Chemistry of Cyclopropanols. V. Stereochemistry of Acid- and Base-Catalyzed Ring Opening[1,2]

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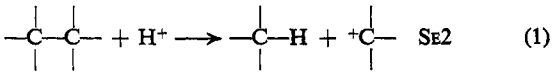
Abstract: *cis*-2-Phenyl-1-methylcyclopropanol undergoes a bimolecular electrophilic ring opening in acid solution leading to a 60:40 mixture of 4-phenyl-2-butanone and 3-phenyl-2-butanone. Stereochemical studies on optically active substrate have shown that this SE2 reaction, the breaking of a carbon–carbon bond by a proton, proceeds with *retention* of configuration. In base the same cyclopropanol rapidly forms only 4-phenyl-2-butanone. This SE1 reaction occurs with *inversion* of configuration. The mechanistic implications of these results are discussed.

One of the simplest imaginable organic reactions, the breaking of a carbon–carbon single bond by a proton, is at the same time one of the least accessible to investigation. Two general mechanistic classes of such a reaction may be envisaged. The first, and in some



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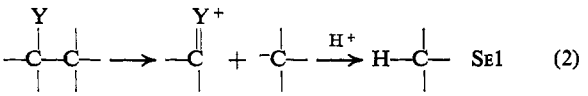


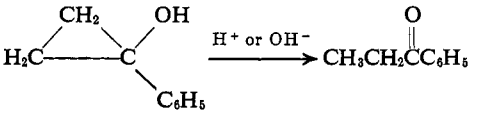
(2)

ways the more fundamental, involves the direct *bimolecular* reaction of a proton with the electrons of a carbon–carbon single bond as shown in eq 1. In such a process a new carbon–hydrogen bond is formed as the carbon–carbon bond is broken. In the Hughes–Ingold terminology this would be an SE2 reaction, bimolecular electrophilic substitution on a saturated carbon. Although reactions belonging to the SE2 class in which a carbon–metal bond is broken by an electrophile are known, only among cyclopropanes is a carbon–carbon single bond so broken.

Cram and co-workers have carried out an extensive study of a second type of electrophilic substitution reaction.[5] In this sequence the breaking of the carbon–carbon bond *precedes* carbon–hydrogen bond formation, so that a carbanion is an intermediate. Since the rate-determining step involves the unimolecular cleavage of the bond, these reactions are classed as SE1.

In earlier papers[6] we have described a number of synthetic methods for the preparation of cyclopropanols, and these compounds have proved to be ideal substrates for an investigation of the mechanism of both SE1 and SE2 reactions. In this paper we will discuss the stereochemistry of these two processes.

Cyclopropanols undergo ring openings in both acidic and basic solution. As a simple example, propiophenone is the product when 1-phenylcyclopropanol is treated either with dilute aqueous base at room temperature or with 1.0 *N* hydrochloric acid in 50:50



dioxane–water solution at 50°. Cyclopropanes themselves undergo ring opening when treated with acids, but cyclopropanols have several advantages as substrates. In the first place the conditions required for the reaction are less drastic than for alkyl- or arylcyclopropanes, stronger acids or higher temperatures being required in the latter cases. Secondly, the hydroxyl group directs the ring opening so that the carbonium ion formed is always adjacent to the electron-rich oxygen atom. It has been generally recognized that Markovnikov's rule applies to cyclopropane ring openings in that the most stable carbonium ion is formed in the course of the reaction.[7] In the case of a cyclopropanol, this is the highly stable conjugate acid of a ketone or aldehyde. Finally, in the normal cyclopropane opening, the carbonium ion formed ordinarily has several paths open for further reaction, some of which may lead to products which are more reactive than the starting material. Not so with cyclopropanols, which lead in quantitative yield to ketones. Cyclopropanols thus are seen to have many advantages as substrates for an investigator of SE2 reactions. Base-catalyzed SE1 reactions of cyclopropanols also proceed rapidly and completely at low temperature so that these compounds provide interesting alternatives for an investigation of this reaction.

Synthesis. 1-Methyl-2-phenylcyclopropanol was chosen as a suitable substrate for the stereochemical study. The synthesis of the important intermediate, 1-methyl-2-phenylcyclopropanecarboxylic acid, was patterned after that of Julia[8] and is outlined in Chart I. Little difficulty was experienced in the synthesis once it was recognized that, contrary to earlier reports, the initial attack of diethyl malonate on styrene oxide does not occur exclusively on the primary carbon, but in fact a 60:40 mixture of lactones is formed. The details of this investigation have been reported previously.[9]

(1) A preliminary account of some of this work appeared as a communication: C. H. DePuy and F. W. Breitbeil, *J. Am. Chem. Soc.*, **85**, 2176 (1963); part IV: C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(2) This work was supported by the National Science Foundation.

(3) Alfred P. Sloan Fellow, 1960–1964; address correspondence to the Department of Chemistry, University of Colorado, Boulder, Colo.

(4) National Science Foundation Undergraduate Research Participant.

(5) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter IV.

