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, $n^{25}D$ 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.), $n^{25}D$ 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°, $[\alpha]^{26}D$ 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.), $n^{25}D$ 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.), $n^{25}D$ 1.4352, $[\alpha]^{25}D$ 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.

CAMBRIDGE, MASSACHUSETTS

[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]

RECEIVED JUNE 5, 1956

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.

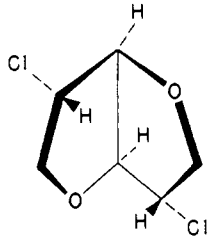
In many syntheses of organic compounds from carbohydrates, the optical activity of the carbohydrate is destroyed during the removal of the hydroxyl groups. This communication reports syntheses of several new heterobicyclic systems from D-mannitol, in which the products were obtained as optically pure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

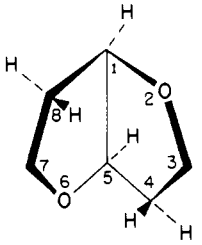
(1) Sharp and Dohme Research Associate.

D-isomannide,[2,3] which has been converted to a dichloride in good yield by treatment with thionyl chloride in pyridine.[3] The configuration of the dichloride has been shown[4,5] to be that represented by formula I, with both chlorine atoms in the *exo* configuration. Accordingly, displacement of the chlorine atoms by a Walden inversion mechanism is difficult because attack at the back of the carbon atoms to which the chlorine atoms are attached is sterically blocked by the rings. The chemical stability of the dichloride I, which can be distilled unchanged from fused potassium hydroxide,[6] undoubtedly is a consequence of these steric factors.

In this investigation, it was sought to find means of replacing the chlorine atoms of the dichloride I by hydrogen to form D-2,6-dioxabicyclo[3.3.0]-octane[7,8] (D-II), and to investigate the chemical reactions of D-II.



I

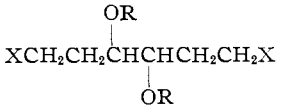


D-II

Reaction of the dichloride I with two moles of lithium aluminum hydride in tetrahydrofuran at the boiling point for two days effected only partial reduction and yielded a mixture of the unchanged dichloride I and a monochloride, presumably D-4-*exo*-chloro-2,6-dioxabicyclo[3.3.0]octane. However, catalytic hydrogenation of I in triethylamine as a solvent at 100° in the presence of Raney nickel proceeded readily and gave D-II in 74% yield. Compound D-II was obtained as a fluid liquid boiling at 153° with a somewhat sweet odor; the specific rotation was +9.0°. The ring system of D-II was relatively stable to hydrogenolysis, but when it was treated with anhydrous hydrogen bromide at room temperature, both tetrahydrofuran rings were cleaved, and the crystalline dibromo glycol, D-1,6-dibromohexane-3,4-diol (D-III), was obtained in 86% yield. The structure of D-III was established by its hydrogenolysis to D-hexane-3,4-diol, $[\alpha]_D$ 22.7°. Treatment of the latter glycol with sodium periodate afforded propionaldehyde, which was characterized as its dimedon derivative, obtained in 71% yield.

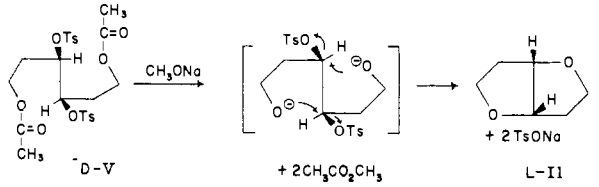
Substituted tetrahydrofurans commonly form a mixture of isomeric products on ring cleavage with acids.[9] In this case, only D-III was isolated from the reaction product of D-II and hydrogen bromide, and the cleavage evidently occurred nearly exclusively in one direction. The formation of the 1,6-dibromide D-III from D-II is analogous to the exclusive formation of 1,6-dichloro compounds from the ring opening of D-isosorbide, D-isomannide and D-isomannide dichloride by fuming hydrochloric acid.[6] Probably all of these ring cleavages are influenced in the same way by the steric nature of the fused ring structures. The configuration D is assigned to the glycol D-III and its derivatives, corresponding to the configuration of the two asymmetric centers (C_3 and C_4) of D-mannitol that remain; the carbon–oxygen bonds of these centers evidently are not affected in the process of ring cleavage.

