

mechanistic picture developed above. As substituents make the benzene ring less susceptible to electrophilic attack, the alternative S_Ei mechanism becomes energetically the more favored one. This is more pronounced the lower the acidity, but when the acidity becomes high enough the A-S_E2 mechanism returns to favor.

Gold and Satchell²¹ have determined the rates of protodeuteration of 4-*d*-anisole, 4-*d*-toluene and deuteriobenzene in sulfuric acid at 25°. Thus direct comparisons can be made with the rates of protodeboronation of benzenboronic acid and the *p*-methoxy and *p*-methyl derivatives. The results are given in Table VIII. In each case de-

boronation is faster than dedeuteration, but the ratio decreases with increasing acidity, except for the marked increase in going from the *p*-methoxy to the *p*-methyl substituent. This latter fact is consistent with the above discussion.

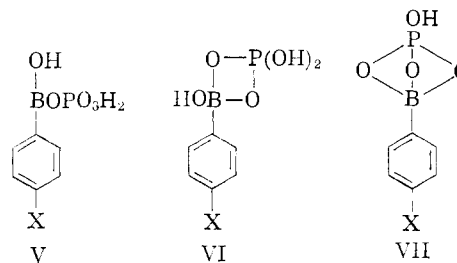
In contradiction to the differences in mechanism outlined above for the hydrolysis of *p*-methoxybenzenboronic and *p*-tolueneboronic acids in sulfuric acid, the activation parameters for these substrates in H₃PO₄ strongly suggest that both are reacting by the same mechanism. The contradiction vanishes, however, if in phosphoric acid essentially all of either substrate is present as any one of the anhydride species V, VI or VII. In

TABLE VIII

RELATIVE RATES OF DEBORONATION AND DEDEUTERATION

X	-H ₀	Deboronation Dedeuteration
<i>p</i> -CH ₃ O	1.60	36
	3.40	20
<i>p</i> -CH ₃	3.02	66
	3.52	51
H	5.60	18
	6.40	15

(21) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 3619 (1955); 2743, 3911 (1956).



view of the ease with which molecular phosphoric acid forms anhydrides, this possibility is at least conceivable.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES 24, CALIF.]

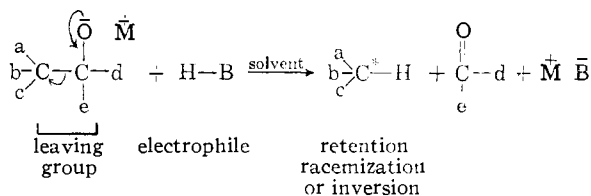
Electrophilic Substitution at Saturated Carbon. VIII. Mixed Solvents and Steric Course¹

BY DONALD J. CRAM AND W. DAVID NIELSEN

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The base-catalyzed cleavage of (-)-2,3-diphenyl-3-methyl-2-pentanol to (+)- or (-)-2-phenylbutane has been used to study the effect of solvent compositions and temperature on the stereochemical course of electrophilic substitution at saturated carbon. Three kinds of steric courses have been observed with lithium *n*-propoxide as base, and different proportions of 1-propanol and dimethyl sulfoxide as solvent. Pure propanol gives 13% net retention, pure dimethyl sulfoxide gives 100% racemization, whereas 80 mole % 1-propanol-20 mole % dimethyl sulfoxide gives 14% net inversion. A qualitatively similar picture is observed with *t*-butyl alcohol-dimethyl sulfoxide solvent mixtures. Three kinds of steric courses have been observed in 36 mole % diethylene glycol, 64 mole % dioxane with potassium diethylene glycolate as catalyst. At 140°, 16% net inversion, at about 175°, 100% racemization, and 220°, 12% net retention was observed. These results are interpreted in terms of mechanisms in which carbanions in an asymmetric environment are captured by proton donors at varying relative rates either from the side of, or the side remote from, the leaving group.

Earlier studies² of carbon as leaving group in electrophilic substitution at saturated carbon revealed that by proper control of solvent and cation, a number of systems that fit the general formulation could be induced to give product that ranged from 99% net retention to 100% racemization to 60% net inversion. A large body of results was accommodated^{2f} by a mechanistic scheme which in all cases involved carbanion intermediates. The



exact composition of the solvent-leaving group envelope determined the stereochemical fate of this intermediate.

