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The Absolute Configurations and Optical Rotations of (−)-4-Hydroxy-2-pentanone and (−)-2,4-Pentanediol

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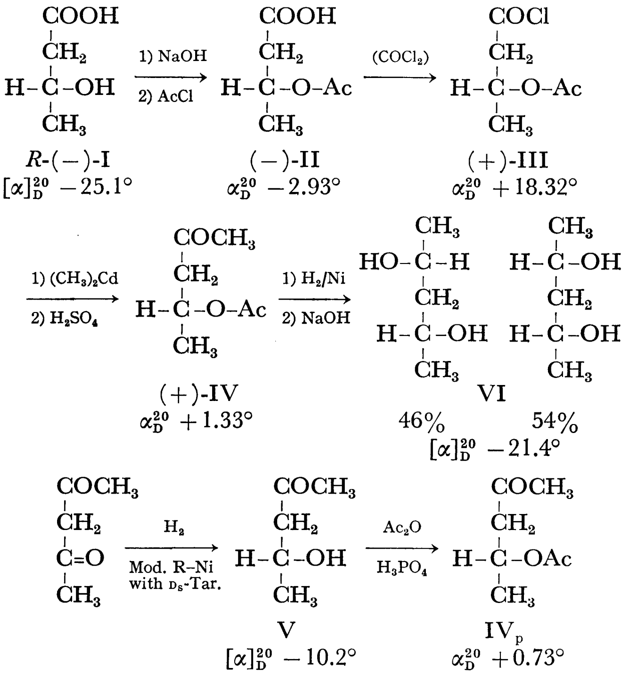
In order to calculate the asymmetric yield and the contents of the stereoisomers of the products obtained by the asymmetric hydrogenation of acetylacetone using Raney nickel catalysts modified with L_s-glutamic acid and D_s-tartaric acid, the absolute configurations and the optical rotations of (−)-4-hydroxy-2-pentanone and (−)-2,4-pentanediol were studied in the present work.

As the direct resolutions of the optical isomers of 2,4-pentanediol were not successful because of difficulty in separating the *racemic* and *meso* compounds, the optical rotation was decided by the following method.



Scheme 1.

Sodium salt of *R*-(D_s)-3-hydroxybutyric acid ((−)-I)[1] ($[\alpha]^{20}_{D}$ −25.1° (*c* 10, water)) was converted into (−)-3-acetoxybutyric acid ((−)-II), which was then treated with oxalyl chloride to yield (+)-3-acetoxybutyryl chloride ((+)-III). By the action of dimethylcadmium, (+)-4-acetoxy-2-pentanone ((+)-IV) was prepared from (+)-III. As IV was a comparatively labile compound under both acidic and alkaline conditions, direct hydrolysis with a base or acid was difficult. (+)-IV was reduced with a Raney nickel catalyst, and the product was hydrolyzed with an aqueous sodium hydroxide solution to yield a mixture of (−)- and *meso*-2,4-pentanediol ((−)- and *meso*-VI). On the other hand, the partially optically-active 4-hydroxy-2-pentanone (V) ($[\alpha]^{20}_{D}$ −10.2°) obtained by the asymmetric hydrogenation of acetylacetone using a Raney nickel catalyst modified with D_s-tartaric acid was acetylated with acetic anhydride in the presence of phosphoric acid to give a partially optically-active IV (IV_p) ($[\alpha]^{20}_{D}$ +0.73°), as is shown in Scheme 1. As (+)-IV and IV_p had the same sign of optical rotation, the absolute configuration of (−)-4-hydroxy-2-pentanone was identified as *R*. From the ratio of the optical rotations of (+)-IV and IV_p, and from the optical rotation of V, the optical rotation of *R*-(−)-4-hydroxy-2-pentanone was calculated to be −18°.

The contents of *R*-(−)- and *meso*-VI were determined to be 46 and 54% respectively by means of the glc and NMR spectroscopy of 2,4-*O*-benzylidene-2,4-pentanediol, which had been derived from *R*-(+)-IV. From the contents of *R*-(−)-VI and the optical rotation of the mixture of *R*-(−)- and *meso*-VI, the optical rotation of *R*-(−)-2,4-pentanediol was calculated to be −47°.