The dibromo glycol D-III was converted in 85% yield into its ditosylate D-IV, m.p. 141°, by treatment with *p*-toluenesulfonyl chloride in pyridine. The dibromo ditosylate D-IV contains two pairs of displaceable groups (bromide and tosylate) situated in the 1,4-positions with respect to each other; such a structure suggested the possibility of re-forming bicyclic ring systems from D-IV by displacement reactions. Such ring closures have been found to take place.



D- and L-III, R = H, X = Br
D- and L-IV, R = $SO_2C_6H_4CH_3$-*p*, X = Br
D-V, R = $SO_2C_6H_4CH_3$-*p*, X = $OCOCH_3$

The dibromo ditosylate D-IV was treated with two molar equivalents of tetraethylammonium acetate to form the crystalline diacetoxyl distosylate D-V in 75% yield. Reaction of D-V with cold sodium methoxide readily gave the L-isomer of D-II (L-II) in 50% yield, $[\alpha]_D$ −9.3°. The formation of the L-isomer may be pictured as a double SN2 displacement of tosylate groups by alkoxide ions derived from the two acetoxyl groups with Walden inversions at both carbon centers. The rotation value of L-II, −9.3° compared to +9.0° for D-II, clearly indicated the high stereospecificity of the ring closure step.[10]



D-V L-II

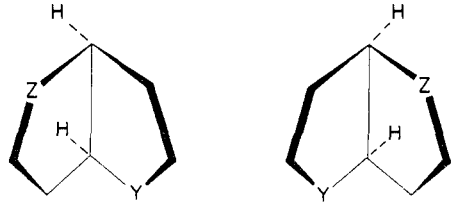
Compound L-II was converted to L-III and L-IV by reactions analogous to the ones used for preparation of the D-isomers. Their rotation values (equal but opposite in direction) also showed that the ring cleavage with hydrogen bromide, as expected, did not affect the two asymmetric carbon centers.

When D-IV was treated with two molar equivalents of sodium sulfide, the sulfur analog of II,

(2) A. Fauconnier, *Bull. soc. chim. France*, [2] **41**, 119 (1884).
(3) L. F. Wiggins, *J. Chem. Soc.*, 4 (1945).
(4) A. C. Cope and T. Y. Shen, THIS JOURNAL, **78**, 3177 (1956).
(5) J. A. Mills, *Advances in Carbohydrate Chem.*, **10**, 1 (1955).
(6) L. F. Wiggins, *ibid.*, **5**, 206 (1950).
(7) An alternative name of D-II is 1,4:3,6-dianhydro-2,5-dideoxy-D-mannitol. This ring system is listed in the Ring Index as hexahydrofuro[3,2-b]furan.
(8) Prefix D or L in this paper denotes the configuration of the compound correlated to carbohydrates.
(9) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 729.
(10) If only one of the two asymmetric centers was inverted during the reaction the product would have a relatively more strained *trans*-fused ring system, which moreover has a center of symmetry and would be optically inactive.

L-2,6-dithiabicyclo[3.3.0]octane (L-VI), was obtained in 58% yield as a low-melting solid, m.p. 25°, $[\alpha]_D$ −136.7°. Likewise the enantiomorph D-VI was obtained from L-IV, $[\alpha]_D$ +132.2°. The configurations of the two isomers were assigned on the assumption that Walden inversions again occurred during the cyclization. In this case the tosylate groups were replaced intramolecularly by mercaptide ions formed from the reaction of the primary bromide groups with sodium sulfide.

