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Determination of the Absolute Configuration of Restricted 1,1'-Binaphthyls by Asymmetric Meerwein–Ponndorf–Verley Reduction[1]

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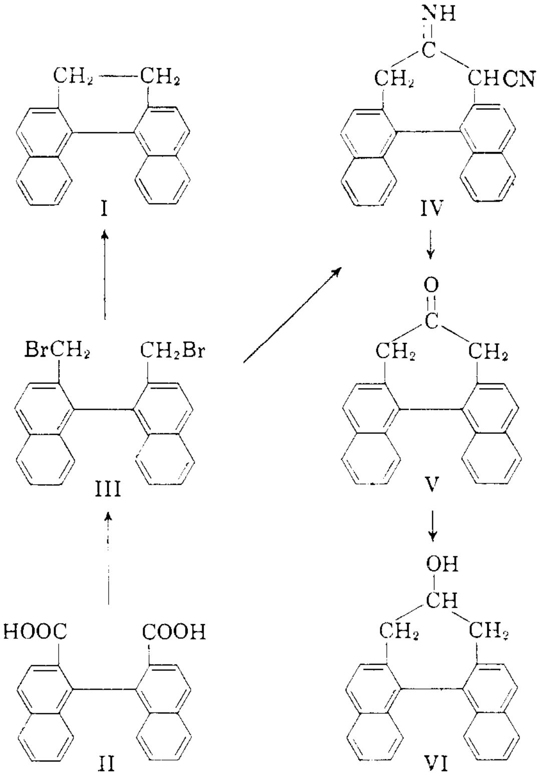
Incomplete reduction of the bridged binaphthyl ketone (±)-V with (+)-(*S*)-2-octanol in the presence of aluminum *t*-butoxide affords the corresponding alcohol (−)-VI, along with unreduced (−)-V. On the basis of these facts, the (*R*)-configuration has been assigned to (−)-VI, to the synthetic precursor of (−)-VI, (+)-1,1'-binaphthalene-2,2'-dicarboxylic acid (II), and to (−)-9,10-dihydro-3,4,5,6-dibenzphenanthrene (I), a derivative of (+)-II. These results provide independent confirmation of configurational assignments made through application of the polarizability of optical activity. The proposed model for the transition state of the reduction has received additional experimental support: the stereospecificity of the asymmetric reduction of (±)-V is virtually identical with that observed in the reduction of the analogous bridged biphenyl ketone (±)-VII under comparable conditions.

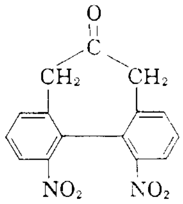
The recent assignment[3] of the (*S*)-configuration[4] to (+)-9,10-dihydro-3,4,5,6-dibenzphenanthrene (I) provided information on the absolute configuration of the synthetic precursor of I, (−)-1,1'-binaphthalene-2,2'-dicarboxylic acid (II), and therefore on the absolute configurations of a number of other structurally symmetrical derivatives of II. These assignments, which derived from a qualitative treatment based on the polarizability theory of optical activity, were subsequently adduced as contributory evidence in support of the generality of an optical displacement rule in the biaryl series.[3]

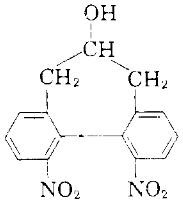
The present work was initiated for a twofold purpose. It was our primary intention to test the reliability of the earlier conclusions through application of our kinetic correlation method.[5] At the same time, it was to be expected that the results would furnish an experimental test for the explicit assumption that the nature of the blocking substituents in the biaryl has a negligible effect on the direction and stereospecificity of the asymmetric reduction, and that the correlation method is therefore a generally applicable one. This assumption, which is basic to our interpretation of the stereochemistry of the reaction, hitherto has rested entirely on the inspection of molecular models.

Accordingly, a study was undertaken of the partial Meerwein–Ponndorf–Verley reduction of the bridged binaphthyl ketone (±)-V by (+)-2-octanol.

