

4-Ethylloxazoline-2-thiol.—When prepared by the usual thiuram disulfide procedure, 7.5 g. (65% theoretical) of slightly impure product was obtained from 15.7 g. of 2-amino-1-butanol (Commercial Solvents, b.p. 178–179°). Fractional precipitation from benzene solution by the addition of petroleum ether, the first oily fraction being discarded, resulted in pure 4-ethylloxazoline-2-thiol, m.p. 74–75°.

Anal. Calcd. for C_6H_9NOS : N, 10.68; S, 24.44. Found: N, 11.06; S, 25.48.

4-Ethylthiazoline-2-thiol.—Treatment of 2-amino-1-butanol by the reflux procedure yielded a viscous yellow oil which, on standing almost a year at room temperature, largely crystallized. Previous attempts at other methods of crystallization of the oil had not been successful. The crystalline product was purified by three recrystallizations from 40% ethanol and then was thrown out of ether solution by the addition of petroleum ether. It melted at 51–52° and gave no m.p. depression when mixed with an authentic sample,¹⁴ m.p. 53–54°.

4,4-Dimethylloxazoline-2-thiol.—The thiuram disulfide was formed from 15.0 g. of 2-amino-2-methyl-1-propanol (Eastman Pract., redistilled, b.p. 163.5–164.5°). The reaction with iodine was too slow for determination of the titration end-point, therefore the theoretical volume of iodine solution was added in 10-ml. portions during a period of 1.25 hours. Each addition was made when the previous one had become decolorized. After the usual decomposition and recovery steps, there was obtained 6.0 g. (59% theoretical) of impure 4,4-dimethylloxazoline-2-thiol. Precipitation from benzene solution by the addition of petroleum ether yielded 5.6 g. of creamy-white needles, m.p. 123–124.5° (lit.⁶ 123–125°).

Products from 2-Amino-2-methyl-1-propanol by Reflux Method.—Twenty-five grams of the aminoalcohol, refluxed with carbon disulfide and alcoholic potassium hydroxide by the method of Bruson and Eastes,⁶ yielded 40 g. of the crude oxazoline derivative. The pale yellow solid, when

(14) Sample and melting point value kindly supplied by L. Onanian, American Cyanamid Company.

boiled with 200 ml. of water, largely dissolved, leaving a heavy yellow oil from which the hot solution was decanted. When cooled, the aqueous solution deposited 10.8 g. of slightly impure 4,4-dimethylloxazoline-2-thiol, m.p. (after purification) 121.5–123°.

The yellow oil remaining from the hot water extraction consisted mainly of the same oxazoline compound, contaminated with 4,4-dimethylthiazoline-2-thiol. The oil was recrystallized from 80 ml. of 75% ethanol. The mother liquor was evaporated to dryness; the residue was leached twice with boiling water, recrystallized from 10 ml. of 50% ethanol, and twice precipitated from benzene solution by addition of petroleum ether. The product was 0.6 g. of 4,4-dimethylthiazoline-2-thiol, m.p. 116–117.5°, no m.p. depression when mixed with an authentic sample,¹⁴ m.p. 115–116° (uncor.).

4,4,6-Trimethyl-5,6-dihydro-1,3,4-oxazine-2-thiol.—The theoretical quantity of iodine was added in preparing the thiuram disulfide from 17.7 g. of 4-amino-4-methyl-2-pentanol (Shell Development), because the reaction proceeded too slowly to permit titration, as in the example above. Decomposition by heating with water in the usual manner resulted in precipitation of 9 g. of a mixture of the heterocyclic product and sulfur. Recrystallization from acetone yielded 6.6 g. (55% theoretical) of nearly pure 4,4,6-trimethyl-5,6-dihydro-1,3,4-oxazine-2-thiol. A single precipitation from ethyl acetate solution by the addition of petroleum ether purified the product, m.p. 212–213° (lit.⁸ 210–211° uncor.). The same compound was recovered as the sole product of reaction under reflux conditions, m.p. 211–212°.

