Studies in Stereochemistry. XLIV. Nucleophilic Substitution at Carbon with Carbon as Leaving Group[1,2]

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Abstract: The stereochemical course of nucleophilic reactions with cyclopropane derivatives, (+)-methyl 1-(*S*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate ((+)-(*E*)-**1**), and (+)-methyl 1-(*R*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate ((+)-(*Z*)-**1**), have been studied. The four stereomers were prepared in an optically pure state: (+)-(*E*)-**1** gave mp 53–54°, $[\alpha]^{25}_{546}$ +251° (*c* 0.54, EtOAc); (−)-(*E*)-**1** gave mp 53–54°, $[\alpha]^{25}_{546}$ −251° (*c* 0.62, EtOAc); (+)-(*Z*)-**1** gave mp 90.5–91.5°, $[\alpha]^{25}_{546}$ +175° (*c* 0.15, EtOAc); (−)-(*Z*)-**1** gave mp 91–91.5°, $[\alpha]^{25}_{546}$ −175° (*c* 0.145, EtOAc). The relative configurations of the *E* and *Z* isomers were established by nmr spectral comparisons, and by $K = 20$ for (*Z*)-**1** ⇄ (*E*)-**1** at 25° (see below). The absolute configurations of the *Z* diastereomers were assigned by converting (+)-(*Z*)-**1** to (+)-methyl 2-(*S*)-phenyl-1-(*S*)-cyclopropanecarboxylate, whose absolute configuration was known. The relative configurations of esters (+)-(*E*)-**1** and (−)-(*Z*)-**1** were established by converting their respective acids to enantiomeric dicyano compounds with a single chiral center. Thus (+)-(*E*)-**1** gave (+)-1,1-dicyano-2-(*R*)-phenylcyclopropane ((+)-**4**), and (−)-(*Z*)-**1** gave (−)-1,1-dicyano-2-(*S*)-phenylcyclopropane ((−)-**4**). When heated in methanol at 126° for 5 days, optically pure (+)-(*E*)-**1** underwent methanolysis to give (−)-methyl 2-cyano-4-methoxy-4-phenylbutanoate ((−)-**5**). This diastereomeric mixture was converted to (−)-methyl 4-(*S*)-methoxy-4-phenylbutanoate ((−)-(*S*)-**6**) of 99% optical purity, whose enantiomer was prepared (maximum rotation) from (+)-(*S*)-mandelic acid of established configuration. These data indicate the methanolysis of (+)-(*E*)-**1** went with 99% inversion of configuration. The reaction is interpreted as occurring through solvated ion-pair intermediates, similar to those observed in solvolyses of open-chain secondary benzyl compounds. Methanolysis kinetics were followed at 100 and 126°, and at 126°, $\Delta H^{\pm} = 19.4 \pm 0.4$ kcal/mol and $\Delta S^{\pm} = -32 \pm 1$ eu. When (*Z*)-**1** was heated in methanol at 126° to 77% reaction, no (*E*)-**1** was produced. In dry dimethylformamide (DMF), (*Z*)-**1** → (*E*)-**1** was catalyzed by lithium halides in pseudo-first-order reactions (first order in free Cl^- and Br^-). At 25° in DMF–0.1 *M* LiBr, optically pure (−)-(*Z*)-**1** was isomerized (9 half-lives) to 99% optically pure (−)-(*E*)-**1**, epimerization occurring solely at the cyanoacetate chiral center. At 34° in DMF–0.1 *M* LiBr, the catalyzed isomerization was ~4000 times faster than thermal isomerization in the same medium, and ~8700 times faster than methanolysis at 34°. At 25° in DMF–0.1 *M* LiBr, (*Z*)-**1** equilibrated with (*E*)-**1** ($K = 20$). At 39° in DMF, the lithium azide catalysis of (*Z*)-**1** to (*E*)-**1** was followed spectroscopically by loss and appearance of methyl (ester) signals in the nmr. A third methyl signal (attributed to the anion derived by proton loss from methyl 4-azido-2-cyano-4-phenylbutanoate (**8**)) appeared after a short time, went through a maximum, and then decreased as the signal of (*E*)-**1** increased. From a reaction mixture, quenched with water at maximum intermediate signal, was isolated **8**. Treatment of a DMF solution of **8** with sodium hydride at 25° gave (*E*)-**1**/(*Z*)-**1** ~ 10. The catalyzed isomerization reactions are interpreted as involving consecutive SN2 reactions. The anionic nucleophile opens the three-membered ring to produce a carbanion, which rotates, and displaces the nucleophile to regenerate the cyclopropane diastereomer.

To our knowledge, the stereochemical course of nucleophilic ring opening of substituted cyclopropanes first was reported in the methanolysis of (+)-methyl 1-(*S*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate ((+)-(*Z*)-**1**).[2] This paper documents the claims of the communication,[2] and extends the study to nucleophilic catalysis of epimerization reactions of the same system.

In an earlier study, optically active methyl 2,2-dimethyl-1-phenylsulfonylcyclopropanecarboxylate was found to undergo solvolysis, racemization, and ring expansion reactions.[3] These transformations were interpreted as going through zwitterionic intermediates, with a carbanion leaving group, and a carbonium ion center subject to nucleophilic reactions. Ring cleavage by nucleophiles of cyclopropane rings containing strong electron distributing substituents have been long known[4] and studied in a variety of systems.[5] The most thorough stereochemical study of nucleophilic three-membered ring opening and closing involves episulfones.[6]

Results

Starting Materials and Their Configurations. Treatment of (*E*)-ethyl 2-cyanocinnamate[7,8] with dimethyloxosulfonium methylide in dimethyl sulfoxide gave (55%) ethyl 1-cyano-2-phenylcyclopropanecarboxylate.[9] Upon hydrolysis, this ester gave (55%) 1-cyano-2-phenylcyclopropanecarboxylic acid as the *E* isomer, (*E*)-**2**.[8] This acid was resolved through its brucine salt to give (−)-(*E*)-**2** (29%) and (+)-(*E*)-**2**

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) A preliminary account of part of this work has appeared: E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 6329 (1970).

(3) D. J. Cram and A. Ratajczak, *ibid.*, **90**, 2198 (1968).

(4) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952).

(5) (a) J. M. Stewart and G. M. Pagenkopf, *J. Org. Chem.*, **34**, 7 (1969), and references to previous work; (b) O. J. Mattson and G. Sundström, *Acta Chem. Scand.*, **24**, 1454, 2219, 3563 (1970); (c) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 820, 821 (1972).

(6) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(7) J. Zabicky, *J. Chem. Soc.*, 683 (1961).

(8) For *Z* and *E* nomenclature, see J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(9) J. Gosselck, L. Beress, and H. Schenk, *Angew. Chem., Int. Ed. Engl.*, **5**, 596 (1966).

(40%) of $[\alpha]^{25}_{546}$ −239° and $[\alpha]^{25}_{546}$ +235° (*c* 0.5–0.8, EtOAc), respectively. Diazomethane and (−)-(*E*)-**2** gave (−)-methyl 1-cyano-2-phenylcyclopropanecarboxylate ((−)-(*E*)-**1** of maximum rotation, mp 53–54°, $[\alpha]^{25}_{546}$ −251° (*c* 0.62, EtOAc). Similarly, (+)-(*E*)-**2** provided (+)-(*E*)-**1**, mp 53–54°, $[\alpha]^{25}_{546}$ +251° (*c* 0.54, EtOAc). Racemic **2** gave racemic **1** as an oil.

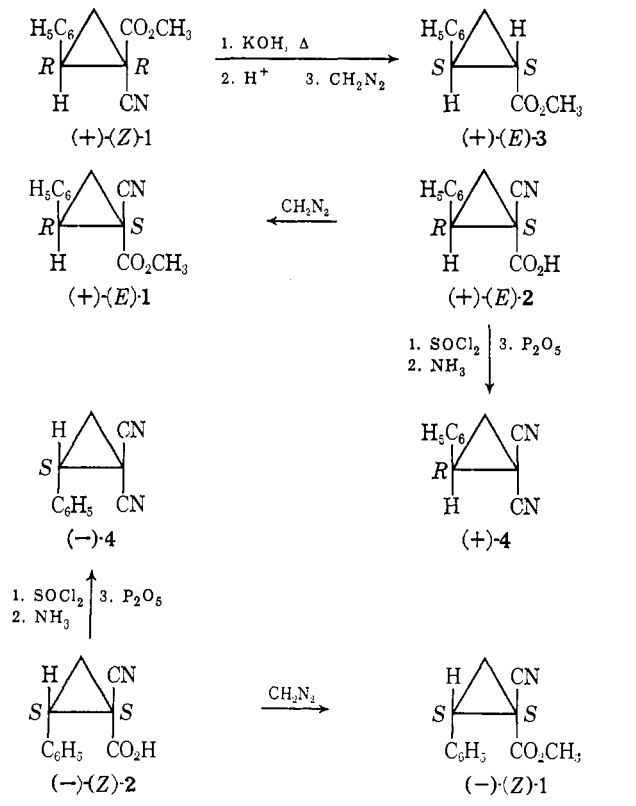
Photolytic isomerization of (*E*)-**1** in acetone gave a 2.2:1 mixture of (*E*)-**1**:(*Z*)-**1**, separated by chromatography to give (20%) (*Z*)-**1**, mp 62–63°. The diastereomeric configurations of (*E*)- and (*Z*)-**1** were initially assigned on the basis of the higher field shift of the methyl group of **1** with mp 62–63°, which came at δ 3.49, as compared with that of the liquid isomer (δ 3.82). The higher field shift of the methyl of (*Z*)-**1** whose phenyl and carbomethoxy groups are cis to one another has considerable precedent.[10] This assignment was confirmed by the observed and predicted (molecular models) much greater thermodynamic stability of (*E*)-**1** (see below).

Ester (*Z*)-**1** was hydrolyzed to acid (*Z*)-**2**, which was incompletely resolved through its quinine salt to give (+)-(*Z*)-**2** (36%) and (−)-(*Z*)-**2** (64%). Each acid with diazomethane gave its ester of the same sign of rotation. Each ester was recrystallized to maximum melting point (90.5–91.5°) and rotation, (−)-(*Z*)-**1**, $[\alpha]^{25}_{546}$ −175° (*c* 0.145, EtOAc), 7% overall, and (+)-(*Z*)-**1**, $[\alpha]^{25}_{546}$ +175° (*c* 0.15, EtOAc), 16% overall.

The configurational assignments were completed with diastereomerically pure but optically impure samples of **1**. Ester (+)-(*Z*)-**1** was hydrolyzed to the potassium salt of (+)-(*Z*)-**2** in ethylene glycol (70° for 1 hr), and this substance was decarboxylated at 200° (1 hr). The cyano group hydrolyzed (185° for 5 hr) to its acid, which was esterified to give (30%) (+)-(*E*)-methyl 2-phenylcyclopropanecarboxylate ((+)-(*E*)-**3**), whose configuration has been established as 2-(*S*),1-(*S*).[11] Thus (+)-(*Z*)-**1** has the 1-(*R*),2-(*R*) configuration. The hydrolysis of (+)-(*Z*)-**1** had to be carried out at the low temperature of 70°, otherwise the cyclopropane ring underwent solvolytic ring opening to give ethers of ethylene glycol (see methanolysis below). Once the carboxylate anion formed, decarboxylation occurred. In methanol, no epimerization at benzyl carbon[12] occurred during methanolysis (see below). It is concluded that the same is true in ethylene glycol.

The relative configurations of (+)-(*E*)-**1** and (−)-(*Z*)-**1** at the benzyl center and, therefore, the absolute configuration of (+)-(*E*)-**1** were determined by the conversion of their respective derived acids to 1,1-dicyano-2-phenylcyclopropane (**4**).[13] Thus, (+)-(*E*)-**2** gave (+)-**4**, and (−)-(*Z*)-**2** gave (−)-**4**. Clearly, (+)-(*E*)-**1** and (−)-(*Z*)-**1** have opposite configurations at the benzyl position, and (+)-(*E*)-**1** has the 1-(*S*),2-(*R*) configuration. Chart I summarizes the configurational relationships. Throughout the series of compounds, including the amide intermediates in the conversions of acids **2** to dinitriles **4**, the signs of rotations of the compounds seem controlled by the configuration at the benzyl carbon.