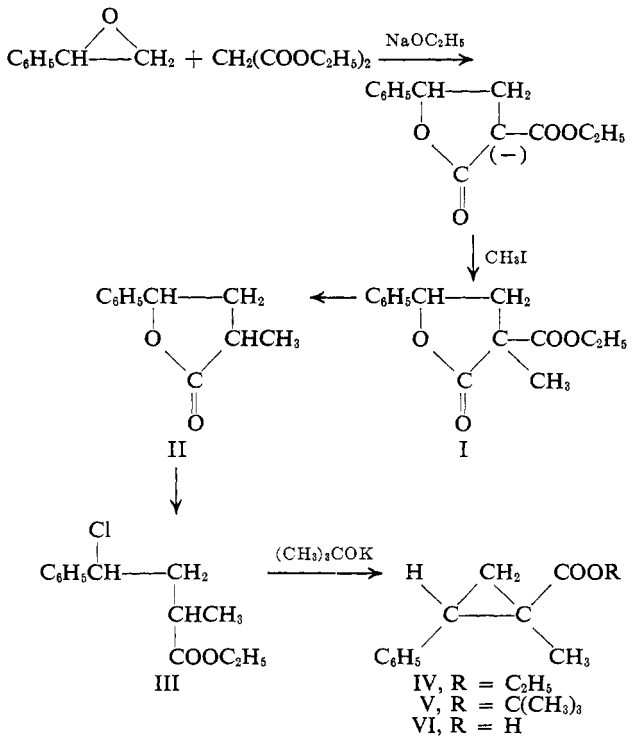
(6) (a) C. H. DePuy and C. R. Mahoney, *J. Am. Chem. Soc.*, **86**, 2653 (1964); (b) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

(7) A. Bhati, *Perfumery Essent. Oil Record*, **53**, 15 (1962).

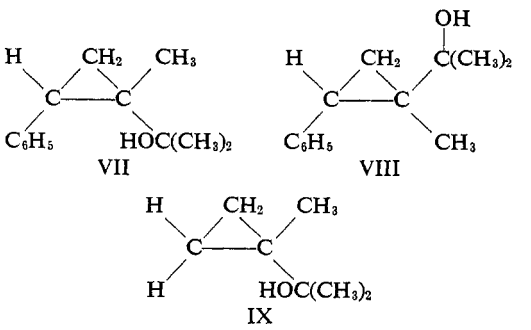
(8) M. Julia, S. Julia, and B. Bermont, *Compt. Rend.*, **245**, 2304 (1957); *Bull. Soc. Chim. France*, 304 (1960).

(9) C. H. DePuy, F. W. Breitbeil, and K. L. Eilers, *J. Org. Chem.*, **29**, 2810 (1964).

Chart I



From this sequence *cis*-1-methyl-2-phenylcyclopropanecarboxylic acid could be isolated as either its ethyl or *t*-butyl ester, depending upon the reaction time. There were certain advantages in allowing sufficient time to form the *t*-butyl ester as this could be converted to the acid merely by heating. It was surprising that only a single stereoisomeric ester is formed, the other isomer being found as less than 1% of the product mixture. This result is reminiscent of those of Zimmerman on the stereoselective formation of epoxides, and may have a similar "overlap control" explanation.[10] A small amount of the isomeric ethyl ester was isolated by careful fractional distillation and hydrolyzed to the acid. The structure of the predominant isomer was shown to have the methyl and phenyl groups *cis* to one another by ozonolysis to the known 1-methyl-*trans*-1,2-cyclopropanedicarboxylic acid. A series of infrared and nmr studies were equally convincing.[11] 1-Methylcyclopropanecarboxylic acid and 1-methyl-2,2-diphenylcyclopropanecarboxylic acid were synthesized and the position of the methyl group absorption measured by nmr. Comparison with the isomeric acids showed that a 2-phenyl group *cis* to the 1-methyl exhibited a shielding effect (see Table IV). The esters were next converted to the corresponding tertiary alcohols by reaction with methyllithium. In the minor isomer (VII) the hydroxyl group showed hydrogen bonding to the phenyl[12] in its infrared spectrum. Finally, the hydroxyl hydrogen absorption in the nmr proved to be indicative of structure. The relevant data are summarized in Table I. Notice that in VII, in which hydrogen bonding is occurring with the adjacent phenyl, the O–H absorption occurs at high field and does not change appreciably



with dilution. In VIII and IX, where such internal hydrogen bonding is absent, the absorption occurs farther downfield and changes sharply upon dilution. The chemical and spectral evidence, taken together, makes a strong case for the assignment of the structure *cis*-2-phenyl-1-methylcyclopropanecarboxylic acid to the major product of the reaction.

