ried beyond the second approximation. This modification resulted from the observation that the factor f is mainly a function of the percentage reaction, and only to a much lesser degree of the relative magnitudes of k_s, k_r and k_p. Thus, from Fig. 5, in which f is plotted against percentage reaction for several combinations of values of k_s, k_r and k_p, it is obvious that a much superior first approximation to f can be made by taking average values from this plot in place of using the constant value of 2. When this was done, the correction involved in going from the first to the second approximation became very much smaller, and the need for a third approximation was usually obviated.

Experimental Part

2-p-Anisyl-1-propyl p-Toluenesulfonate.—2-p-Anisyl-1-propanol, b.p. 80° (0.15 mm.), n^{25}D 1.5278, prepared by lithium aluminum hydride reduction of the corresponding

aldehyde, was converted in the usual way to the p-toluenesulfonate, m.p. 34–35°.

Anal. Calcd. for $C_{17}H_{20}O_4S$: C, 63.72; H, 6.29. Found: C, 63.79; H, 6.44.

Kinetic Measurements.—The anhydrous acetic acid, and the solutions of lithium perchlorate in acetic acid, were the same as those previously described.[4] The usual sealed ampoule technique was employed, the development of p-toluenesulfonic acid being followed by titration with standard sodium acetate in acetic acid using brom phenol blue indicator.[14] Solvolysis was followed to 80–95% completion. Experimental infinity titers agreed with those calculated within an average of 0.2%.

To obtain reaction time intervals from the so-called "true" zero time, the elapsed time interval from immersion in the 50° thermostat was corrected by subtracting an empirically determined "warm-up time" of 66 seconds. This figure was obtained from solvolysis of materials solvolyzing with steady first-order rate constants of 10^{-4} sec.$^{-1}$ or higher.

(14) S. Winstein, E. Grunwald and L. L. Ingraham, THIS JOURNAL, 70, 821 (1948).

LOS ANGELES 24, CALIFORNIA

The Configurational Correlation of Optically Active Biphenyls with Centrally Asymmetric Compounds. The Absolute Configuration of 6,6'-Dinitro-2,2'-diphenic Acid[1]

BY PAUL NEWMAN,[2] PHILIP RUTKIN AND KURT MISLOW[3]

RECEIVED JULY 1, 1957

Incomplete reduction of (±)-4',1''-dinitro-1,2,3,4-dibenz-1,3-cycloheptadiene-6-one (DNDBCH-6-one) with $S(+)$-pinacolyl alcohol and $S(+)$-2-octanol, in the presence of aluminum t-butoxide in dioxane, gives, in each case, a mixture of (+)-DNDBCH-6-one and (−)-DNDBCH-6-ol. These results can be accounted for readily on the basis of a simple model for the transition state of the reduction. Accordingly, (+)-DNDBCH-6-one has been assigned the S-configuration, and, since (+)-DNDBCH-6-one has been prepared from (−)-6,6'-dinitro-2,2'-diphenic acid, the latter compound also has been shown to possess the S-configuration. This method of correlation should be applicable to any optically stable hindered 2,2'-diphenic acid, regardless of the nature of the blocking substituents in the 6,6'-positions. Pseudo-first order rate constants have been obtained for the above transformations, and the difference in free energy of the competing diastereomeric transition states has been estimated.

The optical resolution of 6,6'-dinitro-2,2'-diphenic acid[4] provided the first example of enantiomerism resulting from restricted rotation about a single bond (conformational enantiomerism, Atropisomerie), a phenomenon which has since been amply documented in many diverse cases.[5] The problem of the absolute configuration of such compounds has remained a major one in stereochemistry: although an enormous body of configurational correlations exists in the field of centrally asym-

metric compounds,[6] the area of optically active biphenyls has remained virtually untouched.[7]

The absolute configuration of optically active biphenyls could, in principle, be determined by the

(6) E.g., cf. K. Freudenberg, in K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig and Vienna, 1932, pp. 662 ff.; J. A. Mills and W. Klyne, in W. Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, pp. 177 ff. Recent examples of unusual interest are (a) the chemical correlation of centrally asymmetric carbon with asymmetric quadricoördinate nitrogen, by G. Fodor, J. Toth and I. Vincze, J. Chem. Soc., 3504 (1955), et seq. (cf. also G. Fodor, Tetrahedron, 1, 86 (1957)), and (b) the correlation (by X-ray methods) of centrally asymmetric carbon with centrally asymmetric tricoördinate sulfur, by R. Hine and D. Rogers, Chemistry & Industry, 1428 (1956). The determination of the screw-sense of the polypeptide α-helix (A. Elliott and B. R. Malcolm, Nature, 178, 912 (1956)) by the X-ray method may be regarded as an elegant and important extension in this field.

(7) (a) Through correlating thebaine and phenyldihydrothebaine, J. A. Berson, THIS JOURNAL, 78, 4170 (1956), recently has succeeded in assigning absolute configurations to phenyldihydrothebaine as well as to simpler biphenylic derivatives of the latter; (b) W. Kuhn and K. Bein, Z. physik. Chem., 24B, 335 (1934), on the basis of qualitative arguments derived from their theoretical model, assigned the R-configuration to (−)-6,6'-dinitro-2,2'-diphenic acid; (c) W. Kuhn and R. Rometsch, Helv. Chim. Acta, 27, 1080, 1346 (1944), assigned the R-configuration to (−)-6,6'-dimethyl-2,2'-biphenyldiamine and to (−)-2,2'-dichloro-6,6'-dimethyl-4,4'-biphenyldiamine, on the basis of quantitative, theoretical arguments.

(1) Configurational Studies in the Biphenyl Series. I. Preliminary reports of portions of the work described in this and the following papers: (a) K. Mislow, Trans. N. Y. Acad. Sci., [2] 19, 298 (1957); (b) K. Mislow and P. Newman, THIS JOURNAL, 79, 1769 (1957); (c) K. Mislow, P. Rutkin and A. K. Lazarus, ibid., 79, 2974 (1957).

(2) Trubek Fellow, 1956–1957.

(3) To whom correspondence regarding the article should be addressed.

(4) G. H. Christie and J. Kenner, J. Chem. Soc., 614 (1922).

(5) E.g., cf. G. W. Wheland. "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 202 ff.; R. L. Shriner, R. Adams and C. S. Marvel, in H. Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 343 ff.; M. S. Newman, in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 471 ff.

method of anomalous X-ray diffraction[8]; we were concerned with finding an unequivocal solution to this problem through the use of *chemical* methods. Specifically, we attempted to decide which of the two enantiomeric forms of 6,6'-dinitro-2,2'-diphenic acid has the S-configuration.[9]

Correlation Principle.—The assignment of absolute configuration rests, in the present case, on an analysis of transition states in the Meerwein–Ponndorf–Verley reduction of a dissymmetric biphenylic ketone by centrally asymmetric alcohols of known absolute configuration.[10] The choice of the MPV equilibrium as the basis for the configurational correlation derived in large part from the fact that compelling evidence had been adduced[11] in support of the suggested transition state complex,[12] and from the simplicity of the transition state itself, which in turn permitted detailed and convincing analysis in the present correlation.

The biphenylic ketone, 4',1''-dinitro-1,2,3,4-dibenz-1,3-cycloheptadiene-6-one (DNDBCH-6-one), differs from ketones (R_1COR_2) in the classical MPV reduction in two ways: (a) it can exist in enantiomeric modifications, and (b) hydrogen transfer to *either* face of the carbonyl group (of a given enantiomer) produces the *same* alcohol (DNDBCH-6-ol); *i.e.*, R-DNDBCH-6-one on reduction produces only R-DNDBCH-6-ol. This last property is due to the fact that DNDBCH-6-one is *dissymmetric but not asymmetric;* the produced DNDBCH-6-ol, on the other hand, is asymmetric.[13] A crucial similarity between DNDBCH-6-one and classical unsymmetrical ketones does, however, exist: the two groups attached to the carbonyl carbon differ in their steric requirements toward the approach of the reducing (unsymmetrical) alcohol (R_1R_2-CHOH) in the MPV reduction. Stuart–Briegleb models clearly reveal that *DNDBCH-6-one possesses but a single conformation for a given configuration:* the three-carbon chain bridging the 2,2'-positions distorts the biphenyl from coplanarity,[14] while

the nitro groups in the 6,6'-positions serve to ensure molecular rigidity and optical stability. The transfer of hydrogen by a given enantiomer of R_1-R_2CHOH, *e.g.*, S(+)-pinacolyl alcohol,[15] to either face of the carbonyl carbon will involve, in the case of S-DNDBCH-6-one, compression of *t*-butyl against a jutting phenyl on the left and of methyl against hydrogen on the right, while reduction of the R-isomer will involve compression of *t*-butyl against hydrogen on the left and of methyl against a jutting phenyl on the right.[16] Differential compression against hydrogen being negligible, any asymmetric induction will almost wholly be the result of differential non-bonded compression against the jutting phenyl. Since *t*-butyl >> methyl in bulk size, it is to be expected that reduction of the R-isomer will proceed more rapidly, *initially*, than reduction of the S-isomer. *Incomplete* reduction of RS-DNDBCH-6-one should therefore yield a mixture of DNDBCH-6-ol enriched in R-isomer, and of unreacted DNDBCH-6-one enriched in S-isomer.[17] These relationships are reproduced schematically in Fig. 1. Finally, conversion of optically active 6,6'-dinitro-2,2'-diphenic acid to optically active DNDBCH-6-one completes the desired configurational correlation.[18]

Preparation of DNDBCH-6-one, and Preliminary Asymmetric Reductions.—The preparation of (±)-DNDBCH-6-one was carried out as follows. Methyl (±)-6,6'-dinitro-2,2'-diphenate was reduced to (±)-6,6'-dinitro-2,2'-bis-(hydroxymethyl)-biphenyl[19] by $LiAlH_4$–$AlCl_3$ in ether.[20]

(8) Recently reviewed by R. Pepinsky, *Record Chem. Progr.*, **17**, 145 (1956). No work has been reported thus far bearing on the question of biphenyl configuration.