Nitrogen analogs of II and VI were obtained by treating the dibromo ditosylate D- or L-IV with amines. With *n*-butylamine, L-2,6-di-*n*-butyl-2,6-diazabicyclo[3.3.0]octane (L-VII) was obtained in 89% yield. The corresponding dimethyl compound L-VIII was prepared in 57% yield from methylamine, while D and L-2,6-dibenzyl-2,6-diazabicyclo[3.3.0]octane (D and L-IX) were obtained in 66 and 72% yield, respectively, with benzylamine. In all cases the assignments of configuration were again based on the assumption of Walden inversions in the ring closure step, and the stereospecificity of this reaction was further demonstrated by the optical purity of the D- and L-enantiomorphs which showed identical but opposite optical rotations. The reaction of the dibromo ditosylate D-IV with ammonia failed to give a monomeric product, but the unsubstituted diamine L-X, m.p. 27.5°, $[\alpha]_D$ −43.2°, was obtained from L-IX in 75% yield by hydrogenolysis in the presence of a palladium catalyst. The monobenzyl compound L-XI, m.p. 12–15°, was obtained as one of the products when the hydrogenolysis was interrupted at an intermediate stage. Similarly the diamino glycol L-XII was synthesized by the reaction of D-IV with ethanolamine in 44% yield. It was converted to its dibenzoate dihydrochloride in the usual manner. The pharmacological activity of some of these compounds is being tested and will be reported later.



L-Series D-Series

VI, Y = Z = S VI
VII, Y = Z = N-C_4H_9-*n*
VIII, Y = Z = N-CH_3
IX, Y = Z = N-$CH_2C_6H_5$ IX
X, Y = Z = NH
XI, Y = NH, Z = N$CH_2C_6H_5$
XII, Y = Z = NCH_2CH_2OH

Experimental[11]

D-4,8-*exo*-**Dichloro-2,6-dioxabicyclo[3.3.0]octane** (2,5-dichloro-2,5-dideoxy-1,4,3,6-dianhydro-D-iditol, isomannide dichloride, I) was prepared from D-mannitol according to the procedure of Wiggins.[8] The over-all yield in two steps was 28%.

D-**2,6-Dioxabicyclo[3.3.0]octane** (D-II).—A solution of 55 g. of isomannide dichloride in 200 ml. of triethylamine was placed in a 1.5-liter autoclave equipped with a Pyrex glass liner. About 30 g. of Raney nickel catalyst which had been washed previously with triethylamine was added. The reaction mixture was shaken with hydrogen at 95–105° under 1500–1900 p.s.i. for 18 hours. After cooling to room temperature the autoclave was opened, anhydrous ether (300 ml.) was added, and the catalyst and triethylamine hydrochloride were removed by filtration. The filtrate was fractionated through a 30 × 2.5-cm. Vigreux column. After forerums of ether and triethylamine were separated the product (D-II) was collected at 153–155° (atmospheric pressure) or 55° (18 mm.), $n^{25}D$ 1.4510, $[\alpha]^{25}D$ 9.0° (*c* 4.0, H_2O) as a fluid liquid. The yield was 25.3 g. (74%).

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.84. Found: C, 62.90; H, 8.89.

Lithium Aluminum Hydride Reduction of D-Isomannide Dichloride (I).—A solution of 8.3 g. of isomannide dichloride in 100 ml. of tetrahydrofuran was refluxed with 2.0 g. of lithium aluminum hydride for 48 hours. Excess lithium aluminum hydride was decomposed with water with ice-cooling and the precipitate was collected on a filter and washed thoroughly with ether. The combined ethereal and tetrahydrofuran solutions were dried over anhydrous sodium sulfate and concentrated to a small volume. Fractionation of the residual oil gave: (1) unchanged isomannide dichloride, m.p. 67°, 0.55 g. (6.5%); (2) D-4-*exo*-**chloro-2,6-dioxabicyclo[3.3.0]octane**, b.p. 98° (21 mm.), $n^{25}D$ 1.4781, $[\alpha]^{25}D$ 47.5° (*c* 1.2, $CHCl_3$), 2.92 g. (43%).

Anal. Calcd. for $C_6H_9O_2Cl$: C, 48.49; H, 6.12; Cl, 23.86. Found: C, 48.39; H, 6.12; Cl, 23.47.

In another experiment 9.2 g. of I was refluxed with 4.0 g. of lithium aluminum hydride in tetrahydrofuran for 5 days. A mixture of products was obtained from which only 0.95 g. (17%) of D-II was isolated.

D-**1,6-Dibromohexane-3,4-diol** (D-III).—A steady stream of anhydrous hydrogen bromide was introduced into a solution of 13.0 g. of D-II in 100 ml. of carbon tetrachloride at room temperature for 8 hours. An oily product which gradually separated crystallized after storing overnight at room temperature. The solid was collected on a filter, washed twice with 50-ml. portions of water, and dried over phosphorus pentoxide under reduced pressure. The yield of D-III, m.p. 88–89.5°, was 27.1 g. (86%). The product was recrystallized from benzene or carbon tetrachloride as fine needles, m.p. 89.5–90.0°, $[\alpha]^{27}D$ 58.8° (*c* 2.2, $CHCl_3$).

