TABLE I

Δδ VALUES OBSERVED FOR COMPOUNDS 1–8 IN THE PRESENCE OF Eu(fod)$_3$

Compd	No.	Concn	Proton 1	3	4	5	6	7	8
5-Nitroisoquinoline	1	0.314	29.4	42.5	13.6			4.7	
4,6-Dinitroisoquinoline[d]	2	0.640	22.8	27.7		5.3		3.4	5.4
3,4-Dibromoisoquinoline	3	0.222	2.2						1.8
3-Methylisoquinoline	4	0.203	17.3	22.1[a]	6.1	2.6			3.2
3-Bromoisoquinoline	5	0.131	3.2		3.9				2.0
4-Bromoisoquinoline	6	0.258	29.4	37.6		5.5			6.4
1-Cyanoisoquinoline[c]	7	0.126		2.6	0.7				1.3
Isoquinoline	8	0.446	28.1	29.9	9.7				
Isoquinoline[b]	8a	0.33	23.3	24.1	6.5	3.2	0.6	0.6	3.2

[a] This entry is the gradient observed for the 3-methyl substituent. [b] Data are taken from ref 3 and are the gradients observed for the protons of isoquinoline in the presence of Eu(dpm)$_3$. [c] A. Kaufmann and P. Dändliker, *Ber.*, **46**, 2924 (1923). [d] R. A. Henry, A. T. Nielsen, and D. W. Moore, *J. Org. Chem.*, **37**, 3206 (1972).

as 4,6-dinitroisoquinoline with absolute certainty. Again, the observed coupling constants are in accord with expectations.[3]

In a similar manner, the dibromide **3** was assigned as the 3,4-dibromoisoquinoline. In this case the four protons of the B ring did not reduce to a first-order system, but appear as a complex AA′BB′ system.

In all the isoquinolines examined the shift parameter Δδ [the slope of the straight line obtained by plotting the change of chemical shift in parts per million *vs.* the mole ratio of Eu(fod)$_3$ to substrate] varied monotonically with added shift reagent in the low-shift reagent to substrate domain (ratio less than 0.5). At higher ratios of shift reagent to substrate some deviations from linearity are observed, which are more pronounced for H_1 and H_3, and less severe for protons further removed from the coordination site. The methyl substituent of 3-methylisoquinoline (**4**) shows a marked deviation from linearity. The data for the shift gradients determined for compounds **1–8** are summarized in Table I.

Considerable line broadening was observed for resonances of protons near the coordination site. In the case of 3-methylisoquinoline the methyl resonance, which exhibits a 1.6-Hz line-width at half-height in the absence of Eu(fod)$_3$, is broadened to 22 Hz in the presence of 0.57 molar equiv of Eu(fod)$_3$. Similarly H_1 and H_3 of **1** (see Figure 1b) show extensive broadening in the presence of Eu(fod)$_3$. Protons further removed from the coordination site show little broadening.

Experimental Section

The pmr shifts were measured with a Varian HA-60-IL spectrometer. The solvent, $CDCl_3$, was dried over preheated (110° *in vacuo*) Linde 4 A Molecular Sieve to exclude water and HCl. TMS was used as an internal standard. The probe temperature was 30°. The shifted spectra were obtained by adding small increments of Eu(fod)$_3$.[4] Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,4-Dibromoisoquinoline (3).—This compound was formed in an attempt to prepare 3-bromoisoquinoline from the corresponding 3-amino derivative by using the procedure of Craig[5] for 2-bromopyridine.

3-Aminoisoquinoline (4.11 g, 0.029 mol) was dissolved with stirring and cooling in 32.5 g of 48% hydrobromic acid. Bromine (4.5 ml) was added over 40 min keeping the temperature between −5 and 0°. The perbromide which separated was initially gummy but toward the end of the addition the mass broke down to an easily dispersed orange solid. Sodium nitrite (4.9 g) in 7 ml of water was added over 50 min keeping the temperature below 0°. The mixture was stirred for an additional 2 hr (0°) and then neutralized by the dropwise addition of 11 g of sodium hydroxide in 50 ml of water. The tan product was filtered, washed well with cold water and dried, 6.5 g (80%), mp 86–87°. Recrystallization from 70% ethanol gave the product with mp 92–93°.