The synthesis of V was modelled on the scheme previously employed[5] in the preparation of the analogous restricted biphenyl ketone VII. 2,2'-Bis-(bromomethyl)-1,1'-binaphthyl (III), prepared[6] from II, was converted to the bridged iminonitrile IV through the agency of hot aqueous ethanolic potassium cyanide. Acid hydrolysis of IV yielded the desired ketone V, which could be reduced to the corresponding alcohol VI with lithium aluminum hydride. In a similar sequence of transformations, starting with (+)-II, there was obtained, in order, (+)-III, (−)-IV, (+)-V and (−)-VI. The optically pure forms of V and VI, in contrast to the racemic modifications, could not be obtained in a crystalline state.[7]




VII


VIII

Partial Asymmetric Reductions.—Reductions were carried out at 63.0 and at 82.5°. At each temperature a solution of (±)-V in dioxane,[8] con-

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[1] Configurational Studies in the Biphenyl Series. VI; part V, L. Dvorken, R. B. Smyth and K. Mislow, THIS JOURNAL, **80**, 486 (1958).

[2] John Simon Guggenheim Memorial Fellow, 1957–1958.

[3] D. D. Fitts, M. Siegel and K. Mislow, THIS JOURNAL, **80**, 480 (1958).

[4] Nomenclature according to R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

[5] P. Newman, P. Rutkin and K. Mislow, THIS JOURNAL, **80**, 465 (1958).

[6] D. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1242 (1955).

[7] The similar behavior of VIII already has been commented upon.[5]

[8] Chosen as an indifferent solvent since (±)-V, like (±)-VII, is only slightly soluble in 2-octanol.

taining a 45-molar excess of optically pure (+)-2-octanol, was mixed with a solution of an approximately equimolar quantity of aluminum *t*-butoxide in dioxane. After 0.25 hour the reaction mixture was quenched by addition of dilute HCl, the liquid phase was removed by distillation, and the residual mixture of V and VI was separated by chromatography. In a preliminary experiment with a mixture of known composition, it had been found that V and VI could be smoothly and quantitatively separated by chromatography on alumina: the ketone was eluted with 1:1 hexane–benzene, and the alcohol, in the subsequent fraction, with benzene. A method therefore was given which was suitable for separating the constituents of such a mixture without affecting their optical purity.

In both experiments the infrared spectra of the isolated binaphthyls were identical with those of the authentic substances. The properties of the residual ketone V and of the produced alcohol VI are reported in Table I.

TABLE I

PRODUCTS OF ASYMMETRIC REDUCTIONS

	Residual ketone, V			Produced alcohol, VI				
Temp., °C.	Wt., mg.	$[\alpha]^{20}D$ (benzene)	ω_K[a], %	Wt., mg.	Yield, %	$[\alpha]^{20}D$ (benzene)	ω_A, % Calcd.	ω_A, % Found[b]
63.0	389	− 3.5°	2.6	99	89	−64.7°	10.3	10.2
82.5	128	−46.4°	34.6	549	95	−64.5°	8.1	10.2

[a] $[\alpha_K^0]$ 134° (C_6H_6). [b] $[\alpha_A^0]$ 634° (C_6H_6).

Some features of the information presented in Table I have a bearing on the *reliability* of the data. Thus, considering that the mole-per cent. conversions of V to VI in the two reductions differ widely (20% at 63.0° and 81% at 82.5°), the high yield (about 90%) of VI obtained in both cases speaks for the fact that side-reactions, if any, are of negligible importance. Furthermore, the internal consistency of the data is borne out qualitatively and quantitatively,[9] as follows.

In the asymmetric reduction, the unreduced ketone and the produced alcohol are both levorotatory and therefore of opposite configuration, since it was shown (see above) that (+)-V and (−)-VI have the same configuration. This result is in harmony with the view[5] that moles of (*S*)-biaryl equal moles of (*R*)-biaryl at any time during the reaction. In addition, the optical purities (ω_A) of the produced alcohol calculated from the optical purities (ω_K) of the accompanying residual ketone, according to the equation developed previously,[5] agree satisfactorily with the found values.