This paper reported the results of a study of the steric course of cleavages of 2,3-diphenyl-3-methyl-2-pentanol (I) to give 2-phenylbutane. The relative configurations of these compounds were established earlier.^{2c} The alcohol had previously been found to cleave with net retention in solvents such as dioxane or *t*-butyl alcohol,^{2b,2c} with net inversion in methanol or diethylene gly-

(1) This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to donors of said fund.

(2) (a) D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 570 (1959); (b) D. J. Cram, A. Langemann and F. Hauck, *ibid.*, **81**, 5750 (1959); (c) D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959); (d) D. J. Cram, A. Langemann, W. Lwowski and K. R. Kopecky, *ibid.*, **81**, 5760 (1959); (e) D. J. Cram, F. Hauck, K. R. Kopecky and W. D. Nielsen, *ibid.*, **81**, 5767 (1959); (f) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, *ibid.*, **81**, 5774 (1959).

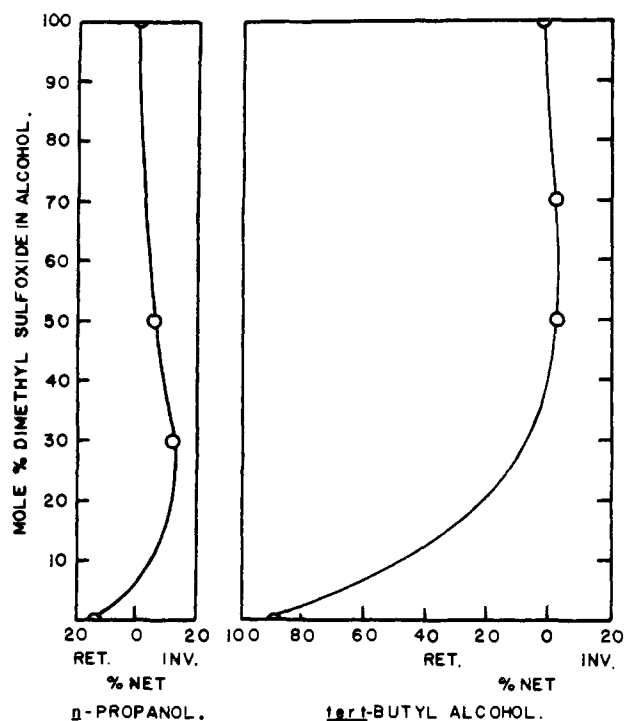


Fig. 1.—Optical results of cleavage of (–)-2,3-diphenyl-3-methyl-2-pentanol to (+)- or (–)-2-phenylbutane in mixtures of dimethyl sulfoxide and 1-propanol (left-hand curve), and of dimethyl sulfoxide and *t*-butyl alcohol (right-hand curve).

dioxane, the curve at 150° indicates about 5% net inversion, and at 200°, 5% net retention. Runs 19 and 20 were conducted with this same solvent composition except that one was at 140° and the other at 220°. The former gave 16% net inversion, and the latter 12% net retention. Thus the predominant steric direction of the reaction can be changed by only a change in temperature, if the medium composition is properly chosen. Equally clear is the fact that the two curves cross, and that the lower temperature favors higher retention in almost pure dioxane, and favors higher inversion in almost pure diethylene glycol.

Runs 21 in dimethyl carbonate as solvent was made to see if the carbonyl group of this ester could be used as a nucleophile. In spite of the fact that carbonate molecules outnumbered proton donors in the medium by a factor of 50, little or no carbonate reacted with the carbanion produced, and 2-phenylbutane was obtained with 74% net retention.