Acknowledgment.—The author is indebted to the late Professor H. S. Fry at whose suggestion and under whose guidance a part of this problem was undertaken. Some of the aminoalcohols were generously supplied by the Commercial Solvents Corp. and the Shell Development Co.

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[CONTRIBUTION FROM HAVEMEYER LABORATORY, COLUMBIA UNIVERSITY]

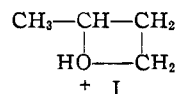
Configurational Interrelationships of Some Secondary Carbinols

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With optically active γ -methoxyvaleric acid as the common reference compound, the configurational interrelationships of 2-butanol, 6-methyl-2-heptanol, 2-octanol and 2-methoxypentane have been established, dextrorotatory compounds having identical configuration. The relationship of the first two carbinols has been established with considerably less jeopardization of the optically active center than the interrelationship previously reported, and is placed on a firmer chemical basis.

The significance of the stereochemistry of the partially asymmetric Meerwein-Ponndorf-Verley reduction depends upon the reliability of the assignment of stereochemical configuration to the secondary carbinols employed as reducing carbinol and reduction product, respectively.² The relationship of 2-butanol and 6-methyl-2-heptanol, one of the pairs used in this study has been established by chemical methods through 4-hydroxypentanoic acid by Levene and co-workers.^{3–6} However, the individual reactions often proceeded with a loss of optical activity, so extensive as to cast considerable

doubt on the validity of the conclusions. Indeed, a number were displacement reactions in which the possibility of 4-membered, neighboring group interaction was not remote and, if operative, could have led either to retention or inversion or both, in varying degree. Particularly suspect in this connection were the reactions of 1-amino-3-butanol with nitrous acid and 1,3-dihydroxybutane with hydrogen iodide, both of which involved extensive racemization and might reasonably have proceeded through the cyclic intermediate (I), the stereochemistry of the formation and of the further reaction of which would be uncertain. It seems



desirable, therefore, to confirm the stereochemical interrelationship by an alternative scheme, using reactions, the stereochemical integrities of which are much more certain and where involvement

(1) From a dissertation submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. R. Melville Cramer Fellow from Dartmouth College, 1947–1949; American Cyanamid Fellow, 1949–1950.

(2) W. von E. Doering and R. W. Young, *THIS JOURNAL*, **72**, 631 (1950).

(3) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **69**, 165 (1926).

(4) P. A. Levene and H. L. Haller, *ibid.*, **69**, 569 (1926).

(5) P. A. Levene, A. Walti and H. L. Haller, *ibid.*, **71**, 465 (1926).

(6) P. A. Levene and H. L. Haller, *ibid.*, **83**, 177 (1929).

of the asymmetric center might be detected easily as a change in substituent.

The starting material, γ -methoxyvaleric acid (II), was prepared from methyl crotonate in four steps. The addition of methanol yielded methyl β -methoxybutyrate (III), which was reduced to 3-methoxy-1-butanol (IV) by lithium aluminum hydride. The corresponding chloride, 1-chloro-3-methoxybutane (V), was converted to the Grignard reagent and carbonated, giving II in an overall yield 34% of theoretical. The resolution of II by crystallization of the quinine salt from water progressed very slowly and was not pressed to completion.

The brominative decarboxylation of the silver salt of (-)- γ -methoxyvaleric acid (II) afforded (-)-1-bromo-3-methoxybutane (VI) which was converted to (-)-2-methoxybutane (VII) by treating the Grignard reagent with water. (+)-2-Methoxybutane having been obtained from (+)-2-butanol by treatment with potassium and methyl iodide⁷ and by treatment with potassium hydroxide and methyl iodide⁸ it follows that (+)- β -methoxyvaleric acid has the same configuration as (+)-2-butanol.

