To the periodate oxidation solution of the polyalcohol, a solution of barium acetate (2.55 g.) was added, and the precipitate of barium iodate and barium periodate removed by centrifugation. The supernatant and washings were neutralized with 0.105 *N* sodium hydroxide and to the neutral solution sodium borohydride (200 mg.) was added in two separate additions of 100 mg. over a period of 4 hours. The solution was allowed to stand for 24 hours and neutralized with glacial acetic acid. The acidity of the solution was increased to approximately 1 *N* by the addition of concentrated hydrochloric acid. The solution was boiled under reflux for 12 hours, cooled and neutralized by successive passage through a cation exchange resin (Amberlite IR-120) and an anion exchange resin (Duolite A4), respectively. The neutral solution was concentrated under diminished pressure to a sirup. The glucose, separated from the other hydrolytic products by paper partition chromatography using 1-butanol:ethanol:water (4:1:5) as the solvent corresponded in R_f to a glucose standard.

Isolation of D-Glucose and Preparation of the *p*-Nitroanilide.—The glucose present in the hydrolysate of the waxy corn starch polyalcohol from experiment II was separated using the sheet paper chromatography technique described in a previous paper.[3] The product obtained in this way was purified by chromatographing on a single sheet of Whatman No. 3 filter paper using the same irrigating solvent. The sirupy product thus obtained was found by polarimetric observation to contain D-glucose (11.2 mg.). Following the procedure of Weygand, *et al.*,[16] there was obtained D-glucose *p*-nitroanilide, m.p. and mixed m.p. 180–182°, $[\alpha]^{23}\mathrm{D}$ $-190°$ in pyridine (*c* 1) (after recrystallization from methanol).

Periodate Oxidation of the β-Limit Dextrin.—The β-limit dextrin (5.0 g.) prepared as described previously,[3] was dissolved in hot water (50 ml.) and allowed to cool to room temperature, after which a solution of sodium periodate (21.4 g.) in water (150 ml.) was added. The volume was quickly adjusted to 250 ml. with water giving a final periodate concentration of 0.4 *M*. The reaction mixture was kept at 2–4° in the dark for 6 days. The formic acid production and periodate consumption were followed in the manner already described.[3] The average chain length as determined by formic acid production was 6 (constant after 24 hours) and the periodate consumed per anhydroglucose unit after 144 hours was 1.09 moles.

Sodium Borohydride Reduction and Hydrolysis of the Polyalcohol.—The polyaldehyde was reduced, hydrolyzed, deionized and concentrated under reduced pressure to a sirup. Qualitative paper chromatographic analysis was carried out for 48 hours using an irrigating solvent of 1-butanol:ethanol:water (4:1:5). The results of spraying with Tollens reagent showed the presence of a small amount of glucose and larger amounts of glycerol and erythritol.

Quantitative Determination of Glucose.—The hydrolysate of the β-limit dextrin polyalcohol was concentrated under diminished pressure to a sirup of constant weight (1.464 g.) which was dissolved in ethanol and made up to 10 ml. in a volumetric flask. An aliquot of this solution (0.048 ml.) was transferred to a sheet of Whatman No. 1 filter paper (8″ × 22″) and separated by paper chromatography, irrigation being carried out for 46 hours with 1-butanol:ethanol:water.

The amount of glucose unattacked by periodate was found to be 0.33% based on the starting weight of β-limit dextrin. This was the average value obtained from four separate analyses carried out in duplicate which gave 0.39, 0.30, 0.33 and 0.29% glucose, respectively.

Acknowledgment.—The authors thank the Northern Utilization Research Branch (Peoria, Ill.) for the waxy corn starch, and Corn Industries Research Foundation for financial support.

ST. PAUL, MINNESOTA

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[16] F. Weygand, W. Perkow and P. Kuhner, *Ber.*, **84**, 594 (1951).

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

The Detosylation of 1,4:3,6-Dianhydrohexitol Ditosylates and Syntheses of 1,4:2,5:3,6-Trianhydro-D-Mannitol

BY ARTHUR C. COPE AND T. Y. SHEN[1]

RECEIVED JUNE 5, 1956

The two *exo*-tosylate groups in 1,4:3,6-dianhydro-L-iditol ditosylate have been removed by treatment with barium methoxide, forming the dianhydride I with retention of configuration. Reactions of 1,4:3,6-dianhydro-D-mannitol ditosylate, which has two *endo*-tosylate groups, with hydroxide, methoxide and hydride ions also resulted in retention of configuration with formation of the dianhydride II. Treatment of 1,4:3,6-dianhydro-D-glucitol ditosylate with sodium ethoxide yielded 14% of the dianhydride III and 60% of 1,4:2,5:3,6-trianhydro-D-mannitol (X), of interest as a hexitol trianhydride. Reaction of the trianhydride X with concentrated hydrochloric acid resulted in cleavage of the 1,4- and 3,6-anhydro rings, and the crystalline dichloro glycol XIV was obtained in 76% yield. The occurrence of "transtosylation," the conversion of an alcohol to the tosylate by reaction with another alkyl or aryl tosylate, has been demonstrated in this series of compounds. This reaction is analogous to the well-known transesterification reaction of carboxylic esters with alcohols.