Table I. Effect of Concentration on the Nmr Peak Position of the Hydroxyl Hydrogen in 2-Cyclopropyl-2-propanols

Compd	Concn, mole % in CCl_4	O–H peak, ppm downfield from TMS
VII	11.62	0.42
	5.37	0.30
	1.62	0.18
	0.43	0.13
VIII	16.29	2.10
	8.00	1.58
	3.85	1.23
	2.30	1.05
	1.23	0.85
	0.50	0.78
IX	16.75	2.05
	8.22	1.52
	4.16	1.13
	2.34	0.85
	0.74	0.65

This *cis* acid was next resolved through its brucine salt according to the procedure of Walborsky and Hornyak.[13] A triangular fractional crystallization from acetone gave, after cutting back the salt, acid of a maximum rotation of $[\alpha]^{25}D$ −155.1° (5% in absolute EtOH). Subsequent reactions were carried out on (+) and (−) acid of varying lesser degrees of optical purity. Treatment of the acid with 2 equiv of methyllithium in ether (Chart II) converted it to the methyl ketone (90% yield).[14] This ketone was oxidized to the acetate with peroxytrifluoroacetic acid and then converted to the alcohol by modifications of the method previously described.[6] Both (+) and (−) alcohols of nearly identical magnitude of rotation (+41.5, −41.9°) were prepared. The degree of optical purity of these alcohols is not known since recrystallizations and other purifications were involved in their preparation from the acid, but it is believed to be high since yields were uniformly good and because the rotation of the ketone formed on ring opening was high (*vide infra*). The structure of the alcohol followed from its mode of

(10) H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **82**, 5459 (1960).

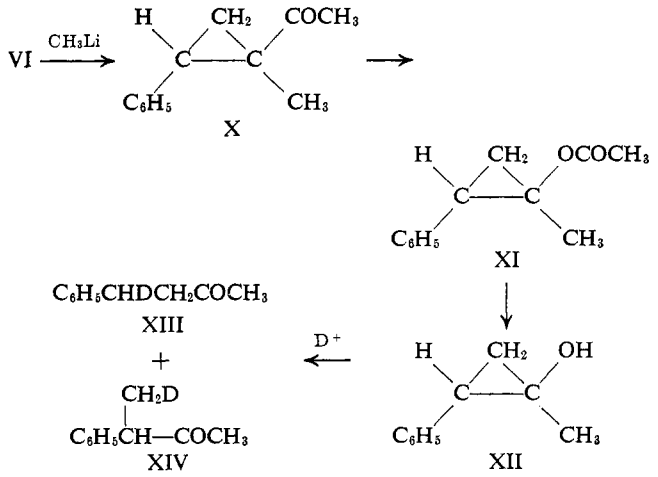
(11) We are grateful to Mr. Donald Barth for these studies.

(12) P. von R. Schleyer, C. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, No. **14**, 1 (1959); I. M. Goldman and R. O. Crisler, *J. Org. Chem.*, **23**, 751 (1958).

(13) H. M. Walborsky and F. M. Hornyak, *J. Am. Chem. Soc.*, **77**, 6026 (1955).

(14) To ensure that no epimerization occurs in this reaction, a sample of ketone from racemic acid was oxidized back to the starting acid by sodium hypochlorite.

Chart II

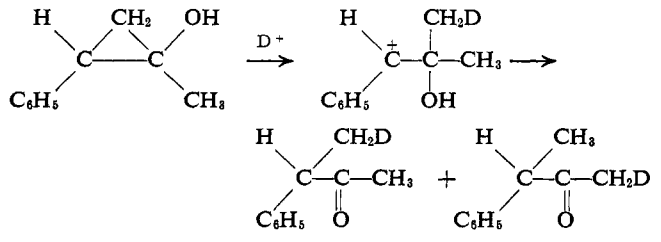


synthesis, its nmr spectrum, and its ring-opening reactions discussed below.

Ring Opening. *cis*-2-Phenyl-1-methylcyclopropanol is a crystalline solid, stable in the pure state but rapidly isomerizing in basic solution. For the stereochemical studies reported, a 50:50 (v/v) dioxane–water medium was chosen for both the acidic and basic reactions. In this medium at 50° the pure alcohol was shown to be stable for an indefinite period of time. In the same medium at 50° in 1 *M* HCl it had a half-life of approximately 40 hr, while in 0.1 *N* NaOH ring opening was instantaneous. The product composition was consistent with the operation of distinct reaction mechanisms in the two cases (Table II). The exclusive production of 4-phenyl-2-butanone from the base-catalyzed opening is consistent with the SE1 mechanism (eq 2), since a benzyl carbanion would be formed. The direct attack of a proton in the SE2 mechanism is apparently less sensitive to the presence of substituents. Further support for the proposed mechanisms was found in the pattern of deuterium labeling, if the reactions were carried out in D_2O–dioxane. The benzyl carbon of 4-phenyl-2-butanone was substituted with a single deuterium atom in both the acid- and base-catalyzed openings. In the 3-phenyl-2-butanone, the CH_3 group contained one deuterium atom.[15]

Since the object of the study was to determine the stereochemistry of the ring openings, optically active alcohol was allowed to react with 1 *N* DCl in 50:50 D_2O–dioxane and with 0.1 *N* NaOD in the same solvent mixture. In this way, an asymmetric center ($C<^{H}_{D}$) was generated in the 4-phenyl-2-butanone. Since the magnitude of rotation due to this center was expected to be small, precautions had to be taken to prevent the accidental inclusion of small amounts of starting alcohol or of 3-phenyl-2-butanone since both of these would be expected to have high rotations. Consequently after ring opening was complete, NaOD was added and the solutions were heated to racemize 3-phenyl-2-butanone and to ensure that any remaining cyclopropanol was destroyed. The desired 4-phenyl-2-butanone was purified by preparative scale gpc and its purity checked by nmr and analytical gpc. Rotations were determined on the neat liquid in a precision Rudolph polarimeter. The results of six experiments, three in base and three in acid, are summarized in Table III.

