

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Stereochemistry of 1,4:3,6-Dianhydrohexitol Derivatives<sup>1</sup>

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The differences in reactivity of the three 1,4:3,6-dianhydrohexitols and their ditosylates have been interpreted in terms of the configurations of the substituents at the 2- and 5-positions of the parent hexitols. In these bicyclic compounds containing two *cis*-fused five-membered rings, displacement of an *exo* group in a  $S_N2$  displacement reaction is shown to be sterically hindered, while displacement of an *endo* group is facile. In transformations of these compounds involving a carbonium ion, the more stable *exo* compounds are formed preferentially. A new synthesis of dianhydro-L-iditol from D-mannitol is described. Revised configurations are suggested for a number of dianhydrohexitol derivatives and other compounds containing bicyclic ring systems with two *cis*-fused five-membered rings on the basis of steric effects observed in this research.

It is well known that the hexitols D-mannitol, D-glucitol and D- and L-iditol readily form 1,4:3,6-dianhydrides under acidic conditions.<sup>2</sup> The dianhydrides, D-isomannide (I), isosorbide (II) and D- and L-isoidide (III), each have two free hydroxyl groups located at the C<sub>2</sub>- and C<sub>5</sub>-positions.<sup>3</sup> The chemical behavior of their ditosylates IV, V and VI has been investigated by previous workers.<sup>4-9</sup> Both tosylate groups in IV have been observed to be reactive, while only one tosylate group in V can be replaced readily and both tosylate groups in VI are relatively unreactive in displacement reactions. Earlier workers<sup>4-8</sup> have attributed the differences in reactivity to the configuration of the hydroxyl groups in the dianhydrides.

Angyal and Matheson<sup>9</sup> in studying the reaction of IV, V and VI with sodium iodide pointed out the effect of steric hindrance upon the reactivity of the three ditosylates. The present paper describes other displacement reactions of the three ditosylates and conclusions that can be drawn concerning their configurations and the configurations of other compounds with similar bicyclic ring systems. According to molecular models the 1,4:3,6-dianhydrohexitols have two nearly planar *cis*-fused five-membered rings in the form of a "V" with the hydroxyl groups situated at the C<sub>2</sub>- and C<sub>5</sub>-positions either inside or outside the "V" shaped wedge. As in other ring systems such as bicyclo[2.2.1]heptane (in norcamphane, for example), the configuration of a group inside the wedge may be designated as *endo* whereas that of one outside the wedge may be designated as *exo*.<sup>10</sup> Accordingly, compound I has two *endo*-hydroxyl groups and II has one *endo* at C<sub>5</sub> and one *exo* at C<sub>2</sub>, while both hydroxyl groups in III are *exo*.

The tosylate groups in IV, V and VI, like other secondary tosylate groups in carbohydrates,<sup>11</sup> are very unreactive under solvolytic conditions.<sup>12</sup> Their substitution reactions probably involve the  $S_N2$  type mechanism,<sup>13</sup> which requires the back side approach of a nucleophilic reagent. The access to the rear of the carbon atom bearing an *exo*-tosylate group is shown by molecular models to be somewhat hindered by the ring system, whereas access to the carbon atom bearing an *endo* group is relatively unhindered. This kind of steric hindrance has been demonstrated in the reaction of IV, V and VI with sodium iodide and lithium chloride, in which a  $S_N2$  type reaction mechanism was considered most likely.<sup>9</sup> We have investigated another typical  $S_N2$  reaction, namely, the reaction with tetraethylammonium acetate.<sup>14</sup>

Treatment of the ditosylate IV with tetraethylammonium acetate in acetone readily afforded the diacetate IX, m.p. 57°, in 79% yield. The configuration of IX was established by its non-identity with the other two possible diacetates, VII<sup>15</sup> and VIII,<sup>16</sup> and by its hydrolysis to L-isoidide (III), further characterized as the dibenzoate. The formation of III from IV clearly showed that Walden inversion had occurred at both the C<sub>2</sub>- and C<sub>5</sub>-positions. On the other hand, in the reaction of V with tetraethylammonium acetate under the same conditions only the C<sub>5</sub>-*endo*-tosyl group was replaced and the acetoxy tosylate X, m.p. 96°, was obtained in 66% yield. Deacetylation of X with methanol followed by tosylation yielded VI, indicating that the *endo*-tosylate group was replaced by an acetoxy group with Walden inversion. As expected, the ditosylate VI was unreactive toward tetraethylammonium acetate; it was recovered in 58% yield after an acetone solution of the reactants was boiled for three days. Although isoidide (III) has been synthesized previously by several routes,<sup>5,17,18</sup> the reaction of IV with tetraethylammonium acetate appears to be the most practical method described to date for preparation

(1) NOTE ADDED IN PROOF: After this manuscript was submitted, similar conclusions concerning the stereochemistry of 1,4:3,6-dianhydrohexitols based on previously known reactions of such compounds have been described by J. A. Mills in *Advances in Carbohydrate Chem.*, **10**, 1 (1955).

(2) L. F. Wiggins, *Advances in Carbohydrate Chem.*, **5**, 191 (1950).

(3) C<sub>2</sub> and C<sub>5</sub> refer to the numbers assigned to the carbon atoms in the original hexitol.

(4) R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 393 (1946).

(5) V. G. Bashford and L. F. Wiggins, *ibid.*, 371 (1950).

(6) L. F. Wiggins and D. J. C. Wood, *ibid.*, 1180 (1951).

(7) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield and R. M. Goepf, Jr., *THIS JOURNAL*, **68**, 927 (1946).