The reaction of an "isolated" secondary sulfonate group in carbohydrates[2] with nucleophilic reagents such as hydroxide and alkoxide ions has been shown[2] to result in desulfonylation with the cleavage of the sulfur–oxygen bond, forming the alcohol with complete retention of configuration[3] as indicated

$$\mathrm{ArSO_2}\,\vdots\,\text{—O—R} + \mathrm{OH}^{\ominus} \longrightarrow \mathrm{ArSO_2OH} + \mathrm{OR}^{\ominus}\ (\mathrm{S_N2S})$$

For the sake of convenience this type of displacement at a sulfur atom is designated in this paper as an SN2S reaction. The prevalence of SN2S reactions in carbohydrates is in direct contrast to the behavior of alkyl sulfonates under similar conditions,[6] except when the alkyl sulfonate group

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[1] Sharp and Dohme Research Associate.

[2] A sulfonate group that has no adjacent hydroxyl or sulfonate group; S. P. Tipson, *Advances in Carbohydrate Chem.*, **8**, 207 (1953).

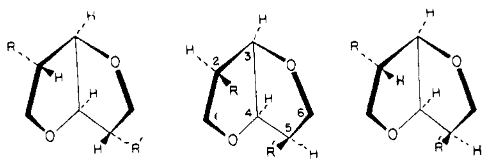
[3] The retention of configuration is not likely to be the result of an SN1 type solvolysis of the sulfonate group with the aid of a neighboring oxygen group participation. An "isolated" secondary sulfonate group in a carbohydrate has been shown[2] to be very unreactive under solvolytic conditions, probably due to the inductive effect of the neighboring oxygen-containing group.[4] The desulfonylation reactions are often carried out with strong nucleophilic reagents. Furthermore, desulfonylation with sodium alkoxide *in dry alcohol affords the hydroxy* compound, frequently in almost quantitative yield,[5] instead of the alkyl ether to be expected from solvolytic reactions.

[4] S. Winstein and co-workers, THIS JOURNAL, **70**, 816 (1948), and later papers.

[5] For example: J. W. H. Oldham and G. J. Robertson, *J. Chem. Soc.*, 685 (1935); D. J. Bell and J. Williamson, *ibid.*, 1196 (1938); W. N. Haworth, E. L. Hirst and L. Panizzon, *ibid.*, 154 (1934).

[6] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 341.

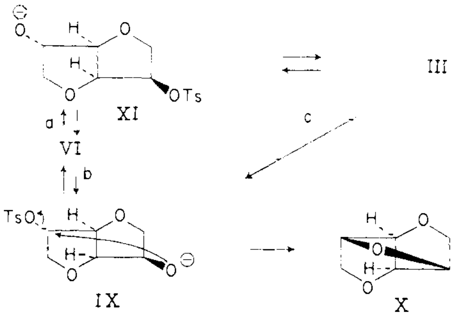
is sterically hindered.[7] Owing to insufficient conformational information about carbohydrates, the SN2S reaction has been attributed to the steric effect of a polyhydroxy compound only in an unspecified manner. The stereochemistry of the three 1,4:3,6-dianhydrohexitols has been elucidated recently.[8–10] This paper describes the detosylation of the ditosylates of these compounds, which differ only in the configuration of the tosylate groups.



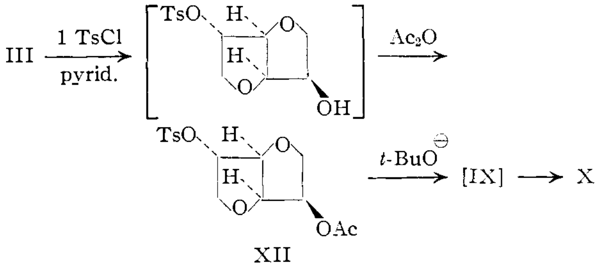
R = R' = OH	I	II	III
R = R' = OTs	IV	V	VI
R = H, R' = OH		VII	
R = R' = H		VIII	