(+)- γ -Methoxyvaleric acid was reduced by lithium aluminum hydride to (+)-4-methoxy-1-pentanol (VIII), which was converted by thionyl chloride to (+)-1-chloro-4-methoxypentane (IX). The Grignard from IX reacted with acetone to give, following distillation, (+)-6-methoxy-2-methyl-2-heptene (X) catalytic hydrogenation of which formed (+)-6-methoxy-2-methylheptane (XI). Methylation of (-)-6-methyl-2-heptanol (XII) as its potassium alkoxide with methyl iodide affording (-)-XI, it follows that (+)- γ -methoxyvaleric acid has the same configuration as (+)-6-methyl-2-heptanol (XII) and, from the first series, (+)-2-butanol.

In addition to this interrelationship, two others were established by way of the Grignard from (+)-1-chloro-4-methoxypentane (IX). Treatment with allyl chloride gave (+)-7-methoxy-1-octene (XIII) which was hydrogenated to (+)-2-methoxyoctane (XIV), previously prepared from (+)-2-octanol.⁹ Furthermore, treatment of the Grignard reagent with water gave (+)-2-methoxypentane (XV). On the assumption that (+)-XV has the same configuration as (+)-2-pentanol, this result supports the interrelationship of (+)-2-pentanol and (+)- γ -hydroxyvaleric acid previously effected.¹⁰ Consequently, (+)- γ -methoxyvaleric acid also has the same configuration as (+)-2-octanol¹¹ and (+)-2-methoxypentane.

We wish to acknowledge the most generous assistance of Dr. Kenneth B. Wiberg in the large-scale preparations.

(7) D. S. Tarbell and M. C. Paulson, *THIS JOURNAL*, **64**, 2842 (1942).

(8) R. Rometsch and W. Kuhn, *Helv. Chim. Acta*, **29**, 1483 (1946).

(9) J. Kenyon and R. A. McNicol, *J. Chem. Soc.*, **123**, 14 (1923).

(10) P. A. Levene, A. Walti and H. L. Haller, *J. Biol. Chem.*, **72**, 591 (1927).

(11) P. A. Levene and S. L. Harris, *ibid.*, **113**, 35 (1936), have related (+)-2-octanol and (+)-2-butanol by physical means, but this seems to be the first chemical interrelationship, although P. A. Levene and R. E. Marker, *ibid.*, **87**, 375 (1930), assert a chemical interrelationship unsupported experimentally then or later.

Experimental¹²

Methyl β -Methoxybutyrate (III).—This procedure is modified from that of Purdie and Marshall.¹³ A solution of 4 kg. of methyl crotonate in 6 l. of methanol in which 23 g. of sodium had been dissolved was refluxed 3 hr., neutralized with concentrated hydrochloric acid and distilled to remove 4 l. of methanol. The addition of 6 l. of water to the cooled reaction mixture separated an organic layer which was united with several hexane extracts (totalling 6 l.) of the aqueous phase. The hexane solution was washed with sodium carbonate solution, dried with calcium chloride and concentrated to a residue which was distilled through an eleven-section, bubble-cap column. There was obtained 3450 g. (66%) of methyl β -methoxybutyrate; b.p. 149–150° (reported¹³ b.p. 146–148°); n_D^{25} 1.4025; d_4^{25} 0.973; *MD*: calcd., 33.21; found, 33.14.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.5; H, 9.2. Found: C, 54.3; H, 9.1.

3-Methoxy-1-butanol (IV).—To a solution of 570 g. of lithium aluminum hydride in 10 l. of anhydrous ether, prepared by stirring 12 hr. in a 22-l. flask equipped with three reflux condensers, 3690 g. of III was added over a period of 8 hr., stirring being continued an additional 15 hr. Following the addition of 6 l. of concentrated hydrochloric acid, the ether solution was siphoned from the flask and the aqueous layer, further diluted with water, was extracted continuously with ether for 3 days. The ether extracts were dried with sodium sulfate and concentrated. Distillation of the residue through the bubble-cap column gave 2200 g. (70%) of 3-methoxy-1-butanol; b.p. 159–160°; n_D^{25} 1.4148; d_4^{25} 0.923; *MD*: calcd., 28.50; found, 28.33.

Anal. Calcd. for $C_6H_{12}O_2$: C, 57.7; H, 11.6. Found: C, 57.6; H, 11.7.

