7-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VIII) could not be ruled out as it might be formed more rapidly than IV and be rather slow to undergo rearrangement. With the encouragement of Dr. Mills we then decided to study the methylenation of volemitol (= D-*glycero*-D-*talo*-heptitol = D-*glycero*-D-*manno*-heptitol, I).

The condensation of volemitol with aqueous formaldehyde, with concentrated hydrochloric acid as catalyst, yielded 43% of a crystalline tri-*O*-methylenevolemitol. From a consideration of the empirical rules, its structure should be either IV or VIII, as already suggested by Mills. Thus, as has been established conclusively, the first preference in the methylenation of a polyhydric alcohol is the formation of a βC-ring[9]; the expected monoacetal, therefore, is the 4,6-acetal, II. The second preference is for a β-ring, and so we should expect the next methylene group to engage either the 1,3- or the 5,7-positions as shown in formulas III and VII, respectively; the empirical rules do not distinguish between these alternatives.[10] If the di-*O*-methylene acetal is III, it should be capable of adding a second β-ring between C5 and C7, whereas if the di-*O*-methylene acetal is VII it should be capable of adding a second β-ring between C1 and C3. The product, in either case, would be the 1,3:4,6:5,7-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VIII) suggested as an alternative possibility by Mills. This cannot be the correct structure, however, for upon acetolysis of our tri-*O*-methylenevolemitol we obtained a substituted di-*O*-methylene derivative, whereas if both terminal hydroxyl groups had been engaged in acetal formation, as in VIII, we should have expected a substituted mono-*O*-methylenevolemitol.

If the intermediate di-*O*-methylenevolemitol is III and it does not proceed to the tri-*O*-methylene acetal VIII, then the only other reaction to be expected with formaldehyde is the closing of a γT-ring between C2 and C5 and the generation of 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV), the structure suggested originally by Mills on the basis of conformational analysis. The acetolysis of this compound would be expected to form 3-*O*-acetoxymethyl-1,7-di-*O*-acetyl-2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (V) whose subsequent deacetylation would yield 2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VI). The last-named compound should be resistant to oxidation with periodate and its tri-*O*-tosyl derivative should exchange two tosyloxy groups

(1) (a) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1909 (1944); (b) see also A. T. Ness, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **70**, 765 (1948) for an extension of these rules.

(2) S. A. Barker and E. J. Bourne, (a) *J. Chem. Soc.*, 905 (1952); (b) *Advances in Carbohydrate Chem.*, **7**, 137 (1952).

(3) For a still later, minor extension of these rules, see E. Zissis and N. K. Richtmyer, *J. Am. Chem. Soc.*, **76**, 5515 (1954).

(4) S. A. Barker, E. J. Bourne, and D. H. Whiffen, *J. Chem. Soc.*, 3865 (1952).

(5) J. A. Mills, (a) *Chemistry & Industry*, 633 (1954); (b) *Advances in Carbohydrate Chem.*, **10**, 1 (1955).

(6) Mills predicted (ref. 5a) that the 1,3:2,4-acetal would be formed in preference to the 2,4:3,5-structure. According to the empirical rules (ref. 2b, p. 182), the 1,3:4,5- and 1,2:3,5-acetals also would be possible. Mills' reasons for excluding these last two were based presumably on the principle that a fused bicyclic system is formed in preference to two isolated acetal rings.

(7) Ref. 3, footnote 1.

(8) J. A. Mills, personal communication to one of us, December 16, 1954.