Chart I



Stereochemical Course of the Methanolysis Reaction of (+)-Methyl 1-(*S*)-Cyano-2-(*R*)-phenylcyclopropanecarboxylate ((+)-(*E*)-1). In run 1, (+)-(*E*)-**1** of maximum rotation when heated in methanol at 126° for 5 days gave (88%) (−)-methyl 2-cyano-4-methoxy-4-phenylbutanoate ((−)-**5**) as a mixture of diastereomers in about equal amounts (nmr integration of two methyl proton signals). The configurational homogeneity and absolute configuration at the benzyl carbon of (−)-**5** were established as follows. The ester was hydrolyzed, and the resulting cyano acid was decarboxylated and hydrolyzed to give the monocarboxylic acid. This substance was isolated and characterized as its ester (75%), (−)-methyl 4-methoxy-4-phenylbutanoate ((−)-**6**), $[\alpha]^{25}_{546}$ −93.8° (*c* 0.78, EtOAc). Ester (−)-**6** has a single chiral center at the benzyl position. Its absolute configuration and maximum rotation were determined as follows.

From (+)-(*S*)-mandelic acid was prepared[14] (+)-(*R*)-3-methoxy-3-phenylpropanoic acid ((+)-(*R*)-**7**), which was brought to optical purity by fractional crystallization of its brucine salt to give acid of sharp melting point (65–66°), whose rotation could not be changed by various further purification procedures. Arndt–Eistert homologation[15] of (+)-(*R*)-**7** of 95.2% optical purity gave (22%) (+)-(*R*)-**6**, $[\alpha]^{25}_{546}$ +90.5° (*c* 0.74, EtOAc), as an oil whose nmr and ir spectra were identical with the (−)-**6** obtained with (+)-(*E*)-**1** as starting material. These data indicate that the (−)-**6** from (+)-(*E*)-**1** was 99% optically pure, and that *the nucleophilic substitution reaction at the benzyl carbon of*

(10) G. L. Krueger, F. Kaplan, M. Orchin, and W. H. Faul, *Tetrahedron Lett.*, 3979 (1965).

(11) (a) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, 20, 1965 (1964); (b) T. Sugita and Y. Inouye, *Bull. Chem. Soc. Jap.*, **39**, 1075 (1966).

(12) (a) E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 6331 (1970); (b) N. E. Howe, E. W. Yankee, and D. J. Cram, *ibid.*, **95**, 4230 (1973).

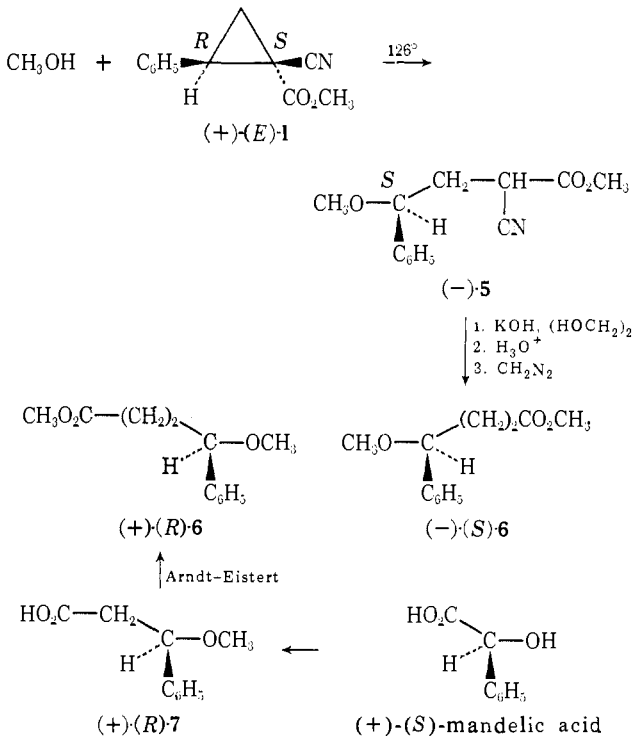
(13) E. Ciganek, *ibid.*, **88**, 1979 (1966).

(14) K. Balenovic, B. Urbas, and A. Deljac, *Croat. Chem. Acta*, **31**, 153 (1959).

(15) T. D. Hoffman and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 1000 (1969).

(+)-(*E*)-**1** *proceeded with essentially complete inversion of configuration.* Chart II traces these conversions.

Chart II



In run 2, racemic (*Z*)-**1** was heated at 126° for 2 hr, and in run 3, for 11 hr. The composition of the products was determined by glc. Run 2 gave 81% (*Z*)-**1**, 19% **5**, and no detectable (< 1%) (*E*)-**1**. Run 3 gave 23% (*Z*)-**1**, 77% **5**, and no detectable (< 1%) (*E*)-**1**. The estimated methanolysis first-order rate constant k_s (one point) in run 2 is 2.94×10^{-5} sec^{-1}, and in run 3, is 3.64×10^{-5} sec^{-1}. The maximum value for k_e (first-order rate constant for (*Z*)-**1** → (*E*)-**1**) based on the minimum amount of (*E*)-**1** that could have been detected in run 3 is 2.32×10^{-7} sec^{-1}. Thus $k_s/k_e > 10^2$.

Kinetics of Methanolysis of (−)-(*E*)-1. The kinetics of methanolysis of (−)-(*E*)-**1** were followed polarimetrically at two temperatures. First-order rate constants (k_s) were determined from least-squares analysis of eight data points in each run that covered 4 reaction half-lives, a point at time = 0, and a point at time = ∞. In each run at $t = \infty$, a glc of the product showed the presence of only the methyl ether, **5**. The ampoule technique (ten per run) was used, and the solutions were 0.01 *M* in (−)-(*E*)-**1**. The limits of error in the rate constants represent two standard deviations. From the rate constants, the activation parameters were calculated at 126°, and their limits of error include both the rate constant and probable temperature errors. In run 4 at 100.4 ± 0.02°, $k_s = 3.72 \pm 0.03 \times 10^{-6}$ sec^{-1}. In run 5 at 126.1 ± 0.05°, $k_s = 21.4 \pm 0.2 \times 10^{-6}$ sec^{-1}, and $\Delta H^{\pm} = 19.4 \pm 0.4$ kcal/mol, and $\Delta S^{\pm} = -32 \pm 1$ eu.

A rough, two-point kinetic run (6) was made with (*Z*)-**1** at 126°. The reaction was followed by glc, with an internal standard, and $k_s \sim 37 \times 10^{-6}$ sec^{-1}. No compounds other than (*Z*)-**1** and **5** were present, and 96–99% of the starting material was accounted for as either **5** or (*Z*)-**1**. Thus at 126°, $k_s^Z/k_s^E \sim 1.8$.

Epimerization of (*Z*)-1 to (*E*)-1 Catalyzed by Lithium Salts in Dimethylformamide. Preliminary, qualitative experiments established that lithium chloride, bromide, iodide, and azide in dimethylformamide (DMF) catalyzed the epimerization of (*Z*)-**1** to (*E*)-**1** with high conversions in hours at 25°. Without salt present, (*Z*)-**1** in DMF at 35° for 24 hr gave no detectable (*E*)-**1** (analytical glc, see below). Reproducible results could be obtained only with carefully dried DMF (<0.003 *M* in water) and salts, and by the use of drybox and sealed vessel techniques. These were used throughout. An analytical and preparative glc for analyzing and separating (*Z*)-**1** and (*E*)-**1** was developed (base line separation) under conditions which controls demonstrated the optically active isomers maintained their configurational integrity. Use of octadecane or tridecane as internal standards demonstrated that 98–100% of synthetic mixtures of isomers could be accounted for in the analytical glc. With calibrated detectors, analyses were ±0.5%. In preparative glc, use of synthetic mixtures demonstrated that about 50% of material put on the columns could be isolated (the remainder was not condensed). No products other than (*Z*)-**1** and (*E*)-**1** were detected in the runs, and use of octadecane or tridecane as an internal standard in the glc analyses showed 98–100% of the starting material was accounted for.

The equilibrium constant for (*Z*)-**1** ⇄ (*E*)-**1** was determined by dissolving (*Z*)-**1** (run 7) and (*E*)-**1** (run 8) in DMF–0.1 *M* LiBr, and allowing the solutions to stand at ~25° until analytical glc showed no further change (~24 hr). Analysis of the equilibrated mixtures gave (*E*)-**1**/(*Z*)-**1** = 20 ± 2. When the change in rotation of a solution of (−)-(*Z*)-**1** (0.1 *M*) in DMF–0.1 *M* LiBr was monitored polarimetrically at 25°, constant rotation was observed in about 1 day, and this rotation stayed constant for 7 days when the experiment was terminated.

Runs were made to determine which center(s) epimerized during the lithium bromide catalyzed conversion of (*Z*)-**1** to (*E*)-**1**. In run 9, a 0.124 *M* solution of optically pure (−)-(*Z*)-**1** in DMF–0.1 *M* LiBr was allowed to stand for 38 hr at 25° (~9 half-lives for epimerization). The (*E*)-**1** isomer was isolated by preparative glc, and was 99% optically pure (−)-(*E*)-**1**. This experiment coupled with the known configurations of the stereomers (Chart I) demonstrated that epimerization occurred only at the cyanoacetate center, within experimental error. Run 10 was identical to 9 except the reaction time was 1 hr. Recovered (−)-(*Z*)-**1** (glc) was optically pure. In run 11, a 0.15 *M* solution of optically pure (+)-(*E*)-**1** in DMF–0.1 *M* LiBr was allowed to stand at 25° for 35 hr. The recovered (preparative glc) (+)-(*E*)-**1** was 98.5% optically pure. In runs 9 and 11, interconversions of *E* and *Z* isomers must have undergone many cycles, and yet configuration at the benzyl center was maintained.

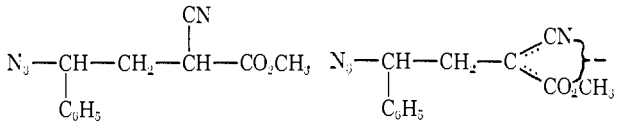
Experiments were conducted in DMF–0.1 *M* LiN_3 at 25° that demonstrated (*Z*)-**1** gave (*E*)-**1**, and (*E*)-**1** gave trace amounts of (*Z*)-**1**. In each case, isomerized product was isolated by preparative glc and compared with authentic material (nmr or melting point). In DMF–0.1 *M* LiN_3, the epimerization of (*Z*)-**1** (0.1 *M*) to (*E*)-**1** was followed in the nmr at 39° in DMF (run 12). The protons of the methyl ester group of *Z* gave a singlet at δ 3.37, whereas those of *E* gave a singlet at δ 3.83.

Two impurities in the DMF with signals at δ 3.91 and 4.08 served as internal standards. Added internal standards in control experiments showed the integral of this impurity was constant with time. The integral of the *Z*-methyl signal decreased in minutes as a new signal at δ 3.12 appeared, followed by the appearance of the *E*-methyl signal. The new signal is attributed to anionic intermediate, A. As time passed, the A-methyl signal integral reached a maximum and declined, the *Z*-methyl signal integral declined sharply, the *E*-methyl signal increased, and the sum of methyl integrals decreased, as tabulated in Table I.