The 1,4:3,6-dianhydrides of L-iditol (I), D-mannitol (II) and D-glucitol (III) each have two *cis*-fused five-membered rings in the form of a "V"-shaped molecule. The ditosylate IV of dianhydro-L-iditol has two *exo*-tosylate groups[9,10] (outside of the "V") which are relatively unreactive under both solvolytic and SN2 types of reaction conditions. The unreactivity toward nucleophilic reagents has been explained on the basis of steric hindrance offered by the V-shaped molecule.[9–11] When IV was treated with barium methoxide, as expected,[12] the *exo*-tosyl groups were removed by an SN2S type of reaction and the dianhydride I was obtained in 52% yield as its known dibenzoate.[9] The ditosylate V of dianhydro-D-mannitol has two *endo*-tosylate groups (inside of the "V") which have been shown to be reactive toward such nucleophilic reagents as tetraethylammonium acetate[9] and metal halides,[8,11] undergoing SN2 displacement reactions (carbon–oxygen cleavage) with Walden inversion. These results substantiate the view that the approach of an anion to the C_2 and C_5 atoms is relatively unhindered. The ditosylate V was recovered after treatment with sodium carbonate in aqueous acetone at the reflux temperature for 48 hours, indicating stability under conditions favoring solvolysis by an SN1 mechanism. However, when V was treated with potassium hydroxide in aqueous ethanol, the tosyl groups were removed and the dianhydride II was obtained in 43% yield (SN2S detosylation with retention of configuration). Likewise the detosylation was effected by treatment with sodium methoxide in dry methanol to afford II in 64% yield. When V was treated with lithium aluminum hydride,[13] the dianhydride II was obtained in 29% yield, and no deoxy compound such as VII or VIII was found in the reaction mixture. Furthermore, reduction of V with sodium in liquid ammonia also afforded II in 41% yield. These results seem to indicate that, even when steric hindrance is relatively unimportant, the reaction of an *endo*-tosylate group with strongly basic nucleophilic reagents such as hydroxide, alkoxide and hydride ions still occurs by SN2S rather than SN2 displacement.

The ditosylate VI of dianhydro-D-glucitol has an *exo*-tosylate group at C_2 and an *endo*-tosylate group at C_5. Reduction of VI with sodium in liquid ammonia yielded the dianhydride III in 31% yield (retention of configuration). However, when VI was treated with sodium ethoxide in ethanol the dianhydride III was isolated in only 14% yield as its diacetate, the main product being a new compound, $C_6H_8O_3$, m.p. 67°, obtained in 60% yield. The infrared spectrum of this compound showed the absence of hydroxyl and carbonyl absorption bands, suggesting a trianhydride structure X. The formation of X can be rationalized as



The formation of the alkoxide IX as the precursor of X is supported by another synthesis of X from III



The dianhydride III was treated with one mole of *p*-toluenesulfonyl chloride and the sirupy product, probably with most of the *exo*-C_2-hydroxy group preferentially tosylated, was converted to a crystalline acetate XII. Treatment of XII with sodium *t*-butoxide afforded the trianhydride X in 44% yield. The formation of X from both VI and XII provides an interesting example of the mech-

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(7) (a) W. Hückel and H. Pietrzok, *Ann.*, **543**, 232 (1940); (b) G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, THIS JOURNAL, **75**, 384 (1953); (c) W. S. Allen, S. Bernstein, M. Heller and R. Littell, *ibid.*, **77**, 4785 (1955); (d) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

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

(9) A. C. Cope and T. Y. Shen, THIS JOURNAL, **78**, 3177 (1956).

(10) J. A. Mills, *Advances in Carbohydrate Chem.*, **10**, 1 (1955).

(11) N. K. Matheson and S. J. Angyal, *J. Chem. Soc.*, 1133 (1952), and ref. 12c.

(12) The detosylation of an *exo*-tosyl group affords the alcohol with retention of configuration. For example: (a) the detosylation of 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-D-xylose by aqueous methanolic potassium hydroxide, P. A. Levene and J. Compton, *J. Biol. Chem.*, **111**, 325 (1935); (b) the detosylation of 5-*O*-methyl-1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-D-xylose and of 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-D-glucofuranose, P. A. Levene and J. Compton, THIS JOURNAL, **57**, 777 (1935); and (c) the desulfonylation of 5-chloro-5-deoxy-2-*O*-methanesulfonyl-1,4:3,6-dianhydro-L-iditol, L. F. Wiggins and D. J. C. Wood, *J. Chem. Soc.*, 1180 (1951).

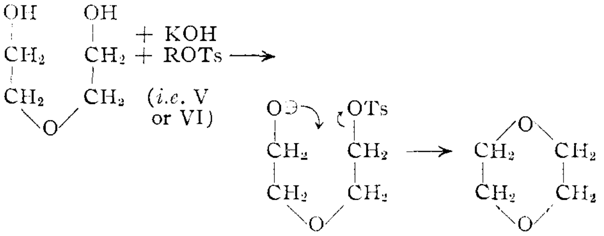
(13) A method for detosylating carbohydrate tosylates; H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949); G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 406 (1950).

anistic similarity between an SN2S type of detosylation and the saponification of a carboxylic ester; the same alkoxide ion evidently was formed in both instances.