Experimental

Determination of the Ratio of racemic *and* meso *2,4-Pentanediols (VI).* *Preparation of* meso-*VI*: A mixture of *racemic* and *meso*-VI was prepared by the hydrogenation of acetylacetone with a Raney nickel catalyst modified with DL-malic acid at pH 5.0, 0 °C.[2] The hydrogenation product was distilled under reduced pressure. Thirty-five grams of the boric ester of VI was prepared from 20 g of VI, 20 g of boric acid, and 4 ml of water according to the method of Nagai *et al.*[3] Twenty grams of the boric ester was recrystallized three times from chloroform; mp 76 °C (lit.,[3] mp 85 °C). Found: C, 45.36; H, 8.61%. Calcd for $C_5H_{11}O_3B$: C, 46.55; H, 8.53%.

Six and a half grams of the boric ester was refluxed with 100 ml of methanol for six hours, and then the methanol and methyl borate were removed under reduced pressure. The residual diol was distilled *in vacuo*. Bp 104 °C/15 mmHg; yield, 3.5 g. Found: C, 56.04; H, 11.90%. Calcd for $C_5H_{12}O_2$: C, 57.66; H, 11.61%. The IR spectrum corresponded with that of *meso*-VI reported in the literature,[3] and the product was used as the standard compound of *meso*-VI.

*Preparation of 2,4-*O*-Benzylidene-2,4-pentanediol (VII)*: A mixture of 1.2 g of *meso*-VI (or a mixture of *racemic* and *meso*-VI) and 5 ml of benzaldehyde was stirred with 0.5 g of anhydrous zinc chloride[4] for 12 hr at room temperature. The reaction mixture was then distilled two times under reduced pressure, and a fraction with a bp of 130—132 °C/

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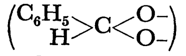
[1] P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 49 (1925).

[2] T. Tanabe, This Bulletin, **46**, 1482 (1973).

[3] E. Nagai, S. Kuribayashi, M. Shiraki, and M. Ukita, *J. Polym. Sci.*, **35**, 295 (1959).

[4] L. Zervas, *Ber.*, **64**, 2293 (1931).

16 mmHg was collected.[5] Found: C, 74.25; H, 8.09%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

Determination of the Contents of meso *and* racemic *VII by Gas Chromatography*: The gas chromatography of VII was carried out under the following conditions: column, 1.5% PEG 20 M on Chromosorb W, 3 m; temp., 140 °C. The retention times of VII from *meso* and *racemic* VI were 5.3 and 7.1 min respectively. The ratio of the areas of *meso* and *racemic* VII in the gas chromatograph was in good agreement with the ratio of the intensities of the signals from the proton of the methine group  $\left(\begin{smallmatrix}C_6H_5\\H\end{smallmatrix}{>}C{<}\begin{smallmatrix}O-\\O-\end{smallmatrix}\right)$ in the NMR spectra. This fact shows that the contents of the *meso* and *racemic* VI can be determined by glc like those of VII.

Preparation of the Sample of VII for Gas-chromatographic Analysis. Twenty to thirty milligrams of VI was dissolved in a solution of 0.4 ml of absolute benzene and 0.2 ml of freshly-distilled benzaldehyde, and then 25 mg of anhydrous zinc chloride and 50 mg of anhydrous potassium carbonate were added to the solution. The mixture was shaken for 1 hr and then allowed to stand for 24 hr at 30 °C. Under these conditions, the conversion of VI to VII was found to be quantitative by gas chromatography.

Determination of the Absolute Configurations and Specific Rotations of (−)-4-Hydroxy-2-pentanone ((−)-V) and (−)-VI. Preparation of (−)-3-Acetoxybutyric Acid ((−)-II): Fifty grams of sodium salt of *R*-($\mathrm{D_s}$)-(−)-3-hydroxybutyric acid ((−)-I) ($[\alpha]^{20}_{\mathrm{D}}$ −25.1° (*c* 10, water)), prepared by the method of Levene *et al.*, and 16 g of anhydrous sodium acetate were dissolved in 100 ml of glacial acetic acid. Forty-two milliliters of acetyl chloride was then stirred into the mixture at 10 °C, after which the stirring was kept up for another hour at room temperature. One hundred and fifty milliliters of ether was then added, and the inorganic salts were removed by filtration. A fraction with a bp of 98—99 °C/1.5 mmHg was collected. 39.3 g $[\alpha]^{20}_{\mathrm{D}}$ −2.93° (without dilution). Found: C, 48.67; H, 6.92%. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90%.