1-Chloro-3-methoxybutane (V).—In a 5-l., three-necked flask with stirrer, thermometer and addition funnel, there were placed 1520 g. of dry pyridine and 2080 g. of IV. To the mixture, cooled to 0° in an ice-bath, 3500 g. of thionyl chloride was added over a 4-hr. period, maintaining the mixture below 20°. With the cooling bath removed, stirring was continued an additional 2 hr., the temperature rising to 60° in the first 15 min. The mixture was poured into 1 kg. of ice and 500 cc. of concentrated hydrochloric acid and extracted with pentane. The pentane solution was washed with water and sodium carbonate solution, dried over calcium chloride, and distilled through the bubble-cap column to give 2084 g. (80%) of 1-chloro-3-methoxybutane; b.p. 125–126°; n_D^{25} 1.4135; d_4^{25} 0.963; *MD*: calcd., 31.80; found, 31.83.

Anal. Calcd. for $C_6H_{11}OCl$: C, 49.0; H, 9.1; Cl, 28.9. Found: C, 48.7; H, 8.8; Cl, 29.2.

γ -Methoxyvaleric Acid (II).—The Grignard reagent from 976 g. of V and 200 g. of magnesium in 9 l. of anhydrous ether was pumped by nitrogen into several 4-l. beakers containing a total of 40 lb. of solid carbon dioxide and allowed to react overnight. The solid complex remaining was decomposed with ice and hydrochloric acid to give an ether layer and an aqueous layer which was continuously extracted with ether for 2 days. The ether solutions were dried over sodium sulfate and concentrated to a residue, distillation of which under reduced pressure afforded γ -methoxyvaleric acid (II), 1800 g. (85%) being obtained from two runs; b.p. 94–96° at 3 mm.; n_D^{25} 1.4258; d_4^{25} 1.014; *MD*: calcd., 33.38; found, 33.09; neut. equiv.: calcd., 132.2; found, 132.2.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.3; H, 9.2; CH_3O , 23.5. Found: C, 54.9; H, 9.1; CH_3O , 23.6.

The resolution was effected by fractional crystallization of the quinine salt from water, the m.p. 118–119° remaining unchanged throughout. The rotation of acid (II), regenerated from the head fractions, rose slowly: fifth recryst-

(12) All m.p. and b.p. determinations are corrected. Unless otherwise stated, rotations are taken in a one-decimeter tube. Analyses are by the Schwarzkopf Microanalytical Laboratory, Middle Village, Long Island, New York. All the experiments reported with optically active materials have been effected as well, often with larger quantities, with racemic materials for the dual purpose of checking both the identity and purity of products and of ascertaining reasonable conditions for the reactions.

(13) T. Purdie and W. Marshall, *J. Chem. Soc.*, **69**, 477 (1891).

tallization, $[\alpha]^{25}_D -3.69^\circ$; twelfth, $[\alpha]^{25}_D -7.42^\circ$; sixteenth, $[\alpha]^{25}_D -10.98^\circ$; eighteenth, $[\alpha]^{25}_D -11.43^\circ$. The resolution was not carried to completion.

Anal. Calcd. for $C_{26}H_{36}N_2O_6$: C, 68.4; H, 8.0; N, 6.1. Found: C, 68.5; H, 7.9; N, 6.0.

1-Bromo-3-methoxybutane (VI).—Silver γ -methoxyvalerate was prepared by treating a hot, aqueous solution of I, $[\alpha]^{25}_D -2.21^\circ$, with one equivalent of 10 *N* sodium hydroxide followed by one equivalent of 10% silver nitrate. The copious white precipitate was dried for 3 days at 0.1 mm. over phosphorus pentoxide. In an atmosphere of nitrogen, 49 g. (0.21 mole) of this salt was added slowly to a solution of 34 g. (0.22 mole) of bromine in 500 cc. of dry carbon tetrachloride, both distilled from phosphorus pentoxide. The reaction became warm and was stirred for 2 hr. whereupon the silver bromide was filtered. The solution was washed with cold aqueous sodium bisulfite and with 10% aqueous sodium carbonate and was dried with calcium chloride. Distillation through an 18-cm. vacuum-jacketed Vigreux column produced 16.2 g. (46%) of VI; $[\alpha]^{25}_D -3.99^\circ$; n^{25}_D 1.4431; d^{25} 1.275; *MD*: calcd., 34.70; found, 34.70.