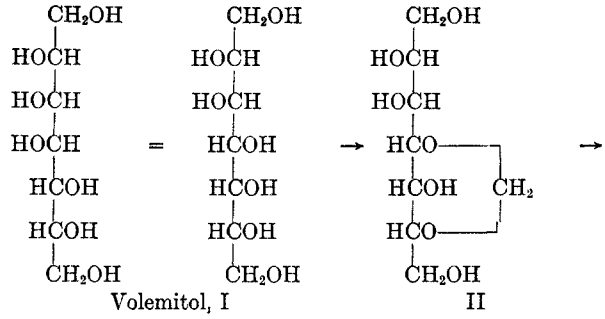
(9) In the notation of Barker and Bourne, the Greek letters signify the relative positions of the two hydroxyl groups engaged in the cyclization, and C and T indicate whether these groups are disposed *cis* or *trans* in the usual Fischer projection formula; C and T are required only when both hydroxyl groups are secondary.

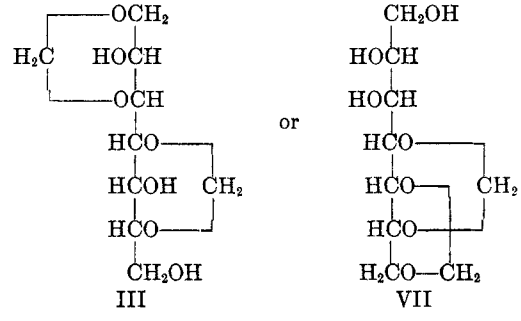
(10) See especially ref. 4, page 3868, on the influence of preformed rings.

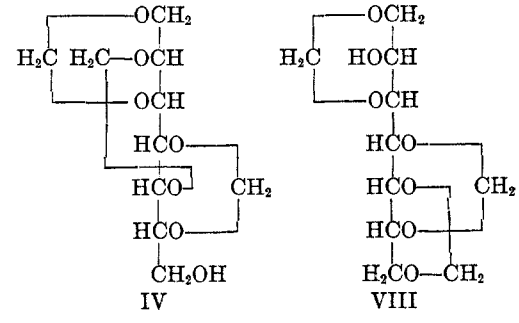
for iodine atoms when it is heated with sodium iodide. The experimental results are in agreement with these expectations and we conclude, therefore, that tri-*O*-methylenevolemitol is 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV).[11]

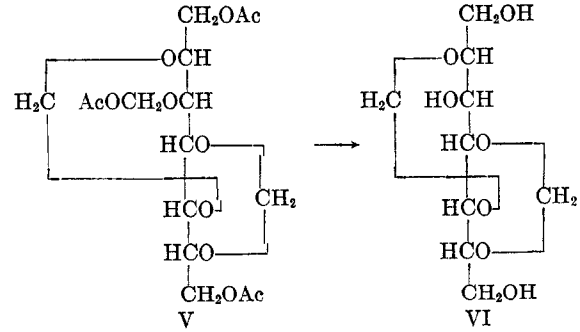
We have thus demonstrated, through a combination of the best-established empirical rules and our own experiments, that the principal product of the methylenation of volemitol under our conditions must be the 1,3:2,5:4,6- rather than the 1,3:4,6:-5,7-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol. As Mills has pointed out, the favored structure (X), like that of the analogous tri-*O*-methylene-D-mannitol (IX), consists of two six-membered acetal rings fused to a seven-membered acetal ring, with the three acetals having a *trans-anti-trans* configuration. The free CH_2OH group in X is equatorial and should confer even greater stability to the structure. The unfavored arrangement, as depicted in XI, consists of two six-membered acetal rings fused with a *trans* junction and resembles *trans*-decalin. It is substituted at the original C4 by an isolated six-membered acetal ring and the two components are then mutually equatorial.

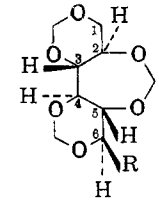
The final formula (XII) represents the 1,3:4,6-di-*O*-methylene acetal (with all ring-substituent groups equatorial) that may be an intermediate compound in the production of tri-*O*-methylenevolemitol just as 1,3:4,6-tri-*O*-methylene-D-mannitol appeared to be an intermediate in the preparation of the analogous tri-*O*-methylene-D-mannitol (IX). Although we succeeded in crystallizing only the tri-*O*-methylenevolemitol, we might expect to find this di-*O*-methylene derivative in the mother liquor[11a] or to obtain it by partial hydrolysis of the triacetal as Fletcher and Diehl[12] were able to do in the D-mannitol series.