Discussion

Previous investigations² demonstrated that three different types of solvents produced three different steric courses for electrophilic substitution in the cleavage of systems such as I. Alcohols of low dissociating power such as *t*-butyl alcohol gave high retention; non-proton-donating solvents of high dissociating power such as dimethyl sulfoxide gave racemization; proton-donating solvents of high dissociating power such as ethylene glycol gave inversion. These results were interpreted in terms of Chart I, in which a process such as $A \rightarrow D \rightarrow G$ provided retention, processes $A \rightarrow D \rightarrow F \rightarrow J$ and

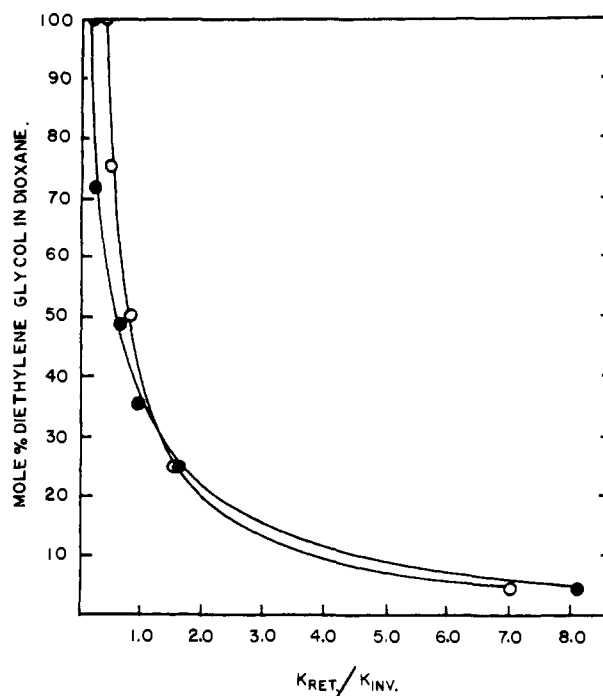


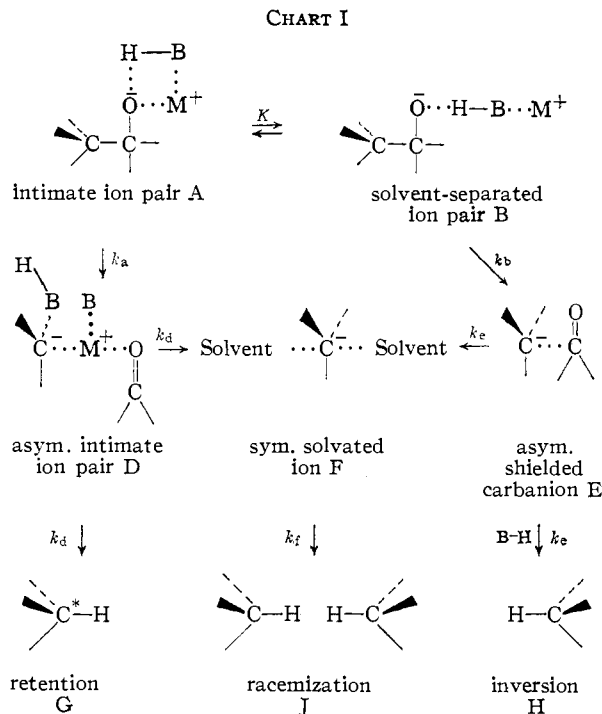
Fig. 2.—Optical results of cleavage of (–)-2,3-diphenyl-3-methyl-2-pentanol to (+)- or (–)-2-phenylbutane in mixtures of diethyleneglycol and dioxane at different temperatures: curve ●, temperature, 150°; curve ○, temperature, 200°.

$B \rightarrow E \rightarrow F \rightarrow J$ provided racemization, and process $B \rightarrow E \rightarrow H$ gave inversion. The fact that appropriate mixtures of a retention and racemization solvent can give net inversion was anticipated by, and supports, this scheme.

Equation 1^{2e,2f} describes in terms of K , k_a and k_b the relative amounts of *D* and *E* produced, the two species which immediately precede product of retained and inverted configuration, respectively. Dilution of either *t*-butyl alcohol or 1-propanol