Table I. Estimates at Different Times of Integrals of Signals Due to Ester's Methyl Protons in Nmr Spectra of 0.1 *M* Lithium Azide Catalyzed Epimerization of (*Z*)-**1** to (*E*)-**1** in DMF at 29° (Run 12)

Time, min	—% integrals relative to internal standards— (*Z*)-**1** methyl	(*E*)-**1** methyl	A methyl	Total methyl
0	95	0	5	100
7.5	45	5	50	100
14	25	25	40	90
26	10	35	35	80
40	5	40	20	65

niques as methyl 4-azido-2-cyano-4-phenylbutanoate. In an additional experiment, (*E*)-**1** was quenched after 3 hr at 25° to give **8**.



8 A

Azide **8** was dissolved in DMF and sodium hydride was added. After 30 min the reaction was quenched with water. A mixture of (*E*)-**1** and (*Z*)-**1** was produced in the ratio (analytical glc), (*E*)-**1**/(*Z*)-**1** ~ 10.

When the epimerization of (*Z*)-**1** to (*E*)-**1** catalyzed by LiCl and LiBr in DMF was followed in the nmr, no signal that resembled A appeared, and the epimerization proceeded with little loss of methyl ester signal.

Kinetics of Epimerization of (*Z*)-1 to (*E*)-1 in DMF Catalyzed by Lithium Halides. The epimerizations were followed through about 1–2 half-lives, either by analytical glc (internal standard) or by nmr integrations of the methyl proton signals against an internal standard. At equilibrium, only about 5% (*E*)-**1** was present. The rate of the reverse reaction ((*E*)-**1** → (*Z*)-**1**) was slow compared to the forward reaction. Thus, the existence of the reverse reaction was disregarded in the calculation of pseudo-first-order rate constants (k_{obsd}). Table II records the conditions and results.

Table II. Lithium Halide Catalysis of Epimerization of (*Z*)-**1** to (*E*)-**1** in Dry Dimethylformamide[a]

Run no.	(*Z*)-**1** concn, *M*	Salt Type	Salt Concn, *M*	Temp, °C	No. points[b]	$10^5 k_{obsd}$, sec^{-1}[c]	*K*[d]	[X$^-$] concn, *M*	$10^4 k_{obsd}$/[X$^-$], l. *M*$^{-1}$ sec^{-1}[d]
16	0.070	LiBr	0.100	41.0 ± 0.2	8	39.7 ± 2.1	0.107	0.064	62.0
17	0.071	LiBr	0.100	25.09 ± 0.03	6	4.52 ± 0.12	0.17	0.071	6.37
18	0.035	LiBr	0.100	34.11 ± 0.03	4	11.1 ± 0.8	0.13	0.066	16.8
19	0.070	LiBr	0.100	34.11 ± 0.03	6	11.2 ± 0.4	0.13	0.066	16.9
20	0.070	LiBr	0.050	34.11 ± 0.03	4	6.18 ± 0.31	0.13	0.039	16.0
21	0.070	LiBr	0.010	34.11 ± 0.03	6	1.59 ± 0.08	0.13	0.0095	16.7
22	0.070	LiCl	0.100	41.0 ± 0.2	10	30.7 ± 1.5			
23	0.070	LiCl	0.100	25.09 ± 0.03	4	3.16 ± 0.08	0.27	0.078	4.06
24	0.070	LiCl	0.051	25.09 ± 0.03	3	1.82 ± 0.06	0.27	0.044	4.11
25	0.070	LiCl	0.010	25.09 ± 0.03	3	0.406 ± 0.016	0.27	0.010	4.06
26	0.070	LiI	0.100	25.09 ± 0.03	4	2.70 ± 0.11			

[a] Water content, ~0.004 *M* by Karl Fischer titration. [b] Runs 16 and 22 were followed by nmr in sealed tubes; runs 17–21 and 23–26 in sealed ampoules, and analyzed by glc. [c] Least-squares first-order rate constants, errors based on two standard deviations (95% confidence). [d] Weaver–Hutchison (ref 16) treatment of data for runs 18–21, and for runs 23–25. For runs 16 and 17, *K* extrapolated from *K* = 0.385 at 0° and *K* = 0.13 at 34.1° (from runs 18 to 21).

Run 13 was the same as 12, except the reaction solution was preheated to 39° before (*Z*)-**1** was added. The second-order rate constant for the appearance of A was estimated to be 0.026 M^{-1} sec^{-1} from the first four points taken during the first 7.5 min of reaction, while the total methyl integrals were still 100%. When subjected to the same conditions, (*E*)-**1** (in run 14) produced a small signal due to A, which never grew to more than 10% of the *E*-methyl signal at $t = 0$. After 35 min, only 60% of the total methyl integrals were present, of which the *E*-methyl signal was 50% and 10% was due to A. No *Z*-methyl signal appeared. Unfortunately, no rate constant estimate could be made of (*E*)-**1** → A.

The structure of A was inferred from the results of an experiment (run 15) in which a mixture of reactants (as in run 13) after 10 min was quenched with ether and water, and the products were separated by preparative glc. Isomers (*E*)-**1** and (*Z*)-**1** were identified by their glc retention times, and a new compound, **8**, was isolated and identified by analytical and spectral tech-

In runs 18–21, when the concentration of lithium bromide was lowered from 0.1 to 0.01 *M*, k_{obsd}/[LiBr] increased by a factor of 1.4. Similarly, when the concentration of lithium chloride was decreased from 0.1 to 0.01 *M*, k_{obsd}/[LiCl] increased by a factor of 1.3 (runs 23–25).

Weaver and Hutchison[16] observed the same behavior for LiBr and LiCl salts in DMF at 0° in their reactions with methyl tosylate. They attributed the apparent deviation from second-order kinetics to reaction only with dissociated halide ion. By a method of successive approximation, with their kinetic data they calculated what *K* for the reaction, LiX → Li$^+$ + X$^-$, would provide the best second-order behavior. They obtained *K* = 0.385 for LiBr, and *K* = 0.18 for LiCl at 0°. Ap-

(16) W. M. Weaver and J. D. Hutchison, *J. Amer. Chem. Soc.*, **86**, 261 (1964).

plication of their treatment to runs 18–21 gave K = 0.13 at 34° for LiBr, and K = 0.27 for LiCl at 25°. A similar treatment of kinetic data for the LiBr catalyzed racemization[17] at 126° of optically active methyl 1-cyano-2,2-diphenylcyclopropanecarboxylate (**10**) gave K = 0.03. A plot of log K for dissociation of LiBr at the three temperatures (0, 34, and 126°) over $1/T$ (absolute) gave curvature consistent with a 126° temperature spread. If the points at the two lower temperatures are extrapolated (assuming linearity) to 126°, the K obtained is 0.02 (instead of the 0.03 calculated from the kinetic data).[17] The internal consistency of these data encourages the conclusion that these estimates of K are realistic. The decrease in K with increasing temperature is consistent with the expected decrease in dielectric constant of DMF with increasing temperature. The values of K estimated from the above plot at 41 and 25° were used to extract second-order rate constants for runs 16 and 17, respectively.

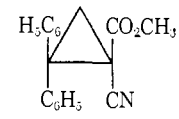
The relationship of the K's obtained from ours and others' data for LiCl $\rightleftarrows$ $Li^+ + Cl^-$ in DMF is less encouraging. Our value at 25° is 0.27, that of Weaver and Hutchison at 0° is 0.18, and that calculated[16] from others' kinetic data[18] at 30° is 0.037. These three values are incompatible, and our value and the assumptions on which it rests are accordingly less secure.

Discussion

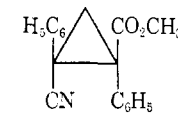
Methanolysis of Stereoisomers of Methyl 1-Cyano-2-phenylcyclopropanecarboxylate (1). When (+)-(*E*)-**1** was heated in methanol at 126°, the cyclopropane ring opened at the benzyl carbon, and ether (−)-**5** was produced with essentially *complete inversion* (99%) of configuration (see Chart II). Thus, carbon, with cyano and carbomethoxy substituents to stabilize negative charge, served as a leaving group in solvolysis of a secondary benzyl system. The closest open-chain analog of this reaction is the methanolysis of optically active α-phenylethyl chloride at 70°. This reaction was reported to occur with 32% net inversion,[19a] but this value is minimal, since racemization of starting material was probably a competing reaction.[19b]

At 25°, K = [(*E*)-**1**]/[(*Z*)-**1**] = 20 in DMF. At 175 and 200° in benzene, the two diastereomers were equilibrated thermally.[12] At 175°, K = [(*E*)-**1**]/[(*Z*)-**1**] = 8.1, and at 200°, K = 7.3. A plot of log K against $1/T$ (absolute) is surprisingly linear. From this plot, at 126°, $K \simeq 10$, and (*Z*)-**1** is ~1820 cal less stable than (*E*)-**1**. At 126°, (*Z*)-**1** and (*E*)-**1** underwent methanolysis with $k_s^Z/k_s^E \sim 1.8$. Thus $\Delta\Delta G^{\pm}$ for methanolysis of the two diastereomers is only 470 cal/mol. In other words, about a quarter of the difference in free energies of the ground states of the two diastereomers is felt in the rate-limiting transition states for methanolysis. The open-chain, methyl ether product (**5**) of methanolysis is the same for the two diastereomers.[20] Thus, as measured by the steric strains of the transition states *vs.* those of the ground states and products, the transition states are three-quarters along the reaction coordinate.

In methanolysis of (*Z*)-**1**, $k_s/k_e > 10^2$ (k_e is the rate constant for epimerization). In methanol, racemization (k_α, first-order rate constant) is faster than solvolysis for **10**, whose structure is the same as **1**, except a benzhydryl has replaced the benzyl of **1**.[17] In **10**, $k_s/k_e < 10^{-2}$. Thus, the additional phenyl of **10** inhibits direct solvent involvement in **10**'s ionization. That the character of the substituent on the carbon leaving group is important to the solvolysis is shown by another comparison. Compound (*Z*)-**11** resembles (*Z*)-**1** structurally, except that a phenyl has replaced the cyano group. Compound (*Z*)-**11** epimerizes at 175° in methanol, and no methanolysis product was detected.[21] The entropies of activation for the reactions of (+)-(*E*)-**1**, **10**, and **11** in methanol are also

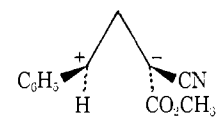


10

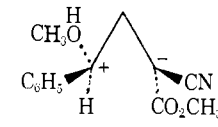


11

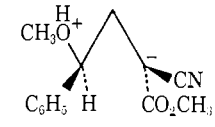
widely different. Thus, methanolysis of (+)-(*E*)-**1** at 126° gave $\Delta S^{\pm} = -32$ eu, racemization of **10** at 126° gave $\Delta S^{\pm} = -14$ eu,[17] and epimerization[21] of **11** at 175° gave $\Delta S^{\pm} = -2$ eu. These differences in $\Delta S^{\pm}$ as well as the differences in products of the three systems point to an increasingly important involvement with methanol in the rate-limiting step in passing from **11** to **10** to **1**. Several possible mechanisms for the methanolysis of (+)-(*E*)-**1** are considered which include *intermediates* (energy minima) B, C, D, and E. Mech-



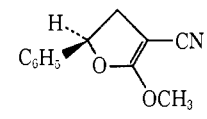
B



C



D



E

anisms that include B are reasonable only if $k_{-1} > k_2$ in the sequences

$$(+)\text{-}(E)\text{-}\mathbf{1} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{B} \xrightarrow{k_2} \mathrm{C} \text{ or } \mathrm{D} \longrightarrow (-)\text{-}\mathbf{5}$$

and if rotations of the two still chiral centers of B are slower by 10^2 than the step represented by k_2. In the sequence formulated, the transition state of highest energy above that of (+)-(*E*)-**1** in methanol is that lying between B and C, or between B and D. Both such steps freeze out solvent, and would make the activation entropy rather negative. These two mechanisms and accompanying assumptions cannot be operationally distinguished from mechanisms (+)-(*E*)-**1** → C → (−)-**5**, (+)-(*E*)-**1** → D → (−)-**5** or (+)-(*E*)-**1** → C → D → (−)-**5**, all of which are simpler. All of these mechanisms share the common feature that the highest energy point on the overall

(17) E. W. Yankee, F. D. Badea, N. E. Howe, and D. J. Cram, *J. Amer. Chem. Soc.*, **95**, 4210 (1973).
(18) P. Casapieri and E. R. Swart, *J. Chem. Soc.*, 4342 (1961).
(19) (a) E. D. Hughes, C. K. Ingold, and A. D. Scott, *ibid.*, 1201 (1937); (b) H. M. R. Hoffmann and E. D. Hughes, *ibid.*, 1244 (1964).
(20) Although **5** is a mixture of diastereomers, they should be very close in free energy to one another since the ethers are open-chain, and the chiral centers are 1,3 to one another.
(21) Alan B. Chmurny and D. J. Cram, *J. Amer. Chem. Soc.*, **95**, 4237 (1973).

potential energy diagram involves formation of a zwitterion that includes a methanol molecule.