(15) This labeling experiment also served to rule out an alternative mechanism for the formation of 3-phenyl-2-butanone. If this path were followed, equal amounts of 4-monodeuterated and 4-undeuterated



ketone would be formed. Of course additional deuteriums were introduced at the α carbons after ring opening.

Table II. Products of Ring Opening of *cis*-2-Phenyl-1-methylcyclopropanol

	$C_6H_5CH_2CH_2$-$COCH_3$, %	$C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCOCH_3$, %
1.0 *N* acid	60	40
0.1 *N* base	100	0

Table III. Rotations of 4-Deuterio-4-phenyl-2-butanone Obtained by Ring Opening of *cis*-2-Phenyl-1-methylcyclopropanol

Run	Alcohol,[a] deg	Ketone,[b] deg	
		1.0 *N* DCl	0.1 *N* NaOD
A	+41.5	−0.351 ± 0.018	+0.339 ± 0.017
B	−41.9	+0.455 ± 0.011	−0.272 ± 0.013
C	−41.6	+0.456 ± 0.014	−0.424 ± 0.016

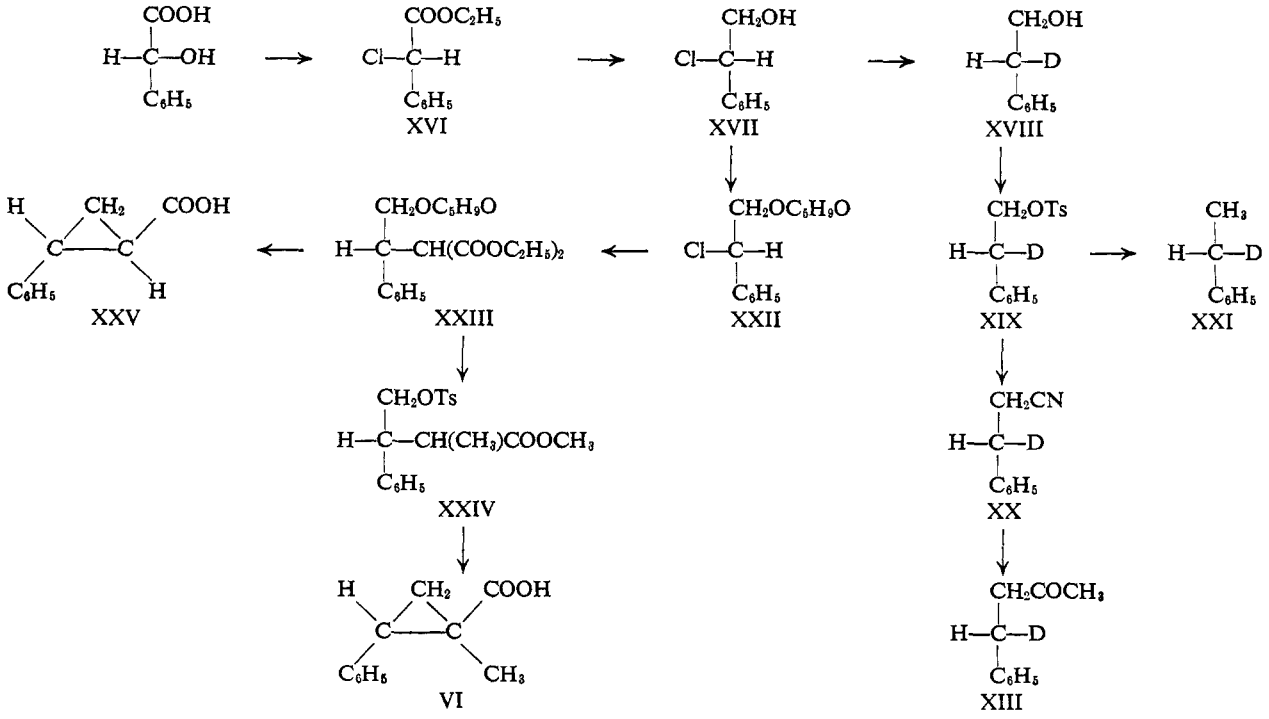
[a] Measured in absolute ethanol solution. [b] Pure liquid, an average of twelve determinations on each sample using a 10-cm cell.

Stereochemistry of the Ring Opening. The results reported in Table III show conclusively that the stereochemistry of the SE1 and SE2 reaction in this system proceeds with *opposite* stereochemical consequences. Obviously one reaction gives predominantly retention of configuration, the other predominantly inversion. Several lines of reasoning show that it is the *SE2 reaction which gives retention, the SE1 process proceeding with inversion.* First, in the extensive studies of Cram, SE1 reactions were shown to give predominantly inversion in solvents of high dissociating power capable of donating protons. This was interpreted to be a result of shielding of the front side of the carbanion by the leaving group and of rapid protonation of the carbanion by the solvent. By analogy, inversion would be expected in our system since the solvent is highly proton donating and the conditions are mild.[16]