(9) The two possible enantiomeric modifications are designed as the S- and R-forms; R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956). Although this nomenclature will be employed throughout, alternative designations have been proposed by G. E. McCasland (private communication; *cf.* also "A New General System for the Naming of Stereoisomers" (1954), p. 21, obtainable from "Chemical Abstracts," Ohio State University, Columbus 10, Ohio), and by A. P. Terentiev and V. M. Potapov, *Tetrahedron*, **1**, 119 (1957).

(10) Asymmetric inductions involving optically active biphenyls are well known; see (a) M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, 1758 (1930); (b) R. Robinson, *Nature*, **160**, 815 (1947); (c) J. A. Berson and E. Brown, THIS JOURNAL, **77**, 450 (1955); (d) J. A. Berson and M. A. Greenbaum, *ibid.*, **79**, 2340 (1957).

(11) (a) W. von E. Doering and T. C. Aschner, Abstracts of Papers, 112th Meeting, A.C.S., New York, Sept. 17, 1947, p. 21-L; *cf.* also E. D. Williams, K. A. Krieger and A. R. Day, THIS JOURNAL, **75**, 2404 (1953); (b) W. von E. Doering and R. W. Young, *ibid.*, **72**, 631 (1950); R. W. Young, Ph.D. Thesis, Columbia University, 1951; *cf.* also L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 2641 (1949).

(12) R. B. Woodward, N. L. Wendler and F. J. Brutschy, THIS JOURNAL, **67**, 1425 (1945).

(13) DNDBCH-6-one has a twofold rotating symmetry axis passing through the carbonyl group; DNDBCH-6-ol has no rotating axis of symmetry. This consideration is important with regard to the general applicability of the correlation method (see below).

(14) The optical activation of 6,6-dicarbethoxy-1,2,3,4-dibenz-1,3-

cycloheptadiene (D. C. Iffland and H. Siegel, *J. Org. Chem.*, **21**, 1056 (1956)) bears out this inference; the observed optical instability suggests that passage through a planar (or equivalent) conformation may occur with ease in the absence of 6,6'-substituents.

(15) Asymmetric Grignard reductions (H. S. Mosher and E. La Combe, THIS JOURNAL, **72**, 3994 (1950); H. S. Mosher and P. K. Loeffler, *ibid.*, **78**, 4959 (1956)) have served to correlate (+)-pinacolyl alcohol and (−)-2-methyl-1-butanol, which has in turn been related to (+)-isoleucine (F. Ehrlich, *Ber.*, **40**, 2538 (1907)). The absolute configuration of (−)-isoleucine has been established by the anomalous X-ray scattering technique (J. Trommel and J. M. Bijvoet, *Acta Cryst.*, **7**, 703 (1954)). (+)-Pinacolyl alcohol also has been assigned the S-configuration through use of the Displacement Rule (P. G. Stevens, THIS JOURNAL, **55**, 4237 (1933)).

(16) In order to visualize the transition state, in which the carbonyl (and carbinol) carbons have a geometry intermediate between sp³ and sp², Stuart–Briegleb models (ref. 1a and 1b) of both DNDBCH-6-one and DNDBCH-6-ol should be consulted, together with models of pinacolyl alcohol and pinacolone, respectively.

(17) *Complete* reduction of RS-DNDBCH-6-one with S(+)-pinacolyl alcohol must yield RS-DNDBCH-6-ol: here again the situation differs from that encountered in the classical MPV reduction, where complete reduction of R_1COR_2 under similar conditions will yield R_1R_2CHOH enriched in one of the enantiomers. In addition, it should be noted that the difference in steric requirements is not a result of compression against *different* groupings, as is the case for the classical MPV asymmetric reduction; rather, the stereoselectivity is a consequence of *the spatial non-equivalence of the two structural identical halves* of the molecule resulting from its twisted geometry.

(18) In an alternative approach, *complete* reduction of *optically active* DNDBCH-6-one with an excess of (±)-pinacolyl alcohol should leave residual pinacolyl alcohol optically active: if dextrorotatory, the enrichment in the S-modification (ref. 15) would lead to the assignment of the S-configuration to the starting DNDBCH-6-one (*i.e.*, S-DNDBCH-6-one is expected to oxidize R(−)-pinacolyl alcohol more rapidly than the S(+)-enantiomer).

(19) This compound has been independently prepared by D. C. Iffland and H. Siegel (ref. 14; Dr. Iffland, private communication). We also prepared the dibromide by NBS-bromination of dinitrobitolyl.

(20) The method was based originally on the successful use of this reagent mixture in the reduction of *p*-nitrobenzaldehyde to *p*-nitrobenzyl alcohol (R. F. Nystrom, THIS JOURNAL, **77**, 2544 (1955)).
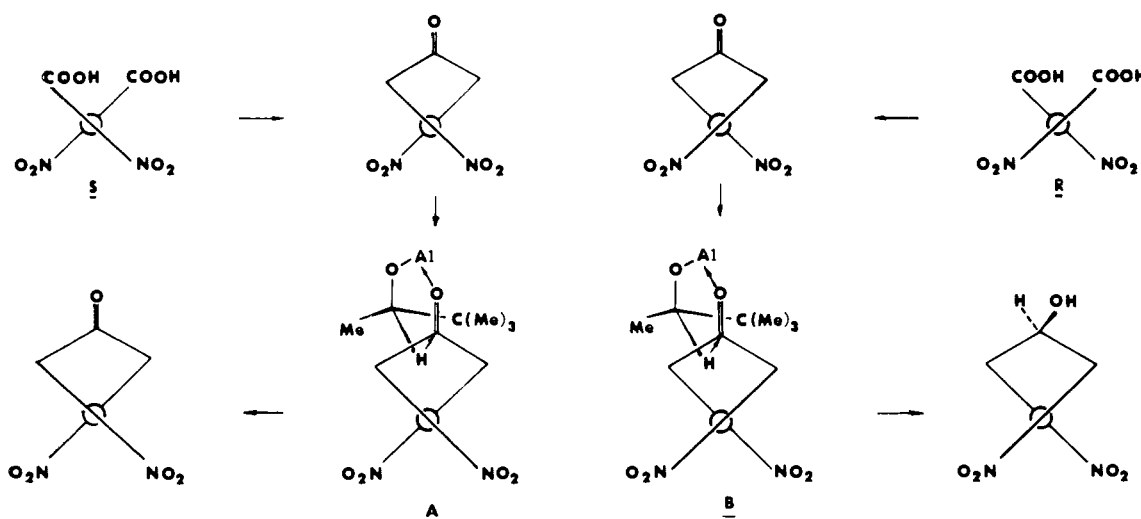
Fig. 1.—Schematic flowsheet illustrating the ideal case of 100% stereoselectivity in the partial MPV reduction of *RS*-DNDBCH-6-one by *S*-pinacolyl alcohol: *S*-DNDBCH-6-one remains unreduced (unfavorable transition state A) while the *R*-form is reduced *via* the favorable diastereomeric transition state B.

The diol, on treatment with concd. HBr, gave (±)-6,6'-dinitro-2,2'-bis-(bromomethyl)-biphenyl,[19] which was converted to (±)-4',1''-dinitro-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine with aqueous ethanolic potassium cyanide.[21] Acid hydrolysis yielded (±)-DNDBCH-6-one. Similar transformations, starting with (−)-6,6'-dinitro-2,2'-diphenic acid, yielded, in order, (−)-methyl 6,6'-dinitro-2,2'-diphenate,[22] (−)-6,6'-dinitro-2,2'-bis-(hydroxymethyl)-biphenyl, (−)-6,6'-dinitro-2,2'-bis-(bromomethyl)-biphenyl,[22] (+)-4',1''-dinitro-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine and (+)-DNDBCH-6-one.