Anal. Calcd for $C_9H_5Br_2N$: Br, 55.69; N, 4.88; mol wt, 285. Found: Br, 56.49; N, 4.99; mol wt (mass spectrum) 285, 287, 289.

3-Bromo- and 3-Hydroxy-4-bromoisoquinoline.—The latter compound precipitated as a hydrated sodium salt in about 22% yield during the preparation of 3-bromoisoquinoline (47% yield) by the method of Case.[6] Recrystallization from 95% ethanol gave yellow needles, mp 254–256° dec.

Anal. Calcd for $C_9H_5BrNONa \cdot 1.5H_2O$: C, 39.58; H, 2.95; Br, 29.26; N, 5.13; Na, 8.42. Found: C, 40.09; H, 2.54; Br, 28.98; N, 5.09; Na, 8.29.

The pure hydroxy compound was recovered by dissolving the salt in hot water and acidifying with acetic acid. A yellow-orange solid was obtained, mp 209–211°. Its spectral properties are similar to those reported for 3-hydroxyisoquinoline.

Anal. Calcd for C_9H_6BrNO: Br, 35.66; N, 6.25; mol wt, 224. Found: Br, 35.68; N, 6.26; mol wt (mass spectrum), 223, 225. Uv (95% ethanol) 229 nm (log ϵ_{max} 4.54), 241 (4.55), 282 (3.43), 294 (3.47), 307 (2.95), 357 (3.28), 428 (3.52); ir (Nujol) C=O, 1625, 1645 cm^{-1} (sh).

The isoquinolines **1**, **4**, **6**, and **8** were commercially available. Purities were checked by nmr and melting point.

Registry No.—**1**, 607-32-9; **2**, 35202-47-2; **3**, 36963-44-7; **4**, 1125-80-0; **5**, 34784-02-6; **6**, 1532-97-4; **7**, 1198-30-7; **8**, 119-65-3; Eu(fod)$_3$, 17631-68-4; 3-hydroxy-4-bromoisoquinoline sodium salt, 36963-49-2; 3-hydroxy-4-bromosioquinoline, 36963-50-5.

(4) Willow Brook Laboratories, Inc., Waukesha, Wis.

(5) L. C. Craig, *J. Amer. Chem. Soc.*, **56**, 231 (1934).

(6) F. H. Case, *J. Org. Chem.*, **17**, 471 (1952).

Mechanism and Stereochemistry of 1,4-Diol Ring Closure to Tetrahydrofuran

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Four principal methods have been employed for the conversion of 1,4-diols to tetrahydrofuran derivatives; the transformation has been accomplished with strong acid,[1] sulfonyl chlorides,[2] alumina,[1a,2c,3] and dimethyl

(1) (a) G. A. Haggis and L. N. Owens, *J. Chem. Soc.*, 389 (1953); (b) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1499 (1954).

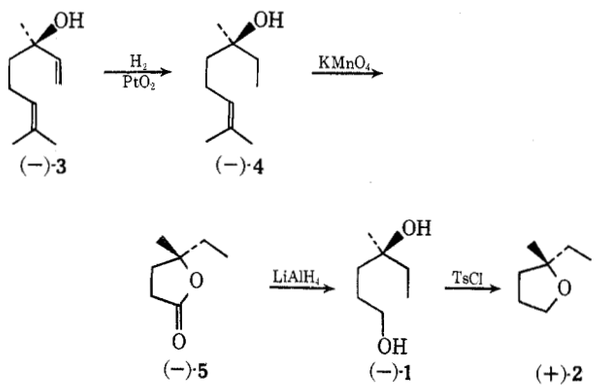
(2) (a) D. D. Reynolds and W. O. Kenyon, *J. Amer. Chem. Soc.*, **72**, 1593 (1950); (b) K. Alder and W. Roth, *Ber.*, **88**, 407 (1955); (c) E. L. Whittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 1218 (1960).