Secondly, Nickon[17] has shown that in 1-hydroxynortricyclene the SE1 reaction occurs with inversion, the SE2 reaction with retention. In this case, diasteriomeric deuterium compounds were formed and the position of deuteration was determined by infrared spectroscopy. Thirdly, SE2 reactions among organometallics have been shown to give retention of configuration under most circumstances.[18]

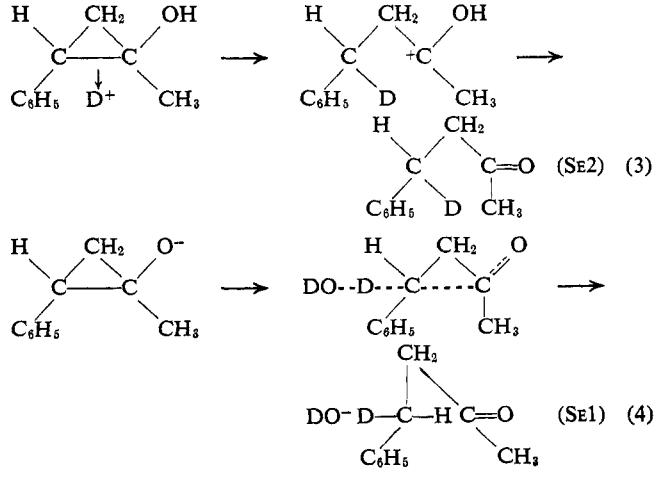
(16) See ref 5, p 153.
(17) A. Nickon, J. H. Hammons, J. L. Lambert, and R. O. Williams, *J. Am. Chem. Soc.*, **85**, 3713 (1963).
(18) See ref 5, p 116.

Chart III



All of the above arguments are merely inferential, however convincing. To prove the point unequivocally, the absolute configuration of both the starting alcohol and the deuterated ketone must be known. That of the latter has been reported by Streitwieser[19] and has been confirmed in the present work. The absolute configurations of 1-methyl-2-phenylcyclopropanol and of the deuterioketone were determined as outlined in Chart III. The starting material in both cases was D-(−)- and L-(+)-mandelic acid which, after esterification, was converted to ethyl chlorophenylacetate (XVI) by the method of Kenyon,[20] using thionyl chloride and pyridine. This method leads to inversion of configuration. The chloro ester was next reduced to the chloro alcohol (XVII) with lithium aluminum hydride.[21] Further reduction of this chloro alcohol with lithium aluminum deuteride produced 2-deuterio-2-phenylethanol (XVIII). Eliel[22] has shown that neither styrene oxide nor phenylacetaldehyde is an intermediate in this reduction, and that a direct displacement, probably by way of a cyclic aluminum alkoxide, is involved. Our results confirm this, since mass spectrometry and nmr showed that the deuterium atom was on the β carbon. The rest of the steps were unexceptional, yielding the deuterated ketone (XIII) with the expected[19] sign of rotation. As a further check, a small amount of 2-deuterio-2-phenylethyl tosylate (XIX) was reduced by lithium aluminum hydride to deuterioethylbenzene (XXI) of the expected sign of rotation.[19]

The same chloroalcohol served as a precursor for the synthesis of 1-methyl-2-phenylcyclopropanol. Unfortunately, some difficulty occurred at the crucial step in the synthesis, the SN2 displacement on the pyranyl ether, and the product obtained (XXIII) had only a small amount of optical activity. Even though a large amount of racemization had occurred, net inversion was demonstrated by conversion of a portion of the product to *trans*-2-phenylcyclopropanecarboxylic acid (XXV) of known[23] configuration. The subsequent steps were patterned after those of the initial synthesis of the 1-methyl-2-phenylcyclopropanecarboxylic acid and are recorded in detail in the Experimental Section. The over-all conclusion is thus unmistakable: (+) alcohol and (−) ketone have the same absolute configuration at the benzyl carbon and therefore the acid-catalyzed SE2 reaction proceeds with retention of configuration. Our preliminary conclusions are thus confirmed and the reaction mechanisms can be expanded to those shown in eq 3 and 4. These results seem reasonable, the electrophilic proton attacking the electrons of the C–C



(SE2) (3)

(SE1) (4)

(19) A. Streitwieser, J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

(20) J. Kenyon, A. G. Lipscomb, and H. Phillips, *J. Chem. Soc.*, 415 (1930).

(21) E. L. Eliel, C. Herrmann, and J. T. Traxler, *J. Am. Chem. Soc.*, **78**, 1194 (1956).

(22) E. L. Eliel and T. J. Prosser, *ibid.*, **78**, 4045 (1956); E. L. Eliel and D. W. Delmonte, *ibid.*, **80**, 1744 (1958); E. L. Eliel and M. H. Rerick, *ibid.*, **82**, 1362 (1960).