Anal. Calcd. for $C_6H_{12}O_2Br_2$: C, 26.11; H, 4.35; Br, 57.91. Found: C, 26.11; H, 4.29; Br, 58.02.

D-**Hexane-3,4-diol.**—A solution of 7.2 g. of the glycol III and 5.5 g. of potassium acetate in 40 ml. of methanol was shaken with hydrogen and 3 g. of 5% palladium-on-Norit catalyst at atmospheric pressure. The hydrogen uptake stopped at 920 ml. (80%) after 24 hours. The mixture was filtered, concentrated, and diluted with 100 ml. of dry ether. The ethereal solution was again filtered and concentrated to a sirup. Fractionation of the sirup through a semi-micro column afforded 1.92 g. (63%) of D-hexane-3,4-diol, b.p. 95° (18 mm.), $n^{25}D$ 1.4469, $[\alpha]^{25}D$ 22.7° (*c* 2.5, H_2O).

Anal. Calcd. for $C_6H_{14}O_2$: C, 60.96; H, 11.85. Found: C, 61.19; H, 11.89.

D-**Hexane-3,4-diol bis-***p*-**nitrobenzoate** was prepared from the glycol and *p*-nitrobenzoyl chloride in pyridine. The mixture was allowed to stand at 5° overnight, and the product was recrystallized from aqueous alcohol as plates, m.p. 111.0–111.5°.

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.75; H, 4.87; N, 6.74. Found: C, 57.68; H, 4.90; N, 6.49.

The glycol (336 mg.) was treated with 15 ml. of 0.3 *M* sodium periodate at 5° for 18 hours. After the removal of iodate and excess periodate as insoluble strontium salts, the filtrate was treated with saturated aqueous dimedon reagent. The yield of propionaldehyde dimedon derivative, m.p. 154–155°, was 615 mg. (71%).

D-**1,6-Dibromohexane-3,4-diol Ditosylate** (D-IV).—To a solution of 33.5 g. of *p*-toluenesulfonyl chloride in 120 ml. of dry pyridine was added in small portions 23.0 g. of D-III, with ice-cooling and occasional shaking. The reaction mixture was kept at 5° for 20 hours, and was then diluted with 500 ml. of ice-water. The white precipitate that separated was collected on a filter and washed with 95% ethanol; m.p. 138–140°, 41.2 g. (84.5%). It was recrystallized from

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

95% ethanol as plates, m.p. 139.5–141°, $[\alpha]^{25}D$ 74.3° (*c* 3.2, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{24}O_6Br_2S_2$: C, 41.10; H, 4.15; S, 10.96. Found: C, 41.40; H, 4.01; S, 11.07.

D-1,6-**Diacetoxyhexane-3,4-diol Ditosylate** (D-V).—A solution of 11.7 g. of D-IV in 200 ml. of acetone was added slowly to a solution of 8.7 g. of tetraethylammonium acetate monohydrate[12] in 150 ml. of acetone over a period of 5 hours at room temperature with stirring. After a few minutes a crystalline ammonium salt began to separate as fine needles. The mixture was stirred overnight and the solution was filtered, concentrated and diluted with water. The product that separated was recrystallized from ethanol as white needles in a yield of 8.12 g. (75%), m.p. 83–84°. A microanalytical sample was prepared by recrystallization from ethanol, m.p. 86.8–87.2°, $[\alpha]^{24}D$ 94.3° (*c* 1.5, $CHCl_3$).

Anal. Calcd. for $C_{24}H_{30}O_{10}S_2$: C, 53.12; H, 5.58; S, 11.80. Found: C, 53.47; H, 5.50; S, 11.99.