With appropriate assumptions involving relative values of microscopic rate constants for various steps, ketene acetal E can be visualized as a possible intermediate, being formed reversibly from intermediates B, C, D, or a number of them. However, any mechanisms in which intermediate E returns to (+)-(*E*)-**1** competitively with steps leading to (−)-**5** are ruled out. If E returns to (+)-(*E*)-**1**, then the sequence (*Z*)-**1** → E → (*E*)-**1** should be observed. In fact, in methanolysis of (*Z*)-**1**, $k_s/k_e > 10^2$.

In mechanisms such as

$$(+)\text{-}(E)\text{-}\mathbf{1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{E} \xrightarrow{k_2} \text{C or D} \longrightarrow (-)\text{-}\mathbf{5}$$

ketene acetal (E) is formed directly from starting material, and subsequently solvolyzes with oxygen as leaving group. In these schemes, $k_2 \gg k_{-1}$. Otherwise epimerization products would be observed. If $k_1 > k_2$, then E would have accumulated, and its rotation would have perturbed the polarimetrically followed first-order kinetics. If $k_2 > k_1$, then the rate-limiting transition state would not have involved ionization or solvation. The high negative entropy of activation for the reaction points to solvent involvement in the rate-determining step. Strong evidence for ionization as a rate-limiting stage in epimerization and racemization reactions of the stereomers of **1** in nonsolvolyzing solvents[12a] is found in the adjacent paper.[12b] Involvement of the (+)-(*E*)-**1** → E stage in the mechanism of methanolysis is highly improbable.

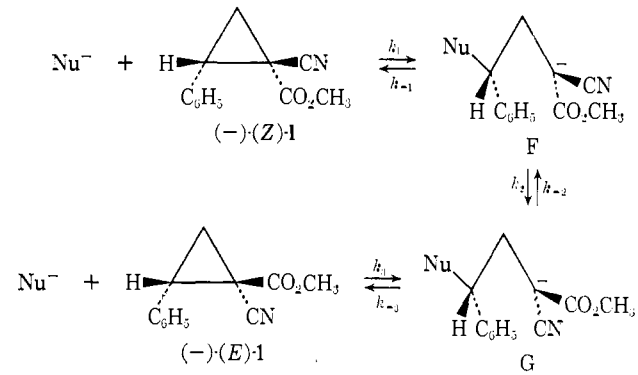
Catalysis of Epimerization Reactions of Methyl 1-Cyano-2-phenylcyclopropanecarboxylate (1) by Lithium Salts in DMF. The kinetics of thermal epimerization of (*Z*)-**1** to (*E*)-**1** in DMF was studied at 100 and 126°.[12] Extrapolation of the first-order rate constant to 34° gives $k_e = 2.86 \times 10^{-8}$ sec^{-1} for the uncatalyzed reaction. In DMF–0.1 *M* LiBr at 34°, the pseudo-first-order rate constant for (*Z*)-**1** → (*E*)-**1** (k_{obsd}) was 11.2×10^{-5} sec^{-1} (run 19). Thus, the lithium bromide catalyzed rate exceeded the thermal rate by a factor of ~4000. Similar rate factors were observed for LiCl and LiI in DMF (runs 23 and 26). Good evidence that the lithium bromide catalyzed reaction was first order in dissociated bromide ion was obtained. That these halide-catalyzed epimerization reactions are extraordinarily fast is indicated by comparison of the methanolysis rate constant for (+)-(*E*)-**1** extrapolated to 34° ($k_s = 1.29 \times 10^{-8}$ sec^{-1}) with the epimerization rate constant for (*Z*)-**1** in DMF–0.1 *M* LiBr at 34° ($k_{obsd} = 11.2 \times 10^{-5}$ sec^{-1}, run 19). The catalyzed epimerization rate exceeded the methanolysis rate by a factor of ~8700. The similarity of the methanolysis rates for (*Z*)- and (*E*)-**1** at 126° suggests that a similarly high factor would have applied had methanolysis of the *Z* isomer been compared with its bromide ion catalyzed epimerization.

A comparison of the rates in DMF of the lithium bromide catalyzed (0.1 *M*) racemization (k_α) of benzhydryl system **10**[17] and epimerization of (*Z*)-**1** (k_{obsd}) is also instructive. Extrapolation of k_α of **10** to 34° gives $k_\alpha \sim 5.27 \times 10^{-8}$ sec^{-1}, and $k_{obsd}/k_\alpha \sim 2100$. Thus, the lithium bromide catalyzed reaction is about three orders of magnitude faster in the benzyl than in the benzhydryl system.

The bromide ion catalysis of (−)-(*Z*)-**1** → (−)-(*E*)-**1** was completely stereospecific in DMF at 25° (run 9), and epimerization occurred exclusively at the cyanoacetate carbon. In DMF–0.1 *M* LiN_3 at 39° (run 13), the ring of (*Z*)-**1** was opened at the benzyl carbon by azide with a second-order rate constant about four times larger than the second-order rate constant for epimerization of (*Z*)-**1** to (*E*)-**1** by 0.1 *M* LiBr in DMF at 41° (run 16). The observation and capture of intermediate azido carbanion A to give **8**, and the regeneration of (*Z*)- and (*E*)-**1** from **8** with base provides additional relevant facts.

Chart III outlines the general mechanism supported

Chart III



by these observations. In an SN2 reaction, Nu^- displaces (k_1) the cyanoacetate leaving group from the benzyl position of (−)-(*Z*)-**1** to give carbanion F. Carbanion F partitions between collapse back to (−)-(*Z*)-**1** (k_{-1}) and 180° rotation of the cyanoacetate group about its bond to methylene (k_2) to give carbanion G. Carbanion G partitions between returning to F (k_{-2}) and collapsing to (−)-(*E*)-**1** by an intramolecular SN2 mechanism (k_{-3}). Although with appropriate assumptions, ketene acetal E could be invoked as an intermediate as well, no evidence supports its inclusion. If it were ever to form, it should from F or G, and would be expected to accumulate and be isolable.

The accumulation of what is undoubtedly an equilibrated mixture of F and G when Nu^- is N_3^- suggests that with the halides as well, k_2 or $k_{-2} \gg k_{-1}$ or k_{-3}. That F ⇄ G accumulates with N_3^- as nucleophile but not with the halides correlates with N_3 being a poorer leaving group than the halides. A mixture of F and G with N_3^- as Nu^- and sodium as counterion was generated from open-chain azide, **8**, by treatment with sodium hydride in DMF. Although the mixture gave (*E*)-**1**/(*Z*)-**1** ~ 10, the presence of sodium instead of lithium, and the uncertainties about the equilibria involved do not allow conclusions to be drawn from this experiment about the values of k_2/k_{-2}, or k_{-1}/k_{-3} of Chart III. The mechanism of Chart III involves complex enough kinetics to exclude any meaningful conclusions to be drawn from the small differences in catalytic activity exhibited by the three lithium halides. The isolation and determination of the structure of open-chain azide **8** demonstrate the epimerization occurs by attack at the benzyl, and not the methylene carbon of (*Z*)-**1**.

Experimental Section

General. All melting points and boiling points are uncorrected. Unless otherwise specified, all solvents and catalysts were reagent grade. Pmr spectra were taken with a Varian A-60 on 10–20% solutions in $CDCl_3$ with tetramethylsilane (1%) as internal standard. Infrared spectra were taken on dilute chloroform solutions with a Beckman IR-5 spectrometer, standardized with polystyrene. Rotations were taken with a Perkin-Elmer 141 polarimeter in a 1-dm thermostated cell, with limits of errors below 1° of ±0.002°. Mass spectra were obtained with an AEI Model MS-9. Thin layer chromatograms (tlc) were taken on Silica Gel 18-F on Baker-Flex plates, and ether (% denoted in text)–pentane was used as developer. Baker chromatographic grade silica gel was used for elution chromatography. Unless otherwise specified, glc was carried out on an F&M Model 720 instrument using 3 ft × 0.25 in. columns packed with 20% SE-30 on 60-80 Firebrick with helium at a flow rate of 60 ml/min.

(*E*)-Ethyl 1-Cyano-2-phenylcyclopropanecarboxylate. To a stirred dry mixture of 7.9 g (0.33 mol) of sodium hydride (after washing with pentane) and 71.3 g of trimethyloxosulfonium iodide[22] under nitrogen was added dropwise 130 ml of dimethyl sulfoxide holding the temperature at 25°. The gray-white mixture was cooled to 15°, and to this was added rapidly a solution of 60 g (0.30 mol) of (*E*)-ethyl 1-cyanocinnamate[23] in 150 ml of dimethyl sulfoxide. The yellow-green mixture was stirred at 15° for 5 min, at 25° for 2 hr, then at 45–50° for 1 hr. The dark green solution was cooled and diluted with ice–water. The cloudy mixture with some precipitated oil was decanted, the decanted mixture was extracted twice with ether, and the ether washings were used to dissolve the residual oil. The ether solution (~800 ml) was washed with brine, dried, and rotary evaporated to give 48.8 g of a yellow, viscous oil. Distillation gave (55%) a colorless, but cloudy oil, bp 131–132° at 65 μ (lit.[24] bp 122° at 5 μ). Preparative glc at 180° (20% SE-30 on 60–80 Firebrick, 6 ft × 0.75 in.) followed by distillation gave an analytical sample. The nmr showed: δ 1.27 (t, 3, 7 Hz), a broad doublet at 2.03 (2, 8 Hz), a broad triplet at 3.12 (1, 8 Hz), 4.23 (q, 2, 7 Hz), and a broad singlet at 7.32 (5). The mass spectrum showed a molecular ion *m/e* of 215. *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.73; H, 6.07; N, 6.60.

(*E*)-1-Cyano-2-phenylcyclopropanecarboxylic Acid (2). A solution of 18.0 g (84 mmol) of crude distilled (*E*)-ethyl 1-cyano-2-phenylcyclopropanecarboxylate, 20 g of potassium hydroxide, 100 ml of ethanol, and 300 ml of water was stirred at 25° for 3 hr. The solution was diluted with water and extracted with ether. The aqueous solution was acidified and extracted with ether. The ether solution was washed with brine, dried, and rotary evaporated to give 17.5 g of a yellow oil which crystallized. Recrystallization of the solid twice from chloroform gave 8.6 g (55%) of white prisms, mp 137–138°. The mass spectrum gave a molecular ion *m/e* of 187. *Anal.* Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.76; H, 4.84; N, 7.29.

(*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*E*)-1). To a solution of 5.5 g (29 mmol) of **2** in 100 ml of ether was added cautiously a solution of diazomethane in ether until the yellow color persisted. The solution was evaporated until the color was discharged, and then rotary evaporated to give 5.9 g of a light yellow oil. Distillation (Kugelrohr) of this material at 115–120° (0.15 mm) gave 5.7 g (97%) of (*E*)-**1** as a colorless oil. The nmr showed: δ 2.09 (d, 2, J = 9 Hz; higher signal split to another d, J = 1.5 Hz), 3.15 (t, 1, J = 9 Hz), 3.82 (s, 3), and 7.32 (s, 5). The ir showed significant bands at 3000 m, 2250 m, 1740 s, 1260–1320 s cm^{-1}. The mass spectrum showed the molecular ion *m/e* of 201. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.37; N, 6.80.