(3) R. C. Olberg, H. Pines, and V. N. Ipatieff, *ibid.*, **66**, 1096 (1944).

sulfoxide (DMSO).[4] We should like to report the mechanism and stereochemistry of each of these transformations.

Absolute Configurations of Reactants and Products. The Mechanism of Tosyl Chloride Ring Closure.—The preparations of 4-methyl-1,4-hexanediol (**1**) and 2-methyl-2-ethyltetrahydrofuran (**2**) are summarized in Chart I. Catalytic semihydrogenation[5] of (−)-(*R*)-

CHART I
PREPARATIVE SCHEME



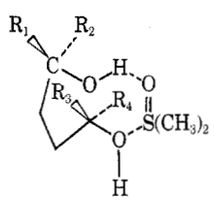
linalool (**3**),[6] with subsequent oxidation of (−)-(*S*)-**4**, afforded the levorotatory lactone (**5**) of (−)-(*S*)-4-hydroxyhexanoic acid.[5] Lithium aluminium hydride reduction of (−)-**5** yields (−)-(*S*)-4-methyl-1,4-hexanediol (**1**).

Treatment of (−)-**1** with *p*-toluenesulfonyl chloride in pyridine afforded (+)-2-methyl-2-ethyltetrahydrofuran (**2**). The absolute configuration of (+)-**2** is not known, but can be inferred from the known selectivity of tosylation reactions. Numerous examples[7] of selective tosylations are known; in general, primary alcohol functionalities form tosyl esters more readily than secondary or tertiary alcohol groups in diols. Thus, for example, 3α,24-cholanediol has been selectively monotosylated to yield 24-tosyloxy-3α-cholanol.[7b]

Granted selectivity in the tosylation of (−)-**1**, the most probable mechanism for the formation of (+)-**2** is tosylation at the primary alcohol functionality with subsequent intramolecular displacement of toluenesulfonate anion by the tertiary oxygen atom. With this sequence, retention of configuration at the chiral center is the expected result; we therefore assign the *S* configuration to (+)-**2**.

Acid-Catalyzed Ring Closure.—Reaction of (−)-(*S*)-**1** with toluenesulfonic acid in benzene with azeotropic distillation of water affords racemic **2**. The most reasonable mechanism for acid-catalyzed ring closure of **1** involves protonation at C-4 hydroxyl (tertiary), formation of an intermediate carbonium ion by loss of water, formation of an oxonium ion intermediate with C-1 hydroxyl, and proton loss. Racemization is explicable by rapid torsion about the C_3–C_4 bond of the intermediate carbonium ion.

DMSO Ring Closure.—Numerous examples of DMSO-catalyzed ring closure of 1,4-diols to THF derivatives have been reported by Gillis and Beck.[4] The mechanism chosen by these authors involved the nine-membered cyclic transition state **6**. With diol **1** two transition states based on **6** (**7** and **8**) become possible. Transition state **7** would yield **2** of retained configuration at C-2, whereas **8** should yield **2** of inverted configuration at C-2. On the basis of nonbonded interactions between reactant and DMSO, **7** should be favored over **8** if a cyclic transition state is operative. The possibility of **7** and **8** being equally probable, with resultant formation of racemic **2**, should be remote. Thus, a cyclic mechanism, if operative, should produce an excess of (+)-**2** *via* transition state **7**.



6

7, $R_1 = CH_3$; $R_2 = Et$; $R_3 = R_4 = H$
8, $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = Et$

Heating of (−)-**1** in DMSO at 165–180° yields racemic **2**. A more prosaic alternative than the previously suggested[4] cyclic mechanism, at least for diols possessing a tertiary alcohol functionality, involves a reaction sequence similar to that proposed for acid-catalyzed ring closure. DMSO is known to promote dehydration of secondary and tertiary benzylic and tertiary aliphatic alcohols, presumably *via* intermediate cations. By analogy to simple tertiary alcohols[8] (−)-**1** should produce an achiral carbonium ion intermediate which will subsequently collapse to racemic **2**.