L-**2,6-Dioxabicyclo[3.3.0]octane** (L-II).—A solution of sodium methoxide prepared from 2.8 g. of sodium and 80 ml. of methanol was added to a suspension of 32 g. of V in 150 ml. of methanol with ice-cooling and stirring. After 0.5 hour a clear solution was formed which was allowed to stand at room temperature overnight. Titration of an aliquot showed that 92% of the sodium methoxide had been neutralized. The solution was concentrated by distillation through a packed column and the residue was diluted with ether. The sodium salt that precipitated was removed by filtration and the filtrate was fractionated to give 0.85 g. (50%) of L-II, b.p. 42° (18 mm.), $n^{25}D$ 1.4528, $[\alpha]^{24}D$ −9.3° (*c* 3.2, H_2O).

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.84. Found: C, 62.87; H, 8.73.

L-1,6-**Dibromohexane-3,4-diol** (L-III).—This compound was prepared in 84% yield from L-II by treatment with dry hydrogen bromide in carbon tetrachloride as described above for the D-isomer. It had m.p. 89.5–90°, $[\alpha]^{26}D$ −60.3° (*c* 1.6, $CHCl_3$).

Anal. Calcd. for $C_6H_{12}O_2Br_2$: C, 26.11; H, 4.35; Br, 57.91. Found: C, 25.95; H, 4.34; Br, 58.16.

The racemic compound III was prepared by mixing equal amounts of the D- and L-isomers and recrystallizing from benzene–petroleum ether as needles, m.p. 93–94.5°. Addition of a small amount of the L-isomer to this racemic compound depressed the m.p. to 91.5–91.8°.

L-1,6-**Dibromohexane-3,4-diol Ditosylate** (L-IV).—This compound was prepared from L-III in 85% yield by tosylation as described before for the D-isomer, and was recrystallized from ethanol as plates, m.p. 141.4–142.2°, $[\alpha]^{25}D$ −75.8° (*c* 1.8, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{24}O_6Br_2S_2$: C, 41.10; H, 4.15; S, 10.96. Found: C, 40.94; H, 4.09; S, 11.13.

L-**2,6-Dithiabicyclo[3.3.0]octane** (L-VI).—To a solution of 17.5 g. (0.03 mole) of D-IV in 80 ml. of ethanol was added a solution of 15 g. (0.063 mole) of sodium sulfide monohydrate in 40 ml. of ethanol at room temperature. After a few seconds a mild exothermic reaction took place with development of an orange color and separation of a small amount of a yellow solid. The mixture was heated on a steam-bath for 1 hour, concentrated under reduced pressure to 50 ml., diluted with 350 ml. of water, and extracted with ether. The ethereal extract was dried over sodium sulfate, concentrated, and the residue was fractionated through a semi-micro column, yielding 2.55 g. (58%) of L-VI, b.p. 57° (0.4 mm.), $n^{25}D$ 1.5875, $[\alpha]^{25}D$ −136.7° (*c* 4.4, $CHCl_3$). It crystallized on cooling, m.p. 24–24.5°.

Anal. Calcd. for $C_6H_{10}S_2$: C, 49.30; H, 6.90; S, 43.80. Found: C, 49.59; H, 6.62; S, 43.45.

D-**2,6-Dithiabicyclo[3.3.0]octane** (D-VI).—This compound was prepared in 57% yield by cyclization of L-IV with sodium sulfide in the manner described for the L-isomer. It had b.p. 73° (1.0 mm.), $n^{25}D$ 1.5873, $[\alpha]^{24}D$ 132.0° (*c* 3.0, $CHCl_3$).

Anal. Calcd. for $C_6H_{10}S_2$: C, 49.30; H, 6.90; S, 43.80. Found: C, 49.31; H, 6.79; S, 43.55.

L-**2,6-Di-*n*-butyl-2,6-diazabicyclo[3.3.0]octane** (L-VII).—To a solution of 10.0 g. of D-IV in 100 ml. of dioxane at the reflux temperature was added slowly 7.5 g. of *n*-butylamine over a period of 30 minutes. After refluxing for 2 hours the solution was diluted with 300 ml. of water and extracted four times with 100-ml. portions of ether. The combined extracts were washed with 30 ml. of water, dried over potassium carbonate, concentrated, and fractionated through a semi-micro column. The product (L-VII) was obtained in a yield of 3.42 g. (89%), b.p. 84° (0.3 mm.), $n^{25}D$ 1.4685, $[\alpha]^{25}D$ 62.5° (*c* 2.6, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{28}N_2$: C, 74.91; H, 12.56; N, 12.49. Found: C, 75.00; H, 12.44; N, 12.51.