(23) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).

bond, probably at the edge of the ring where they are thought to bulge out in "banana bonds."[24]

From our results it is not possible to be quite as certain about the amount of racemization, if any, accompanying the ring openings. The results in Table III are reported in the order obtained and the absolute magnitude of the observed rotations are believed to be more reliable in the third experiment. Especially is this so in the base-catalyzed reaction where we took greater pains to avoid locally high concentration of either cyclopropanol or base. Since the ring opening in base is so rapid, locally high concentrations of protons might result in formation of some undeuterated ketone, or the carbanion might be more prone to racemization. With the utmost care, however, the optical rotation of the ketone is the same, within experimental error, when obtained from either acid- or base-catalyzed reaction. The simplest explanation of this result is that both proceed with substantially 100% stereospecificity. The actual magnitudes of the rotations point in the same direction, since the maximum rotation of the deuterated ketone is thought to be 0.44 ± 0.03.[19] Taken together with Nickon's[17] study in which >95% stereospecificity was observed, we believe that both the SE2 and SE1 reactions of cyclopropanols proceed with complete stereospecificity, the former with *retention*, the latter with *inversion* of configuration.

Experimental Section

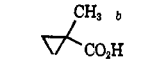
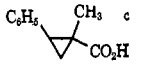
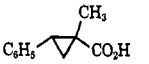
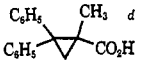
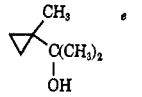
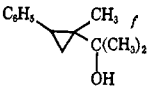
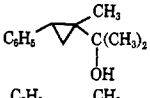
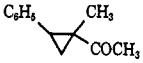
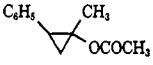
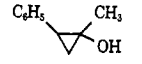
All melting points and boiling points reported in this section are uncorrected. The nmr spectra of pertinent cyclopropane compounds are recorded in Table IV.

α-Methyl-γ-phenyl-γ-butyrolactone (II). To a solution of 55 g (2.4 g-atoms) of sodium in 200 ml of anhydrous ethanol was added 310 g (1.9 moles) of diethyl malonate. The solution was heated to reflux and 230 g (1.9 moles) of styrene oxide was added over a 2-hr period. After refluxing for an additional 2 hr, 320 g (2.2 moles) of methyl iodide in 200 ml of absolute ethanol was added slowly. The solution was refluxed 20 hr to effect decarbethoxylation.[25] To this cooled solution was cautiously added 40 g (1.0 mole) of sodium hydroxide in 1700 ml of water. Most of the ethanol was distilled, 300 ml (3.6 moles) of concentrated hydrochloric acid was carefully added, and the organic layer was extracted with ether and dried. The ether was evaporated and the residual oil was vacuum distilled at 0.25 mm to give 258 g of product (71% yield); bp 105–108°, $n^{25}D$ 1.529, d^{27} 1.106, molar refractivity 49.09 (calcd, 49.15); $\nu_{max}^{CHCl_3}$ 1772 (s) cm^{-1}.[26]

Ethyl 4-Chloro-2-methyl-4-phenylbutanoate (III). Three hundred grams (2.5 moles) of thionyl chloride and 258 g (1.4 moles) of II were dissolved in 900 ml of benzene and the solution was heated at reflux for 8 hr. The reaction mixture was cooled and 500 ml of absolute ethanol saturated with anhydrous hydrogen chloride was cautiously added. The reaction mixture was refluxed for 4 hr and then most of the solvent was removed by distillation. Vacuum distillation of the residue at 0.25 mm gave 223 g (70% yield) of a product that was largely[27] the desired product: bp 104–106°, $n^{27}D$ 1.511, d^{27} 1.064, ν_{max} 1735 (s) cm^{-1}. The major product can exist in the *erythro* and *threo* forms and the lactone arising from β attack of malonate on styrene oxide could, on ring opening, yield two racemic modifications. No effort was made to separate the isomers since the γ elimination of all isomers would give the desired product. The gpc results might be misleading since at the column temperature used, elimination of HCl should occur readily.[28]

cis-1-Methyl-2-phenylcyclopropanecarboxylic Acid (VI). A solution of potassium *t*-butoxide in *t*-butyl alcohol was prepared by dissolving 46.8 g (1.2 g-atom) of potassium in 1000 ml of dry *t*-butyl alcohol. To this refluxing solution was added, with stirring, 223 g (0.93 mole) of III over a 4-hr period. The solution was heated at reflux for an additional 16 hr and then 750 ml of *t*-butyl alcohol was removed by distillation while maintaining anhydrous conditions. The residue was cooled, 500 ml of water was added cautiously, and the reaction mixture was extracted with ether. The ether extracts were shaken with 100-ml portions of 5% $KMnO_4$ solution until the aqueous layer retained a purple color, washed with a saturated solution of sodium chloride, and dried over anhydrous $MgSO_4$. The ether was removed and the residue was distilled through an efficient column at 0.60 mm to give 155 g (0.67 mole) of the *t*-butyl ester: bp 92°, $n^{25}D$ 1.4990. The ester was heated at 200° until evolution of isobutylene ceased, and the almost clear residue was taken up in 5% sodium hydroxide solution and ex-

Table IV. Summary of Chemical Shifts[a] of Characteristic Groups on Cyclopropane Compounds Synthesized in This Investigation

Compound	CH_3	CO_2H	C_6H_5	$C(CH_3)_2$	$\overset{O}{\overset{\|}{C}}CH_3$
	75.4	764.0	...	...	...
	58.5	767.0	431.0	...	...
	84.4	707.0	425.6	...	...
	69.0	665.0	435.0	...	...
	62.7	...	...	70.0	...
	43.2	...	426.0	77.0	...
	71.8	...	432.0	65.9	...
	49.0	...	430.0	...	115.0
	70.0	...	432.0	...	116.0
	71.0	...	441.0	...	...