$$\omega_A = \omega_K \left(\frac{K_S + K_R}{A_S + A_R}\right)$$

Stereoselectivity in the Asymmetric Reductions.—Treating the reaction as a unimolecular irreversible process, it is possible to derive expressions[5] for the pseudo-first-order rate constants, k_R and k_S, corresponding to the reduction of the (*R*)-resp. (*S*)-biaryl. Calculated[10] values are listed in Table II, together with the corresponding data[5] for VII. Significantly, under comparable conditions[11] the values of k_R/k_S for VII and for V are the same, within experimental error, despite a fivefold difference[12] in the rate constants themselves. The two ketones V and VII are structurally identical above the central plane (defined as the plane which contains the long biphenyl axis and which is perpendicular to the twofold symmetry axis), but differ drastically in the nature of the blocking substituents; we therefore regard these results as experimental vindication of the view[5] that the stereochemical efficiency (k_R/k_S, or $\Delta\Delta F^{\ddagger}$ of the two diasteromeric transition states) of the reaction is governed by the environment above the central plane to the virtual exclusion of that below it. We note that E_{act} *ca.* 22 kcal./mole for the reduction of V within the temperature range studied; k_R/k_S remains approximately constant.

TABLE II

EFFICIENCY IN ASYMMETRIC REDUCTIONS

Temp., °C.	Ketone	k_R, hr.$^{-1}$	k_S, hr.$^{-1}$	k_R/k_S
63.0	VII	5.4	3.9	1.4
63.0	V	1.0	0.8	1.3
82.5	V	8.3	5.5	1.5

Absolute Configuration of the 1,1′-Binaphthyls.—Following the same arguments which were used[5] in the assignment of absolute configurations to (+)-VII and to (−)-VIII, we now assign the (*S*)-configuration to (−)-V, the unreduced ketone, and the (*R*)-configuration to (−)-VI, the alcohol produced in the partial asymmetric reduction of (±)-V by (+)-(*S*)-2-octanol.[13] It follows that the (*R*)-configuration has been established for (+)-II, the synthetic precursor of (−)-VI, as well as for the structurally symmetrical derivatives of (+)-II, including (−)-I. The earlier configurational assignments[3] thus have been confirmed.

Insofar as (*R*)-IV and (*R*)-VI are both strongly levorotatory ($[M]_D$ −2780° resp. −1970°), ancillary experimental support has been secured for the optical displacement rule[3]; at the same time, however, we also have encountered in (*R*)-V ($[M]_D$ +413°) the first clear-cut exception to that rule.[14] Since the polarizability theory of optical activity takes into account only electric dipole–dipole interactions, and since a large magnetic dipole is associated with the carbonyl group, it is not overly surprising that the theory fails to give reliable results in a case where there may be significant interaction between the magnetic dipole moment and the electric dipole moment of the same elec-

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(9) These and other quantitative considerations rest on the presumption that neither the two biaryls V and VI nor the 2-octanol[5] suffer significant racemization in the course of the reaction.

(10) Equations 10 and 11 (ref. 5) and values listed in Table I; t = 0.25 hr.

(11) Temperature, concentration of reagents in dioxane, molar quantities of aluminum *t*-butoxide (1) and of 2-octanol (43–45) relative to ketone, optical purity (99–100%) of 2-octanol, contact time (15–20 minutes).

(12) Possibly ascribable to polar factors.

(13) Regarding the absolute configuration of (+)-2-octanol, see ref. 5, footnote 28.

(14) The ethyl ester of (*R*)-1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylic acid, $[M]_D$ +7.6° (D. C. Iffland and H. Siegel, THIS JOURNAL, **80**, 1947 (1958); ref. 5) must be regarded as a borderline case: while the compound is dextrorotatory, in violation of the optical displacement rule, the magnitude of the rotation is such that the compound is exempted from consideration by that rule. It is preferable to reserve judgment in this instance, however, for the compound is optically labile and the quoted rotation might thus possibly refer to largely racemized substance.

tronic transition.[15] On a more empirical level, the generality of the optical displacement rule, as originally stated,[3] has been somewhat impaired by the quoted exception. Obviously, the original formulation requires modification or refinement. Further investigations are in progress.