(*Z*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*Z*)-1). A stirred solution of 3.0 g (15 mmol) of (*E*)-**1** in 200 ml of acetone in a Pyrex housing was irradiated for 3.5 hr with a 450-W medium-pressure Hanovia lamp, immersed in a water-jacketed, quartz well containing a Vycor filter (1 mm thickness). The yellow solution obtained was rotary evaporated to give 3.5 g of yellow oil. Glc of an acetone solution at 160° showed two peaks at 8 and 10.5 min, respectively (ratio 1/2.2). The more abundant, longer retention time peak corresponded to (*E*)-**1**. A tlc (20%) of the original mixture showed a barely discernible second spot, moving 0.5 R_f faster than (*E*)-**1**. The oil was chromatographed on 400 g of silica gel, and 100-ml fractions were collected: 1-l. pentane, 2-l. 5% (ether in pentane), 2-l. 10%, 4-l. 15% (ether in pentane). Oils (some early fractions crystallized) were obtained beginning toward the end of the 10% and finishing well before the end of the 15% ether in pentane fractions. By glc, 0.56 g of a pure new compound, 0.6 g of a mixture (1:3, respectively) of the new compound and 0.4 g of pure starting material were obtained. The isomerically pure photoproduct, (*Z*)-**1**, crystallized from ethanol to give 0.4 g (20%) of soft white needles, mp 62–63°. The nmr showed: δ 1.8–2.4 (mult, 2), 3.25 (t, 1, J = 9 Hz), 3.49 (s, 3), 7.27 (s, 5). The mass spectrum showed the molecular ion *m/e* of 201. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.72; H, 5.67; N, 6.79.

Photoequilibration of (*E*)- and (*Z*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*E*)-1 and (*Z*)-1). Solutions of 0.5 g of each ester in 200 ml of acetone contained in a Pyrex flask with a well were irradiated for 6 hr by immersing a water-jacketed tube containing a Corex filter and a medium-pressure, 450-W Hanovia lamp. Analysis by glc (160°) of the crude product showed a ratio of 1.5:1 of *E*:*Z* isomers from each starting ester.

Resolution of (*E*)-1-Cyano-2-phenylcyclopropanecarboxylic Acid ((*E*)-2). To a dry mixture of 10.0 g (53.5 mmol) of (*E*)-**2** and 21.2 g (53.5 mmol) of brucine (recrystallized from acetone) was added 200 ml of methanol. The mixture was heated until clear, and the solution was stored at 25° and then 0° for several days. The solid that separated was recrystallized 4 times from boiling methanol to give 9.0 g of well-formed hard needles, $[\alpha]^{25}_{546}$ −110° (*c* 0.268, $CHCl_3$). The rotation of the salt did not change with another recrystallization to give 7.1 g of needles. The free acid was obtained by shaking 7.1 g of the salt with 50 ml of ether and 50 ml of 1 *M* hydrochloric acid. The aqueous layer was extracted three times more with ether; the combined ether extracts were washed with brine, dried, and evaporated to give 2.2 g of white solid, mp 135–138° (*cf.* 137–138° for racemic acid), $[\alpha]^{25}_{546}$ −239° (*c* 0.500, EtOAc). *Anal.* Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.42; H, 4.89; N, 7.52.

From the brucine salt mother liquors, the positive enantiomer was obtained by evaporating the methanol and recrystallizing the residue four times from hot acetone. From 12 g of residue was obtained 8.4 g of a yellow-white solid, $[\alpha]^{25}_{546}$ +74.6° (*c* 0.232, $CHCl_3$). The rotation did not change with another recrystallization to give 6.6 g of yellow-white solid. The 6.6 g of salt was converted to 2.0 g of a white solid, $[\alpha]^{25}_{546}$ +239° (*c* 0.575, EtOAc). That the acid obtained was not optically pure was indicated by changes of rotation upon repeated recrystallizations from chloroform (+239°, +241°, +238°, +235°), mp 139–140°. *Anal.* Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.80; H, 4.94; N, 7.35.

Optically Pure (−)- and (+)-(*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((−)-(*E*)-1 and (+)-(*E*)-1). The (−)-enantiomer was obtained by treating an ether solution of 0.35 g of (*E*)-**2** of $[\alpha]^{25}_{546}$ −241° (*c* 0.555, EtOAc) with diazomethane, and isolating the (−)-(*E*)-**1** by the usual procedure. The light yellow oil obtained slowly crystallized. Recrystallization of this material from ethanol gave 0.20 g of white, fibrous needles, $[\alpha]^{25}_{546}$ −251° (*c* 0.620, EtOAc), mp 53–54°. Another recrystallization from ethanol to give 0.11 g did not change the rotation or melting point. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.69; H, 5.51; N, 6.76.

The (+)-enantiomer was obtained as above from 0.80 g of acid, $[\alpha]^{25}_{546}$ +240° (*c* 0.615, EtOAc). The material was recrystallized from pentane to give 0.55 g of long thin needles, $[\alpha]^{25}_{546}$ +251° (*c* 0.545, EtOAc), mp 53–54°. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.45; N, 6.69.

(*Z*)-1-Cyano-2-phenylcyclopropanecarboxylic Acid ((*Z*)-1). A mixture of 2.0 g (9.9 mmol) of (*Z*)-**1**, 2.0 g (30 mmol) of potassium hydroxide, 10 ml of ethanol, and 30 ml of water was stirred at 25° for 1 hr, and the product was isolated in the usual way as 2.1 g of a white solid. Recrystallization of this material from chloroform afforded 1.85 g (99%) of white powdery solid, mp 151° dec (gas). The nmr (chloroform-*d*, acetone-d_6) showed: δ 1.8–2.4 (mult, 2), 3.25 (t, 1, J = 9 Hz), 5.5 (broad s), 7.26 (s, 5). The ir showed significant bands at 3400–2700 m, 2250 m, 1725 s, 1480–1300 m (several) and 1180 m cm^{-1}. The mass spectrum gave the molecular ion *m/e* of 187. *Anal.* Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 64.15–65.70; H, 4.51–4.61; N, 6.28–6.85. Because of the poor analysis, a portion of the analytical sample was converted back to (*Z*)-**1**, mp and mmp (with original material) 62–63°.

(22) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(23) J. Zabicky, *J. Chem. Soc.*, 683 (1961).
(24) J. Gosselck, L. Beress, and H. Schenk, *Angew. Chem., Int. Ed. Engl.*, **5**, 596 (1966).

Resolution of (*Z*)-1-Cyano-2-phenylcyclopropanecarboxylic Acid ((*Z*)-2). To a dry mixture of 1.1 g (5.9 mmol) of (*Z*)-2 and 1.95 g (5.9 mmol) of quinine was added 50 ml of methanol. The mixture was heated to clarity and stored at 25°. The salt that separated was recrystallized twice to give 1.1 g of soft, long needles, $[\alpha]^{25}_{546}$ −106° (*c* 0.228, $CHCl_3$). The free acid was obtained in the usual way to give 0.4 g (36%) of an off-white solid, $[\alpha]^{25}_{546}$ +199° (*c* 0.158, EtOAc).

From the quinine salt mother liquors, the negative enantiomer of (*Z*)-2 was recovered as 0.7 g (64%) of a yellow solid, $[\alpha]^{25}_{546}$ −143° (*c* 0.282, EtOAc). These optically impure acids were esterified (see below) without further purification.

Optically Pure (+)- and (−)-(*Z*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((+)-(*Z*)-1 and (−)-(*Z*)-1). The (+)-enantiomer was obtained by treating an ether solution of 0.2 g of (*Z*)-2 of $[\alpha]^{25}_{546}$ +199° (*c* 0.158, EtOAc) with diazomethane in the usual way to give a light yellow solid. This material was recrystallized once from ethanol to give 0.123 g (44%) of thin platelets, $[\alpha]^{25}_{546}$ +176° (*c* 0.150, EtOAc), mp 90.5–91.5°. One further recrystallization gave 95 mg of thin square platelets of (+)-(*Z*)-1, $[\alpha]^{25}_{546}$ +175° (*c* 0.221, EtOAc). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.44; H, 5.39; N, 6.81.

The negative enantiomer was obtained from 0.5 g of optically impure (−)-(*Z*)-2 of $[\alpha]^{25}_{546}$ −143° (*c* 0.280, EtOAc) and diazomethane. The initially obtained oil was dissolved in ethanol and (−)-(*Z*)-1 crystallized at −30° to give 0.386 g of a white powder, $[\alpha]^{25}_{546}$ −55.4° (*c* 0.590, EtOAc). Of this, 285 mg was recrystallized six times to give 20 mg (7%) of square thin platelets, $[\alpha]^{25}_{546}$ −175° (*c* 0.145, ethyl acetate), mp 91–91.5°. Further recrystallization changed neither the rotation nor melting point. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.73; H, 5.48; N, 6.87.

Decarboxylation–Hydrolysis of (+)-(*Z*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((+)-(*Z*)-1). A mixture of 0.108 g (0.54 mmol) of (+)-(*Z*)-1 of $[\alpha]^{25}_{546}$ +65.4° (*c* 0.208, EtOAc) and 0.05 g of potassium hydroxide in 4.0 ml of ethylene glycol was stirred at 60–80° for 45 min, and then at 200° for 1 hr. Water (1 ml) was added and the solution refluxed for 3 hr. While the solution was refluxing, an additional 0.1 g of potassium hydroxide was added, and the solution was refluxed 2 hr more. The yellow solution was cooled and shaken with 50 ml of water and ether, and the ether layer was washed once with water. The aqueous solutions were combined and acidified with 1 *M* hydrochloric acid. The resulting acidic solution was extracted four times with ether; the combined ether washings were extracted once with brine, dried, and evaporated to give 0.2 g of a viscous, yellow oil. An ether solution of the oil was treated with excess diazomethane. The ester was obtained as 0.100 g of a yellow oil. Analytical glc (160°) showed only two components in the ratio of 9:1, with the more abundant having the shorter retention time. Kugelrohr distillation of the crude product at 75–95° (0.12 mm) gave 72 mg of a colorless oil, $[\alpha]^{25}_{546}$ +125° (*c* 0.740, EtOAc). The nmr spectrum of the distilled product showed in addition to the expected compound (see below) two equal-intensity singlets at δ 3.34 and 3.77. Preparative tlc (20%, 8 in. × 8 in. × 1 mm, Merck silica gel G) of the material followed by distillation at 75–80° (0.12 mm) (Kugelrohr) gave 40 mg (30%) of a colorless oil, $[\alpha]^{25}_{546}$ +134° and $[\alpha]^{25}_{D}$ +111° (*c* 0.287, EtOAc). That this compound was (*E*)-methyl 2-phenylcyclopropanecarboxylate ((+)-(*E*)-3) was demonstrated by its spectral properties: nmr δ 1.0–2.0 (mult, 3), 2.3–2.7 (mult, 1), 3.70 (s, 3), 7.1–7.3 (mult, 5); ir 3000 w, 1720 s, 1180 s cm^{-1}. *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.84; H, 6.91.