(8) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepf, Jr., and S. Soltzberg, *ibid.*, **68**, 930 (1946).

(9) S. J. Angyal and N. K. Matheson, *J. Chem. Soc.*, 1133 (1952).

(10) R. Adams and B. L. Van Duuren, *THIS JOURNAL*, **76**, 6379 (1954), used the terms *cis* and *trans* to denote the configuration of substituent groups with reference to the hydrogen atoms at the ring juncture in pyrrolizidine bases.

(11) R. S. Tipson, *Advances in Carbohydrate Chem.*, **8**, 107 (1953).

(12) A. C. Cope and T. Y. Shen, to be published.

(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 377-381.

(14) J. Steigman and L. P. Hammett, *THIS JOURNAL*, **59**, 2536 (1937); J. D. Roberts, W. G. Young and S. Winstein, *ibid.*, **64**, 2160 (1942); L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4035 (1952).

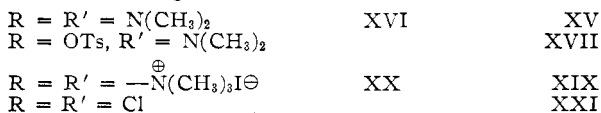
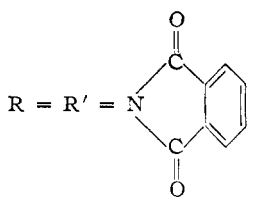
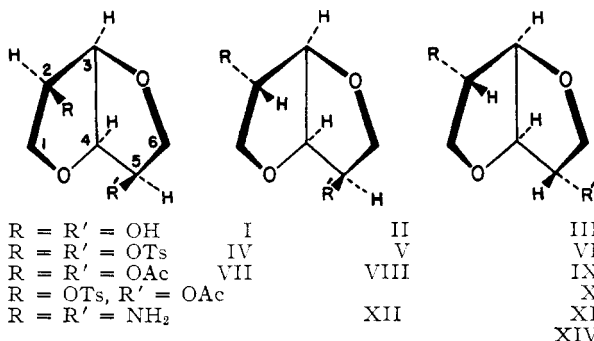
(15) A. Fauconnier, *Bull. soc. chim. France*, [2] **41**, 119 (1884).

(16) R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 237 (1948).

(17) H. G. Fletcher, Jr., and R. M. Goepf, Jr., *THIS JOURNAL*, **67**, 1042 (1945); **68**, 939 (1946).

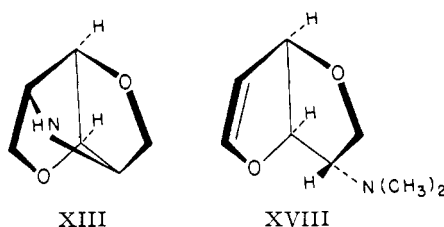
(18) L. F. Wiggins, *J. Chem. Soc.*, 1403 (1947).

of this rather inaccessible dianhydride. The synthesis of III from IV by basic hydrolysis cannot be realized, for the reaction proceeds with cleavage of the sulfur-oxygen bond and with retention of configuration rather than inversion at C<sub>2</sub> and C<sub>5</sub>.<sup>12</sup>



All three ditosylates (IV, V and VI) have been converted to amino derivatives<sup>4,5</sup> by treatment with methanolic ammonia at 170° in a sealed vessel. The diamines XI and XII were obtained from IV and V, respectively, in fair yields, while a tricyclic secondary amine XIII was obtained from VI in good yield. As C<sub>2</sub> and C<sub>5</sub> in XIII can only be bridged by an *endo*-imino linkage, Bashford and Wiggins suggested the occurrence of Walden inversion during the reaction. Although these investigators originally assigned configurations to the diamines prepared from IV and V on the assumption that there was retention of configuration at C<sub>2</sub> and C<sub>5</sub>, it appears to us more likely that inversion occurred in both instances and accordingly that the diamine prepared from IV has configuration XI, with both amino groups *exo*. The diamine derived from V would have configuration XII if either complete inversion or complete retention occurred. In the present work, the same diamine (XI) that is obtained from IV and ammonia also was obtained by converting IV to the diphthalimido compound XIV with potassium phthalimide in dimethylformamide,<sup>19</sup> followed by treatment with hydrazine.<sup>20</sup>

In additional studies of the relative reactivities of *exo*- and *endo*-tosylate groups in IV and V, these compounds have been treated with dimethylamine. At 120° the ditosylate IV reacted with dimethylamine to form the diamine XV, m.p. 55°, in 45% yield. Under similar conditions only one tosylate group in V, presumably the *endo* group at C<sub>5</sub>, was replaced, and a 44% yield was obtained of



the dimethylamino tosylate XVII, characterized as the picrate and methiodide. A small amount of an unsaturated amine, probably XVIII, in which the unreactive tosylate group was eliminated,<sup>21</sup> also was isolated. However, when the reaction temperature was raised to 165°, both tosylate groups in V were replaced, and the diamine XVI, m.p. 54.6–55.5°, was obtained in 67% yield.<sup>22</sup> In order to establish the configuration of these two tertiary amines, the primary amine XII was exhaustively methylated by excess methyl iodide, and the dimethiodide XX obtained was reduced by lithium aluminum hydride<sup>23</sup> to the tertiary amine XVI. Since this method of methylation avoids the possibility of configurational change at the carbon atoms attached to the amino groups, this result shows that XVI, like XII, has an *exo* group at C<sub>2</sub> and an *endo* group at C<sub>5</sub>. The configurations of XI and XV were shown to be the same by converting both to the same methiodide, XIX. The primary amines XI and XII also were methylated by formic acid and formaldehyde,<sup>24</sup> and in each case the tertiary amine of the same configuration was obtained.<sup>25</sup>