Alumina-Catalyzed Ring Closure.—Heating (−)-**1** with alumina (Alcoa, grade F-20) at 165–180° results in the formation of (+)-**2**, $[\alpha]^{24}D$ +0.33° (neat), *i.e.*, with net retention at C-2 of product. The most plausible rationalization of this result involves selective adsorption[9] of C-1 hydroxyl with subsequent nucleophilic displacement of hydroxide (or its equivalent) by C-4 hydroxyl.

The mechanism can be thought of as the surface equivalent of the tosylate reaction (*vide supra*). The lower degree of stereospecificity in this reaction as compared to the tosylate reaction is indicative of the incursion of minor, alternate mechanisms; the relatively high degree of stereospecificity signalizes that the selective adsorption scheme is the major pathway. This mechanism demands inversion at C-1 of the reactant (C-4 of product).

(4) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

(5) (a) P. Vlad and M. Soucek, *Collect. Czech. Chem. Commun.*, **27**, 1726 (1962); (b) H. Mayer, P. Schudel, R. Ruegg, and O. Isler, *Helv. Chim. Acta*, **46**, 963 (1963).

(6) The absolute configuration of **3** was determined by correlation with mevalonic acid: R. H. Cornforth, J. W. Cornforth, and V. Prelog, *Justus Liebigs Ann. Chem.*, **634**, 197 (1960).

(7) (a) I. Scheer, M. J. Thompson, and E. Mosettig, *J. Amer. Chem. Soc.*, **78**, 4733 (1956); (b) R. T. Blickenstaff and F. C. Chang, *ibid.*, **80**, 2726 (1958); (c) R. T. Blickenstaff and F. C. Chang, *ibid.*, **81**, 2835 (1959); (d) W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *ibid.*, **85**, 1409 (1963).

(8) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964), and references cited therein.

(9) L. R. Snyder, *J. Chromatogr.*, **16**, 55 (1964).

Synthetic Utility.—The yields of the ring closure of **1** with tosyl chloride, *p*-toluenesulfonic acid, DMSO, and alumina are 92, 90, 67, and 48%, respectively. Thus, for **1**, the optimal yield, both product and optical, is obtained with tosyl chloride; for the preparation of THF derivatives this route is highly recommended both on the basis of yield and ease of laboratory manipulations.

Experimental Section

Dihydrolinalool (**4**) was prepared as previously described, $[\alpha]^{23}D$ −2.40 ± 0.03° (neat), bp 85–90° (15 mm) (Kugelrohr) [lit.[5b] bp 88° (17 mm)].

The lactone of 4-methyl-4-hydroxyhexanoic acid (**5**) was prepared as previously described,[5] $[\alpha]^{24}D$ −7.73 ± 0.02° (*c* 8.2, chloroform), bp 81–82° (3 mm) (Kugelrohr) [lit.[5] bp 100° (20 mm)].

4-Methyl-1,4-hexanediol (**1**) was prepared by the reduction of 5.4 g (0.042 mol) of (−)-**5** with 1.6 g (0.042 mol) of lithium aluminum hydride in 100 ml of ether at 0° for 16 hr. A saturated solution of sodium sulfate in water (25 ml) was added dropwise to the reaction mixture, followed by *ca.* 10 g of anhydrous sodium sulfate. The precipitated aluminum salts were removed by vacuum filtration. Removal of ether from the filtrate under reduced pressure afforded crude **1**. Kugelrohr distillation (105°, 0.4 mm) of the crude product gave 4.3 g (77%) of **1**, $[\alpha]^{24}D$ −2.35 ± 0.16° (*c* 12.8, CCl_4) [lit. bp 102° (4 mm),[10] 129–130.5° (12 mm)].[11]