Preparation of (+)-3-Acetoxybutyryl Chloride ((+)-III): Fifteen milliliters of oxalyl chloride[6] was added to 20 g of (−)-II in 10 ml of absolute benzene,[7] and the resulting solution was allowed to stand for 12 hr at room temperature. The benzene was removed under reduced pressure, and the residual liquid was distilled. Bp 79—81 °C/12 mmHg; yield, 21.3 g; $[\alpha]^{20}_{\mathrm{D}}$ +18.32° (neat) IR: 1730, 1800 $\mathrm{cm^{-1}}$ (C=O).

Preparation of (+)-4-Acetoxy-2-pentanone ((+)-IV): Nineteen grams of (+)-III in 50 ml of benzene was added at 0 °C, over a period of twenty seconds, to a benzene solution of dimethylcadmium prepared from 6.2 g of magnesium, 20.8 g of methyl iodide, and 26 g of anhydrous cadmium chloride.[8] The reaction mixture was then kept for 15 min at room temperature, carefully decomposed with 80 g of ice water, and acidified with 1.5 M sulfuric acid. The organic layer was separated, washed with water and then with saturated sodium hydrogencarbonate solution, and dried over anhydrous sodium sulfate. After the removal of the benzene, the residue was distilled *in vacuo*. A fraction with a bp of 80—90 °C/14 mmHg was redistilled. Bp 85—90 °C/14 mmHg; yield, 6.3 g.

(+)-IV was obtained by further purification using silica gel column chromatography. (Column: Kiesel Gel, 0.05—0.2 mesh, 1.6×75 cm. Eluent solvent: benzene.) Bp 92 °C/20 mmHg; yield, 2.3 g, $[\alpha]^{20}_{\mathrm{D}}$ +1.33° (neat). Found: C, 56.43; H, 8.33%. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39%.

Preparation of IV from Partially Optically-active 4-Hydroxy-2-pentanone (V) and Calculation of the Specific Rotation of Optically-pure V: Five milliliters of partially optically-active V ($[\alpha]^{20}_{\mathrm{D}}$ −10.2° (d^{20} 0.986), neat), prepared by the asymmetric hydrogenation of acetylacetone using a modified Raney nickel catalyst with $\mathrm{D_s}$-tartaric acid at pH 5.0, 100 °C,[2] was acetylated with 6 ml of acetic anhydride and a catalytic amount of phosphoric acid.[9] After the removal of the acetic acid under reduced pressure, partially optically-active IV ($\mathrm{IV_p}$) was obtained by distillation *in vacuo*. Bp 43 °C/2 mmHg; yield, 4 g, $[\alpha]^{20}_{\mathrm{D}}$ +0.73° (neat).

The specific rotation of (−)-4-Hydroxy-2-pentanone was calculated by the following procedure; $[\alpha]^{20}_{\mathrm{D}}$ of V×($[\alpha]^{20}_{\mathrm{D}}$ of (+)-IV/$[\alpha]^{20}_{\mathrm{D}}$ of $\mathrm{IV_p}$) = −10.2°×(1.33/0.73) = −18°.

Preparation of a Mixture of (−)- and meso*-VI and the Specific Rotation of (−)-VI*: Two grams of (+)-IV ($[\alpha]^{20}_{\mathrm{D}}$ +1.33°) in 5 ml of methanol was reduced using 0.6 g of a Raney nickel catalyst in an autoclave at 70 °C under an initial pressure of 90 kg/cm^2.[10] The product was hydrolyzed with 0.6 g of sodium hydroxide in 0.6 ml of water and 3 ml of methanol. The resulting solution was neutralized with 3 M hydrochloric acid and concentrated *in vacuo*, and then the VI was extracted with acetone. After the acetone had been removed, the residue was distilled. Bp 107—108 °C/17 mmHg; yield, 0.6 g, $[\alpha]^{20}_{\mathrm{D}}$ −21.4° (*c* 10.5, ethanol). Found: C, 56.27; H, 11.57%. Calcd for $C_5H_{12}O_2$: C, 57.66; H, 11.61%. The content of (−)-VI was 46%. The specific rotation of optically-pure (−)-2,4-pentanediol was calculated by means of the following equation: −21.4°×(100/46) = −47° (*c* 10.5, ethanol).

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[5] As, under these conditions, the conversion of VI to VII was not perfect, and as the distillation process changed the diastereomeric component ratio of VII, the method is inadequate for the preparation of samples for diastereomeric analysis by glc.

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