According to the reaction scheme above the trianhydride X was formed when the *endo*-tosylate group was detosylated first (route b). The high yield of X seemed to indicate that the *endo*-tosylate group, although sterically more hindered, was preferentially detosylated. However, a more plausible explanation may be based on the assumption that a "transtosylation" took place during the reaction. The "transtosylation" may be considered as a reversible SN2S type of displacement between an alkoxide ion and a tosylate ester, analogous to the base-catalyzed transesterification reaction of carboxylic esters with alcohols.

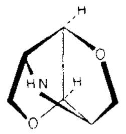
Transtosylation of III by VI or of XI by VI followed by SN2S cleavage at C_5 would yield IX, thus increasing the final yield of X. The validity of this postulation was shown by treating the disodio derivative of III with the tosylate V[14]; the trianhydride X was indeed formed in 50% yield. Similarly treatment of the disodio derivative of III with phenyl *p*-toluenesulfonate afforded the trianhydride X in 37% yield. The transtosylation was further demonstrated by treating the disodio derivative of I with phenyl *p*-toluenesulfonate; the ditosylate IV was isolated in 23% yield.

In an earlier experiment it was observed that when either V or VI was heated with potassium hydroxide in β,β′-dihydroxyethyl ether, 1,4-dioxane was obtained in about 40% yield based on the amount of the tosylate present. Since control experiments showed that in the absence of a tosylate β,β′-dihydroxyethyl ether was not dehydrated by potassium hydroxide to form 1,4-dioxane, a rationalization based on transtosylation is suggested[15]

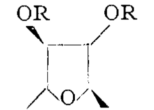


The trianhydride X appears to be the first monomeric trianhydrohexitol to be reported. A similar tricyclic compound (XIII) with a 2,5-imino bridge has been described by Bashford and Wiggins.[16] The formation of X further illustrates the proximity of C_2 and C_5 in a 1,4:3,6-dianhydrohexitol molecule.

The trianhydride X remained unchanged on treatment with 2 *N* hydrochloric acid at room temperature for 24 hours. However, when X was treated with concentrated hydrochloric acid at 100°, ring cleavage took place and a crystalline glycol, $C_6H_{10}O_3Cl_2$, m.p. 88°, was obtained in 76% yield, and was characterized as its dimethanesulfonate. The glycol was recovered almost quantitatively after shaking with acetone and cupric sulfate for 24 hours. The chlorine atoms in the molecule were very unreactive toward either silver acetate or sodium acetate in acetic anhydride at the reflux temperature; only traces of chloride ion were detected in the reaction mixture after heating for 24 hours. The product was isolated as a dichloro diacetate in 82% yield. The dichloro glycol reacted with one molar equivalent of sodium periodate, showing that the hydroxyl groups were located on adjacent carbon atoms. The optical rotatory power of the solution increased during the reaction, indicating that the product was optically active. Hydrogenolysis of the dichloro diacetate in triethylamine in the presence of a Raney nickel catalyst formed a diacetate, $C_{10}H_{16}O_5$, in 73% yield. On the basis of these data it is suggested that the dichloro glycol has structure XIV.



XIII



XIV, R = H; R′ = Cl
XV, R = $COCH_3$; R′ = Cl
XVI, R = $COCH_3$; R′ = H

The configuration of XIV is assigned on the assumption that the 1,4- and the 3,6-anhydro rings in X were cleaved preferentially.[17,18] The optical activity of the product (not isolated) obtained by periodate cleavage of XIV indicates that the groups at C_2 and C_5 have a *trans* relationship, as shown. The formation of two primary chloride groups is analogous to ring cleavage reactions of similar fused-ring systems.[19]

Experimental[20]

Detosylation of 2,5-Di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-L-iditol (IV) with Barium Methoxide.—A solution of 2.30 g. of IV and 30 meq. of barium methoxide in 100 ml. of dry methanol was refluxed for 8 hours. After cooling to room temperature, the reaction mixture was treated with excess powdered Dry Ice, centrifuged, and evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml. of dry pyridine and treated with 2 g. of benzoyl chloride at 5° for 18 hours. The mixture was

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[14] A tosylate suitable for such a transtosylation reaction must be one that is capable of undergoing an SN2S type of reaction with an alkoxide ion, such as the "isolated" secondary tosylate group of a carbohydrate, or an aryl sulfonate. C. A. Bunton and Y. F. Frei, *J. Chem. Soc.*, 1872 (1951), have shown that potassium hydroxide in O^{18}-enriched water cleaved the sulfur–oxygen bond of phenyl sulfonate exclusively. Methyl sulfonates are unsuitable. Treatment of the disodio derivative of III with methyl *p*-toluenesulfonate yielded the dimethyl ether of III in 86% yield and no X was obtained.