IX (R = H) = 1,3:2,5:4,6-Tri-*O*-methylene-D-mannitol
X (R = CH_2OH) = 1,3:2,5:4,6-Tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV)

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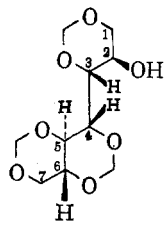
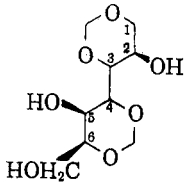
(11) We have considered also three other possibilities: (*a*) the formation from III of a 1,3:2,7:4,6-triacetal, but introduction of the 2,7-acetal ring would be highly improbable, and the compound, if formed, would give only a mono-*O*-methylene derivative on acetolysis; (*b*) the formation from VII of a 1,2:4,6:5,7-triacetal; and (*c*) of a 2,3:4,6:5,7-triacetal. However, the introduction of an α- or an αC-ring would seem to be extremely unlikely while it is still possible to establish an isolated β-acetal linkage between C1 and C3. Furthermore, the 1,2:4,6:5,7-tri-*O*-methylenevolemitol, if formed, would yield only a mono-*O*-methylene derivative on acetolysis.

(11a). *Note added August 2, 1957.* After submitting this paper for publication we succeeded in isolating from the mother liquor 1.2 g. (2%) of a crystalline di-*O*-methylenevolemitol. Because the compound is not oxidized by periodate it cannot be the 4,6:5,7-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VII) but must be the expected intermediate 1,3:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (III = XII). Its crystalline triacetate is different from that of the isomeric 2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VI). On further methylenation it was converted to the tri-*O*-methylenevolemitol (IV).

(12) H. G. Fletcher, Jr., and H. W. Diehl, *J. Am. Chem. Soc.*, **74**, 3797 (1952).



XI = 1,3:4,6:5,7-Tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VIII)



XII = 1,3:4,6-Di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (III)

EXPERIMENTAL

1,3:2,5:4,6-Tri-O-*methylene*-D-glycero-D-manno-*heptitol* (IV) (=*Tri*-O-*methylenevolemitol*). A solution of 48 g. of volemitol (I)[13] in a mixture of 100 ml. of concentrated hydrochloric acid and 200 ml. of 37% aqueous formaldehyde was heated overnight in an oven at 70°, left at room temperature for a day, and then allowed to evaporate in a crystallizing dish in an evacuated desiccator over concentrated sulfuric acid and solid potassium hydroxide. After 3 weeks the waxy residue was extracted three times by boiling with 75 ml. of water. The cooled extracts deposited 15.3 g., and the concentrated mother liquors an additional 8.7 g., making a total of 24.0 g. (42.7%) of tri-*O*-methylenevolemitol (IV). In spite of repeated recrystallizations from water, the analytical data were not satisfactory until the compound had been converted to its acetate and the latter deacetylated catalytically with sodium methoxide in methanol. Two recrystallizations from water then afforded a pure product as clusters of needles, with m.p. 181–182° and $[\alpha]_D^{20}$ −60.8° in water (*c*, 0.7).

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50. Found: C, 48.23; H, 6.44.

7-O-*Acetyl-1,3:2,5:4,6-tri*-O-*methylene*-D-glycero-D-manno-*heptitol*. When a mixture of 8.5 g. of the tri-*O*-methylenevolemitol (IV), 1.7 g. of fused sodium acetate, and 51 ml. of acetic anhydride was heated for 2 hr. on the steam bath, the acetal dissolved and then the acetate began to crystallize. After dilution of the solution with ice water, the product was isolated by filtration; wt. 7.5 g. (75.5%). The acetyl derivative was recrystallized from 500 parts of acetone, then from 100 parts of ethanol, and finally from acetone again; the needles melted at 200–201° and showed $[\alpha]_D^{20}$ −60.6° in chloroform (*c*, 1).