In preliminary experiments, solutions of (±)-DNDBCH-6-one (0.04–0.07 g.), containing a 30–40 molar excess of pinacolyl alcohol (0.5–0.7 g., $[\alpha]^{25}D$ +8.1°), in 1.5–2 ml. of dioxane[23] at 63° were

(21) (a) Ring closure occurred readily without isolation of the expected intermediate, 6,6'-dinitro-2,2'-bis-(cyanomethyl)-biphenyl; the corresponding ring closure starting from 2,2'-bis-(bromomethyl)-biphenyl requires more drastic conditions (R. Weitzenböck, *Monatsh.*, **34**, 193 (1913)), 2,2'-bis-(cyanomethyl)-biphenyl being the usual product (J. Kenner and E. G. Turner, *J. Chem. Soc.*, 2101 (1911)) isolated. Furthermore, since 6,6'-dimethyl-2,2'-bis-(bromomethyl)-biphenyl yields 6,6'-dimethyl-2,2'-bis-(cyanomethyl)-biphenyl under similar conditions, conversion to 4',1''-dimethyl-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine requiring the agency of sodium ethoxide (*cf.* Experimental Part), it is concluded that the electron-withdrawing power of the nitro groups, rather than some steric effect, must be held accountable for the present result. (b) It is noteworthy that no condensation between methylene and nitro occurred under these conditions, to give (A). A similar ring closure has been reported in the at-

NC—C=N—O⊖
(diagram)
⊖O—N=C—CN

(A)
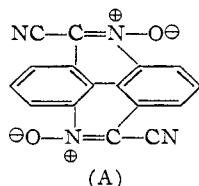
tempted preparation of 2-nitro-2'-cyanomethylbiphenyl (C. W. Muth, J. C. Ellers and O. F. Folmer, Abstract of Papers, 130th Meeting, A.C.S., Atlantic City, N. J., Sept. 16, 1956, p. 38-O).

(22) The (+)-forms were similarly prepared; the diol and dibromide have been independently synthesized (ref. 19).

(23) Chosen as an indifferent common solvent since DNDBCH-6-one is only very slightly soluble in pinacolyl alcohol at 63°.

mixed with equimolar quantities (0.03–0.05 g.) of aluminum *t*-butoxide in 0.5 ml. of dioxane at 63°. The mixtures were quenched, after various intervals of time, by addition of dilute HCl. The solvent mixture was distilled and the residual solid ("biphenylic mixture"), after washing with water and drying, was examined polarimetrically. The results, presented in Fig. 2 (circles), proved that the reduction was stereospecific, as shown analytically below.

At any time, *t*, during the reduction, the rotation of the biphenylic mixture, $[\alpha_M]$, can be expressed[24,25] as

$[\alpha_A]$ and $[\alpha_K]$ = specific rotation
$[\alpha^0_A]$ and $[\alpha^0_K]$ = specific rotation of optically pure substance
n_A and n_K = mole fraction (*cf.* ref. 25)
ω_A and ω_K = optical purity
A_R and K_R = moles of substance having the *R*-configuration
A_S and K_S = moles of substance having the *S*-configuration
$T = A_R + K_R + A_S + K_S$
k_R and k_S = spec. rate const. for reducn. of *R*- and *S*-DNDBCH-6-one

$$[\alpha_M] = n_K[\alpha_K] + n_A[\alpha_A]$$

or

$$[\alpha_M]T = (K_R + K_S)[\alpha_K] + (A_R + A_S)[\alpha_A]$$

Since

$$\omega_A = \frac{A_R - A_S}{A_R + A_S} = \frac{[\alpha_A]}{[\alpha_A^0]} \quad (1)$$

and

$$\omega_K = \frac{K_S - K_R}{K_S + K_R} = \frac{[\alpha_K]}{[\alpha^0_K]} \quad (2)$$

it follows that

$$[\alpha_M]T = (K_S - K_R)[\alpha^0_K] + (A_R - A_S)[\alpha^0_A]$$

(24) In this and the subsequent discussions, these symbols will be employed (*A* refers to the alcohol DNDBCH-6-ol, and *K* to the ketone DNDBCH-6-one)

(25) Since the molecular weights of DNDBCH-6-one (298) and of DNDBCH-6-ol (300) differ by less (0.7%) than any errors in measurement in the present work, the molecular weights will be taken as identical (*i.e.*, mole fraction ≅ weight fraction) in the derivation of equation 8.
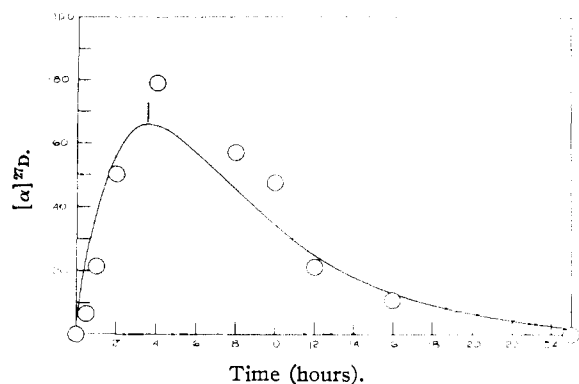
Time (hours).

Fig. 2.—Specific rotation of DNDBCH-6-one/6-ol mixtures as a function of time in MPV reduction by (+)-pinacolyl alcohol; experimental points (circles), calcd. by eq. 8 in text (curve). The arrow marks t_{max}.

However, at any time during the reaction

$$A_R + K_R = A_S + K_S$$

or

$$A_R - A_S = K_S - K_R \qquad (3)$$

Therefore

$$[\alpha_M]T = ([\alpha^0_K] + [\alpha^0_A])(K_S - K_R)$$

This expression may be transformed if we treat the reduction as a unimolecular, irreversible process,[26] so that

$$- dK_R/dt = k_R K_R \qquad (4)$$

and

$$- dK_S/dt = k_S K_S \qquad (5)$$

Setting the limits $(K_R = K_S = \frac{1}{2}T$ at $t = 0)$ after integration gives

$$K_R = \frac{T}{2} \exp(-k_R t) \qquad (6)$$

and

$$K_S = \frac{T}{2} \exp(-k_S t) \qquad (7)$$

where k_R and k_S are pseudo-first-order rate constants. Substitution of (6) and (7) for K_R and K_S yields

$$[\alpha_M] = \frac{([\alpha^0_K] + [\alpha^0_A])}{2} (\exp(-k_S t) - \exp(-k_R t)) \qquad (8)$$

According to equation 8, which has the kinetic form of a first-order consecutive reaction,[27] $[\alpha_M] = 0$ at $t = 0$ and $t = \infty$ (when all of the ketone has been reduced to (±)-DNDBCH-6-ol), but $[\alpha_M] \neq 0$ at other times unless $[\alpha^0_K] = -[\alpha^0_A]$ or $k_S = k_R$. The observed (Fig. 2) $[\alpha_M]$ was indeed zero at $t = 0$ and $t = 25$ hr.; since the mixture was levorotatory for intermediate values of t, it has thus been demonstrated that $k_R \neq k_S$; i.e., the reduction is stereoselective.

(26) This assumption is justified if the ratio of aluminum t-butoxide to DNDBCH-6-one remains the same in all of the runs, and if a constant, large molar excess of optically pure reducing alcohol is employed. Such conditions were very nearly fulfilled. A further simplification is the non-effectiveness of the MPV equilibrium S-6-one + S-6-ol ⇄ S-6-ol + S-6-one (and of the mirror image equilibrium), and the fact that the equilibrium S-6-one + R-6-ol ⇄ S-6-ol + R-6-one does not alter with the validity of equation 3. These circumstances are a unique property of the system employed.

(27) S. Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 1055. The "intermediate" species is here represented by the optical activity, $[\alpha_M]$.
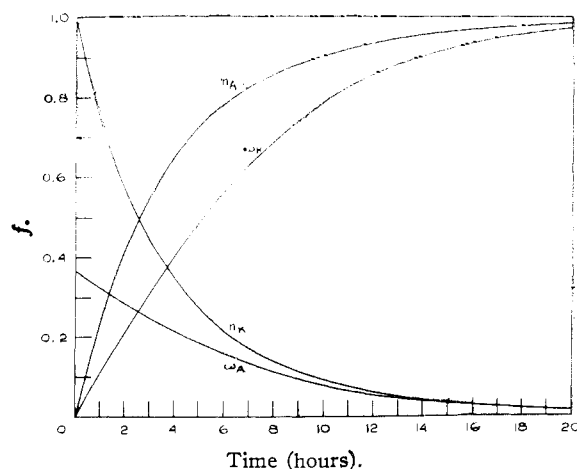

Time (hours).