The dichloride XXI was prepared in good yield by the reaction of I with thionyl chloride in pyridine,<sup>26</sup> and it also has been obtained by the reaction of IV or the corresponding dimethanesulfonate with lithium chloride. Only a monochloride was obtained from II and thionyl chloride in pyridine,<sup>27</sup> or V and lithium chloride,<sup>6</sup> while neither III nor VI formed chloro compounds on treatment with thionyl chloride in pyridine and lithium chloride, respectively. Considering the results noted above, it appears likely that the reaction of I with thionyl chloride in pyridine proceeds by a S<sub>N</sub>2 displacement with inversion and that the two chlorine atoms in XXI have the *exo* configuration.

Both diamines XI and XII have been converted to III with two *exo*-hydroxyl groups by the action of nitrous acid.<sup>5</sup> The deamination reaction is be-

(21) Other examples of elimination of an unreactive tosylate group: K. Freudenberg and A. Doser, *Ber.*, **56**, 1243 (1923); K. Freudenberg and H. Hess, *Ann.*, **448**, 121 (1926); K. Freudenberg and K. Smeykal, *Ber.*, **59**, 100 (1926); T. M. Reynolds, *J. Chem. Soc.*, 2626 (1931); see also ref. 5.

(22) Although the tertiary amines XV and XVI have almost identical melting points, a mixture of the two melted at room temperature. Their infrared spectra also showed marked differences.

(23) A procedure based on one described by G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 406 (1950), and further developed by A. C. Cope and M. A. P. Meisinger, to be published.

(24) H. T. Clark, H. B. Gillespie and S. Z. Weisshaus, *THIS JOURNAL*, **55**, 4571 (1933).

(25) This result shows that no tautomerism of the type  $>CH-N=CH_2 \rightleftharpoons >C=N-CH_3$  was taking place during the methylation, for otherwise a mixture of the more stable diamine XV and XVI could be obtained from XII.

(26) L. F. Wiggins, *J. Chem. Soc.*, 4 (1945).

(27) W. G. Overend, R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 2201 (1948).

(19) Conditions previously employed for similar reactions of halides by J. C. Sheehan and W. A. Bolhofer, *THIS JOURNAL*, **72**, 2786 (1950).

(20) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

TABLE I

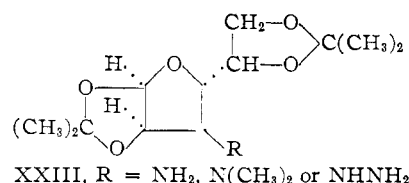
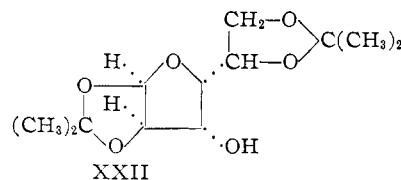
Compound	Revised configuration	Ref.
5-Chloro-5-deoxy(?) -1,4:3,6-dianhydro-D-glucitol	5-Chloro-5-deoxy-1,4:3,6-dianhydro-L-iditol	27
x-Iodo-x'-O-p-toluenesulfonyl-1,4:3,6-dianhydro-D-glucitol	5-Iodo-5-deoxy-2-O-p-toluenesulfonyl-1,4:3,6-dianhydro-L-iditol	7
2,5-Dichloro-2,5-dideoxy-1,4:3,6-dianhydro-D-mannitol	2,5-Dichloro-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol	26
2-Chloro-2-deoxy-5-O-methanesulfonyl-1,4:3,6-dianhydro-D-mannitol	2-Chloro-2-deoxy-5-O-methanesulfonyl-1,4:3,6-dianhydro-D-glucitol	30
2-Chloro-2-deoxy-5-phenylcarbonyl(?) -1,4:3,6-dianhydro-D-mannitol	2-Chloro-2-deoxy-5-phenylcarbonyl-1,4:3,6-dianhydro-D-glucitol	31
2,5-Diiodo-2,5-dideoxy-1,4:3,6-dianhydro-D-mannitol	2,5-Diiodo-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol	8
2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-D-mannitol and derivs.	2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol and derivs.	4
2,5-Dithio-2,5-dideoxy-1,4:3,6-dianhydro-D-mannitol and derivs.	2,5-Dithio-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol and derivs.	29

lied to proceed through an intermediate containing a trigonal carbonium ion.<sup>28</sup> The formation of III as the only isomer isolated indicates that the product with the more stable *exo* configuration is preferentially formed, probably for steric reasons. We have also investigated the reaction of nitrosyl chloride with the diamines XI and XII. In each case a mixture was obtained, from which the dichloride XXI was isolated by chromatography in small yield.

In summary, the reaction of I and II with thionyl chloride in pyridine and the reaction of the ditosylates IV, V and VI with nucleophilic reagents such as sodium iodide, lithium chloride, tetraethylammonium acetate, potassium phthalimide, ammonia and dimethylamine all appear to proceed by a mechanism of the S<sub>N</sub>2 type. The relative reactivities of the *endo* and *exo* groups support this conclusion, and configurations of the reaction products provide supporting evidence. By analogy the reaction of the dimethanesulfonate of I with potassium thiolacetate<sup>29</sup> probably proceeds similarly. The structures of many 1,4:3,6-dianhydrohexitol derivatives have been assigned with the assumption of complete retention of configuration in displacement reactions in the absence of configurational information. In the light of the present work, a suggested revision of several configurational assignments is listed in Table I.