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 14.83. Found: C, 49.63; H, 6.43; CH_3CO, 14.75.

1,3:2,5:4,6-Tri-O-*methylene*-7-O-p-*tolylsulfonyl*-D-glycero-D-manno-*heptitol*. A solution of 0.38 g. of the tri-*O*-methylenevolemitol (IV) and 0.6 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine was left at room temperature for 10 days and then poured onto cracked ice. The crystalline product (0.27 g.; 44%) was recovered by filtration. The tosylate was recrystallized once from hot 95% ethanol and then twice from chloroform-pentane. The clusters of prisms melted at 139–140° and showed $[\alpha]_D^{20}$ −40.1° in chloroform (*c*, 0.6).

Anal. Calcd. for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51; S, 7.97. Found: C, 50.71; H, 5.53; S, 7.70.

3-O-*Acetoxymethyl-1,7-di*-O-*acetyl-2,5:4,6-di*-O-*methylene*-D-glycero-D-manno-*heptitol* (V). To a mixture of 35 ml. of acetic anhydride, 15 ml. of glacial acetic acid, and 0.5 ml of concentrated sulfuric acid, chilled in ice, was added 5 g of the tri-*O*-methylenevolemitol (IV). After 45 min. in the ice bath the solution was poured onto cracked ice. The product began to crystallize immediately. It was left overnight in the refrigerator and then filtered and washed with cold water; the dry product weighed 6.4 g. (81%). It was recrystallized three times from 8 parts of 95% ethanol, forming silky needles melting at 124–126° and showing $[\alpha]_D^{20}$ +19.2° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{16}H_{24}O_{11}$: C, 48.98; H, 6.16; CH_3CO, 32.91. Found: C, 48.87; H, 6.18; CH_3CO, 32.81.

1,3,7-Tri-O-*acetyl-2,5:4,6-di*-O-*methylene*-D-glycero-D-manno-*heptitol*. Deacetylation of 4.5 g. of the acetoxymethyldiacetyl derivative (V) with sodium methoxide in methanol, followed by deionization and concentration of the solution, left 2.9 g. of amorphous, powdery 2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VI); it was not oxidizable by periodate. Acetylation of 0.75 g. of this material with acetic anhydride and fused sodium acetate yielded 0.8 g. (70%) of the triacetate. It was recrystallized from 5 parts of 95% ethanol and then from chloroform-pentane, separating as needles with m.p. 130–131° and $[\alpha]_D^{20}$ −38.8° in chloroform (*c*, 1).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 35.64. Found: C, 49.72; H, 6.11; CH_3CO, 35.53.

1,3,7-Tri-O-*benzoyl-2,5:4,6-di*-O-*methylene*-D-glycero-D-manno-*heptitol*. The benzoylation of 1 g. of the amorphous di-*O*-methylene derivative (VI) with excess benzoyl chloride in pyridine for 15 min. on the steam bath produced a gum that was apparently not completely benzoylated. However, by repeated recrystallizations, twice from 95% ethanol, twice from chloroform-pentane, and then four times from 95% ethanol, we were able to isolate 0.1 g. of prismatic needles of the pure tribenzoate. It melted at 147–148° and showed $[\alpha]_D^{20}$ +15.3° in chloroform (*c*, 1.1).

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15. Found: C, 65.73; H, 5.05.

2,5:4,6-Di-O-*methylene-1,3,7-tri*-O-p-*tolylsulfonyl*-D-glycero-D-manno-*heptitol*. The reaction between 1.5 g. of amorphous di-*O*-methylenevolemitol (VI) and 13 g. of *p*-toluenesulfonyl chloride (10.7 molar equivalents) in 25 ml. of dry pyridine for 4 days at room temperature yielded 3.3 g. of a sirup whose sulfur content (12.03%) indicated incomplete tosylation. However, when a solution of this sirup in chloroform-pentane was kept at −5° it deposited slowly a mixture of sirup and crystals. The solid material was separated successfully by 3 recrystallizations from chloroform-pentane and 2 from ethanol, and 0.44 g. of the pure tri-*O*-tosyl derivative was finally obtained. The needles melted at 136–138° and showed $[\alpha]_D^{20}$ −18.5° in chloroform (*c*, 1.5).