As a further structure proof, the ester was hydrolyzed to its carboxylic acid by stirring a mixture of 20 mg of ester, 50 mg of potassium hydroxide, 1 ml of ethanol, and 3 ml of water at 25° for 4 hr. The product was isolated by the usual procedure to give 18 mg of an oil. An ir (KBr) spectrum was the same as that published for *trans*-2-phenylcyclopropanecarboxylic acid.[25]

(*E*)-1-Cyano-2-phenylcyclopropanecarboxamide. To a mixture of 0.5 g (2.7 mmol) of (*E*)-1-cyano-2-phenylcyclopropanecarboxylic acid, 0.5 g (5.0 mmol) of thionyl chloride, and 2 ml of chloroform at 25° was added 3 drops (40 mg, 0.5 mmol) of dry dimethylformamide (redistilled from Sieves). The mixture was refluxed for 10 min. The intense yellow solution was then quickly cooled and poured rapidly, but cautiously, into 75 ml of concentrated aqueous ammonia at −10°. The resulting mixture was shaken for 5 min. The layers were separated and the aqueous solution was extracted once more with chloroform. The combined organic solutions were washed once with brine and rotary evaporated to give 0.3 g of a solid. Recrystallization of this material from ethanol gave 0.2 g (40%) of white crystals, mp 184–185°. The nmr (DMSO-d_6) showed: δ 1.8–2.3 (mult, 2), 3.0 (t, 1, *J* = 8 Hz), 7.3 (s, 5), 7.4–7.6 (broad s). The ir showed significant bands at 3200–3600 (d) m, 3000 m, 2250 m, 1700 s, 1620 m, 1400 m, 1350 m, 1200 m cm^{-1}. The mass spectrum showed the molecular ion at *m/e* of 186. *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.86; H, 5.38; N, 15.07.

(+)-(*E*)-1-Cyano-2-phenylcyclopropanecarboxamide. From 0.3 g (1.6 mmol) of (+)-(*E*)-2 of $[\alpha]^{25}_{546}$ +234° (*c* 0.546, EtOAc) by the above procedure was obtained 0.25 g of a yellow solid. The solid was sublimed at 110–120° and 10 μ and then recrystallized once from ether to give 0.11 g (37% yield) of white platelets, $[\alpha]^{25}_{546}$ +235° (*c* 0.625, acetone), mp 121–123°. The nmr spectrum was identical with the racemic amide. *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.94; H, 5.48; N, 15.06.

Dehydration of (*E*)-1-Cyano-2-phenylcyclopropanecarboxamide to 2-Phenylcyclopropanedicarbonitrile (4). In a dry flask, 0.7 g (5 mmol) of phosphorus pentoxide was covered with 5 g of dry sand. To this mixture, a solution of 0.2 g (1.1 mmol) of the above amide in 15 ml of chloroform (freshly distilled from phosphorus pentoxide) was added. To this mixture was added 3 ml of triethylamine (redistilled from sodium hydroxide) causing an exothermic reaction. The mixture was stirred and refluxed under a drying tube (Drierite) for 2 hr. The yellow-orange mixture was decanted and the residue washed successively with water and chloroform. The combined chloroform solutions (50 ml) were washed twice with 1 *M* hydrochloric acid, once with saturated sodium bicarbonate and once with brine, and finally rotary evaporated to give a watery, yellow oil. The mixture was dissolved in water–ether, and the ether was washed with brine, dried, and rotary evaporated to give 0.15 g of a yellow oil. The oil was absorbed on 1.6 g and chromatographed on 25 g of silica gel (25-ml fractions cut): 100-ml pentane, 200-ml 1% (ether in pentane), 1-l. 2%, 400-ml 5%, 400-ml 10%, 100-ml 20% (ether in pentane). The product from the 10% ether in pentane fractions (waxy solid) was sublimed at 35° and 20 μ to give 70 mg (39%) of white crystals, mp 42–42.5° (lit.[9] mp 61°). The nmr and ir spectra were identical with those reported for 2-phenylcyclopropanedicarbonitrile.[13] The mass spectrum showed a molecular ion at *m/e* of 168. *Anal.* Calcd for $C_{11}H_6N_2$: C, 78.55; H, 4.79. Found: C, 78.78; H, 4.83.

Dehydration of (+)-(*E*)-1-Cyano-2-phenylcyclopropanecarboxamide to (+)-2-Phenylcyclopropanedicarbonitrile ((+)-4). By the above procedures, 0.10 g (0.54 mmol) of the above amide of $[\alpha]^{25}_{546}$ +235° (*c* 0.625, acetone) was converted to 0.14 g of crude (+)-4 as an orange viscous oil. The oil was twice chromatographed as before, to give 25 mg of a light yellow oil. Careful Kugelrohr distillation at 0.1 mm and 85–95° gave 16 mg (18%) of (+)-4 as a colorless oil, $[\alpha]^{25}_{546}$ +227° (*c* 0.137, acetone). The nmr spectrum was identical with that of racemic 4. *Anal.* Calcd for $C_{11}H_6N_2$: C, 78.55; H, 4.79. Found: C, 78.57; H, 4.90.

(*Z*)-1-Cyano-2-phenylcyclopropanecarboxamide. From 0.3 g (1.6 mmol) of (*Z*)-2 by the above procedure was produced 0.3 g of a light orange oil that slowly crystallized. Tlc (50%) showed some (*E*)-amide (R_f 0.2) with another major spot (R_f 0.3). The crude product was absorbed on 3 g and chromatographed on 30 g of silica gel (25-ml fractions): 100-ml pentane, 100-ml 1% (ether in pentane), 200-ml 2%, 200-ml 5%, 500-ml 10%, 200-ml 20%, 200-ml 40%, and 1-l. 50% (ether in pentane). The last fractions contained 40 mg of the *E* isomer and 0.12 g of the *Z* isomer. Recrystallization of the (*Z*)-amide from ethanol–water (minimum) gave 84 mg (28%) of white flakes, mp 121–122°. The nmr showed: δ 1.7–2.5 (mult, 2), 3.1 (t, 1, *J* = 9 Hz), 5.7–6.2 (broad, 2), and 7.24 (s, 5). The ir showed significant bands at 3200–3500 (d) m, 3000 m, 2250 m, 1710 s, 1600 s, 1380 s, 1220 cm^{-1}. The mass spectrum showed a molecular ion of *m/e* of 186. *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.07; H, 5.43; N, 15.08.

(−)-(*Z*)-1-Cyano-2-phenylcyclopropanecarboxamide. Application of the above procedure to 98 mg (0.52 mmol) of (−)-(*Z*)-2 of $[\alpha]^{25}_{546}$ −17.2° (*c* 0.615, ether) gave 91 mg of a yellow solid. Tlc (50%) showed only the presence of the *Z* isomer (1% sensitivity). The product was sublimed at 100° and 10 μ to give 74 mg (75%) of a microcrystalline solid, $[\alpha]^{25}_{546}$ −17.5° (*c* 0.630, ether), mp 115–120°. The nmr was identical with that of the racemic (*Z*)-amide. *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.09; H, 5.49; N, 14.87.

(25) Sadtler Standard Spectra, 29509 (1967).

Dehydration of (−)-(*Z*)-1-Cyano-2-phenylcyclopropanecarboxamide to (−)-2-Phenylcyclopropanedicarbonitrile ((−)-4). By the above procedure, from 65 mg (0.35 mmol) of (−)-(*Z*)-amide of $[\alpha]^{25}_{546}$ −17.5° (*c* 0.630, ether) was obtained 79 mg of crude oil. Two Hickman distillations (50 μ) and one Kugelrohr distillation (0.15 mm, 90–110°) of this material gave 38 mg (65%) of (−)-**4** as a colorless oil, $[\alpha]^{25}_{546}$ −10.1° (*c* 3.77, acetone). The sample was homogeneous by glc (160°) and gave the same retention time as the (+)-**4** reported above, and gave an nmr spectrum identical with that of (+)-**4** prepared from (*E*)-amide. *Anal.* Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79. Found: C, 78.70; H, 4.94.

Methanolysis of (*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*E*)-1) to Give Methyl 1-Cyano-4-methoxy-4-phenylbutanoate (5). A solution of 3.0 g (15 mmol) of (*E*)-**1** in 15 ml of methanol (distilled from Molecular Sieves) was twice frozen (liquid nitrogen) and thawed in a heavy-walled Pyrex tube. The tube was evacuated to <0.1 mm, dry oxygen-free nitrogen admitted, the solution again frozen, thawed, frozen, and sealed at <0.1 mm nitrogen pressure. The tube was annealed carefully. The ampoule was heated at 126° for 3 days. Evaporation of the resulting yellow solution gave 3.5 g of residue, distillation of which at 50 μ and 105–110° gave 3.0 g (86%) of a mixture of diastereomers of open-chain ether, **5**. The structure was apparent from its spectral and analytical properties: nmr δ 2.0–2.7 (mult, 2), 3.17 and 3.20 (two singlets, 3), 3.77 and 3.80 (two singlets, 3), 3.5–4.1 (mult, 1), 4.2–4.5 (mult, 1), and 7.34 (s, 5); ir 3000 m, 2250 w, 1740 s, 1420 m, 1200–1310 s, 1120 m, and 1060–1110 s cm^{-1}. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.88; H, 6.48; N, 5.76.

Methanolysis of (+)-(*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((+)-(*E*)-1, Run 1). A solution of 0.509 g (2.5 mmol) optically pure (−)-(*E*)-methyl 1-cyano-2-phenylcyclopropanecarboxylate of $[\alpha]^{25}_{546}$ +251° (*c* 0.545, EtOAc) in 10 ml of methanol (distilled from Sieves) was sealed in a heavy-walled Pyrex tube as above. The solution was heated at 126° for 5 days. Evaporation of the yellow solution gave 0.5 g of an oil, $[\alpha]^{25}_{546}$ −74.2° (*c* 0.665, EtOAc). Kugelrohr distillation at 110–120° (0.14 mm) gave 0.52 g (88%) of (−)-**5** as a colorless oil, $[\alpha]^{25}_{546}$ −75.9 ± 0.4° (*c* 0.630, EtOAc) which had an nmr spectrum identical with the **5** prepared from racemic (*E*)-**1** (see above). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.86; H, 6.41; N, 6.04.

Methanolysis of (*Z*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*Z*)-1, Runs 2 and 3). A sample of 0.5 g of (*Z*)-**1** was dissolved in 15 ml of methanol (distilled from magnesium). Two samples of 5.0-ml each were sealed in a heavy-walled Pyrex tube after degassing as before, and placed in a constant-temperature bath at 126°. One tube was removed after 2.0 hr; analysis by glc showed 81% (*Z*)-**1** and 19% **5**, with good base line separation. The second tube was withdrawn after 11.0 hr; glc showed 23% (*Z*)-**1** and 77% **5**. No other products were visible. Control glc experiments with synthetic mixtures of (*Z*)-**1**, (*E*)-**1**, and **5** demonstrated that had it been present in the above experiment, <1% of (*E*)-**1** could have been detected.

Run 6. This run was conducted as were runs 2 and 3, except the two tubes were withdrawn after 150 min and after 600 min, and the contents were analyzed by glc with tridecane as internal standard (97–99% of starting material was accounted for). No (*E*)-**1** was detected (<1% sensitivity). Calculated first-order rate constant from tube 1 was 3.6×10^{-5} sec^{-1}, and from tube 2, 3.9×10^{-5} sec^{-1}.

Decarboxylation–Hydrolysis of Methyl 1-Cyano-4-methoxy-4-phenylbutanoate (5). A solution of 0.20 g (0.86 mmol) of **5** and 0.3 g of potassium hydroxide in 5.0 ml of ethylene glycol was stirred at 100° for 2 hr and then at 200° for 20 hr. To the hot solution was added 1.0 ml of water, and the solution was refluxed at 180° for 6 hr. The solution was cooled and shaken with a mixture of 20 ml of water and ether. The aqueous solution was acidified and extracted three times with ether. The combined ether solution was washed with brine, dried, and evaporated. The residue was treated with excess diazomethane in ether, and the resulting solution was rotary evaporated to give 0.24 g of an orange liquid. Kugelrohr distillation of the material at 75–85° and 75–80 μ gave 0.17 g (94%) of a colorless liquid. The spectral and analytical data indicated the compound was methyl 4-methoxy-4-phenylbutanoate (**6**): nmr δ 1.8–2.6 (mult, 4), 3.20 (s, 3), 3.64 (s, 3), 4.17 (t, 1, J = 7 Hz), and 7.33 (s, 5); ir 3000 m, 1730 s, 1200–1300 s, 1150 s, 1100 s cm^{-1}. *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.25; H, 7.87.