A number of other bicyclic compounds containing two *cis*-fused five-membered rings are known. For example, 1,2:5,6-diisopropylidene-D-glucofuranose (XXII), a well known compound, contains an *exo*-hydroxyl group. The tosylate of XXII has been converted into amine derivatives by reaction with ammonia,<sup>32</sup> hydrazine<sup>33</sup> and dimethylamine<sup>34</sup> under conditions similar to those used for similar reactions of IV and V. The configurations

of the reaction products were tentatively designated as the same as the original tosylate. By analogy with the present work, inversion probably occurred at C<sub>3</sub>, and the products (XXIII) probably have the D-allose configuration.



Another well investigated bicyclic system is the one present in the naturally occurring pyrrolizidine bases, the stereochemistry of which recently has been summarized by Adams and Van Duuren.<sup>10</sup> The 7-*endo*-hydroxyl group in platynecine (XXIV) as well as the primary hydroxyl group reacted with thionyl chloride to form a dichloride. Similarly retronecanol (XXV) which also has a 7-*endo*-hydroxyl group was converted to a chloride. On the other hand, dihydroxyheliotridane (XXVIII) which has a 7-*exo*-hydroxyl group only formed a monochloride. Since the reaction of thionyl chloride with pyrrolizidine bases is likely to proceed with a displacement by chloride ion, it is of interest to note that the steric effect is parallel to those observed in the dianhydrohexitol field. By analogy it might be suggested that the 7-*endo*-hydroxyl group in both XXIV and XXV have been replaced with inversion to give the products XXVI and XXVII, respectively, with a 7-*exo*-chlorine atom. Also, the monochloride obtained from XXVIII is likely to have the configuration of XXIX,<sup>35</sup> not XXX.<sup>10</sup>

(35) Adams and Van Duuren<sup>10</sup> also pointed out that the 7-hydroxyl group in the monobenzoate of XXVIII was dehydrated by boiling thionyl chloride, a fact clearly indicating that the 7-hydroxyl group of XXVIII was unreactive toward thionyl chloride.

(28) Reference 12, p. 397.

(29) P. Bladen and L. N. Owen, *J. Chem. Soc.*, 585 (1950).

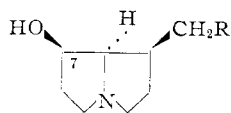
(30) R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 2204 (1948).

(31) P. Carré and P. Mauclerc, *Compt. rend.*, **192**, 1587 (1931).

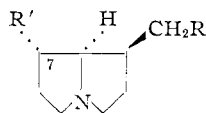
(32) K. Freudenberg, O. Burkhart and E. Braun, *Ber.*, **59**, 714 (1926). The 3-*exo*-tosylate group of XXII did not react with liquid ammonia at 100°; it was replaced at 170°.

(33) K. Freudenberg and F. Brauns, *Ber.*, **55**, 3233 (1922).

(34) K. Freudenberg and K. Smeykal, *ibid.*, **59**, 100 (1926).



XXIV, R = OH  
XXV, R = H



XXVI, R = R' = Cl  
XXVII, R = H, R' = Cl  
XXVIII, R = R' = OH  
XXIX, R = Cl, R' = OH  
XXX, R = OH, R' = Cl

### Experimental<sup>36</sup>

**1,4:3,6-Dianhydro-L-iditol Diacetate (IX).**—A solution of 35 g. of the ditosylate IV and 40 g. of tetraethylammonium acetate monohydrate in 400 ml. of acetone was heated under reflux on a steam-bath for 70 hr. The reaction mixture was concentrated to 100 ml., diluted with 400 ml. of water, and extracted with chloroform. The extract was dried over sodium sulfate, concentrated and distilled in a short path distillation apparatus at 0.7 mm. with a bath temperature of 120–150°. The distillate crystallized on cooling, m.p. 56–57°. The yield of the diacetate IX was 14.1 g. (79%). Redistillation of the product at a bath temperature of 100–110° (0.5 mm.) raised the melting point to 57–57.6°,  $[\alpha]^{25}_D$  89.6° (*c* 1.5, chloroform).

*Anal.* Calcd. for  $C_{10}H_{14}O_6$ : C, 52.17; H, 6.13. Found: C, 52.16; H, 6.14.

**1,4:3,6-Dianhydro-D-mannitol diacetate (VII)** was prepared by treating 4.0 g. of isomannide (I) with 12 ml. of acetic anhydride and 15 ml. of pyridine at 0–5° for 2 days. The solution was diluted with water and extracted with chloroform. Distillation of the extract in a semi-micro column yielded 5.63 g. (89%) of the diacetate, b.p. 118° (0.5 mm.),  $n^{25}_D$  1.4680,  $[\alpha]^{25}_D$  194.5° (*c* 6.7, chloroform). Only b.p. 197° (28 mm.) has been reported previously for this compound.<sup>15</sup>

*Anal.* Calcd. for  $C_{10}H_{14}O_6$ : C, 52.17; H, 6.13. Found: C, 52.03; H, 6.09.

**1,4:3,6-Dianhydro-L-iditol (III).**—To a solution of 12.5 g. of the diacetate IX in 90 ml. of dry methanol was added 10 ml. of 1 *N* barium methoxide in methanol at 0°. The mixture was allowed to stand at 5° for 18 hr. Powdered Dry Ice was added to precipitate barium carbonate and the solution was centrifuged until clear. Evaporation of the solvent followed by distillation at a bath temperature of 140–160° (0.4 mm.) afforded 7.1 g. (89%) of III, which crystallized in the receiver, m.p. 43–45.5°,  $[\alpha]^{25}_D$  18.7° (*c* 2, water).