Experimental Part[16]

(±)- and (−)-5-Cyano-2′,1′:1,2;1″,2″:3,4-dinaphth-cyclohepta-1,3-diene-6-imine (IV).—A mixture of 30 g. of (±)-2,2′-bis-(bromomethyl)-1,1′-binaphthyl[6] (III), m.p. 151–153°, 5.7 g. of potassium cyanide, 30 ml. of water and 90 ml. of ethanol was refluxed for six hours, cooled, and poured into a large volume of water. The product precipitated as an oil which solidified on standing. There was thus obtained 16 g. of material, m.p. 260–265°. In order to ensure complete conversion to the desired iminonitrile, the following treatment was resorted to. A solution of 4.0 g. of sodium in 100 ml. of anhyd. ethanol was added slowly to a refluxing solution of the above product in 60 ml. of ethanol; during this operation the system was flushed with nitrogen gas. After the addition the solution was refluxed for 1.5 hours and then cooled in an ice–salt mixture. The resulting solid was collected by filtration to give 15.5 g. (68%) of crude product, m.p. 258–263°. Two recrystallizations from acetonitrile raised the m.p. to 269–271°. The infrared spectrum (KBr pellet) exhibited strong bands at 3266, 3170 (N—H), 2167 ($C\equiv N$) and 1646 cm.$^{-1}$ $C=N$.

Anal. Calcd. for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43. Found: C, 86.45; H, 5.00; N, 8.24.

The (−)-form was prepared similarly from (+)-III (m.p. 182–186°, $[\alpha]^{28}\mathrm{D}$ +161.8° (*c* 0.89, benzene)), which had in turn been prepared[6] from (+)-1,1′-binaphthalene-2,2′-dicarboxylic acid (II), $[\alpha]^{30}\mathrm{D}$ +77.9° (*c* 0.73, 0.1 *N* NaOH). The product melted at 296–298° (after two recrystallizations from acetonitrile) and had $[\alpha]^{20}\mathrm{D}$ −837° (*c* 0.62, pyridine).

Anal. Calcd. for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43. Found: C, 86.82; H, 5.02; N, 8.51.

(±)- and (+)-2′,1′:1,2;1″,2″:3,4-dinaphth-cyclohepta-1,3-diene-6-one (V).—A mixture of 14.4 g. of the racemic iminonitrile, (±)-IV, 750 ml. of glacial acetic acid and 750 ml. of 85.9% phosphoric acid was refluxed for five hours, cooled, and poured into a large volume of water. The resulting precipitate (14 g.) was collected by filtration, dried, and chromatographed on 450 g. of silica gel, benzene being used as the eluent. There was thus obtained 6.7 g. (50%) of a product, m.p. 204–208°; two recrystallization from benzene gave faintly yellow crystals, m.p. 207–210°. The infrared spectrum (5% chf. solution) exhibited the pronounced carbonyl band at 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{16}O$: C, 89.58; H, 5.23. Found: C, 89.72; H, 5.33.

The (+)-form was obtained similarly from (−)-IV. Chromatography on silica gel (benzene as eluent) or neutral alumina (Woelm, activity III, 3:1 hexane–benzene as eluent) produced an oil which could not be induced to crystallize; although the oil hardens to an amorphous glass which softens at about 100°, the substance oils out from the common solvents. An analytical sample, obtained on distillation at 160° (bath temp.) and 0.005 mm., had $[\alpha]^{20}\mathrm{D}$ + 134° (*c* 0.40, benzene). The infrared spectrum (5% chf. solution) was identical with that of the racemic modification.

Anal. Calcd. for $C_{23}H_{16}O$: C, 89.58; H, 5.23. Found: C, 89.41; H, 5.39.

(±)- and (−)-2′,1′:1,2;1″,2″:3,4-dinaphth-cyclohepta-1,3-diene-6-ol (VI).—A solution of 0.147 g. of the racemic ketone, (±)-V, in 15 ml. of anhyd. ether was added dropwise to a solution of 0.075 g. of lithium aluminium hydride in 15 ml. of ether. After the addition was complete, the mixture was stirred and refluxed for 30 minutes and then was decomposed through addition of water and dilute sulfuric acid. The ether layer was separated, washed with 5% potassium bicarbonate solution, dried over potassium sulfate, and evaporated to dryness. The residual oil (0.148 g., 100%), after drying at 100° (15 mm.), was purified by chromatography on neutral alumina (Woelm, activity III, benzene as eluent) followed by two recrystallizations from hexane. The resulting colorless product, m.p. 162–163°, is exceedingly soluble in the common solvents. The infrared spectrum, characteristically different from that of the ketone V, exhibits no trace of the carbonyl band. The ultraviolet spectrum features λ_{max}^{EtOH} 219 mμ (log ϵ 5.03), 230.5 mμ (log ϵ 4.92), 305 mμ (log ϵ 4.13).