[15] It is of interest to note that the formation of 1,4-dioxane also was observed during the reaction of alkyl sulfonates with lithium fluoride; W. F. Edgell and L. Parts, THIS JOURNAL, **77**, 4902 (1955).

[16] V. G. Bashford and L. F. Wiggins, *J. Chem. Soc.*, 371 (1950).

[17] If the 1,4-(or 3,6-) and the 2,5-anhydro rings were cleaved preferentially, the product would have two *cis*-hydroxyl groups and two adjacent chlorine atoms, structural features which are incompatible with the observed chemical behavior of XIV.

[18] Since 1,4:3,6-dianhydroxhexitols are stable toward concentrated hydrochloric acid at the reflux temperature, the formation of XIV from X indicates that the stability of the 1,4- and the 3,6-anhydro rings was decreased by the presence of the 2,5-anhydro ring.

[19] For example, 1,4:3,6-dianhydro-D-glucitol and 1,4:3,6-dianhydro-D-mannitol have been converted by treatment with fuming hydrochloric acid to the corresponding 1,6-dichloro-1,6-dideoxyhexitol, L. F. Wiggins, ref. 7. Also D- and L-2,6-dioxabicyclo[3.3.0]octane have been converted by treatment with anhydrous hydrogen bromide to D- and L-1,6-dibromohexane-3,4-diol; A. C. Cope and T. Y. Shen, ref. 8.

[20] Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

poured into 200 ml. of ice and water and the product was collected on a filter, washed with cold water, and recrystallized from aqueous ethanol as plates, m.p. 110.5–111.2°. This product was identified as 1,4:3,6-dianhydro-L-iditol dibenzoate by mixed melting point with an authentic specimen,[9] m.p. 110.6–111.2°. The over-all yield was 0.93 g. (52%).

Detosylation of 2,5-Di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-mannitol (V) with Potassium Hydroxide.—A solution of 9.05 g. of V and 5 g. of potassium hydroxide in 200 ml. of 80% aqueous ethanol was refluxed for 18 hours. The solution was deionized by passing it through a column of 150 g. of Amberlite IR-120 resin and a column of 150 g. of Amberlite IRA-400 resin successively. The effluent was evaporated under reduced pressure to a sirup, which was distilled through a semi-micro column to afford 1.25 g. (43%) of 1,4:3,6-dianhydro-D-mannitol (II), b.p. 95–99° (0.8 mm.), m.p. 85.5°–86.8°. Mixed m.p. with an authentic sample was not depressed.

Detosylation of V with Sodium Methoxide.—To a solution of sodium methoxide prepared from 4.6 g. of sodium and 200 ml. of methanol was added 9.0 g. of V and the mixture was refluxed for 4 hours. The insoluble sodium salt was removed by filtration and the filtrate was concentrated under reduced pressure, diluted with chloroform, filtered and again concentrated to a sirup. Distillation of the residue through a semi-micro column afforded 1.87 g. (64%) of II, m.p. and mixed m.p. with an authentic sample 85.5–86.8°.

Detosylation of V with Lithium Aluminum Hydride.—To a solution of 1.2 g. of lithium aluminum hydride in 200 ml. of ether at 0° was added in small portions 9.04 g. of the ditosylate V with stirring. The reaction mixture was kept at 0° for 2 hours, at room temperature for 16 hours and finally at the reflux temperature for 2 hours. The excess lithium aluminum hydride was destroyed by ethyl acetate with ice-cooling. After the ethereal solution was decanted, the precipitate was dissolved in dilute hydrochloric acid saturated with sodium chloride and extracted continuously with chloroform for 48 hours. The ethereal and chloroform solutions were combined, dried over sodium sulfate, and concentrated through a 10-cm. Vigreux column to a sirup. Fractionation through a semi-micro column afforded 0.85 g. (29%) of II, b.p. 95° (0.3 mm.), m.p. and mixed m.p. with an authentic sample 84.0–86.0°. About 5 g. of nonvolatile residue remained in the distillation flask and was not investigated.

Reduction of V with Sodium in Liquid Ammonia.—To a suspension of 13.6 g. of V in 150 ml. of liquid ammonia was added 5.8 g. of sodium in small portions at −33°. The sodium reacted readily with the ditosylate to form an orange-yellow paste; a persistent blue color appeared after approximately 4 equivalents of sodium had been added per tosylate group. After stirring for 1 hour excess solid ammonium chloride was added, and the colorless solution was allowed to evaporate overnight. The white residue was extracted with two 100-ml. portions of ether and three 100-ml. portions of boiling chloroform. The ethereal extract was dried over sodium sulfate and fractionated through a semi-micro column to afford: (1) 1.45 g. (26%) of toluene, b.p. 108°, n^{25}_{D} 1.4930; (2) 0.88 g. (12%) of *p*-thiocresol, b.p. 80° (20 mm.), m.p. 42°; and (3) 0.35 g. of crude II, b.p. 95° (0.2 mm.), which partially crystallized on seeding. Distillation of the chloroform extract yielded 1.87 g. of crude II, b.p. 100° (0.2 mm.), which crystallized on seeding. Recrystallization of the combined 1,4:3,6-dianhydro-D-mannitol fractions from ethyl acetate–ethanol afforded 1.81 g. (41%) of pure II, m.p. 86–87°. Mixed m.p. with an authentic sample was not depressed.