Decarboxylation–Hydrolysis of (−)-Methyl 1-Cyano-4-methoxy-4-phenylbutanoate ((−)-5). A solution of 0.102 g of (−)-**5** having $[\alpha]^{25}_{546}$ −75.9° (*c* 0.630, EtOAc) and 0.15 g of potassium hydroxide in 4.0 ml of ethylene glycol was stirred at 100° for 2 hr and then at 200° for 20 hr. To the hot solution was added 1.0 ml of water, and the solution was refluxed at 180° for 6 hr. The product was isolated and esterified as with racemic material (see above) to give 0.102 g of a yellow liquid. Preparative tlc of this material (20%, 8 in. × 8 in. × 1 mm, Merck silica gel G) gave 68 mg (75%) of a yellow liquid. Hickman distillation at 0.15 mm of this oil gave 25 mg of (−)-**6** as a colorless liquid, $[\alpha]^{25}_{546}$ −93.8 ± 0.4° (*c* 0.781, EtOAc), which had an nmr spectrum identical with that of **6** (see above). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.12; H, 7.62.

Optically Pure (+)-3-Methoxy-3-phenylpropanoic Acid ((+)-7). A solution of 1.85 g (9.53 mmol) of (+)-methyl 4-methoxy-4-phenylpropanoate[14] having $[\alpha]^{25}_{546}$ +65.7° (*c* 0.530, EtOAc), 2.0 g of potassium hydroxide, 20 ml of ethanol, and 10 ml of water was refluxed for 1 hr. The solution was cooled, poured into water, and extracted with ether. The ether extracts were washed with water. The combined aqueous solution was acidified with hydrochloric acid, and the resulting mixture was extracted with ether. The ether was washed with brine, dried, and evaporated to give 1.6 g of an oil, which crystallized. Two recrystallizations of the solid from pentane–benzene gave 1.2 g (70%) of optically impure (+)-**7** as white soft crystals, $[\alpha]^{25}_{546}$ +67.8 ± 0.1° (*c* 0.960, EtOAc), and $[\alpha]^{25}_{546}$ +68.7 ± 0.1° (*c* 0.233, EtOAc), mp 57–65°. *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.63.

To a dry mixture of 0.10 g (0.56 mmol) of the above sample of (+)-**7** and 0.22 g (0.56 mmol) of brucine (recrystallized from acetone) was added 25 ml of acetone. The mixture was heated until clear. When cooled to 0°, the solution deposited a solid which, after three crystallizations, gave 0.15 g of salt of constant rotation, $[\alpha]^{25}_{546}$ −41.2° (*c* 0.312, $CHCl_3$). Treatment of this material with 1 *M* hydrochloric acid and ether gave, after evaporation of the dried ether solution, 60 mg of a solid. One recrystallization of the solid from pentane gave 48 mg of hard, light-yellow spurs, $[\alpha]^{25}_{546}$ +74.1° (*c* 0.208, EtOAc), mp 64.5–66°. Recrystallization of this material from pentane–benzene gave 38 mg of small, hard white needles of (+)-**7**, $[\alpha]^{25}_{546}$ +72.3 ± 0.9° and $[\alpha]^{25}_{D}$ +58.3 ± 1.0° (*c* 0.227, EtOAc), mp 65–66°. One more recrystallization from pentane–benzene did not change the melting point or the rotation. *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.65; H, 6.67.

(+)-Methyl 3-Methoxy-3-phenylpropanoate. To an ether solution of 0.20 g (1.1 mmol) of (+)-3-methoxy-3-phenylpropanoic acid having $[\alpha]^{25}_{546}$ +67.8° (*c* 0.960, EtOAc), 95.2 ± 1.2% optically pure, was added an excess of diazomethane. The ester was isolated as usual. After Kugelrohr distillation at 80–85° and 50 μ, 0.15 g (70%) of a colorless liquid was obtained, $[\alpha]^{25}_{546}$ +64.9° (*c* 0.590, EtOAc) and $[\alpha]^{24.0}_{D}$ +65.8° (*c* 3.04, benzene). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.24; H, 7.33.

Arndt–Eistert Homologation of 3-Methoxy-3-phenylpropanoic Acid (7). A solution of 0.30 g (1.7 mmol) of **7**, 2 ml of chloroform, 50 drops of purified thionyl chloride, and 5 drops of dimethylformamide (distilled from Sieves) was refluxed for 4 min. After cooling, the intense yellow solution was rotary evaporated at 25° to a liquid and a heavy oil. Two additions of 10-ml portions of benzene followed by rotary evaporation at 25° gave a mixture of a liquid and a solid. This material was dissolved in 40 ml of ether; the solution was filtered through glass wool and added dropwise over a period of 1.5 hr to 150 ml of ether–0.7 *M* in diazomethane stirred at 0°. The resulting solution was stirred at 0° for 0.5 hr, and then at 25° for 16 hr. The yellow solution was boiled on a steam bath in a hood until the intense yellow color had faded, and the solution was filtered through Celite. The filtrate was rotary evaporated at 25° to give 0.5 g of a yellow liquid whose spectral properties showed it to be the desired diazo ketone: nmr δ 2.5–2.9 (mult, 2), 3.19 (s, 3), 4.64 (mult 1), 5.31 (s, 1), and 7.32 (s, 5); ir 3000 m, 2110 s, 1640–1670 (2) s, 1360 s, 1100 s.

A 0.1 g (0.49 mmol) portion of the diazo ketone was added dropwise (neat) to a stirred solution of 0.30 g (2.45 mmol) of *s*-collidine and 0.26 g (2.45 mmol) of benzyl alcohol contained in a vial immersed in an oil bath at 175°. After the first drop, there was an induction period of about 2 sec followed by vigorous gas evolution. All of the diazo ketone was added in about 2 min. Gas evolution continued for an additional 5 min. The dark solution was heated for 5 min longer, cooled to 25°, and added to 10 ml of 0.1 *M* hydrochloric acid. The resulting mixture was extracted three times with ether; the ether was combined, washed with brine, dried, and evaporated to give 0.5 g of an oil. This material was dissolved in 1 ml of methanol, 0.1 g of potassium hydroxide and 1 ml of water were added, and the

mixture was refluxed for 3 hr. The solution was cooled, diluted with 20 ml of water, and washed twice with ether–pentane. The combined organic washings were extracted once with water. The combined aqueous solution was acidified with hydrochloric acid and extracted with ether. The ether solution was washed with brine, dried, and evaporated to give 0.2 g of an oil. This oil was esterified with diazomethane in the usual way to give 0.2 g of an oil. The glc (170°) showed only benzyl alcohol and one other component. Preparative tlc (20%) of the material gave 29 mg of yellow liquid. Hickman distillation of the material at 50 μ gave 20 mg (18%) of methyl 4-methoxy-4-phenylbutanoate (**6**) as an oil. The nmr and ir spectra of this material were as follows: nmr δ 1.8–2.6 (mult, 4), 3.20 (s, 3), 3.64 (s, 3), 4.17 (t, 1, J = 7 Hz), and 7.33 (s, 5); ir 3000 m, 1730 s, 1200–1300 s, 1150 s, and 1100 s cm^{-1}. No contamination with unhomologated ester could be seen by nmr. These spectra are identical with those exhibited by the sample of (−)-**6** prepared from (−)-**5** (see above). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.27; H, 7.78.

Arndt–Eistert Homologation of (+)-3-Methoxy-3-phenylpropanoic Acid ((+)-7). From 0.30 g (1.7 mmol) of (+)-**7** (95.2 ± 1.2% optically pure), $[\alpha]^{25}_{546}$ +68.7 ± 0.1° (*c* 0.233, EtOAc), by the above procedure was obtained 77 mg (22%) of (+)-**6** as a colorless oil, $[\alpha]^{25}_{546}$ +90.5 ± 0.2° (*c* 0.743, EtOAc). The nmr and ir spectral properties of this material were identical with those of the samples of **6** and (−)-**6** prepared above. *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.13; H, 7.63.

Kinetics of Methanolysis of (−)-(*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((−)-(*E*)-1). From a solution of 50 mg of (−)-(*E*)-**1** of $[\alpha]^{25}_{546}$ +244° (*c* 0.251, EtOAc) in 25 ml of dry methanol (distilled from Molecular Sieves) were withdrawn 20 1.1-ml aliquots. The solutions were sealed *in vacuo* in dry heavy-walled Pyrex tubes after the freeze–thaw degassing cycles described above. Ten tubes were used at each of the two temperatures, 126.1 and 100.4°, with tubes withdrawn periodically and frozen. Rotations of the spent samples were determined at 25° at λ 546 nm. The infinity points were determined by allowing one tube to remain at 126.1° for 6.0 days and a second tube to remain at 100.4° for 180 hr and then at 150° for 15 hr. The temperatures were determined by using thermometers previously calibrated by the National Bureau of Standards. The temperature errors were determined from a Beckmann differential thermometer. The first-order rate constants were determined from a least-squares analysis of the raw data. The results are given in the text.

Techniques General to Equilibria and Kinetic Experiments Conducted in Dimethylformamide. Reagent grade dimethylformamide (DMF) was distilled under nitrogen atmosphere once from calcium hydride and once from barium oxide in carefully dried equipment, and was stored in a drybox. Karl Fischer titration showed the presence of ~0.004 *M* water. This material was used throughout the following experiments except for the kinetics. For the rate studies, DMF was further purified by passing it through a column of activity one alumina (Woelm, dried at 650°) in a drybox. Karl Fischer titration showed this DMF to be <0.003 *M* in water. Lithium salts were reagent grade, LiN_3 Eastman, and LiCl, LiBr, and LiI were MCB. These were carefully dried, stored, and manipulated in a drybox. Glc analyses were performed with an F&M Model 720 instrument with an 8-ft, 20% SE-30 on Chromosorb W, 80–100 mesh column with helium as carrier gas. The cut-and-weigh technique was employed. The detector was calibrated against known mixtures of (*Z*)-**1**, (*E*)-**1** and octadecane or tridecane, which were used as internal standards. The response was linear from about 20 to 80% (*Z*)-**1** in (*E*)-**1**, and unknowns were corrected to known synthetic mixtures. Analyses were good to ±0.5%. Preparative glc separations were performed with the same instrument on a 3-ft column of 20% SE-30 on Chromosorb W, 80–100 mesh with good base line separation between (*E*)-**1** and (*Z*)-**1**. With known mixtures, only about 50% of the material put through the column could be condensed from the helium carrier gas. All volumetric equipment and ampoules were thoroughly dried and manipulated in the drybox, where weighing operations were performed. Calibrated thermometers (precision of 0.01°) were used to measure the rate bath temperatures.

Equilibration of (*Z*)- and (*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*Z*)- and (*E*)-1) in DMF–0.1 *M* LiBr (Runs 7 and 8). Solutions of 15 mg of (*Z*)-**1** (run 7) and of (*E*)-**1** (run 8) in 3 ml of 0.10 *M* lithium bromide in DMF were prepared under nitrogen in a drybox, and allowed to stand (~25°) in stoppered flasks in the drybox for 24 hr. The solutions were then shaken with a water–ether mixture. The ether layer was dried over sodium sulfate, filtered through a short plug of silica gel, and submitted to glc analysis. Run 7 gave 5% (*Z*)-**1** and 95% (*E*)-**1** whereas run 8 gave 4.5% (*Z*)-**1** and 95.5% (*E*)-**1**.