Anal. Calcd. for $C_5H_{11}BrO$: C, 35.9; H, 6.6; Br, 47.8. Found: C, 36.0; H, 6.9; Br, 47.8.

2-Methoxybutane (VII).—1-Bromo-3-methoxybutane (15 g., 10.09 mole; $[\alpha]^{25}_D -3.99^\circ$) was added slowly to 2.5 g. (0.10 atom) of magnesium in 50 cc. of *n*-butyl ether. The reaction mixture was refluxed for 30 min., cooled in ice, treated with hydrochloric acid, washed with 10% aqueous sodium carbonate, dried over calcium chloride and distilled through a jacketed Vigreux column. The product, 1.9 g. (24%), b.p. 60–70°, was redistilled from sodium to give VII; b.p. 61–63°; $[\alpha]^{25}_D -1.63^\circ$; n^{25}_D 1.3702; d^{25} 0.737; *MD*: calcd., 26.93; found, 27.03. Bennett and Philip¹⁴ report b.p. 59°, d^{20} 0.762, d^{20} 0.742.

Anal. Calcd. for $C_5H_{12}O$: C, 68.1; H, 13.7. Found: C, 67.8; H, 13.8.

4-Methoxy-1-pentanol (VIII).—In a procedure typical of many, using acid of varying optical purity, (+)-II ($[\alpha]^{25}_D +3.27^\circ$) was reduced with an equimolecular quantity of lithium aluminum hydride in ether. The reaction mixture was decomposed with concentrated hydrochloric acid and extracted continuously with ether to give (+)-VIII; $[\alpha]^{25}_D +1.48^\circ$ (*l* 2) in 80–85% of theoretical yield; b.p. 185–186°; n^{25}_D 1.4232; d^{25} 0.912; *MD*: calcd., 33.19; found, 32.95.

Anal. Calcd. for $C_6H_{14}O_2$: C, 61.0; H, 11.9. Found: C, 60.9; H, 11.9.

1-Chloro-4-methoxypentane (IX).—In a typical procedure, (+)-VIII ($[\alpha]^{25}_D +1.48^\circ$) was treated with thionyl chloride in pyridine to give (+)-IX in 70–75% of theoretical yield; $[\alpha]^{25}_D +1.38^\circ$ (*l* 2); b.p. 154–155°; n^{25}_D 1.4229; d^{25} 0.957; *MD*: calcd., 36.42; found, 36.38.

Anal. Calcd. for $C_6H_{13}ClO$: C, 52.7; H, 9.6; Cl, 26.0. Found: C, 53.2; H, 9.5; Cl, 25.7.

6-Methyl-2-methoxyheptane (XI).—To the Grignard reagent from 22 g. of (+)-IX ($[\alpha]^{25}_D +1.38^\circ$) and 4.0 g. of magnesium in 100 cc. of dry ether, prepared by slow addition of the chloride and refluxing for 2 hr., 12 g. of dry acetone was added. The reaction mixture was poured into a mixture of 40 cc. of concentrated sulfuric acid and 100 g. of ice, and extracted thrice with ether. The ether solutions,

dried with potassium bisulfate, were concentrated to a residue which was distilled from a small amount of iodine in an 18-cm. jacketed Vigreux column. Distillation of the dried product from sodium gave 6-methoxy-2-methyl-2-heptene (X); 14 g. (61%); b.p. 161–162°; $[\alpha]^{25}_D +1.19^\circ$ (*l* 2); n^{25}_D 1.4245; d^{25} 0.806; *MD*: calcd., 44.94; found, 45.10.¹⁵

Anal. Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.8. Found: C, 76.2; H, 12.7.