$$D/E = k_a/k_bK \quad (1)$$

with dimethyl sulfoxide should increase the value of K , since dimethyl sulfoxide with its much higher dielectric constant is a better dissociating solvent than either alcohol. Furthermore, the value of k_a/k_bK should decrease with increasing concentration of dimethyl sulfoxide, since cleavage occurs in pure dimethyl sulfoxide much faster than in any of the alcohols.^{2f} In mixtures that contain appreciable amounts of dimethyl sulfoxide, *E* is presumed to be the intermediate that accounts for the major amount of product. This species can partition between process $E \rightarrow F \rightarrow J$, which leads to racemic product, and process $E \rightarrow H$ which gives inverted product. Dimethyl sulfoxide, although capable of solvating anions, is not a proton donor and therefore must favor the racemization process. After stage *E* is reached, the two alcohols as proton donors favor the inversion process. Thus dimethyl sulfoxide enhances inversion by favoring cleavage of *B* over *A*, and the alcohol in the mixture provides the concentration of proton donors on which the inversion process finally depends. As might be expected, 1-propanol as a



superior proton donor (in both an electronic and steric sense) gives a higher maximum inversion than *t*-butyl alcohol when mixed with dimethyl sulfoxide.

A previous study^{2f} demonstrated that in mixtures of methanol (inversion solvent) and dimethyl sulfoxide (racemization solvent), compound I gave II with varying amounts of inversion, but no mixtures gave net retention. The mechanism of Chart I provides no means by which combination of an inversion and racemization solvent could give net retention, so again the compatibility of theory and experiment has been demonstrated.

Striking temperature effects are visible in Fig. 2. At 36 mole % diethylene glycol in dioxane, variation of temperature from 140 to 220° changed the steric result from $k_{ret}/k_{inv} = 0.51$ to 1.6. This result demonstrates conclusively that at this solvent composition, two stereospecific processes, one inversion and the other retention, are competing with one another to produce a net process which would be just balanced ($k_{ret}/k_{inv} = 1$) at a temperature of about 165°. Since these two processes have different temperature coefficients, the net steric direction of the reaction can be altered by simple temperature variation.

The mechanistic picture of Chart I readily accounts for these observations. The retention process involves cleavage of intimate ion pair A and the inversion process, cleavage of the solvent separated ion pair B. The observed enhancement of the retention process in the middle range of solvent composition by higher temperature is attributed to the value of k_a/k_bK decreasing with increasing temperature, since the dielectric constant and dissociating power of the solvent decrease with increasing temperature.

The second interesting effect of temperature is the observation (Fig. 2) that in both extreme in-

version and retention solvents (diethylene glycol and dioxane, respectively), the lower temperature produces the higher stereospecificities. In terms of Chart I, this means that in extreme retention solvents only A cleaves, and in extreme inversion solvents only B cleaves, and both k_d/k_d' and k_e/k_e' , which control the stereochemical fates of D and E, decrease with increasing temperature. Clearly these two types of temperature effects are superimposed on one another, and only the composition is visible in Fig. 2.

Experimental

Starting Materials and Solvents.—Alcohol I was prepared as reported previously^{2a} by addition of methylmagnesium bromide to optically pure (+)-1,2-diphenyl-2-methyl-1-butanone. The material (I) employed in all experiments had $[\alpha]^{25}_D -17.4^\circ$ (*c* 41, benzene). The alcohols used as solvents were all distilled from their sodium or potassium salts before use. Dimethyl sulfoxide was passed through Linde Molecular Sieves, 4A, 14 by 30 mesh, distilled under reduced pressure in an efficient column, again passed over Molecular Sieves and distilled through a short path Claisen head just prior to use. Dioxane was purified by the method of Fieser.⁴ Dimethyl carbonate was dried with Molecular Sieves, and fractionally distilled before use.

Cleavage Reactions.—All of the reactions were carried out in sealed heavy walled glass tubes in Wood metal-baths. Solvents and tubes were flushed with pure dry nitrogen before use. All runs but 21 involved about the same procedure, which is illustrated by that employed for run 7.