Stereospecificity of Lithium Bromide Catalyzed Epimerization of Optically Pure Isomers of Methyl 1-Cyano-2-phenylcyclopropanecarboxylate (1) in DMF (Runs 9–11). In run 9, 25.0 mg of (−)-(*Z*)-**1**, $[\alpha]^{25}_{546}$ −175° (*c* 0.15, EtOAc), was weighed into a 1-ml volumetric flask, and enough 0.10 *M* LiBr in DMF added to give 1 ml of solution. The flask was stoppered and allowed to stand in the drybox (~25°) for 38 hr. The solution was shaken with ether and water; the ether layer was washed with water and concentrated. The concentrate was submitted to preparative glc to give 12.5 mg (Cahn balance) of (−)-(*E*)-**1**, $[\alpha]^{25}_{546}$ −247° (*c* 0.13, EtOAc). Run 10 was identical with 9 except that the reaction was quenched after 1 hr. Preparative glc gave 9.8 mg (Cahn balance) of recovered (−)-(*Z*)-**1**, $[\alpha]^{25}_{546}$ −178° (*c* 0.10, EtOAc). Run 11 was identical with 9 except 30 mg of (+)-(*E*)-**1** was used, $[\alpha]^{25}_{546}$ +251° (*c* 0.15, EtOAc), and the reaction was run 35 hr. Preparative glc gave 12.6 mg (Cahn balance) of recovered (+)-(*E*)-**1**, $[\alpha]^{25}_{546}$ +248° (*c* 0.13, EtOAc).

Lithium Azide Catalyzed Epimerization of the Isomers of (*Z*)- and (*E*)-Methyl 1-Cyano-2-phenylcyclopropanecarboxylate ((*Z*)-1 and (*E*)-1). A solution of 0.201 g of (*E*)-**1** in 10 ml of DMF–0.10 *M* in lithium azide was allowed to stand under nitrogen for 2 hr in a stoppered flask in a drybox (~25°), and then shaken with a mixture of ether and water. The ether layer was washed with water, dried, concentrated, and submitted to preparative glc. Three materials were collected with retention times corresponding to (*Z*)-**1** (4 mg, mp 61–62°), (*E*)-**1** (40 mg, nmr identical with authentic sample), and **8** (trace, ir identical with authentic material). A solution of 0.040 g of (*Z*)-**1** in 2 ml of DMF–0.1 *M* lithium azide was similarly prepared, quenched after 45 min, and submitted to isolation and preparative glc. The three peaks corresponding to (*Z*)-**1**, (*E*)-**1**, and **8** were again observed, and that corresponding to (*E*)-**1** was collected (15 mg, nmr identical with authentic material).

Lithium Azide Catalyzed Epimerizations in DMF of (*Z*)-1 and (*E*)-1 and Formation of Intermediate A Monitored by Nmr Spectroscopy (Runs 12–14). Preliminary experiments showed that solutions of (*Z*)-**1** in DMF gave methyl ester proton signals at δ 3.37, and (*E*)-**1** methyl ester proton signals at δ 3.83. Two impurities in the DMF with signals at δ 3.91 and 4.08 were shown by addition of several internal standards not to change with time. These impurities were used as internal standards to monitor the growth and disappearance of methyl ester signals. In run 12, a solution of 2.00 ml of 40.2 mg of (*Z*)-**1** in DMF–0.01 *M* LiN_3 was quickly prepared, and syringed into an nmr tube which was capped with Teflon tape. The tube was quickly removed from the drybox and put into the probe (39°) of an A-60-D nmr machine. Initially only the signals of the methyl of (*Z*)-**1** and a small new methyl ester signal (intermediate A) at δ 3.12 were visible. As time passed, the signal for (*Z*)-**1** decreased, that of A increased to a maximum and then decreased, and that of (*E*)-**1** more slowly appeared and then decreased. Periodically the three signals and that of the internal standard were integrated. Table I records the results. Run 13 was identical with 12 except the DMF–0.10 *M* LiBr solution was preheated to 39° before dissolving the (*Z*)-**1**; the solution was mixed and put in the probe in less than 1 min. The kinetics of formation of A were followed with four points during the first 7.5 min of the reaction while the methyl ester integrals still totalled 100% (see text for rate constant estimate). Run 14 was the same as 13 except (*E*)-**1** was used. Although the signal of A appeared, its rate of growth was not high enough compared to the total loss of methyl signals to even estimate a rate constant.

Conversions of (*Z*)-1 to Methyl 1-Azido-2-cyano-4-phenylbutanoate (8, Run 15) and of 8 to 1. To 60 mg of (*Z*)-**1** was added 3 ml of DMF–0.10 *M* LiN_3. A drying tube was fitted to the flask; the flask was removed from the drybox and immersed in a 40° bath for 10 min. The solution was then shaken with an ice-water–ether mixture; the ether layer was washed with water, dried, evaporated, and submitted to preparative glc to give ~5 mg of **8** as an oil. This material was combined with **8** isolated from an experiment in which (*E*)-**1** was substituted for (*Z*)-**1**, and the reaction was quenched after 3 hr at 25° (~10% yield). The substance was characterized as follows: nmr δ 7.5 (s, 5), 5.85 (t, 1, J = 8 Hz), 3.9 (s, 3), 3.8 (t, 1, J = 4 Hz), 2.45 (t, 2, J = 9 Hz); ir 2350 (C≡N), 1750 (CO_2), 2120, 1430, and 720 (N_3) cm^{-1}. The mass spectrum exhibited no molecular ion, but gave major peaks at 216 (P − 28) and 201 (P − 43). *Anal.* Calcd for $C_{12}H_{12}O_2N_4$: C, 59.02; H, 4.92. Found: C, 58.72; H, 4.85.

Azide **8** was reconverted to (*E*)-**1** and (*Z*)-**1** as follows. To a solution of ~5 mg of **8** dissolved in 5 ml of dry DMF was added 50 mg of

sodium hydride (drybox, under nitrogen). Bubbles appeared, and after stirring for 35 min, the mixture was shaken with ice–water and ether. The ether layer was washed with water, dried, and evaporated, and the mixture was submitted to glc. The ratio of the weights of the peak with (*E*)-**1** retention time to that with (*Z*)-**1** in one determination was 9.4, and in a second was 11.2. In a larger run, the (*E*)-**1** produced from **8** was isolated by preparative glc and shown to possess an nmr spectrum identical with that of authentic material.

Kinetics of Epimerizations of (*Z*)-1 to (*E*)-1 Catalyzed by Lithium Halides in DMF (Runs 16–26). Runs 16 and 22 carried out in nmr tubes resembled run 13 except 42.0 mg of (*Z*)-**1** was weighed in a 3-ml volumetric flask that was filled to the mark with 0.100 *M* LiBr or LiCl in dry DMF at 41° in a drybox (time 0). The solution was immediately syringed into an nmr tube at 41°; the tube was capped with Teflon tape and transferred from the drybox to the probe of an A60D nmr machine. The signals of the methyl protons of (*Z*)-**1** and (*E*)-**1** were integrated at time intervals and compared to the internal standard impurities in the DMF. No other methyl signals were observed. In run 16, the sum of the integrals at the end of the run (75% conversion) was equal to that at the beginning. In run 22, the sum at the end (80% conversion) was 0.94 that at the beginning. Table I records the results.

In runs 17, 19–21, and 23–26, 42.0 mg of (*Z*)-**1** was weighed into a 3-ml volumetric flask, and in run 18, 21.0 mg was used. Solutions of LiBr, LiCl, or LiI in dry DMF freshly prepared under nitrogen in the drybox were added to the mark, the flasks were shaken, and a clean, dry syringe was filled with solution. The syringe was quickly removed from the drybox, and the content was delivered into clean dry ampoules attached to a sealing apparatus under dry argon. The solutions were immediately frozen (liquid nitrogen). Manipulations from mixing to freezing took 20–30 sec. The solutions were degassed with three freeze–thaw cycles and the ampoules sealed at <0.01 mm. The ampoules were first warmed to 0° to melt the liquid, and then placed in a constant-temperature bath. The first tube (time 0) was withdrawn after 5 min and immediately frozen, and additional tubes were removed at appropriate intervals covering about 2 half-lives. The tubes were opened and added to a water–ether mixture (10 ml of each containing a weighed amount of octadecane or tridecane as an internal standard). The ether layer was washed with water and dried with a small amount of sodium sulfate, and the volume of ether was reduced through a distillation column to about 3 ml. This solution was subjected to glc analysis. Less than 3% loss of (*E*)-**1** and (*Z*)-**1** as measured against the internal standards was observed. Most data points fell between 20 and 80% conversion of (*Z*)-**1** to (*E*)-**1**. The pseudo-first-order rate constants were calculated by a least-squares computer program, and errors are reported with two standard deviations. Table I reports these results.

Studies in Stereochemistry. XLV. Zwitterionic Transition States in Epimerization Reactions of Substituted Cyclopropanes[1,2]

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Abstract: An operational criterion was developed to differentiate between zwitterionic and singlet diradical transition states in thermal, geometric isomerization reactions of substituted cyclopropanes in solution. Changes in rates and products with changes in solvent polarity served as criteria for differentiating between zwitterion and diradical paths at the orthogonal point (transition state of highest energy) on the reaction coordinate. Epimerization rates (first order) were measured for each chiral center of optically active (+)-methyl 1-(*R*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate ((+)-(*Z*)-**1**) in dimethylformamide (DMF) and in benzene at two temperatures. The product of epimerization at the cyanoacetate center (k_a) was (+)-methyl 1-(*S*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate ((+)-(*E*)-**1**). Epimerization at the benzyl center (k_b) gave (−)-methyl 1-(*R*)-cyano-2-(*S*)-phenylcyclopropanecarboxylate ((−)-(*E*)-**1**). Racemization rates of (+)-(*Z*)-**1** were also estimated in DMF and measured in benzene at two temperatures. These rates were much slower in DMF than the epimerization rates, and comparable in benzene. The values of the equilibrium constant, *K*, for (*Z*)-**1** ⇄ (*E*)-**1** were measured at 175° (*K* = 8.1) and at 200° (*K* = 7.3) in benzene, and were already known in DMF at 25° (*K* = 20). Interpolation of these values to 126° gave *K* = 10, and to 100° gave *K* = 12. From the rate and equilibrium data, the following rate ratios were calculated: $(k_a^{DMF}/k_a^{C_6H_6})_{126°} \sim 4 \times 10^4$; $(k_b^{DMF}/k_b^{C_6H_6})_{126°} \sim 7 \times 10^3$; $(k_a^{DMF}/k_b^{DMF})_{100°} \sim 86$; $(k_a^{DMF}/k_b^{DMF})_{126°} \sim 27$; $(k_a^{C_6H_6}/k_b^{C_6H_6})_{175°} \sim 5$; $(k_a^{C_6H_6}/k_b^{C_6H_6})_{197°} \sim 5$. Each kind of epimerization passes through a different face-to-edge structure at some point on the reaction path, in which the original bonding orbitals of the starting material become orthogonal to one another. The ~10^4 greater rate of epimerization at each chiral center in the more polar DMF as compared to benzene as solvent indicates the transition states are close to being orthogonal, and are zwitterionic rather than singlet diradical. In both media, the cyanoacetate group rotates faster than the benzyl, the opposite of what is expected sterically (hydrogen of edge turned inward toward cyanoacetate face of the edge-to-face structure). Charge separation is less in the zwitterionic, orthogonal state in which the carboxymethoxyl group carrying most of the negative charge is turned inward in the edge of the face-to-edge structure. This zwitterionic transition state explains the thermal results. In an acetone-sensitized, photolytic stereoisomerization reaction, (+)-(*Z*)-**1** gave racemic (*E*)-**1** and largely racemized (*Z*)-**1**; (+)-(*E*)-**1** gave racemic (*Z*)-**1** and largely racemized (*E*)-**1**. The photochemical results are interpreted as involving triplet state, open-chain trimethylene derivatives of long enough life to undergo multiple rotations at both chiral centers before collapsing to the covalent ground state.

Conceivably, reaction coordinates for geometric or optical isomerization reactions of 1,2-substituted cyclopropanes might involve singlet structures A–D or a number of triplet structures summarized by E. Structure A is a face-to-face singlet whose orbital geometry and proximity allow different blends of diradical and zwitterionic character. Structure B is a face-to-edge singlet diradical whose orbitals do not overlap since

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