Reduction of 2,5-Di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-glucitol (VI) with Sodium in Liquid Ammonia.—A solution of 12 g. of VI in 250 ml. of ammonia was treated with 5 g. of sodium at −33° and the product was isolated in a manner similar to the one described in the preceding paragraph. Fractionation yielded: (1) 1.3 g. of toluene, (2) 0.83 g. of *p*-thiocresol and (3) 1.18 g. (31%) of 1,4:3,6-dianhydro-D-glucitol, m.p. 61–63°. Mixed m.p. with an authentic sample of III was not depressed.

Reaction of VI with Sodium Ethoxide.—To a solution of sodium ethoxide prepared from 2.3 g. of sodium and 200 ml. of absolute ethanol was added 22.6 g. of VI and the mixture was heated under reflux with stirring. At the end of 5 hours titration of an aliquot showed that about 95% of sodium ethoxide had been consumed. The mixture was filtered and the filtrate was concentrated through a 20-cm. Vigreux column to a volume of 80 ml. The residue was diluted with 300 ml. of ether and the solution was again filtered and concentrated to a sirup. Distillation of the sirup afforded 3.79 g. (59%) of **1,4:2,5:3,6-trianhydro-D-mannitol (X)**, b.p. 101° (18 mm.), m.p. 64–65.5°. A microanalytical sample was prepared by sublimation at a bath temperature of 60° (20 mm.) as white prisms, m.p. 66.5–67.2°, $[\alpha]^{31}_{D}$ 128.4° (*c* 4.2, H_2O).

Anal. Calcd. for $C_6H_8O_3$: C, 56.25; H, 6.31; mol. wt., 128. Found: C, 56.11; H, 6.31; mol. wt., 143.

The distillation residue was treated with 15 ml. of pyridine and 10 ml. of acetic anhydride at 5° for 18 hours. The reaction mixture was poured into ice and water and extracted with chloroform. After concentration under reduced pressure the residue was distilled in a short-path distillation apparatus at a bath temperature of 160° (0.3 mm.) to afford 1.62 g. (14%) of 2,5-diacetyl-1,4:3,6-dianhydro-D-glucitol, m.p. and mixed m.p. with an authentic sample, 59.6–60.8°.

5-*O*-Acetyl-2-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-glucitol (XII).—To a solution of 45 g. of III in 400 ml. of dry pyridine at 0° was added 65 g. of *p*-toluenesulfonyl chloride slowly in small portions over a period of 4 hours with stirring. The reaction mixture was kept at 5° for 40 hours and was then poured into 1 l. of water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and concentrated to a small volume. The residue was dissolved in 450 ml. of 95% ethanol and stored in a refrigerator overnight, yielding 23.3 g. of the ditosylate VI, m.p. 96–98°. The mother liquor was evaporated to a sirup under reduced pressure, the last trace of moisture being removed by distillation with benzene. The sirup was treated with a mixture of 70 ml. of acetic anhydride and 100 ml. of pyridine at 5° for 40 hours. The solution was diluted with water and extracted with chloroform. The extract was washed with dilute hydrochloric acid and with dilute sodium bicarbonate, dried over sodium sulfate, and concentrated to a sirup under reduced pressure. The sirup partially crystallized on standing, and was recrystallized from aqueous methanol. The product (XII) amounted to 9.55 g. (28%), m.p. 64–65°, $[\alpha]^{25}_{D}$ 50.5° (*c* 3.5, chloroform).

Anal. Calcd. for $C_{15}H_{18}O_7S$: C, 52.63; H, 5.29; S, 9.37. Found: C, 52.71; H, 5.18; S, 9.20.

1,4:2,5:3,6-Trianhydro-D-mannitol (X) from XII.—A solution of 7.5 g. of XII in 30 ml. of *t*-butyl alcohol was added to a solution of sodium *t*-butoxide prepared by dissolving 0.58 g. of sodium in 50 ml. of *t*-butyl alcohol. The mixture was refluxed for 18 hours; during the interval a large amount of precipitate separated. The solution was filtered, concentrated by distillation through a 25-cm. Vigreux column, and fractionated through a semi-micro column. The product (1.42 g., 44%) was collected at b.p. 102–105° (20 mm.), and crystallized in the receiver, m.p. 62–65°.

The infrared spectrum of this compound was identical with that of X described in the preceding paragraph. Mixed m.p. showed no depression.