[a] Nmr spectra were obtained from a Varian HR-60 spectrometer using TMS as an internal standard and the side-band technique to calibrate the spectra. Carbon tetrachloride was the sample solvent. [b] The properties of the acid were in agreement with those reported by S. Siegel and C. G. Bergstron, *J. Am. Chem. Soc.*, **72**, 3815 (1950). [c] K. L. Eilers, Ph.D. Dissertation, Iowa State University of Science and Technology, 1963. [d] The properties of the acid were in agreement with those reported by H. M. Walborsky and F. M. Hornyak, *J. Am. Chem. Soc.*, **77**, 6026 (1955). [e] Prepared by the reaction between methyllithium and 1-methylcyclopropanecarboxylic acid: C. H. DePuy and D. E. Barth, unpublished results. [f] Prepared by the reaction between methyllithium and methyl (1-methyl-*cis*-2-phenylcyclopropyl) ketone: C. H. DePuy and F. W. Breitbeil, unpublished results.

(24) C. A. Coulson and W. Moffitt, *Phil. Mag.*, **40**, 1 (1949); A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

(25) G. V. Fyl and E. E. van Tamelen, *J. Am. Chem. Soc.*, **72**, 1357 (1950).

(26) Gas phase chromatography (Carbowax 20 M 1:5 on 60–80 Chromosorb W) showed that the product was a mixture of at least three isomers, which arise from α and β attack of diethyl malonate on styrene oxide plus the possibility of *cis–trans* isomerism in the product lactones.[9]

(27) Gas phase chromatography (same conditions as ref 26) of the product showed three peaks of comparable retention time presumably arising from the four possible racemic modifications.

(28) J. Cason, C. E. Adams, L. L. Bennett, Jr., and U. D. Register, *J. Am. Chem. Soc.*, **66**, 1764 (1944).

Table V. Resolution Results

	Weight, g		[α],[a] deg		
	Brucine salts	Cyclopropane acid	Brucine salts	Cyclopropane acid	Purity,[b] %
(−)-Enantiomer	70.9	21.5	−87.9 ± 0.2	−114.6 ± 0.4	74
(+)-Enantiomer	73.7	20.6	+22.0 ± 0.3	+152.7 ± 0.4	98
Supernatant	40.4	11.3	...	−57.7 ± 0.4	37

[a] Determined as 2% solution in absolute ethanol. [b] These values are based on 100% optically pure acid obtained by a small-scale triangular crystallization of the brucine salt. Constant specific rotations of the recrystallized salt in acetone and finally in absolute ethanol were the criterion of optical purity. The maximum specific rotation of the salt in acetone is $[\alpha]^{25}D - 91.2 \pm 0.4°$; in absolute ethanol, $[\alpha]^{25}D -91.8 \pm 0.4°$. Maximum specific rotation of the free acid in absolute ethanol is $[\alpha]^{25}D -155.1 \pm 0.4°$.

tracted with ether. The aqueous layer was acidified and extracted with ether, and the ether extracts were washed with saturated sodium chloride solution and dried over anhydrous $MgSO_4$. After removal of the ether, the viscous semisolid crystallized to give a 70% yield of acid, which after recrystallization from hexane or water gave fine white needles: mp 80.5–81.0°, $\nu_{max}^{CHCl_3}$ 1687 (s) cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.84. Found: C, 75.03; H, 6.72.

If the ring closure reaction is worked up as soon as all the chloro ester is added, the ethyl rather than the *t*-butyl ester is obtained. Thus in one run the product was carefully fractionated at 0.75 mm on a 3-ft spinning-band column. The first two fractions were predominantly ethyl *trans*-1-methyl-2-phenylcyclopropanecarboxylate (bp 89°, $n^{25}D$ 1.5062) followed successively by ethyl *cis*-1-methyl-2-phenylcyclopropanecarboxylate (IV) (bp 90°, $n^{25}D$ 1.5107), starting material, and lactone precursor. The *trans* ethyl ester was hydrolyzed with base in ethanol–water to give upon neutralization the free acid, which upon recrystallization from hexane melted at 103.5–104.0°, $\nu_{max}^{CCl_4}$ 1690 (s) cm^{-1}. The *cis* ethyl ester was hydrolyzed similarly and afforded the *cis* acid, mp 80.5–81.0°.

Resolution of VI. Best results were obtained when the reagents were of high quality. The acid was recrystallized to a sharp melting point from hexane (80–81°) and the brucine resolving agent was recrystallized from 1:1 ethanol–water and dried in a vacuum oven at 100° for 24 hr before use.