**1,4:3,6-Dianhydro-L-iditol dibenzoate** was prepared by shaking 350 mg. of the diacetate IX with 5 ml. of 20% potassium hydroxide and 1 ml. of benzoyl chloride for 20 minutes. The white solid was collected on a filter, washed with water and recrystallized from aqueous ethanol as flakes (386 mg.), m.p. 110.6–111.4°,  $[\alpha]^{25}_D$  134.2° (*c* 3, chloroform). Reported physical constants for the dibenzoate are m.p. 110–111°,  $[\alpha]^{15}_D$  139° (*c* 2.8, chloroform).<sup>17</sup>

**1,4:3,6-Dianhydro-L-iditol di-*p*-toluenesulfonate (VI)** was prepared by treating 1.46 g. of III with 4.5 g. of *p*-toluenesulfonyl chloride in 15 ml. of pyridine at 0–5° for 18 hr. The reaction mixture was diluted with ice-water and the precipitate was collected on a filter, washed with water and recrystallized from methanol, yielding 3.96 g. (85%), m.p. 105.5–106°,  $[\alpha]^{25}_D$  33.2° (*c* 2.5, chloroform). Reported physical constants for VI are m.p. 106°,  $[\alpha]^{35}_D$  +33° (*c* 2.0, chloroform).<sup>9</sup>

**5-*O*-Acetyl-2-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-L-iditol (X).**—A solution of 9.0 g. of V and 5.0 g. of tetraethylammonium acetate was heated on a steam-bath under reflux for 72 hr. The solution was concentrated, diluted with water and extracted with chloroform. The extract was dried over sodium sulfate and concentrated to a residue which crystallized. The product was recrystallized from methanol, yielding 4.54 g. (66.5%) of X, m.p. 95–96°. A microanalytical sample was prepared by recrystallization from methanol, m.p. 95.5–96.3°,  $[\alpha]^{25}_D$  50.5° (*c* 4.7, chloroform).

*Anal.* Calcd. for  $C_{15}H_{18}O_7S$ : C, 52.62; H, 5.29; S, 9.37. Found: C, 52.96; H, 5.18; S, 9.59.

(36) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

**Deacetylation and Tosylation of 5-*O*-Acetyl-2-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-L-iditol.**—To a solution of 1.0 g. of X in 10 ml. of dry methanol was added 10 ml. of 0.1 *N* barium methoxide in methanol at 0°. After 18 hr. the solution was neutralized by powdered Dry Ice, centrifuged and evaporated to an oily residue under reduced pressure. The residue was treated with 1.0 g. of *p*-toluenesulfonyl chloride in 10 ml. of pyridine at 5° for 18 hr. The reaction mixture was poured into ice-water and the precipitate was collected on a filter, washed with water and recrystallized from methanol, yielding 0.67 g. (51%) of 1,4:3,6-dianhydro-L-iditol di-*p*-toluenesulfonate (VI), m.p. 105–106°. Mixed melting point with an authentic sample of VI was not depressed.

**Treatment of 1,4:3,6-Dianhydro-L-iditol Di-*p*-toluenesulfonate with Tetraethylammonium Acetate.**—A solution of 3.8 g. of VI and 1.75 g. of tetraethylammonium acetate monohydrate in 50 ml. of acetone was heated under reflux on a steam-bath for 72 hr. The solution was concentrated to 20 ml. and diluted with water; an oily product separated which soon crystallized. The solid was recrystallized from methanol and yielded 2.19 g. (58%) of unchanged VI, m.p. 104.5–105.3°. The mother liquor contained some unstable product which developed a dark green color on standing at room temperature; it was not investigated further.

**2,5-Dipthalimido-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (XIV).**—A mixture of 22.6 g. of IV, 20 g. of potassium phthalimide and 300 ml. of dimethylformamide was heated in an oil-bath at 110° for 40 hr. The pale brown solution was diluted with 1.5 l. of water, and the precipitate was collected on a filter. The solid was extracted with 300 ml. of boiling ethanol to remove the more soluble fraction, leaving 6.9 g. (34%) of the insoluble dipthalimide derivative XIV, m.p. 242–243.2°. A microanalytical sample was prepared by recrystallization from ethyl acetate-ethanol as prisms, m.p. 243.4–243.6°,  $[\alpha]^{25}_D$  168° (*c* 1, chloroform).

*Anal.* Calcd. for  $C_{22}H_{16}O_8N_2$ : C, 65.34; H, 3.99; N, 6.92. Found: C, 65.22; H, 4.21; N, 6.84.

**2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (XI).**—A mixture of 8.08 g. of XIV, 1.51 g. of 85% hydrazine hydrate and 200 ml. of ethanol was heated under reflux on a steam-bath for 2 days. After 20 ml. of 4 *N* hydrochloric acid had been added, boiling was continued for another hour. The precipitate formed was removed by filtration and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml. of water, filtered to remove a small amount of an insoluble substance and treated with an excess of freshly prepared silver carbonate to remove chloride ion. The solution was treated with Darco, filtered and acidified with aqueous oxalic acid to pH ~4.5. Dilution of the aqueous solution with ethanol precipitated the oxalate, m.p. 242–243° dec. (2.1 g., 43%). The oxalate was dissolved in water, treated with 0.7 g. of sodium hydroxide in water, filtered and distilled through a semi-micro column. The diamine XI, b.p. 110° (0.2 mm.), solidified in the receiver (m.p. 59–60°) and was obtained in a yield of 0.97 g. (78%). It formed a picrate, m.p. 227.8–228.1° dec. Reported physical constants are m.p. 59–62° for the diamine, m.p. 246–247° for the oxalate and m.p. 227–228° dec. for the picrate.<sup>4</sup>