Reaction of 1,4:3,6-Dianhydro-D-glucitol (III) with 2,5-Di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-mannitol (V).—To a solution of sodium *t*-butoxide prepared from 1.5 g. of sodium and 200 ml. of *t*-butyl alcohol was added 2.92 g. of III and the mixture was stirred at room temperature for 0.5 hour. After addition of 13.5 g. of the ditosylate V, the mixture was heated under reflux for 18 hours. The solution was filtered, concentrated through a 20-cm. Vigreux column, and diluted with 200 ml. of ether. The ethereal solution was again filtered and concentrated by distillation through the Vigreux column. Distillation of the residue afforded a crude product which was sublimed at a bath temperature of 70–80° (18 mm.) to yield 1.27 g. (50%) of X, m.p. and mixed m.p. with an authentic sample 66.2–67.0°.

Reaction of 1,4:3,6-Dianhydro-D-glucitol (III) with Phenyl *p*-Toluenesulfonate.—To a solution of sodium *t*-butoxide prepared from 0.92 g. of sodium and 200 ml. of *t*-butyl alcohol was added 2.92 g. of III and the mixture was stirred at room temperature for 0.5 hour. After addition of 4.96 g. of phenyl *p*-toluenesulfonate, the mixture was heated under reflux for 18 hours. The solution was filtered, concentrated by distillation through a 20-cm. Vigreux column, and diluted with 200 ml. of ether. The ethereal solution was again filtered and concentrated. Distillation of the residue afforded a crude product containing phenol, which was chromatographed on an alumina column using petroleum ether (b.p. 30–60°) as the eluant. The product was purified by sublimation to yield 0.95 g. (37%) of pure X, m.p. and mixed m.p. with X prepared from VI and sodium ethoxide, 64.7–66.0°.

Reaction of 1,4:3,6-Dianhydro-L-iditol (I) with Phenyl *p*-Toluenesulfonate.—A solution of 0.845 g. of I in 50 ml. of tetrahydrofuran was heated under reflux with 0.30 g. of sodium hydride for 4 hours. To the suspension was added 2.88 g. of phenyl *p*-toluenesulfonate, and the mixture was refluxed for 40 hours. The solution was filtered and concentrated under reduced pressure to a sirup which partly crystallized on trituration with ethanol. The solid was recrystallized from ethanol to furnish 0.603 g. (23%) of IV, m.p. and mixed m.p. with an authentic sample[9] 104–104.5°. The infrared spectrum of this product was identical with that of an authentic sample.

Reaction of V with Potassium Hydroxide in 2,2′-Dihydroxyethyl Ether.—Potassium hydroxide (15 g.) was dissolved in 50 ml. of 2,2′-dihydroxyethyl ether with heating at about 160° and about 5.2 g. of water was removed by distillation. To the cooled solution was added quickly 18.1 g. of the ditosylate V and the mixture was heated in an oil-bath at 160–190°. After a few minutes a moderate reaction took place and a volatile product, b.p. 95–97°, was collected in the receiver. The reaction soon subsided and only water distilled on further heating. The volatile product was dried over Drierite and redistilled through a semi-micro column to give 3.4 g. (48%, based on the amount of sulfonate group present) of 1,4-dioxane, $n^{25}\text{D}$ 1.4188, identified by its infrared spectrum.

Reaction of VI with Potassium Hydroxide in 2,2′-Dihydroxyethyl Ether.—Potassium hydroxide (15 g.) was dissolved in 50 ml. of redistilled 2,2′-dihydroxyethyl ether at 160–180°. The solution was maintained at 180° for 10 minutes and about 2.1 g. of water distilled but no 1,4-dioxane was formed. To the cooled solution was added 18.1 g. of VI and the mixture was heated to 180°. A moderate reaction soon took place; 2.9 g. (41%) of 1,4-dioxane was isolated by the procedure described above.

1,6-Dichloro-1,6-dideoxy-2,5-anhydro-D-mannitol (XIV).—A solution of 2.0 g. of X in 60 ml. of concentrated hydrochloric acid was heated on a steam-bath for 18 hours. The solution was filtered to remove a small amount of an insoluble residue and concentrated under reduced pressure to a sirup. The product was distilled through a semi-micro column, b.p. 128° (0.2 mm.), $n^{25}\text{D}$ 1.5193, and crystallized on standing, m.p. 86–87°, yield 2.38 g. (76%). An analytical sample was prepared by two recrystallizations from benzene as prisms, m.p. 87.6–88°, $[\alpha]^{26}\text{D}$ 14.2° (*c* 1.2, CH_3OH).

Anal. Calcd. for $C_6H_{10}O_3Cl_2$: C, 35.85; H, 5.02; Cl, 35.32. Found: C, 35.54; H, 5.24; Cl, 35.31.