Run 7.—To an oven-dried glass Carius tube of about 50-ml. capacity was added 17.8 ml. (0.238 mole) of purified 1-propanol. After saturating this alcohol with dry, oxygen-free nitrogen, 0.07 g. (0.01 g. atom) of lithium ribbon (cleaned under pentane, weighed under dry mineral oil, and recleaned under pentane prior to use) was introduced and dissolved under nitrogen. When solution was complete, 7.2 ml. (0.101 mole) of purified dimethyl sulfoxide was introduced followed by 1.2 g. (0.005 mole) of alcohol I. The final volume was assumed to be 25 ml. for purposes of calculating concentrations of base and substrate. The solution, thus prepared, was cooled to -78° , and the tube was sealed. When the solution had warmed to room temperature, the glass tube was immersed in a Wood metal-bath previously heated to 170° where it remained for 96 hours. The tube was then cooled to -78° and opened. The contents were shaken with 50 ml. of pentane and 50 ml. of water. The aqueous layer was extracted twice more with pentane. The combined pentane layer was washed several times with water and finally concentrated through a Vigreux column to about 15 ml. The concentrate was then chromatographed on 100 g. of Activity I alumina with pentane as eluant. The first 300 ml. of eluate was collected. The pentane was removed by distillation, and the residue flash distilled yielding 0.280 g. (42%) of 2-phenylbutane, $n^{25}_D 1.4876$, $\alpha^{25}_D + 2.76^\circ$ (neat, 1 dm.), 11.3% net inversion.

Runs 1-4.—In these four runs, 25 ml. of the appropriate alcohol was introduced into the glass tube and saturated with nitrogen. The potassium, freshly cut and weighed under pentane, was dissolved at -78° . The remainder of the procedure was exactly as described under run 7.

Runs 5 and 10.—These runs were prepared just as runs 1-4 except that lithium was dissolved in the pure solvent at room temperature instead of potassium at -78° .

Runs 6, 8, 9, 11-13.—The model procedure for these runs is described in detail under run 7 using the appropriate volumes of each of the solvent components.

Runs 14-20.—The technique of preparing the mixed solvent for these runs is described under run 7 with diethylene glycol as the first component to react with the potassium at room temperature. After the reaction period, the products were isolated as described above.

Run 21.—In an oven-dried glass Carius tube flushed with nitrogen was placed 10 ml. of dry *t*-butyl alcohol followed by 0.38 g. (0.01 g. atom) of freshly cut (under pentane)

(4) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 369.

potassium. When the potassium had reacted, the excess *t*-butyl alcohol was evaporated and the resulting white solid was dried in the tube under vacuum overnight. A nitrogen atmosphere was again provided and 25.0 ml. of dimethyl carbonate added followed by 1.25 g. (0.005 mole) of alcohol I. The tube was sealed in the usual manner and then immersed in a Wood metal-bath at 180° for 72 hours. At the end of the reaction, a crystalline solid was observed at the bottom of the tube. When opened at -78°, a gas was evolved.

The basic solution was extracted with pentane. Examination of the aqueous layer revealed the absence of any acid. The pentane concentrate was chromatographed on 100 g. of Activity I alumina, and the first two 100-ml. fractions contained 2-phenylbutane, weight 0.160 g. (24%), n_D^{20} 1.4877, α_D^{25} - 18.08° (neat, 1 dm.), 74% net retention. The developer was changed to pentane-ether (one-to-one), and six fractions of eluant were collected. After removal of the solvent from the combined six fractions, the oily residue was saponified with 10% sodium hydroxide and the resulting acid purified. Sublimation of this solid acid gave 0.062 g. of impure benzoic acid, m.p. 112-118°. Recrystallization of the sublimate from water produced white crystals, m.p. 121-122°, undepressed by admixture with an authentic sample. When 2-phenylbutane was subjected to the same reaction conditions, no ester was formed.

Control Runs.—Previously,^{2b} 2-phenylbutane was found not to racemize when heated at 240° for 24 hours in a 1 *M* solution of potassium diethylene glycoxide in diethylene glycol. This result serves as a control for runs 1-5 conducted at 170-200° with primary alkoxide catalysts. As a control for runs 6 and 7 (conditions for the latter run were the more drastic, since dimethyl sulfoxide enhances the activity of the base), 2-phenylbutane (α_D^{25} + 3.48°, neat, 1 dm.) was submitted to the conditions of run 7. Recovered material was not racemized (α_D^{25} + 3.45°, neat, 1 dm.). As a control for runs 8 and 9, 2-phenylbutane (α_D^{25} + 23.50° neat, 1 dm.) was submitted to the conditions of run 9 except that potassium was substituted for lithium. Recovered material was 88% racemized (α_D^{25} + 2.82° neat, 1 dm.). Previously,^{2b} 2-phenylbutane was found to racemize only 5% when heated for 20 hours in an 0.8 *M* solution of potassium *t*-butoxide at 200°. Extensive unpublished work has established that potassium alkoxides racemize 2-phenylbutane at rates either faster than or equal to the rates for lithium alkoxides. Clearly no racemization could have occurred in runs 10 or 21. As a control for runs 11-13, 2-phenylbutane (α_D^{25} + 6.90°, neat, 1 dm.) was found to racemize only 17% when submitted to the conditions of run 13. As a control for runs 14-20, 2-phenylbutane (α_D^{25} + 5.82°, neat, 1 dm.) was submitted to the conditions of run 20, and the recovered material was only 3% racemized (α_D^{25} + 5.64°, neat, 1 dm.).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES 24, CALIF.]