L-**2,6-Di-*n*-butyl-2,6-diazabicyclo[3.3.0]octane dipicrate** was prepared from L-VII and picric acid in ether and was recrystallized from ethanol as plates, m.p. 163.2–164.2°.

Anal. Calcd. for $C_{26}H_{34}O_{14}N_8$: C, 45.74; H, 5.02; N, 16.42. Found: C, 45.87; H, 5.26; N, 16.53.

L-**2,6-Dimethyl-2,6-diazabicyclo[3.3.0]octane** (L-VIII).—A stream of dry methylamine was introduced into a refluxing solution of 17.5 g. of D-IV in 100 ml. of dioxane during a period of 2 hours. The solution was refluxed for another hour and allowed to stand at room temperature overnight. After filtration, the solution was concentrated and fractionated through a semi-micro column, yielding 2.42 g. (56%) of the diamine L-VIII, b.p. 88° (16 mm.), $n^{25}D$ 1.4673.

Anal. Calcd. for $C_8H_{16}N_2$: C, 68.53; H, 11.50; N, 20.00. Found: C, 68.31; H, 11.51; N, 19.76.

L-**2,6-Dimethyl-2,6-diazabicyclo[3.3.0]octane methiodide** was prepared from a solution of the diamine L-VIII in ether and excess methyl iodide at room temperature. The precipitate that formed was recrystallized from ethanol as long prisms, m.p. 226.8–227.2°.

Anal. Calcd. for $C_9H_{19}N_2I$: C, 38.30; H, 6.74; N, 9.92. Found: C, 37.88; H, 6.64; N, 9.60.

L-**2,6-Dimethyl-2,6-diazabicyclo[3.3.0]octane dimethiodide** was prepared by treating 0.5 g. of the diamine L-VIII with 5 ml. of methyl iodide in 50 ml. of methanol at room temperature for 2 days. The well formed crystals were collected and recrystallized from 80% ethanol, m.p. 249.5–250.0° dec., yield 1.31 g. (88%).

Anal. Calcd. for $C_{10}H_{22}N_2I_2$: C, 28.32; H, 5.23; N, 6.61. Found: C, 28.41; H, 5.41; N, 6.54.

L-**2,6-Dibenzyl-2,6-diazabicyclo[3.3.0]octane** (L-IX).—A solution of 5.0 g. of D-IV in dioxane was treated with 5.5 g. of benzylamine in a manner similar to the one described above for *n*-butylamine. The product was collected at 155–170° (0.5 mm.), and crystallized on cooling, m.p. 32–34°. The yield was 1.85 g. (72%). The product was recrystallized from aqueous methanol as needles, m.p. 37.5–38.0°, $[\alpha]^{25}D$ 62.7° (*c* 1.8, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.15; H, 8.29; N, 9.58. Found: C, 82.36; H, 8.45; N, 9.49.

L-**2,6-Dibenzyl-2,6-diazabicyclo[3.3.0]octane dipicrate** was prepared from the diamine and picric acid in ether and recrystallized from ethanol; m.p. 207.5–208.0° dec.

Anal. Calcd. for $C_{32}H_{30}O_7N_8$: C, 51.25; H, 4.02; N, 14.95. Found: C, 51.04; H, 4.31; N, 15.06.

L-**2,6-Dibenzyl-2,6-diazabicyclo[3.3.0]octane dihydrochloride** was prepared from the diamine and hydrogen chloride in ether and recrystallized from ethanol; m.p. 243.5–245.2° dec.

Anal. Calcd. for $C_{20}H_{26}N_2Cl_2$: C, 65.76; H, 7.18; N, 7.67. Found: C, 65.85; H, 7.17; N, 7.69.

L-**2,6-Dibenzyl-2,6-diazabicyclo[3.3.0]octane dimethiodide** was prepared from the diamine and methyl iodide in methanol and recrystallized from ethanol as prisms, m.p. 193.0–193.8°.

Anal. Calcd. for $C_{22}H_{30}N_2I_2$: C, 45.85; H, 5.25; N, 4.87. Found: C, 45.70; H, 5.22; N, 4.94.