Fig. 3.—Calculated fractional (f) optical purities (ω_A and ω_K) and mole fractions (n_A and n_K) of DNDBCH-6-ol and 6-one, resp., as functions of time in the MPV reduction by (+)-pinacolyl alcohol.

Isolation of Products in Asymmetric Reductions.—Two large-scale reductions were performed under conditions closely resembling those described for the preliminary experiments.

In the first reduction, 951 mg. of (±)-DNDBCH-6-one was heated at 63° for 7 hours with a 44-molar ratio of 99% optically pure S(+)-pinacolyl alcohol,[15] in the presence of an approximately equimolar quantity of aluminum t-butoxide in dioxane. The biphenylic mixture obtained could be smoothly separated by chromatography on silica gel; the ketone was eluted quantitatively with 1:3 ethyl acetate–benzene, and the alcohol, in the following fraction, with 1:1 ethyl acetate–benzene. Both fractions were identified by elemental analysis and infrared spectrum (characteristically different; Fig. 4, Experimental Part), and both were pure accord-
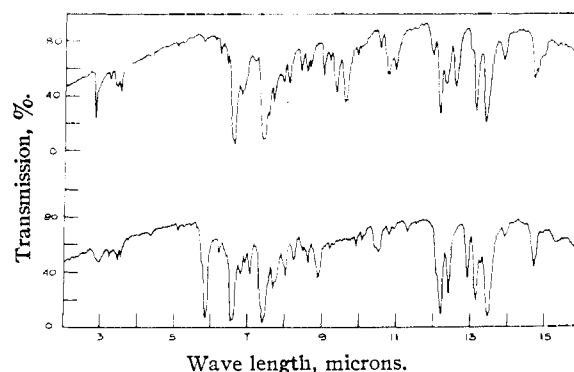

Wave length, microns.

Fig. 4.—Infrared spectra (KBr wafer) of racemic DNDBCH-6-ol (upper curve) and DNDBCH-6-one (lower curve).

ing to these criteria. Weights and rotations of residual ketone and produced alcohol are reported in Table I.

In a second experiment, 641 mg. of (±)-DNDBCH-6-one was heated at 63° for 20 minutes with a 4:1-molar ratio of 99% optically pure S(+)-2-octanol,[28] in the presence of an approximately equimolar

(28) The absolute configuration of (+)-2-octanol has been unequivocally established. Pertinent correlations are: (+)-2-octanol with (+)-2-methoxyoctane (J. Kenyon and R, A. McNicol, J. Chem.

TABLE I

PRODUCTS OF ASYMMETRIC REDUCTIONS

Reducing alcohol	Residual DNDBCH-6-one Wt., mg.	$[\alpha]^{25}_D$ (EtOAc)	ω_K	Product of reduction of residual DNDBCH-6-one $[\alpha]^{25}_D$ (EtOAc)	Calcd.	ω_A Found[a]	Wt., mg.	Produced DNDBCH-6-ol $[\alpha]^{25}_D$ (EtOAc)	Calcd.	ω_A Found[a]
(+)-Pinacolyl	139	+136°	0.624	+498°	0.624	0.715 (0.623)	665	−109°	0.131	0.157 (0.136)
(+)-2-Octanol	120	+ 52°	0.239	+212°	0.239	0.305 (0.265)	427	− 54°	0.068	0.078 (0.068)

[a] Figures are based on the observed value of $[\alpha^0_A]$ +696° and, in parentheses, on the "possible" value (ref. 30) of +800°.

quantity of aluminum *t*-butoxide in dioxane. The products were separated and characterized as before; weights and rotations of the two fractions are reported in Table I.

In both experiments, the excess unreacted reducing alcohol was recovered: in the case of (+)-2-octanol, the alcohol had retained 97% of its original optical purity; in the case of (+)-pinacolyl alcohol, the recovered product could not be obtained in chemically pure form, so that the apparent extent of racemization (27%) cannot be regarded as a reliable figure. It is likely that the pinacolyl alcohol suffered only negligible racemization.[11b] We are assuming, therefore, virtual constancy in the optical purity of reducing alcohol in the course of both reductions.

Quantitative Consistency of the Data.—In both experiments, the residual (+)-DNDBCH-6-one was completely reduced (Al(*i*-PrO)₃/*i*-PrOH) to (+)-DNDBCH-6-ol. The optical purities (ω) of starting material and product[29] (Table I) agree satisfactorily, as anticipated.[30]

According to equation 3, the molar excess of *R*-enantiomer in the alcohol fraction equals the molar excess of *S*-enantiomer in the ketone fraction. Since (+)-DNDBCH-6-one gives (+)DNDBCH-6-ol on reduction, signs and configurations are related; the fact that, in both experiments, residual (+)-DNDBCH-6-one was accompanied by pro-

Soc., **14** (1923)); (+)-2-methoxyoctane with (+)-4-methoxypentanoic acid, and (−)-4-methoxypentanoic acid with (−)-2-methoxybutane (W. von E. Doering and R. W. Young, THIS JOURNAL, **74**, 2997 (1952)); (+)-2-methoxybutane with (+)-2-butanol (D. S. Tarbell and M. C. Paulson, *ibid.*, **64**, 2842 (1942), R. Rometsch and W. Kuhn, *Helv. Chim. Acta*, **29**, 1483 (1946)); (+)-2-butanol with (+)-lactic acid (K. W. Wiberg, THIS JOURNAL, **74**, 3891 (1952)); (+)-lactic acid with (−)-glyceraldehyde (M. L. Wolfrom, R. U. Lemieux, S. M. Olin and D. I. Weisblat, *ibid.*, **71**, 4057 (1949)); (+)-glyceraldehyde with (−)-tartaric acid (A. Wohl and F. Momber, *Ber.*, **50**, 455 (1917)). The absolute configuration of (+)-tartaric acid has been established by the anomalous X-ray scattering technique (J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature*, **168**, 271 (1951)).

(29) Calculated on the basis of $[\alpha^0_K]$ +218° (EtOAc) and $[\alpha^0_A]$ +696° (EtOAc); we assume that no racemization took place in the preparation starting from optically pure (−)-6,6'-dinitro-2,2'-diphenic acid.

(30) These comparisons are made possible because all of the materials described in Table I were isolated in a state of high purity by chromatography only. Recrystallizations, which might well have altered the optical integrity of these substances, were altogether avoided. That the found ω_A is in every case *ca.* 13% higher than the calculated value might be ascribed to the error inherent in $[\alpha^0_K]$ and $[\alpha^0_A]$; a slightly lower value for the former and/or a slightly higher value for the latter would lead to more precise agreement. As pointed out by a referee, it is also possible that the optically pure reference DNDBCH-6-ol, whose isolation in solid form was attended by experimental difficulties, was contaminated by some substance(s) which escaped detection by elemental and infrared analysis, with the result that $[\alpha^0_A]$ was lowered from 800° to a value within experimental error of the observed figure. Granted the higher value, the agreement between calculated and found ω_A (figures in parentheses, Table I) is indeed excellent.

duced (−)-DNDBCH-6-ol therefore bears out equation 3 qualitatively. In addition, however, *it is possible to calculate the optical purity of the produced alcohol using only the optical data for the accompanying residual ketone.*

Dividing equation 1 by 2, and combining with 3

$$\omega_A = \omega_K \left(\frac{K_S + K_R}{A_S + A_R}\right) \qquad (9)$$

Since moles of residual ketone and produced alcohol are calculable from the corresponding weights (Table I), comparisons[30] of calculated and found ω_A are thus possible; the agreement for both experiments is gratifying (Table I).

A final measure of internal consistency is the fit of the kinetic data, as described in the following section.

Kinetics and Efficiency of the Asymmetric Reduction.—Combination of equations 2 and 6, resp. 7, gives

$$k_S = \frac{1}{t}\ln\frac{[\alpha^0_K]T}{(K_S + K_R)([\alpha^0_K] + [\alpha_K])} \qquad (10)$$

and

$$k_R = \frac{1}{t}\ln\frac{[\alpha^0_K]T}{(K_S + K_R)([\alpha^0_K] - [\alpha_K])} \qquad (11)$$

With appropriate substitutions,[31] values for the specific rate constants k_R and k_S may be obtained (Table II). In both reductions, $k_R > k_S$, *i.e.*, *R*-DNDBCH-6-one is reduced more rapidly than the *S*-isomer at the same concentration; it is significant that the values for *both* rate constants in the (+)-2-octanol experiment considerably exceed the corresponding values for the (+)-pinacolyl alcohol experiment, *i.e.*, a lower free energy of activation[32] is required for the reduction of *either* enantiomer of DNDBCH-6-one by (+)-2-octanol than for reduction by (+)-pinacolyl alcohol. Further, the *ratio* of rates, k_R/k_S, and the derived *difference* in free energies of activation for the competing diastereomeric transition states (Fig. 1, A and B)[33] is less in the reduction by (+)-2-octanol than in the reduction by (+)-pinacolyl alcohol (Table II). These results are in complete harmony with our view of the transition state: compression of the *t*-butyl group against jutting phenyl is more prohibitive a process than compression of *n*-hexyl against jutting phenyl,[34] and pinacolyl alcohol is accordingly the

(31) For the pinacolyl alcohol and 2-octanol reductions, *t* = 7.0 and 0.33 hr., respectively; $[\alpha^0_K]$ = 218° (ref. 29); all other values are obtained from the data in Table I, in conjunction with the known molecular weights.