Electrophilic Substitution at Saturated Carbon. IX. Stereochemistry at Secondary Carbon¹

BY DONALD J. CRAM AND BRUCE RICKBORN

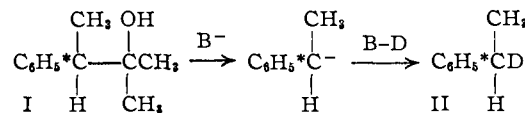
RECEIVED OCTOBER 4, 1960

Optically active phenylethane-1-*d* was produced by the base-catalyzed cleavage of (-)-2-methyl-3-phenyl-2-butanol in *t*-butyl alcohol-*O-d* and ethylene glycol-*O,O'-d*, whose preparation is described. The reaction proceeded with about 75% predominating retention in the tertiary alcohol and 50% predominating inversion in the glycol. Cleavage of (+)-2,3-diphenyl-3-methyl-2-pentanol in *t*-butyl alcohol-*O-d* gave 2-phenylbutane-2-*d* with 87% predominating retention, and over 80% deuterium in the α -position. The same system in ethylene glycol-*O,O'-d* gave 2-phenylbutane-2-*d* with 65% predominating inversion and 91% deuterium in the α -position. These results indicate that solvent serves as proton or deuterium donor in these reactions, and that electrophilic substitution at secondary and tertiary benzyl systems involve similar stereochemical paths.

The change of reaction site from tertiary to secondary to primary carbon is a logical and time-honored approach to the study of stereochemistry and reaction mechanism of substitution at saturated carbon. When the reaction in question involves a carbanion rather than a carbonium ion as intermediate, the problem of leaving group and electrophile is more troublesome than the corresponding problem of leaving group and nucleophile in nucleophilic substitution. In contrast to the long list of nucleophiles, only a few electrophiles are available, the best of which are proton donors. Although hydroxylic solvents react with tertiary carbanions to produce optically active products,² reactions with secondary carbanions lead to products incapable of optical activity, irrespective of stereochemical course. However, deuterium donors can in principle react with asymmetric secondary carbanions to give asymmetric products, as is illustrated by the system chosen for the present study.

(1) This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(2) D. J. Cram, J. Allinger and A. Langemann, *Chemistry & Industry*, 919 (1955).



The advantages of this system are manifold: (1) The base-catalyzed cleavage of systems such as III and IV have been studied in detail, and provide a basis for comparison of the behavior of secondary and tertiary carbanions.³ (2) Reaction product II is the simplest secondary benzyl system capable of optical activity, and has been shown to possess a small but measurable rotation.⁴ (3) The absolute configuration of II has been demonstrated,⁵ and that of I is established by its synthesis from

(3) (a) D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 5740 (1959); (b) D. J. Cram, A. Langemann and F. Hauck, *ibid.*, **81**, 5750 (1959); (c) D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959); (d) D. J. Cram, A. Langemann, W. Lwowski and K. R. Kopecky, *ibid.*, **81**, 5760 (1959); (e) D. J. Cram, F. Hauck, K. R. Kopecky and W. D. Nielsen, *ibid.*, **81**, 5767 (1959); (f) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, *ibid.*, **81**, 5774 (1959).

(4) E. L. Eitel, *ibid.*, **71**, 3970 (1949).

(5) These configurational correlations are summarized by J. A. Mills and W. Klyne in "Progress in Stereochemistry," edited by J. Klyne, Butterworths Scientific Publications, London, 1954, p. 187.