The theoretical quantity of hydrogen was absorbed when 11.6 g. of (+)-X was reduced with platinum in acetic acid. The product was obtained by neutralization of the acetic acid solution with aqueous sodium carbonate, extraction with pentane, drying over calcium sulfate and distilling. Two distillations from sodium afforded 9 g. (77%) of (+)-6-methyl-2-methoxyheptane (XI); $[\alpha]^{25}_D +1.07^\circ$ (*l* 2); b.p. 153–154°; n^{25}_D 1.4049; d^{25} 0.778; *MD*: calcd., 45.48; found, 45.41.

Anal. Calcd. for $C_9H_{20}O$: C, 74.9; H, 14.0; CH_3O , 21.3. Found: C, 75.1; H, 13.9; CH_3O , 21.4.

Authentic (–)-6-methyl-2-methoxyheptane (XI) was prepared from (–)-XII ($[\alpha]^{25}_D -6.53^\circ$) by treatment of the potassium salt in benzene with methyl iodide in an atmosphere of nitrogen. Two distillations of the product from sodium gave pure XI; $[\alpha]^{25}_D -6.31^\circ$ (*l* 0.5); n^{25}_D 1.4052; d^{25} 0.778; *MD*: calcd. 45.48; found, 45.42.

Anal. Calcd. for $C_9H_{20}O$: C, 74.9; H, 14.0; CH_3O , 21.5. Found: C, 75.2; H, 13.9; CH_3O , 21.7.

2-Methoxyoctane (XIV).—To the Grignard reagent from 27.2 g. (0.2 mole) of 4-methoxy-1-chloropentane (IX, $[\alpha]^{25}_D +1.55^\circ$), pumped by nitrogen through a fritted glass plate into a three-necked flask, there was added 23.4 g. (0.3 mole) of allyl chloride. After 15 hr. stirring, the magnesium chloride was filtered from the solution which was concentrated on the steam-bath and distilled from sodium to give 12 g. (42%) of 7-methoxy-1-octene (XIII); b.p. 160–161°; $[\alpha]^{25}_D +1.68^\circ$; n^{25}_D 1.4183; d^{25} 0.793; *MD*: calcd., 36.42; found, 36.38.

Anal. Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.8. Found: C, 75.9; H, 12.8.

The hydrogenation of 10 g. (0.07 mole) of XIII with platinum in acetic acid was worked by neutralizing with aqueous sodium carbonate, extracting with pentane, drying over calcium sulfate and distilling from sodium to give 7 g. (70%) of XIV; b.p. 162–163°; $[\alpha]^{25}_D +1.02^\circ$; n^{25}_D 1.4068; d^{25} 0.779; *MD*: calcd. 45.4; found, 45.6.

Anal. Calcd. for $C_9H_{20}O$: C, 74.9; H, 14.0; CH_3O , 21.5. Found: C, 75.1; H, 14.1; CH_3O , 21.5.

2-Methoxypentane (XV).—The Grignard reagent from 13.6 g. (0.1 mole) of 4-methoxy-1-chloropentane, $[\alpha]^{25}_D +1.55^\circ$, was treated with 20 cc. of concentrated hydrochloric acid, the resulting ethereal solution then being dried with calcium sulfate and concentrated. Distillation of the product from sodium gave 5 g. (50%) of XV; b.p. 91–92°; $[\alpha]^{25}_D +2.52^\circ$; n^{25}_D 1.3805; d^{25} 0.750; *MD*: calcd., 31.55; found, 31.51.

Anal. Calcd. for $C_6H_{14}O$: C, 70.6; H, 13.8; CH_3O , 30.4. Found: C, 70.7; H, 13.9; CH_3O , 30.0.

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(15) This material may be a mixture of the 2- and 1-heptene isomers similar to that prepared by B. Helferich, *Ber.*, **52**, 1800 (1919), by methylation of methylheptenol (from citral) and for which he reports b.p. 163.5°; n^{18}_D 1.4281; d^{18} 0.8103.

(14) G. M. Bennett and W. G. Philip, *J. Chem. Soc.*, 1930 (1928).