(32) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 14.

(33) $\Delta\Delta F^{\ddagger}$ (= $-RT\ln k_S/k_R$) is a measure of the efficiency of the asymmetric reduction.

(34) The "compression" involves both loss of internal degrees of freedom and, separately, an increase in potential energy. Taft's

slower, more stereoselective reducing agent of the two employed.

Reducing alcohol	k_R, hr.$^{-1}$	k_S, hr.$^{-1}$	k_R/k_S	$\Delta\Delta F\pm$	t_{max}, hr.	$\omega_A(t_0) = \omega_K(t_{max})$
(+)-Pinacolyl	0.39	0.18	2.2	0.51	3.66	0.365
(+)-2-Octanol	5.4	3.9	1.4	0.21	0.217	0.157

Given values (Table II) for k_R and k_S, it is now possible to calculate $[\alpha_M]$, n_K, n_A, ω_K and ω_A as functions of time.[24,35] The calculated curve for $[\alpha_M]$ (Fig. 2) fits the experimental points surprisingly well, considering the roughness of the data, and thus further credence is lent to the soundness of the quantitative treatment. Curves expressing n_K, n_A, ω_K and ω_A as functions of time, presented in Fig. 3, deserve additional comment.

At $t = 0$, when $n_K = 1$, $\omega_K = 0$ since $K_R = K_S$. The optical purity of the infinitesimal amount of alcohol produced at $t = dt$ is calculable: substitution of $k_R K_R$ and $k_S K_S$ for A_R and A_S, respectively, in equation 1 gives

$$\omega_A(t_0) = \frac{k_R - k_S}{k_R + k_S} \qquad (10)$$

since $K_R = K_S$.

Initially, R-ketone is reduced more rapidly than S-ketone since $k_R > k_S$ while $K_R = K_S$ (eq. 4 and 5). At the "inversion point," $-dK_R/dt$, $= -dK_S/dt$, whence (eq. 4 and 5) $K_S = k_R K_R/k_S$. Substitution into eq. 2 gives

$$\omega_K(t_{max}) = \frac{k_R - k_S}{k_R + k_S} \qquad (11)$$

The inversion of rates occurs at a time corresponding to the maximum development of optical activity $[\alpha_M]$ in the biphenylic mixture (Fig. 2, arrow), as shown analytically by substitution of t_{max} (from eq. 8)[36] into the expression[35] for ω_K; $\omega_K(t_{max}) = \omega_A(t_0)$ (eq. 10 and 11) regardless of the values for k_R and k_S.

As the reduction proceeds (Fig. 3), ω_K rises from zero to a value, at t_{max}, identical with that for ω_A at t_0. Beyond this, the inversion point, as ω_K continues to increase and ω_A continues to decrease, S-ketone will be reduced *more* rapidly than R-ketone. Numerical solutions for $\omega_K(t_{max})$ and for t_{max} are recorded in Table II.[37] Both large-scale reductions were run, fortuitously, for times exceeding t_{max}; hence, in both cases, ω_K of the isolated residual ketone (Table I) was larger than $\omega_K(t_{max})$. The ω_A of

steric parameter (R. W. Taft, Jr., THIS JOURNAL, **74**, 3120 (1952), *et seq.*) might well provide a quantitative measure of steric compression in the present asymmetric reduction (E_s of n-$C_5H_{13} \sim -0.4$; E_s of t-$C_4H_9 \sim -1.5$). We hope to investigate such a relationship in greater detail at a future date.

(35) (a) $[\alpha_M]$ from equation 8; $[\alpha^0_K]$ and $[\alpha^0_A]$ refer to solvent pyridine (Experimental). (b) $n_K = (K_S + K_R)/T$; substitution of eq. 6 and 7 gives $n_K = (\exp(-k_S t) + \exp(-k_R t))/2$. (c) $n_A = 1 - n_K$. (d) Combination of eq. 2, 6 and 7 gives $\omega_K = (\exp(-k_S t) - \exp(-k_R t))/(\exp(-k_S t) + \exp(-k_R t))$. (e) Combination of eq. 1, 3, 6 and 7 gives $\omega_A = (\exp(-k_S t) - \exp(-k_R t))/(2 - (\exp(-k_S t) + \exp(-k_R t)))$.

(36) $t_{max} = (\ln k_S/k_R)/(k_S - k_R)$, in complete analogy to a first-order consecutive reaction (ref. 27); obtained by setting $d[\alpha_M]/dt = 0$.

(37) It must be emphasized that k_S, k_R and t_{max} are dependent on the particular reaction conditions (solvent, concentration of aluminum t-butoxide, temperature, etc.) employed; reported values (Table II) refer, of course, to the reaction conditions chosen in this work.

isolated produced alcohol (Table I) was, of course, less than $\omega_A(t_0)$.
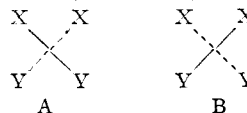
Absolute Configuration of 6,6'-Dinitro-2,2'-diphenic Acid.—The absolute configurations of the reducing alcohols have been independently and unequivocally established.[15,28] Since $S(+)$-2-octanol and $S(+)$-pinacolyl alcohol each produce residual $S(+)$-DNDBCH-6-one, and since the latter has been related to $(-)$-6,6'-dinitro-2,2'-diphenic acid, the S- and R-configurations can be assigned to $(-)$- and $(+)$-6,6'-dinitro-2,2'-diphenic acid, respectively. This result is in disagreement with the conclusions of Kuhn and Bein,[7b] but it must be remarked that these authors did not appear to have attempted a quantitative theoretical treatment of this problem.

The absolute configuration of all compounds related to 6,6'-dinitro-2,2'-diphenic acid is automatically established.[38] Included are the intermediates in synthesis reported in the present work, as well as the bridged biphenyls prepared by Iffland and Siegel[14,39]; absolute configuration has therefore been assigned to an optically unstable, bridged biphenyl (Ic).[39]

General Applicability of the Correlation Method.—In our view, based on the inspection of models,[16] the reaction sphere (including compression areas) lies entirely above the plane which contains the long biphenyl axis and which is perpendicular to the twofold symmetry axis; we do not regard the nature of the blocking substituents in the 6,6'-positions as influential in the course of the asymmetric reduction, other than in their function to ensure optical stability and molecular rigidity. The method of correlation is expected to apply, in general, to any optically stable 4',1"-disubstituted DBCH-6-one, and hence to any 6,6'-disubstituted 2,2'-diphenic acid (or compound relatable to a 6,6'-disubstituted 2,2'-diphenic acid).

In the event that the 4',1"-substituents are not identical, as they are in DNDBCH-6-one, the correlation principle still applies, but the method requires slight modification. The original symmetry attributes[13] no longer obtain, for the DBCH-6-one

(38) It is to be noted in connection with material presented in this and the following papers that, according to the system of nomenclature here employed (ref. 9), any biphenyl of geometry A has the S-configuration, and of geometry B the R-configuration, regardless of the priority number of X and Y. Since, furthermore, exchange of X and Y on

both rings yields the identical configuration, the problem of configurational designation is remarkably simple one.

(39)
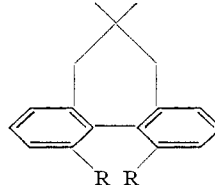
Ia, R = NO$_2$
b, R = NH$_2$
c, R = H

$(-)$-Ia, $(-)$-Ib and $(+)$-Ic were prepared starting from $(+)$-6,6'-dinitro-2,2'-diphenic acid (we are greatly indebted to Dr. Iffland for releasing this information to us prior to publication). All of these compounds therefore possess the R-configuration.

is now asymmetric, and the corresponding DBCH-6-ol can exist in four stereomeric modifications: incomplete reduction of such a racemic DBCH-6-one with, say, S-2-octanol would be expected to yield nearly equal quantities of two diastereomeric alcohols, with, say, R-DBCH-6-ol predominating in each to nearly the same extent. The separation problem might appear formidable, but it will be quite sufficient to separate both alcohols from the ketone and to examine the latter alone; the residual DBCH-6-one should be enriched in the S-form.[18] The generality of our method therefore remains unimpaired.