L-**2,6-Diazabicyclo[3.3.0]octane** (L-X).—A solution of 7.5 g. of L-VIII in ethanol was hydrogenolyzed in the presence of 3 g. of palladium-on-Norit catalyst at 60° with stirring. After 17 hours two moles of hydrogen had been absorbed, and the solution was filtered and concentrated. The residue was fractionated through a semi-micro column, yielding 2.2 g. (75%) of the diamine L-X, b.p. 53° (0.8 mm.), $n^{25}D$ 1.5070–1.5084. The product was purified by redistillation: b.p. 40° (0.5 mm.), $n^{25}D$ 1.5082, m.p. 27.5–

(12) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4035 (1952).

28.0°, $[\alpha]^{25}D$ −37.0° (*c* 2.5, H_2O), −43.2° (*c* 2.2, CH_3OH).

Anal. Calcd. for $C_6H_{12}N_2$: C, 64.28; H, 10.71; N, 24.97. Found: C, 64.54; H, 10.86; N, 24.82.

L-2,6-Diazabicyclo[3.3.0]octane dipicrate was prepared from the diamine and picric acid in ethanol and recrystallized from aqueous ethanol as plates, m.p. 279° dec.

Anal. Calcd. for $C_{18}H_{18}O_{14}N_8$: C, 37.90; H, 3.19; N, 19.66. Found: C, 38.14; H, 3.33; N, 19.67.

L-2-Benzyl-2,6-diazabicyclo[3.3.0]octane (L-XI).—In a hydrogenolysis of L-IX, which was interrupted before completion, distillation of the product gave a 24% yield of L-X and a 53% yield of L-XI. The monobenzylamine L-XI had b.p. 106° (0.5 mm.), $n^{25}D$ 1.5470, m.p. 12–15°, $[\alpha]^{26}D$ 33.4° (*c* 3.4, CH_3OH).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.16; H, 9.02; N, 13.87. Found: C, 77.14; H, 9.28; N, 13.97.

L-2-Benzyl-2,6-diazabicyclo[3.3.0]octane dipicrate was prepared from the diamine and picric acid in ether and recrystallized from aqueous alcohol as plates, m.p. 227.5° dec.

Anal. Calcd. for $C_{22}H_{24}N_8O_{14}$: C, 45.46; H, 3.67; N, 16.98. Found: C, 45.65; H, 3.86; N, 17.03.

L-2-Benzyl-2,6-diazabicyclo[3.3.0]octane *p*-toluenesulfonamide was prepared from the diamine L-XI and *p*-toluenesulfonyl chloride in pyridine at 5°, and was recrystallized from alcohol, m.p. 84.0–85.5°.

Anal. Calcd. for $C_{20}H_{24}O_2N_2S$: C, 67.40; H, 6.78; N, 7.86. Found: C, 67.46; H, 7.09; N, 7.84.

L-2,6-Bis-(β-hydroxyethyl)-2,6-diazabicyclo[3.3.0]octane (L-XII).—A solution of 7.3 g. of ethanolamine in 20 ml. of dioxane was added slowly to a refluxing solution of 11.7 g. of D-IV in 100 ml. of dioxane over a period of 2 hours. The solution was refluxed for another 3 hours and concentrated to 30 ml. After addition of 40 ml. of 2 *N* sodium hydroxide the product was extracted with ether continuously for 72 hours. The extract was dried over potassium carbonate, concentrated, and distilled in a short-path distillation apparatus with a bath temperature of 160° (1.0 mm.). The yield of L-XII, a clear viscous liquid, amounted to 1.75 g. (44%), $n^{25}D$ 1.5180.

Anal. Calcd. for $C_{10}H_{20}O_2N_2$: C, 59.96; H, 10.06; N, 13.99. Found: C, 59.68; H, 10.17; N, 14.16.

L-2,6-Bis-(β-hydroxyethyl)-2,6-diazabicyclo[3.3.0]octane dibenzoate was prepared by heating 1.50 g. of the glycol L-XII with 5 g. of benzoyl chloride in 75 ml. of chloroform under reflux for 7 days. The crystalline mass that separated was collected, dissolved in dilute sodium bicarbonate, and extracted with ether. Evaporation of the ethereal solution afforded the dibenzoate, m.p. 60–62°. It was recrystallized from pentane as prisms, m.p. 65°.