Anal. Calcd. for $C_{23}H_{18}O$: C, 89.00; H, 5.85. Found: C, 88.94; H, 5.88.

Similarly, reduction of (+)-V afforded (−)-VI in 92% yield. The product oils out from the common solvents and could not be prepared in a crystalline form; after drying under vacuum at 100° subsequent to the chromatography, the substance was obtained in the form of a hard, colorless, glassy foam, $[\alpha]^{20}\mathrm{D}$ −634° (*c* 2.2, benzene). Although we were unable to prepare an analytical sample, the ultraviolet and infrared (5% chf. solution) spectra of the product in the glassy state were identical in every respect with those of the racemic modification.

Separation of a Mixture of Ketone V and Alcohol VI.—A mixture of 63 mg. of (±)-V and of 63 mg. of (±)-VI, dissolved in 5 ml. of 1:1 hexane–benzene, was chromatographed on 10 g. of neutral alumina (Woelm, activity III), using 1:1 hexane–benzene as eluent. The first four 10-ml. fractions contained, in order, < 1, 63, < 1 and 0 mg. of eluate, identified as (±)-V by m.p. (207–211°) and infrared spectrum (identical with that of authentic V). The eluent was changed to benzene, and the following seven 10-ml. fractions, contained in order, 0, < 1, 39, 18, 5, 2 and 0 mg. of eluate, identified as (±)-VI by m.p. (160–163°) and infrared spectrum (identical with that of authentic VI).

Asymmetric Reduction of Ketone V.—To a mixture of 0.701 g. (2.3 mmoles) of (±)-V, 20.0 ml. of dioxane[17] and 13.20 g. (102 mmoles) of 2-octanol[18] ($[\alpha]^{21}\mathrm{D}$ + 9.66° (homogeneous), 100% optically pure[19]) was added a solution of 0.548 g. (2.2 mmoles) of aluminum *t*-butoxide (m.p. 197–198°) in 7.0 ml. of dioxane[17] at 82.5°. The resulting solution was kept at 82.5° for 15 minutes. The reaction mixture was cooled, 15 ml. of 2 *M* hydrochloric acid was added, and the mixture was taken to dryness at 10 mm. The solid was leached with benzene, the benzene extracts were evaporated to dryness, and the residue, dissolved in 1:1 hexane–benzene, was chromatographed on 60 g. of neutral alumina as described in the previous section. Weights and rotations of eluted V and VI are reported in Table I.

The reduction was repeated by mixing a solution of 0.393 g. (1.6 mmoles) of aluminum *t*-butoxide in 5.0 ml. of dioxane with a soluion of 0.500 g. (1.6 mmoles) of (±)-V and 9.37 g. (72 mmoles) of optically pure (+)-2-octanol in 14.0 ml. of dioxane at 63.0°, and keeping the reaction mixture at that temperature for 15 minutes. The mixture was quenched and the binaphthyls V and VI were worked up as described above. Weights and rotations of eluted V and VI are recorded in Table I.

In both experiments the eluates, V and VI, were identified by their infrared spectra (5% chf. solution), which were identical with those of the authentic substances.

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(15) D. D. Fitts, private communication; see also W. Kauzmann, "Quantum Chemistry," Academic Press, Inc., New York, N. Y., 1957, pp. 715–722.

(16) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by the Microanalytical Laboratory of the E.T.H. (under the direction of W. Manser).

(17) Purified according to the procedure of K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(18) Resolved according to the directions of A. W. Ingersoll, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 400.

(19) Calculated using the data of M. K. Hargreaves, *J. Chem. Soc.*, 2953 (1953).