1,6-Dichloro-1,6-dideoxy-3,4-dimethanesulfonyl-2,5-anhydro-D-mannitol was prepared by the treatment of 0.8 g. of X with 2.0 g. of methanesulfonyl chloride in 10 ml. of pyridine at 5° for 18 hours. The mixture was poured into 100 ml. of ice and water and the dimethanesulfonate was collected on a filter and recrystallized from ethanol, m.p. 98.0–99.0°. The yield was 1.15 g. (81%). An analytical sample was prepared by recrystallization twice from ethanol as prisms, m.p. 98.2–99.2°.

Anal. Calcd. for $C_8H_{14}O_7S_2Cl_2$: C, 26.92; H, 3.93; Cl, 19.85. Found: C, 27.02; H, 4.05; Cl, 19.95.

Periodate Oxidation of XIV.—The dichloro glycol XIV (0.660 g.) was treated with 100 ml. of 0.05 *M* sodium periodate at 25°. Titration of aliquots at time intervals with 0.1 *N* sodium arsenite and iodine showed the number of moles of sodium periodate consumed per mole of glycol XIV as follows: 1 minute, 0.098; 5 minutes, 0.273; 15 minutes, 0.425; 25 minutes, 0.525; 40 minutes, 0.758; 55 minutes, 0.836; 70 minutes, 0.882; 100 minutes, 0.926; 145 minutes, 0.964; 190 minutes, 0.980. Treatment of the remaining reaction mixture with dimedon reagent after the removal of the iodate and periodate as their insoluble strontium salts did not precipitate a dimedon derivative.

1,6-Dichloro-1,6-dideoxy-3,4-diacetyl-2,5-anhydro-D-mannitol (XVI).—A mixture of 8.0 g. of XIV, 10 g. of anhydrous sodium acetate and 200 ml. of acetic anhydride was heated on a steam-bath for 1.5 hours. The cooled solution was poured into 500 ml. of ice-water and stirred for 0.5 hour. The product was extracted with chloroform, dried over sodium sulfate, and concentrated under reduced pressure. The residue was distilled, b.p. 152° (0.2 mm.), $n^{25}\text{D}$ 1.4750, yield 9.32 g. (82%).

Anal. Calcd. for $C_{10}H_{14}O_5Cl_2$: C, 42.13; H, 4.94. Found: C, 42.46; H, 5.35.

1,6-Dideoxy-3,4-diacetyl-2,5-anhydro-D-mannitol (XVII).—A solution of 3.90 g. of XVI in 30 ml. of triethylamine was placed in a 300-ml. autoclave equipped with a Pyrex glass liner. About 2 g. of Raney nickel catalyst which had been washed previously with triethylamine was added. The reaction mixture was shaken with hydrogen at 100° under 1500 p.s.i. for 18 hours. After cooling to room temperature the autoclave was opened, and 150 ml. of ether was added. The ethereal solution was filtered, dried over sodium sulfate, and concentrated by distillation through a 20-cm. Vigreux column. Distillation of the residue through a semi-micro column furnished 2.14 g. (73%) of XVII, b.p. 110° (12 mm.), $n^{25}\text{D}$ 1.4352, $[\alpha]^{25}\text{D}$ 15.1° (*c* 8.2, CH_3OH).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.45. Found: C, 55.79; H, 7.55.

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

Syntheses of D- and L-2,6-diheterobicyclo[3.3.0]octanes

BY ARTHUR C. COPE AND T. Y. SHEN[1]

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D-Isomannide dichloride has been converted to D-2,6-dioxabicyclo[3.3.0]octane (D-II) by hydrogenolysis. Cleavage of D-II by hydrogen bromide yielded D-1,6-dibromohexane-3,4-diol (86%), which was converted to a ditosylate, D-IV. Treatment of the ditosylate D-IV with two moles of tetraethylammonium acetate formed D-1,6-diacetoxyhexane-3,4-diol ditosylate, D-V, which reacted with sodium methoxide to form the L-enantiomorph of D-II. Cyclization of D- and L-IV with sodium sulfide gave L- and D-2,6-dithiabicyclo[3.3.0]octane, respectively. Similarly on treatment of D- or L-IV with primary amines several derivatives of L- or D-2,6-diazabicyclo[3.3.0]octane were obtained. In all ring-closure reactions of IV Walden inversions appeared to have taken place at both asymmetric centers. The stereospecificities of the transformations were indicated by the optical purity of the enantiomorphs.

In many syntheses of organic compounds from carbohydrates, the optical activity of the carbohydrate is destroyed during the removal of the hydroxyl groups. This communication reports syntheses of several new heterobicyclic systems from D-mannitol, in which the products were obtained as optically pure compounds by stereospecific transformations.

It is well known that D-mannitol can be dehydrated readily by heating with mineral acids to form a 1,4:3,6-dianhydride, commonly known as

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