Anal. Calcd. for $C_{24}H_{28}O_4N_2$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.78; H, 6.90; N, 7.17.

L-2,6-Bis-(β-hydroxyethyl)-2,6-diazabicyclo[3.3.0]octane dibenzoate dihydrochloride was prepared by treating the dibenzoate with 5% methanolic hydrogen chloride and recrystallizing from ethanol as prisms, m.p. 195°.

Anal. Calcd. for $C_{24}H_{30}O_4N_2Cl_2$: C, 59.86; H, 6.28; N, 5.82. Found: C, 59.90; H, 6.42; N, 5.47.

D-2,6-Dibenzyl-2,6-diazabicyclo[3.3.0]octane (D-VIII).—This compound was prepared by cyclization of L-IV with benzylamine as described before for the L-isomer in 66% yield, m.p. 37.5–37.8°, $[\alpha]D$ −63.1° (*c* 1.8, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.15; H, 8.29; N, 9.58. Found: C, 82.03; H, 8.40; N, 9.83.

D-2,6-Dibenzyl-2,6-diazabicyclo[3.3.0]octane dihydrochloride was prepared from the diamine D-VIII and hydrogen chloride in ethanol and recrystallized from the same solvent as long prisms, m.p. 241.8–243.0°.

Anal. Calcd. for $C_{20}H_{26}N_2Cl_2$: C, 65.76; H, 7.18; N, 7.69. Found: C, 65.63; H, 7.36; N, 7.75.

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The Stereochemistry of α-Lipoic Acid[1]

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The absolute configuration of (+)-α-lipoic acid has been established.

Current interest in α-lipoic acid (5-[3-(1,2-dithiolanyl)]-pentanoic acid) derives in the main from recognition of its importance as a factor in vital biochemical processes. First isolated, characterized and named by Reed and co-workers,[2] α-lipoic acid appears to assume crucial roles in photosynthesis[3] as well as in the (related) tricarboxylic acid cycle.[2] Available evidence[2,4,5] indicates that biological activity is confined to the naturally occurring (dextrorotatory) isomer.

While the gross structure of α-lipoic acid is now known with certainty, not only through numerous syntheses of the racemate[6] but most convincingly through a synthesis of the enantiomeric forms,[4] there still remains the problem of assigning absolute configurations to these forms. The present paper provides a basis for a decision between the alternative configurations I and II (Chart I) conceivable for (+)-α-lipoic acid.

The Merck synthesis[4] involves conversion of (+)-3-acetylthio-7-carbethoxyheptanoic acid (III) and of its enantiomer IV into (+)-α-lipoic acid (I) and the (−)-isomer II, respectively.[7] In the present work saponification, under mild conditions, of III and IV gave, respectively, (−)- and (+)-3-thioloctanedioic acids (V and VI, respectively). Since none of these transformations affect the asymmetric center, the configurations of I and II may properly be discussed in terms of those of V and VI, respectively.

For the task of relating V and VI to a substance

(1) A preliminary account of this work appeared in THIS JOURNAL, **78**, 2341 (1956).

(2) L. J. Reed, B. G. De Busk, I. C. Gunsalus and C. S. Hornberger, Jr., *Science*, **114**, 93 (1951) *et seq.* (THIS JOURNAL). Concurrent studies have been contributed by the Lederle group (J. A. Brockman, Jr., E. L. R. Stokstad, E. L. Patterson, J. V. Pierce, M. Macchi and F. P. Day, *ibid.*, **74**, 1868 (1952) *et seq.*) who have proposed the designation 6-thioctic acid.

(3) Recently reviewed by M. Calvin, *Angew. Chem.*, **68**, 253 (1956); *J. Chem. Soc.*, 1895(1956).

(4) E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly and K. Folkers, THIS JOURNAL, **76**, 4748 (1954); **77**, 5144 (1955).

(5) I. C. Gunsalus, L. S. Barton and W. Gruber, *ibid.*, **78**, 1763 (1956).

(6) *E.g.*, E. A. Braude, R. P. Linstead and K. H. R. Wooldridge, *J. Chem. Soc.*, 3074(1956); and cited references.

(7) In order to simplify the discussion, it will be assumed that the projection formulas I–VIII are in correct reference to signs of rotation, as measured.