Experimental Part[40]

(−)- and (+)-Methyl 6,6'-Dinitro-2,2'-diphenate.—Hydrogen chloride gas was passed into a stirred solution of (−)-6,6'-dinitro-2,2'-diphenic acid[41] (18.5 g., $[\alpha]^{23}$D −125° (c 2.1, methanol), m.p. 230–233°) in 500 ml. of methanol. Passage was maintained for two hours, under reflux with external heating. The solvent was removed and the residue was triturated with cold 10% sodium carbonate. The mixture was filtered and the residual solid was washed with water and dried, giving 19.6 g. of material, m.p. 135.5–137.5°. Four recrystallizations from 95% ethanol gave the desired product,[42] m.p. 141–142°, $[\alpha]^{28}$D −113° (c 4.9 ethyl acetate).

Anal. Calcd. for $C_{16}H_{12}N_2O_8$: C, 53.4; H, 3.4; N, 7.8. Found: C, 53.6; H, 3.2; N, 8.2.

The other enantiomer, prepared in the same manner, had m.p. 141–142°, $[\alpha]^{27}$D +113° (c 5.1, ethyl acetate).

Anal. Calcd. for $C_{16}H_{12}N_2O_8$: C, 53.4; H, 3.4; N, 7.8. Found: C, 53.6; H, 3.2; N, 7.6.

(±)- and (−)-6,6'-Dinitro-2,2'-bis-(hydroxymethyl)-biphenyl.—Into a three-neck flask equipped with reflux condenser, dropping funnel and Tru-Bore stirrer was placed, in the order given, 173 ml. of a filtered solution containing 6.5 g. of lithium aluminum hydride in abs. ether, 31.1 g. of aluminum chloride in 500 ml. of abs. ether and, over a period of 80 minutes, a solution of 21.0 g. of methyl 6,6'-dinitro-2,2'-diphenate[41] in 2.75 l. of abs. ether. After addition was complete, the mixture was stirred for two hours. Water (50 ml.) was added, the ether was concentrated to 1 l., 100 ml. of 9 M sulfuric acid was added, and the organic phase was separated, washed with 10% sodium carbonate, dried and evaporated. The residue (10 g.) was recrystallized from benzene to give 8.0 g. (45%) of product, m.p. 142–144°.

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: C, 55.3; H, 4.0; N, 9.2. Found: C, 55.5; H, 3.9; N, 9.0.

In a similar manner, starting with (−)-methyl 6,6'-dinitro-2,2'-diphenate, the (−)-diol was obtained.[42] The product, purified by chromatography on alumina (Woelm, acid (anionotropic), activity grade 1; a 2% solution of methanol in benzene was used as eluent) followed by recrystallization from benzene, had m.p. 120–121°, $[\alpha]^{20}$D −65° (c 0.71, ethyl acetate).

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: C, 55.3; H, 4.0; N, 9.2. Found: C, 55.5; H, 3.7; N, 9.1.

(±)-, (−)- and (+)-6,6'-Dinitro-2,2'-bis-(bromomethyl)-biphenyl.—(A) A mixture of 5.0 g. of 6,6'-dinitro-2,2'-dimethyl biphenyl,[43] 6.5 g. of N-bromosuccinimide, 50 mg. of benzoyl peroxide and 60 ml. of carbon tetrachloride was refluxed for ten hours with the intermittent addition, every two to three hours, of small quantities (25–50 mg.) of benzoyl peroxide. The mixture was filtered while hot; the residue was leached with hot carbon tetrachloride. The combined solution was freed of solvent and the residue (6.5 g.) recrystallized four times from ethanol to give 0.82 g. (10%) of desired product, m.p. 183–185°.

(40) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(41) A. W. Ingersoll and J. R. Little, THIS JOURNAL, **56**, 2123 (1934).

(42) Kindly prepared by Dr. A. K. Lazarus.

(43) G. Wittig and O. Stichnoth, *Ber.*, **68**, 928 (1935).

Anal. Calcd. for $C_{14}H_{10}Br_2N_2O_4$: C, 39.1; H, 2.3; N, 6.5. Found: C, 39.0; H, 2.5; N, 6.3.

(B) A mixture of 8.0 g. of 6,6'-dinitro-2,2'-bis-(hydroxymethyl)-biphenyl and 360 ml. of 48% hydrobromic acid was refluxed for 40 minutes, cooled, and filtered. The residue was washed with water and dried. The crude solid (10.3 g., m.p. 177–183°) was recrystallized from ethyl acetate to give 6.5 g. (58%) of crystals, m.p. (183–185°) undepressed by admixture of product from A.

The (−)-dibromide, similarly prepared[42] from (−)-6,6'-dinitro-2,2'-bis-(hydroxymethyl)-biphenyl, and purified by chromatography on silica gel (Davison, 100–200 mesh; ethyl acetate was used as eluent) followed by recrystallization from ethyl acetate, had m.p. 171.5–172.5°, $[\alpha]^{32}$D −8.9° (c 2.0, tetrahydrofuran).

Anal. Calcd. for $C_{14}H_{10}Br_2N_2O_4$: C, 39.1; H, 2.3; N, 6.5. Found: C, 39.3; H, 2.1; N, 6.7.

The other enantiomer, prepared in like manner from crude (+)-6,6'-dinitro-2,2'-bis-(hydroxymethyl)-biphenyl, had m.p. 172–173°, $[\alpha]^{32}$D +8.3° (c 6.3, tetrahydrofuran).

Anal. Calcd. for $C_{14}H_{10}Br_2N_2O_4$: C, 39.1; H, 2.3; N, 6.5. Found: C, 39.8; H, 2.8; N, 6.9.

(±)- and (+)-4',1''-Dinitro-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine.—To a refluxing solution of 0.500 g. of 6,6'-dinitro-2,2'-bis-(bromomethyl)-biphenyl in 78 ml. of 95% ethanol was added a solution of 0.182 g. of potassium cyanide in 8.7 ml. of water. The solution was kept at reflux under nitrogen for 90 minutes; a dark yellow color had developed during this period. The solution was cooled, made just acid to Hydrion paper with glacial acetic acid, and, after addition of 5 ml. of water, distilled under aspirator vacuum to one-quarter of its volume. The golden yellow material (m.p. 210–260° dec.) which precipitated was leached four times with 5-ml. portions of hot benzene. The yellow-green residue (0.228 g., 61% yield, m.p. 295–300° dec.) was recrystallized from acetonitrile to give intensely canary-yellow crystals, m.p. 304° dec. The infrared spectrum (KBr wafer) exhibited strong bands at 3325 (N–H), 1635 (C=N) and 2190 cm.$^{-1}$ (C≡N).

Anal. Calcd. for $C_{16}H_{10}N_4O_4$: C, 59.6; H, 3.1; N, 17.4. Found: C, 59.8; H, 3.2; N, 17.1.

The (+)-form, similarly prepared from (−)-6,6'-dinitro-2,2'-bis-(bromomethyl)-biphenyl, had m.p. 295–300° dec. (after three recrystallizations from acetonitrile–benzene and one recrystallization from acetonitrile), $[\alpha]^{28}$D +837° (c 1.0, pyridine).

Anal. Calcd. for $C_{16}H_{10}N_4O_4$: C, 59.6; H, 3.1; N, 17.4. Found: C, 60.1; H, 3.7; N, 17.4.

(+)-6,6'-Dimethyl-2,2'-bis-(cyanomethyl)-biphenyl.—(+)-6,6'-Dimethyl-2,2'-bis-(bromomethyl)-biphenyl[44] (6.1 g., m.p. 54–57°, $[\alpha]^{28}$D +54° (c 0.80, benzene)) was added over a period of 5.5 hours to a refluxing solution of 2.6 g. of KCN in 5.9 ml. of water and 17.3 ml. of ethanol. After an additional two hours of refluxing, the solution was cooled, water was added until no further precipitation occurred, and the mixture, after cooling in ice for two hours, was filtered. The residue (m.p. 103–117°), after recrystallization from ethanol, gave product, m.p. 122–123°, $[\alpha]^{29}$D +20° (c 1.1, pyridine).

The infrared spectrum (KBr wafer) exhibited the nitrile band (2255 cm.$^{-1}$), but no bands associated with N–H and C=N.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.0; H, 6.2; N, 10.8. Found: C, 83.5; H, 6.1; N, 10.9.

(+)-4',1''-Dimethyl-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine.—A 0.6-ml. portion of a solution of 1 g. of sodium in 25 ml. of ethanol was added to a refluxing solution of 3.3 g. of (+)-6,6'-dimethyl-2,2'-bis-(cyanomethyl)-biphenyl in 16.5 ml. of absolute ethanol. A stream of nitrogen was passed over the solution, and refluxing was maintained for one hour. The mixture was cooled in ice, filtered, and the residue washed with cold ethanol. The solid (2.2 g., 66%, m.p. 249–253° dec.) on recrystallization from acetonitrile gave product, m.p. 254–256° dec., $[\alpha]^{29}$D +496° (c 1.1, pyridine). The infrared spectrum (KBr wafer) showed marked absorption at 3333 (N–H), 1635 (C=N) and 2174 cm.$^{-1}$ (C≡N).