**2,5-Bis-dimethylaminomethyl-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (XV).**<sup>37</sup>—A solution of 39 g. of IV and 70 g. of anhydrous dimethylamine in 500 ml. of tetrahydrofuran was heated in a steel bomb at 120° with shaking for 72 hr. The bomb was opened at room temperature and the red solution was concentrated, treated with 100 ml. of 20% sodium hydroxide and extracted four times with 100 ml. of ether. The ethereal extracts were combined, dried over sodium hydroxide and concentrated. The sirupy residue was distilled, b.p. 80–100° (0.2 mm.), and solidified in the receiver, m.p. 57–59°, yield 7.5 g. (44%). An analytical sample was prepared by sublimation at 40° (0.2 mm.), m.p. 57.5–58.5°,  $[\alpha]^{25}_D$  30.0° (*c* 2.1, water).

*Anal.* Calcd. for  $C_{10}H_{20}N_2O_2$ : C, 59.97; H, 10.07; N, 13.99. Found: C, 59.65; H, 10.13; N, 13.94.

**2,5-Bis-dimethylaminomethyl-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol dimethiodide (XIX)** was prepared from XV and excess methyl iodide in boiling methanol. It was recrystallized from aqueous ethanol as a monohydrate, m.p. 260° (dec. without melting),  $[\alpha]^{25}_D$  33.3° (*c* 2.2, water).

(37) We are indebted to H. H. Lee for this preparation.

*Anal.* Calcd. for  $C_{12}H_{28}N_2O_3I_2$ : C, 28.70; H, 5.62; N, 5.58; I, 50.37;  $H_2O$ , 3.59. Found: C, 28.93; H, 5.48; N, 5.77; I, 50.37;  $H_2O$ , 3.58.

**2,5-Bis-dimethylaminomethyl-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol dipicrate** was prepared from III and picric acid in water. It was recrystallized from aqueous ethanol, m.p. 222° dec.

*Anal.* Calcd. for  $C_{22}H_{36}N_8O_{16}$ : C, 40.13; H, 3.98; N, 17.02. Found: C, 40.08; H, 4.27; N, 16.89.

**Reaction of 1,4:3,6-Dianhydro-D-glucitol Di-*p*-toluenesulfonate (V) with Dimethylamine.**—(a) A solution of 45.2 g. of V and 100 g. of anhydrous dimethylamine in 600 ml. of tetrahydrofuran was heated in a steel bomb at 120–130° with shaking for 50 hr. After cooling to room temperature, the bomb was opened and the solution was concentrated, treated with 150 ml. of 20% sodium hydroxide and extracted with ether. The extract was dried over potassium hydroxide, concentrated and distilled at 0.3 mm. There was obtained 0.68 g. of a crude low-boiling fraction, b.p. 41° (0.3 mm.), and 14.5 g. of a non-volatile residue. The distillate was treated with methyl iodide in methanol, and the methiodide that was formed was treated with activated charcoal and recrystallized three times from ethanol as plates, m.p. 202–203° dec.,  $[\alpha]_D^{25}$  33.1° (*c* 2.5, water). The yield was 1.13 g. (3.8%).

*Anal.* Calcd. for  $C_9H_{16}O_2NI$ : C, 36.39; H, 5.43; N, 4.72. Found: C, 36.55; H, 5.29; N, 5.08.

The infrared spectra of both the crude distillate and the methiodide showed very strong absorption at 1610  $cm^{-1}$ , probably the enol-ether band. This compound is believed to be 5-dimethylamino-5-deoxy-1,4:3,6-dianhydro-1,2-L-iditoleen (XVIII).

The non-volatile residue was dissolved in ether and washed once with water. The ethereal solution was dried over potassium hydroxide and concentrated to a brown sirup.

**2-*O*-*p*-Toluenesulfonyl-5-dimethylamino-5-deoxy-1,4:3,6-dianhydro-L-iditol picrate** was prepared from the brown sirup and picric acid in 95% ethanol, m.p. 178.5–179.5°. Two recrystallizations from ethanol raised the m.p. to 179.4–180.8°.

*Anal.* Calcd. for  $C_{21}H_{34}O_{12}N_4S$ : C, 45.32; H, 4.35; N, 10.08. Found: C, 45.54; H, 4.55; N, 10.21.

**2-*O*-*p*-Toluenesulfonyl-5-dimethylamino-5-deoxy-1,4:3,6-dianhydro-L-iditol methiodide** was prepared from the sirup and methyl iodide in methanol, m.p. 173–175°. An analytical sample was recrystallized from ethanol twice as prisms, m.p. 177.6–178.6°.

*Anal.* Calcd. for  $C_{18}H_{24}O_5NSI$ : C, 40.96; H, 5.16; N, 2.98. Found: C, 41.13; H, 5.30; N, 3.28.