2-Methyl-2-ethyltetrahydrofuran (**2**) was prepared by the addition of a solution of 5.71 g (0.03 mol) of *p*-toluenesulfonyl chloride in 10 ml of anhydrous pyridine to an ice-cooled solution of 3.5 g (0.027 mol) of (−)-**1** in 40 ml of anhydrous pyridine. The reaction mixture (0°) was stirred overnight and poured into a mixture of 100 ml of cold 10% aqueous hydrochloric acid and 100 ml of ether. The ether layer was washed with cold 10% hydrochloric acid until acidic, neutralized with aqueous saturated sodium carbonate, and dried over anhydrous magnesium sulfate. The solution was filtered and the ethyl ether was removed by distillation through a 10-cm Vigreux column. Subsequent distillation of the residue yielded 2.8 g (92%) of (+)-**2**, homogeneous by tlc and vpc analysis (FFAP, 30 ft), $[\alpha]^{24}D$ +0.44 ± 0.03° (neat),[12] bp 118–120° [lit.[12] bp 120–121° (760 mm)].

***p*-Toluenesulfonic Acid Ring Closure of** (−)-**1**. A solution of 3.0 g (0.023 mol) of (−)-**1**, $[\alpha]^{24}D$ −2.35° (CCl_4) and 0.1 g of *p*-toluenesulfonic acid in 30 ml of anhydrous benzene was refluxed into a Dean–Stark trap for 18 hr. The benzene solution was poured into 25 ml of 5% aqueous sodium bicarbonate. It was separated from the aqueous layer, washed with 30 ml of water, dried over anhydrous magnesium sulfate, filtered, and distilled. The fraction with bp 118–120° was collected (1.8 g, 90% of theoretical yield). Nmr, vpc, and tlc analysis indicated that this material was homogeneous **2**, $\alpha^{24}D$ +0.02 ± 0.03° (neat, *l* 1).

DMSO Ring Closure of (−)-**1**.—A solution of 5.0 g (0.038 mol) of (−)-**1**, $[\alpha]^{24}D$ −2.35° (CCl_4), in 34 ml of anhydrous DMSO was heated under reflux at 180° for 18 hr. The reaction mixture was poured into 100 ml of H_2O and the resultant solution was extracted with three 50-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed by distillation. The distillation residue (bp >35°) was fractionated to yield 2.9 g (67% of theoretical yield) of *dl*-**2**, bp 118–119°, $\alpha^{24}D$ −0.02 ± 0.03° (neat, *l* 1), identical in spectral parameters with an authentic sample of **2**.

Alumina Ring Closure of (−)-**1**.—An intimate mixture of 5.0 g (0.038 mol) of (−)-**1**, $[\alpha]^{24}D$ −2.35° (CCl_4), and 10 g of anhydrous alumina (Alcoa F-20) was heated at 165–180°. A mixture of **2** and olefins (nmr vinylic absorption) distilled over a period of 2 hr. The distilled material was fractionated and the material boiling at 118–120° (2.1 g, 48% of theoretical yield) was collected. The spectral properties (nmr and ir) of this material were identical with those of an authentic sample of **2**. The material exhibited $[\alpha]^{24}D$ +0.33 ± 0.02° (neat).

Registry No.—(−)-**1**, 37102-84-4; (+)-**2**, 37102-85-5.

(10) I. N. Nararov, I. L. Kotlyarevskii, and V. F. Ryabchenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 960 (1956); *Chem. Abstr.*, **51**, 5019 (1957).

(11) T. A. Favorskaya and O. V. Sergievskaya, *Zh. Obshch. Khim.*, **28**, 87 (1958); *Chem. Abstr.*, **52**, 12757 (1958).

(12) The density of *dl*-**2** is 0.8562: N. I. Shuikin, L. F. Bel'skii, and R. A. Karakhanov, *Z. Chem.*, **3**, 226 (1963); *Chem. Abstr.*, **59**, 9948 (1964).