Anal. Calcd. for $C_{30}H_{34}O_{13}S_3$: C, 51.56; H, 4.90; S, 13.76. Found: C, 51.64; H, 4.95; S, 13.64.

1,7-Dideoxy-1,7-diiodo-2,5:4,6-di-O-*methylene-3*-O-p-*tolylsulfonyl*-D-glycero-D-manno-*heptitol*. A mixture of 369 mg. of the tri-*O*-tosyl derivative just described and 700 mg. of sodium iodide in 35 ml. of 2-butanone was refluxed for 7 hr. The precipitated sodium *p*-toluenesulfonate weighed 207 mg. (calcd. for 2 replaceable tosyloxy groups: 205 mg.) and not more than a trace of additional precipitate was obtained on heating for another 5 hr. Water was added to the filtrate, the 2-butanone was allowed to evaporate overnight, and the oily product was extracted with chloroform. The extract, washed with water, dried with sodium sulfate, and concentrated *in vacuo*, left a sirup that crystallized spontaneously when warmed with aqueous ethanol. The product weighed 262 mg. (81%); upon recrystallization from ethanol and then from chloroform-pentane the diiodo compound separated as needles that melted at 141–142° and showed $[\alpha]_D^{20}$ +6.6° in chloroform (*c*, 1.1).

Anal. Calcd. for $C_{16}H_{20}I_2O_7S$: C, 31.49; H, 3.30; I, 41.59; S, 5.25. Found: C, 31.65; H, 3.48; I, 41.74; S, 5.37.

(13) L. C. Stewart, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **74**, 2206 (1952).

*Added August 2, 1957. 1,3:4,6-Di-*O*-methylene-*D*-glycero-*D*-manno-heptitol* (III, XII). By fractional crystallization from aqueous ethanol of the material remaining after separation of the 24 g. of tri-*O*-methylenevolemitol (IV), we have isolated 1.2 g. (2%) of a new di-*O*-methylenevolemitol. This compound, like the tri-*O*-methylene derivative, was purified through its acetate; the deacetylated product was then recrystallized twice from methanol, once from 95% ethanol (as prismatic needles), and finally from aqueous acetone (as long rectangular plates). It melted at 203–212° and showed $[\alpha]_D^{20}$ −45.2° in water (*c*, 1.1). It was not oxidized by periodate.

Anal. Calcd. for $C_9H_{16}O_7$: C, 45.76; H, 6.83. Found: C, 45.87, 45.87; H, 6.87, 6.77.

Proof that this compound was a derivative of volemitol was established by heating 0.50 g. of it with concentrated hydrochloric acid and 37% aqueous formaldehyde for 5 hr. on the steam bath. From this reaction mixture we obtained 0.06 g. (11%) of once-recrystallized tri-*O*-methylenevolemitol (IV), identified by melting point and mixed melting point.

*2,5,7-Tri-*O*-acetyl-1,3:4,6-di-*O*-methylene-*D*-glycero-*D*-manno-heptitol.* The 1.2 g. of crude di-*O*-methylenevolemitol (III) was acetylated with acetic anhydride and fused sodium acetate to yield 1.6 g. (87%) of the triacetate, which was recrystallized from 95% ethanol (as plates) and then from chloroform-pentane (as prismatic needles). It melted at 171–173° and showed $[\alpha]_D^{20}$ −9.6° in chloroform (*c*, 1.0).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 35.6. Found: C, 50.06, 50.05; H, 6.15, 6.13; CH_3CO, 35.9.

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