(b) A solution of 45.2 g. of V and 100 g. of anhydrous dimethylamine in 600 ml. of tetrahydrofuran was heated in a steel bomb at 165° with shaking for 48 hr. After cooling to room temperature, the bomb was opened and the solution was concentrated, treated with 150 ml. of 20% sodium hydroxide and extracted with ether. The extract was dried over potassium hydroxide, concentrated and distilled through a simple distillation head with a bath temperature of 120–180° (0.5 mm.). The product was redistilled to yield 13.4 g. (67%) of 2,5-bis-dimethylamino-2,5-dideoxy-1,4:3,6-dianhydro-D-glucitol (XVI) which crystallized on cooling, m.p. 54.0–55.2°. An analytical sample was prepared by passing a solution of the product in petroleum ether (b.p. 30–60°) through a column of activated alumina to remove traces of red colored impurities. The effluent was evaporated to dryness under reduced pressure and the residue was sublimed at a bath temperature of 80° (0.5 mm.) as white prisms, m.p. 54.6–55.4°,  $[\alpha]_D^{25}$  106.3° (*c* 1.6, water).

*Anal.* Calcd. for  $C_{10}H_{20}O_2N$ : C, 59.96; H, 10.07; N, 13.99. Found: C, 59.95; H, 10.38; N, 13.87.

**Methylation of 2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-D-glucitol (XII).**—(a) A solution of 1.17 g. of the crystalline oxalate of XII in 10 ml. of 98% formic acid and 8 ml. of 37% formaldehyde was heated under reflux for 18 hr.; 10 ml. of 4 *N* hydrochloric acid was added and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml. of 1 *N* sodium hydroxide and extracted with ether. The extract was dried over potassium hydroxide, concentrated and the residue was completely sublimed at a bath temperature of 80° (0.5 mm.) as

prisms, 0.67 g. (65%), of XVI, m.p. 54–54.5°. Mixed melting point with a sample of XVI described in the preceding paragraph showed no depression, but a mixture with an equal amount of XV melted at room temperature.

**2,5-Bis-dimethylamino-2,5-dideoxy-1,4:3,6-dianhydro-D-glucitol dimethiodide** was prepared by heating the diamine with excess methyl iodide in methanol, and the product was recrystallized from aqueous methanol as a monohydrate, m.p. 292–295° dec.

*Anal.* Calcd. for  $C_{12}H_{28}O_3N_2I_2$ : C, 28.69; H, 5.58; N, 5.58. Found: C, 28.73; H, 5.82; N, 5.54.

(b) A solution of 3.0 g. of XII and 25 g. of methyl iodide in 100 ml. of dry methanol was heated under reflux in the presence of 4 g. of sodium carbonate with stirring for 48 hr. The solution was acidified with 48% hydroiodic acid and evaporated to dryness under reduced pressure. The residue was recrystallized from aqueous methanol to remove sodium iodide, yielding 9.25 g. (89%) of the dimethiodide monohydrate XX, m.p. 289–294° dec.

The dimethiodide was dissolved in 100 ml. of dry *N*-methylmorpholine which had been redistilled over lithium aluminum hydride. A slurry of 2 g. of lithium aluminum hydride in 20 ml. of *N*-methylmorpholine was added slowly with stirring and cooling. After the initial exothermic reaction subsided the mixture was heated in an oil-bath at 90–95° for 48 hr. Excess lithium aluminum hydride was destroyed by the addition of ethyl acetate with ice-cooling. The precipitate was collected by centrifugation, dissolved in 10% sodium hydroxide and extracted with ether. The extract was combined with the *N*-methylmorpholine solution and dried over potassium hydroxide. Fractionation of the extract through an 8-inch Vigreux column followed by sublimation of the residue afforded 2.73 g. (74%) of the diamine XVI, m.p. 51.5–53.5°, slightly contaminated with an oily impurity. The crude product was purified by drying on a porous plate followed by sublimation; m.p. and mixed m.p. with a sample prepared by method a, 54.3–55.2°. The infrared spectrum of the crude product was identical with that of a pure sample and contained no characteristic bands of its isomer XV.

In an attempted purification of the crude product by Hinsberg's method, 1.0 g. of the diamine XVI was warmed with 2.0 g. of *p*-toluenesulfonyl chloride in 20 ml. of 10% sodium hydroxide on a steam-bath for 15 minutes until a clear solution was obtained. From the solution only 135 mg. (13.5%) of the pure diamine XVI was recovered, m.p. 54.3–55.3°.

**Methylation of 2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (XI).**—(a) A solution of 0.72 g. of XI in 10 ml. of 98% formic acid and 6 ml. of 37% formaldehyde was heated under reflux for 18 hr. The product was isolated in a manner similar to the one described above. The yield of the diamine XV was 0.72 g. (72%), m.p. 52–54°; mixed m.p. with an authentic sample of XV prepared by the reaction of dimethylamine with the ditosylate IV as described above was not depressed.

(b) A solution of 0.320 g. of XI and 5 g. of methyl iodide in 20 ml. of dry methanol was heated under reflux for 65 hr. in the presence of 0.85 g. of sodium bicarbonate. The solid was collected on a filter, washed with 95% ethanol and recrystallized from aqueous ethanol as prisms, 0.667 g. (60%), m.p. 225–228° dec. The infrared spectrum of XIX from this source was identical with a sample prepared by the reaction of methyl iodide with the diamine XV as described above.