(44) G. Wittig and H. Zimmermann, *ibid.*, **86**, 629 (1953).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.0; H, 6.2; N, 10.8. Found: C, 83.0; H, 5.8; N, 11.5.

(±)- and (+)-4',1''-Dinitro-1,2,3,4-dibenz-1,3-cyclohep-tadiene-6-one (DNDBCH-6-one).—A mixture of 0.53 g. of (±)-4',1''-dinitro-5-cyano-1,2,3,4-dibenz-1,3-cyclohepta-diene-6-imine, 10 ml. of water, 10 ml. of glacial acetic acid and 10 ml. of sulfuric acid was refluxed for 1.25 hours, cooled, and poured into 40 ml. of water. The resulting emulsion soon turned into a solid suspension. The solid (0.32 g., 65%) was filtered and washed with water. A total of 2.7 g. of crude ketone thus obtained was chromatographed twice on alumina (Woelm, acid (anionotropic), activity grade 1; 1:1 ethyl acetate–benzene was used as eluent) and then recrystallized once from ethyl acetate to give 2.1 g. of stout, light yellow prisms, m.p. 234–236° dec. The infrared spectrum exhibited pronounced bands at 1700 cm.$^{-1}$ (C=O), and at 1345 and 1515 cm.$^{-1}$ (NO$_2$); cf. Fig. 4.

Anal. Calcd. for $C_{15}H_{10}N_2O_5$: C, 60.4; H, 3.4; N, 9.4; mol. wt., 298. Found: C, 60.4; H, 3.3; N, 9.2; mol. wt., 280.

The (+)-form, similarly prepared from (+)-4',1''-dini-tro-5-cyano-1,2,3,4-dibenz-1,3-cycloheptadiene-6-imine, had m.p. 227–229° dec., $[\alpha]^{25}$D +218° (c 1.1, ethyl acetate), $[\alpha]^{25}$D +209° (c 0.9, pyridine), infrared spectrum identical with that of the (±)-form.

Anal. Calcd. for $C_{15}H_{10}N_2O_5$: C, 60.4; H, 3.4; N, 9.4. Found: C, 61.0; H, 3.8; N, 9.5.

(±)- and (+)-4',1''-Dinitro-1,2,3,4-dibenz-1,3-cyclohep-tadiene-6-ol (DNDBCH-6-ol).—A mixture of 1.0 g. of DNDBCH-6-one, 2.1 g. of aluminum isopropoxide and 125 ml. of isopropyl alcohol was refluxed for three hours and then made acid with 2 *M* hydrochloric acid. The mixture was concentrated by distillation and the solid which crystallized on cooling was collected and washed with water. The crude product (1.0 g.) was recrystallized from benzene to give 0.55 g. (55%) of thin plates, m.p. 199–200°. The infrared spectrum (KBr wafer) exhibited pronounced bands at 3540 (OH), 1515 (NO$_2$) and 1345 cm.$^{-1}$ (NO$_2$); cf. Fig. 4.

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.0; N, 9.3. Found: C, 60.0; H, 3.5; N, 9.2.

The (+)-form, similarly prepared from (+)-DNDBCH-6-one, was obtained as an oil which could be solidified by scratching *but which could not be crystallized from common solvents* owing to its persistent tendency to oil out. The solid, after washing with cold benzene, had m.p. 133–137°,[45] $[\alpha]^{27}$D +696° (c 0.23, ethyl acetate), $[\alpha]^{26}$D +674° (c 0.22, pyridine). The infrared spectrum was identical with that of the racemate (Fig. 4).

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.0; N, 9.3. Found: C, 60.2; H, 4.3; N, 9.3.

Preliminary Reductions of DNDBCH-6-one with (+)-Pinacolyl Alcohol.—A number of small-scale reductions were run as described in the text. A typical procedure follows.

A mixture of 0.0572 g. (0.19 mmole) of (±)-DNDBCH-6-one, 1.54 g. of dioxane[46] and 0.660 g. (6.4 mmoles) of (+)-pinacolyl alcohol [n^{25}D 1.4130, $[\alpha]^{25}$D +8.10° (homogeneous) (lit.[11b] $[\alpha]^{25}$D +8.03°, n^{25}D 1.4133 and $[\alpha]^{20}$D +7.71°[47]); prepared *via* the hydrogen phthalate brucine salt, $[\alpha]^{28}$D −3.2° (c 2.9, 95% ethanol), lit.[47] $[\alpha]$D −4.2° and $[\alpha]$D −2.98°[11b]] was kept in a thermostated bath at 63° for 15 minutes. A second mixture, consisting of 0.0436 g. (0.18 mmole) of aluminum *t*-butoxide and 0.52 g. of dioxane, was also brought to 63°. The two solutions were mixed at 63° and kept at that temperature for two hours. The reaction mixture was cooled, 1 ml. of 2 *M* hydrochloric acid was added, and the solvent mixture was removed by distillation under vacuum. The residual solid was washed with water and dried. This material (0.0303 g., m.p. 198–222° dec.; the infrared spectrum (KBr wafer) exhibited bands for OH, C=O and NO$_2$) was made up to 1.00 ml. with pyridine and the resulting solution, after centrifugation of a small amount (ca. 1 mg.) of suspended aluminum hydroxide, had α^{27}D −0.78° (l 0.5), or $[\alpha]^{27}$D −51° (c 3.0, pyridine).

The results of similar runs are summarized in Fig. 2. In one experiment, the reaction was allowed to proceed for 36 hours at 100°; the product (0.030 g. from 0.062 g. of starting DNDBCH-6-one), m.p. 195–200°, was recrystallized from benzene to give DNDBCH-6-ol, m.p. 199–200°, infrared spectrum identical with that of authentic material.

Partial Asymmetric Reduction of DNDBCH-6-one with (+)-Pinacolyl Alcohol.—To a mixture of 0.951 g. (3.2 mmoles) of (±)-DNDBCH-6-one, 40.2 g. of dioxane[46] and 13.97 g. (137 mmoles) of pinacolyl alcohol ($[\alpha]^{18}$D +8.32°, $[\alpha]^{25}$D +7.98°, $[\alpha]^{29}$D +7.73° (homogeneous), 99% optically pure based on $[\alpha]^{25}$D +8.10° as the maximum reported rotation (see above), n^{25}D 1.4130), at 63° was added a solution of 0.717 g. (2.9 mmoles) of aluminum *t*-butoxide in 12.2 g. of dioxane at 63°, and the resulting mixture was kept at 63° for seven hours. The reaction mixture was cooled, 20 ml. of 2 *M* hydrochloric was added, and the solution was taken to dryness at 5 mm. (pot temperature 30–50°).

The distillate was made alkaline with 15% sodium carbonate solution. The organic layer was separated, dried over barium oxide and distilled through a Podbielniak concentric tube column. The liquid distilled over a range (110–117°); the last portion (1 ml., b.p. 117°) had $[\alpha]^{29}$D +5.6° (homogeneous), n^{25}D 1.4133. The infrared spectrum (neat, 0.1-mm. cell) exhibited pronounced bands at 874 and 890 cm.$^{-1}$ which were absent in the spectrum of authentic pinacolyl alcohol.

Anal. Calcd. for $C_6H_{14}O$: C, 70.6; H, 13.8. Found: C, 69.5; H, 13.3.

The poor analysis, and the evidence of the infrared spectrum, indicate contamination.

The solid residue was leached with hot ethyl acetate. The remaining white solid (0.603 g.) was soluble in water (aluminum chloride hydrate). The combined leachings (70 ml.) were mixed with 210 ml. of benzene, and the solution was chromatographed on 162 g. of silica gel (Davison, 100–200 mesh, grade 923), using 1:3 ethyl acetate–benzene as eluent.[48] The eluate contained 0.139 g. of DNDBCH-6-one, $[\alpha]^{26}$D +136° (c 0.68, ethyl acetate), infrared spectrum (KBr wafer) identical with that of authentic ketone.

Anal. Calcd. for $C_{15}H_{10}N_2O_5$: N, 9.4. Found: N, 9.1.

The material remaining on the column was eluted with 1:1 ethyl acetate–benzene, to give 0.665 g. DNDBCH-6-ol, $[\alpha]^{26}$D −109° (c 3.1, ethyl acetate), infrared spectrum (KBr wafer) identical with that of authentic alcohol.

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: N, 9.3. Found: N, 9.6.

A portion of the residual ketone, 0.108 g., $[\alpha]^{26}$D +136°, was reduced by the procedure described for the preparation of (±)-DNDBCH-6-ol. The product was isolated by chromatography on silica gel. A small amount of unreacted material was first removed by elution with 1:3 ethyl acetate–benzene, and the pure DNDBCH-6-ol was obtained in the following fraction by elution with 1:1 ethyl acetate–benzene. The product (0.063 g., 58%) had $[\alpha]^{26}$D +498° (c 1.1, ethyl acetate), infrared spectrum (KBr wafer) identical with that of authentic alcohol.

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: N, 9.3. Found: N, 9.1.

Partial Asymmetric Reduction of DNDBCH-6-one with (+)-2-Octanol.—To a mixture of 0.641 g. (2.1 mmoles) of (±)-DNDBCH-6-one, 29.6 g. of dioxane[46] and 11.3 g. (90 mmoles) of 2-octanol[49] ($[\alpha]^{26}$D +9.41° (homogeneous), n^{26}D 1.4240, b.p. 90–91° (28 mm.), 99% optically pure[50]) at 63°, was added a solution of 0.508 g. (2.1 mmoles) of aluminum *t*-butoxide in 9.43 g. of dioxane at 63°, and the resulting mixture was kept at 63° for 20 minutes. The reaction mixture was cooled, 5 ml. of 2 *M* hydrochloric acid was added, and the solution was taken to dryness at 5 mm. The distillate was made alkaline with 15% sodium carbonate solu-

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(45) It is remarkable that the active alcohol melts ca. 65° lower than the racemate.

(46) Purified according to L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 369.

(47) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1115 (1914).

(48) In preliminary experiments it had been found that chromatography under similar conditions served to separate cleanly and quantitatively synthetic mixtures of (±)-DNDBCH-6-one and (±)-DNDBCH-6-ol.

(49) Kindly prepared by Mr. L. Dvorken.

(50) Based on the maximum reported rotation, $[\alpha]^{17}$D +9.9° (R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 2058 (1907); J. Kenyon, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 418), after applying a temperature correction derived from the data of M. K. Hargreaves, *J. Chem. Soc.*, 2953 (1953).

tion; the organic layer was separated, dried over potassium hydroxide and distilled, giving 2-octanol, b.p. 84–86° (28 mm.), $[\alpha]^{26}D$ +9.10° (homogeneous), $n^{26}D$ 1.4236.

The solid residue was leached with a total of 62 ml. of hot ethyl acetate, and the leachings, combined with 186 ml. of benzene, were chromatographed on 137 g. of silica gel. (+)-DNDBCH-6-one (0.120 g., $[\alpha]^{26}D$ +52° (c 1.1, ethyl acetate)) and (−)-DNDBCH-6-ol (0.427 g., $[\alpha]^{26}D$ −54° (c 4.2, ethyl acetate)) were recovered as described for the previous experiment. Both fractions had infrared spectra

(KBr wafer) identical with authentic materials. Reduction of 0.100 g. of the (+)-DNDBCH-6-one and isolation of product DNDBCH-6-ol (0.061 g., 61%, $[\alpha]^{26}D$ +212° (c 0.24, ethyl acetate), infrared spectrum (KBr wafer) identical with authentic alcohol) followed the procedure described in the previous section.

The Configurational Intercorrelation of Optically Active Biphenyls by Thermal Analysis[1]

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The configurations of 6,6'-dinitro-, 6,6'-dichloro- and 6,6'-dimethyl-2,2'-diphenic acid have been correlated by the method of thermal analysis, in the first application of any indirect method to intercorrelations in the biphenyl series. In conjunction with previous work,[1] the S-configuration has thence been assigned to (−)-6,6'-dichloro- and to (+)-6,6'-dimethyl-2,2'-diphenic acid. The method has been extended successfully to the correlation of 6,6'-dichloro- and 6,6'-dimethyl-2,2'-bis-(hydroxymethyl)-biphenyl.

While absolute configuration may now be assigned to key compounds in the series of optically active biphenyls through use of the general method earlier developed,[1] the same purpose also may be served by configurational intercorrelation within the series, employing $S(−)$-6,6'-dinitro-2,2'-diphenic acid as the absolute standard. Anticipating the difficulties which are likely to be encountered in direct chemical interconversions, we were particularly concerned with developing a physical method for achieving the desired end.

Scrutiny of the literature disclosed that in most instances the melting points of the enantiomeric forms of the hindered biphenyls lie below those of the racemic modifications[3]: racemate formation appears to be the general case. This observation encouraged investigation of the method of thermal analysis[4] as a means for arriving at configurational relationships within the biphenyl series.

Optically Active 2,2'-Diphenic Acids.—A major limitation of the method, as applied to hindered biphenyls, was recognized at the outset: for optically unstable biphenyls, the relatively high temperatures involved in the establishment of solid–liquid equilibria are likely to cause enantiomeric interconversions and consequent vitiation of results. The compounds which were employed in testing the

method, 6,6'-dinitro-, 6,6'-dichloro- and 6,6'-dimethyl-2,2'-diphenic acid, are, however, optically stable[5]; furthermore (a) they are similarly constituted dicarboxylic acids, i.e., expected on the basis of previous work[4] to exhibit significant differences in phase behavior, and (b) the absolute configuration of one of their number is known.[1]

Thermal analysis of mixtures of the three racemates with the corresponding optically active forms revealed no peculiarities. The phase diagrams each exhibit simple eutectics, with some evidence of partial solid solution formation, and no evidence of partial racemate formation[6]; the only compound formed between the enantiomeric species is the 1:1 racemate.

The phase diagrams of (+)-6,6'-dimethyl-2,2'-diphenic acid vs. (+)- and (−)-6,6'-dichloro-2,2'-diphenic acid (Fig. 1, curves A and B, respectively), (+)-6,6'-dimethyl-2,2'-diphenic acid vs. (+)- and (−)-6,6'-dinitro-2,2'-diphenic acid (Fig. 2, curves A and B, respectively) and (+)-6,6'-dichloro-2,2'-diphenic acid vs. (−)- and (+)-6,6'-dinitro-2,2'-diphenic acid (Fig. 3, curves A and B, respectively) serve as unambiguous evidence for the desired configurational correlation. In each case, one, the quasi-enantiomeric, pair forms a congruent and pronounced 1:1 compound (quasi-racemate; arrow, curves A),[7] while the other, configurationally related, pair exhibits continuous solid solution formation (curves B). This type of a difference in phase behavior provides a measure of internal consistency,

(1) Configurational Studies in the Biphenyl Series II. Part I, P. Newman, P. Rutkin and K. Mislow. THIS JOURNAL, **80**, 465 (1958).

(2) To whom correspondence regarding the article should be addressed.

(3) Among the several exceptions: (±)-methyl 6,6'-dinitro-2,2'-diphenate, m.p. 132–133° (J. Kenner and W. V. Stubbings, J. Chem. Soc., 593 (1921)), (+)- and (−)-forms, m.p. 141–142° (Part I (ref. 1)); 6,6'-dimethyl-2,2'-biphenyldiamine, m.p. 136°, (+)- and (−)-forms, m.p. 156° (J. Meisenheimer and M. Höring, Ber., **60**, 1425 (1927)).

(4) The method, introduced by J. Timmermans (Rec. trav. chim., **48**, 890 (1929)), has been brilliantly exploited by A. Fredga ("The Svedberg," Almqvist and Wiksells, Uppsala, 1944. p. 261) and his collaborators at Uppsala. For incisive reviews, cf. especially J. Timmermans, J. chim. phys., **49**, 162 (1952); H. Lettré, Erg. Enzymforsch., **9**, 1 (1943); and, more recently, K. Petterson, Arkiv Kemi, **10**, 297 (1956). For previous work in this Laboratory, cf. K. Mislow and M. Heffler. THIS JOURNAL, **74**, 3668 (1952); K. Mislow and W. C. Meluch, ibid.. **78**, 5920 (1956). Thus far, only centrally asymmetric compounds have been correlated by this powerful method.

(5) (a) R. Kuhn and O. Albrecht, Ann., **455**, 272 (1927), have reported on the extreme stability of 6,6'-dinitro-2,2'-diphenic acid. (b) The optical stability of methyl 6,6'-dimethyl-2,2'-diphenate has been commented on by D. Aziz and J. G. Breckenridge, Can. J. Research, **28B**, 26 (1950). (c) The interference radius of Cl (1.89) is intermediate between that of NO_2 (1.92) and CH_3 (1.73) (G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 210), hence (cf. a and b) 2,2'-dichloro-2,2'-diphenic acid is also optically stable.

(6) M. Bergmann and M. Lissitzin, Ber., **63**, 310 (1930); cf. however M. Tomita and Y. Seiki, J. Biochemistry (Japan), **30**, 101 (1939).

(7) The maximum in curve 1A is far less satisfactorily expressed and defined than are those in curves 2A and 3A. The possibility of, for example, incongruent melting cannot be unequivocally ruled out on the basis of the present data. Our conclusions remain unaffected.