**Reaction of 2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-L-iditol (XI) with Nitrosyl Chloride.**—To a mixture of 0.72 g. of XI and 3 ml. of concentrated hydrochloric acid in 30 ml. of glacial acetic acid was added slowly 2.0 g. of *n*-butyl nitrite, with ice-cooling and stirring. After a few minutes gas bubbles gradually evolved from the brown solution and the suspended solid slowly dissolved. The solution was allowed to stand in the ice-bath for 0.5 hr. and at room temperature for 18 hr. The colorless solution was concentrated under reduced pressure, diluted with water and extracted with chloroform. The extract was dried over sodium sulfate, filtered and evaporated to a sirup. The sirup was distilled at a bath temperature of 130° (0.2 mm.) in a short path distillation apparatus as an oil, which did not crystallize. The oil was chromatographed on 10 g. of activity II alumina using petroleum ether (b.p. 30–60°)–ether (5:1) as the eluent. The dichloride XXI was obtained from

the first 60 ml. of effluent, in an amount of 103 mg. (11.2%), m.p. and mixed m.p. with an authentic sample prepared by the reaction of thionyl chloride in pyridine with D-isomannide (I),<sup>20</sup> 67°.

Reaction of 2,5-Diamino-2,5-dideoxy-1,4:3,6-dianhydro-

D-glucitol (XII) with Nitrosyl Chloride.—The deamination was carried out in a manner similar to the one described above. Chromatography of the product yielded 87 mg. of XXI from 0.72 g. of XII; the yield was 9.5%.

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## Chromate Esters. II. Reactions of Di-2-methylfenchyl Chromate<sup>1,2</sup>

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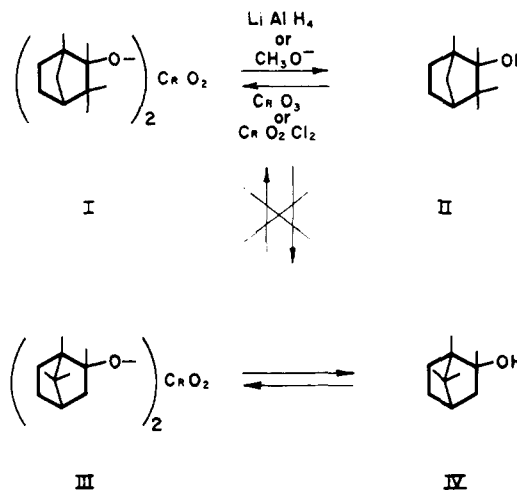
The behavior of the chromate ester of 2-methylfenchol under varied solvolytic conditions has been examined. These results, together with those obtained from the chromic acid oxidation of 2-methylfenchol itself and of a mixture of 1-methylcamphene and 1-methyl- $\alpha$ -fenchene, are used to delineate the path by which tertiary alcohols are oxidized and tertiary chromates react as oxidizing agents.

In the first paper of this series<sup>4</sup> the formation and solvolysis of an aliphatic tertiary chromate ester are demonstrated to occur with retention of configuration at the tertiary carbon atom. In the present paper we describe the chemical properties of a very stable bicyclic tertiary chromate ester in order to delineate as closely as possible the path by which tertiary alcohols are oxidized. As a corollary to these studies the function of tertiary chromate esters as oxidizing agents is adduced.

The first chromate ester to be isolated by Wienhaus, di-2-methylfenchyl chromate (I), was prepared by the usual methods<sup>5</sup> and also by the use of chromyl chloride<sup>4</sup> from 2-methylfenchol (II). Since our preparation commenced with almost racemic  $\alpha$ -fenchone, the chromate ester with which we worked was a mixture of *exo* and *endo* isomers.<sup>19,20</sup> However, the stereoisomeric composition of the ester is quite reproducible as are the results, kinetic<sup>9</sup> and chemical, obtained with it. By analogy with the isoborneol-borneol system it may be anticipated that the *exo* (C-2 methyl) forms of the diester will rearrange more rapidly than the *endo* forms during reaction. However, both types of esters should decompose to the same products, albeit in different ratios, and thus produce no difficulties in the interpretation of the results.

Reduction of this red, crystalline ester with lithium aluminum hydride provided structurally pure II, spectroscopically similar in the infrared region to that purified *via* the half phthalate ester and subsequent reduction with the same reagent. This reaction cycle ensures the absence of rearrangement of the fenchyl structure to that of bornyl and establishes the fact that it resides intact in the chromate ester. Further, it confirms the stereochemical evidence for the observed maintenance of asymmetric identity in optically active 2,4-dimethyl-4-hexanol throughout a similar cycle.<sup>4</sup> The structural isomer of II, 2-methylborneol (IV), like-

wise failed to undergo rearrangement under equivalent circumstances. Then also, the action of methoxide ion on I regenerated II without rearrangement.



The diester I was solvolyzed in methanol at 25, 46 and 65°, and, although the products were the same regardless of the temperature, at 25° less than 20% of I had reacted after 4 days. At 46° reaction was substantially complete in this period of time, and at 65° methanolysis time was less than 24 hours. The products from a sealed tube reaction at 65° were the parent alcohol II, a mixture of 1-methylcamphene (V) and 1-methyl- $\alpha$ -fenchene (VI), an apparent mixture of the methyl ethers of II and IV, formaldehyde and an insoluble organochromium compound analyzing for trimethoxychromium. The presence of methyl ether is indicated by comparison of the 8.5–9.5  $\mu$  infrared region of the product with that of an authentic sample of the methyl ether of II; and it is inferred that a mixture of the ethers of II and IV is present on the basis of the reasonable mechanism proposed below. The main product was 2-methylfenchol (61%) unaccompanied by IV. In the incomplete run at 25° the recovered ester I contained none of III. It is concluded, therefore, that the decomposition of I is irreversible with respect to any process involving the reformation of I subsequent to or during the

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(2) Taken from the Ph.D. dissertation of D. A. Pease, Jr., Yale University, 1954, and presented in part at Los Angeles, Calif., March 18, 1953, *Abstr., 123rd Meeting, Am. Chem. Soc.*, p. 30M.

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