Powdered, recrystallized, dry brucine (119.7 g, 0.304 mole) was dissolved in 2 l. of reagent acetone in a 4-l. beaker. The acid (53.5 g, 0.304 mole) was dissolved in 250 ml of reagent grade acetone, heated to reflux, and added to the refluxing brucine solution. The beaker was placed on a cork ring and set aside without a cover. After 5 days, small cubic crystals began forming (volume was down to 1 l.). The beaker was covered and the crystals were permitted to grow for another week. The supernatant was transferred to a 1-l. beaker along with a small amount of acetone used to wash the crystals, and this was set aside to crystallize without a cover. The crystals were treated with just enough refluxing acetone to put them into solution in an open 1-l. beaker. Crystal growth began after cooling to ambient and was allowed to continue until half the original volume remained. The supernatant was decanted along with two acetone washes and the crystals were dried to give 70.9 g of brucine acid salt. The supernatant from the first batch of crystals crystallized into a mass of well-defined, cubic crystals after one-third of the solvent evaporated. Recrystallization from acetone with washing and drying gave 73.7 g of brucine acid salt. The supernatant from this recrystallization was combined with the supernatant from the recrystallization of the first batch of crystals and the solvent was evaporated giving what we term "supernatant" brucine acid salt. The three batches of brucine acid salts were each treated separately with 200 ml of 1 *M* HCl solution and 200 ml of hexane and stirred with warming to hasten the neutralization. The two phases were separated and the hexane layer was washed several times with small amounts of water, dried over anhydrous $MgSO_4$, and stripped of solvent to give resolved and "supernatant" acids. Weights, specific rotations, and optical purity are given in Table V.

(+)-*trans*-Acetyl-1-methyl-2-phenylcyclopropane [(+)-X]. Four hundred milliliters of a 1.12 *M* solution of methyllithium in ether was added over a period of 30 min to a magnetically stirred solution of 39.5 g (0.224 mole) of 56% optically pure (+)-VI in 100 ml of anhydrous ether. After addition of the first 200 ml a white precipitate formed which on further addition became difficult to stir. The reaction mixture was stirred at room temperature for 15 hr and then 500 ml of a saturated solution of NH_4Cl was added, very slowly at first. The two-phase system was stirred until the two layers became clear; they were separated and the aqueous layer was extracted twice with ether. The combined extracts were washed with a saturated solution of NaCl and dried with anhydrous $MgSO_4$. The ether was removed and the residue was distilled through a small packed column at 0.14 mm to yield 35.0 g of ketone (90% yield): bp 70°, $n^{25}D$ 1.5298, $[\alpha]^{25}D$ +173.3 ± 0.6° (2% absolute ethanol), ν_{max} 1692 (s) cm^{-1}; 2,4-dinitrophenylhydrazone derivative mp 165.0–165.5°.

Anal. (derivative). Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.92; H, 5.07; N, 15.91.

***cis*-1-Methyl-2-phenylcyclopropyl Acetate (XI).** Cold trifluoroperacetic acid, prepared by dropwise addition of 22 ml of 90% hydrogen peroxide to 136.2 g (0.648 mole) of trifluoroacetic anhydride in 250 ml of dry dichloromethane at 0–10°, was added slowly to 37.5 g (0.215 mole) of *trans*-1-acetyl-1-methyl-2-phenylcyclopropane (X) in a stirred slurry of 1 lb of anhydrous granular Na_2HPO_4 in 600 ml of dry dichloromethane. The reaction temperature was maintained below 10°. After addition of the trifluoroperacetic acid the reaction mixture was allowed to warm to room temperature over 6 hr and then filtered. The Na_2HPO_4 was washed twice with dry solvent and the filtrate was washed with a saturated solution of $NaHCO_3$, and a saturated solution of NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was distilled at 0.30 mm to give 31.6 g (77% yield) of product: bp 68°, $n^{26}D$ 1.4991, ν_{max} 1746 (s) cm^{-1}.

This reaction, when carried out on a smaller scale using (+)-X, $[\alpha]^{25}D$ 173.3° (2% absolute ethanol), yielded the desired product, $[\alpha]^{25}D$ +27.2° (2% absolute ethanol).

(−)-*cis*-1-Methyl-2-phenylcyclopropanol [(−)-XII]. Ten grams (0.0526 mole) of (−)-XI, $[\alpha]^{25}D$ −36.7° (1% absolute ethanol), in 50 ml of anhydrous ether was stirred and treated with 170 ml of 0.631 *M* methyllithium in ether over a period of 30 min. After stirring for an additional 30 min, the solution was transferred to a dropping funnel and added rapidly with stirring to a suspension of a large excess of boric acid in 200 ml of water. After addition was completed, just enough water was added to dissolve excess boric acid and the organic layer was separated. The aqueous layer was extracted twice with ether and the combined ether extracts were washed twice with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the ether was stripped off *without* heating. The viscous residue crystallized. The white, crystalline mass was triturated with 15 ml of hexane while cooling the flask in an ice bath, and was filtered, washed with a small amount of cold hexane, and sucked dry to give 5.52 g of product (70% yield). Recrystallization from hexane gave a product without carbonyl impurities, $[\alpha]^{25}D$ −41.9 ± 0.4° (2% absolute ethanol). In another synthesis, racemic XII was prepared: mp 80–81°, ν_{max} 3700 (s), 3450 (s), and 1613 (s) cm^{-1}. A *p*-nitrobenzoate derivative was prepared and analyzed.

Anal. (derivative). Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.09. Found: C, 68.22 (68.33); H, 5.01 (5.08).

Acid- and Base-Catalyzed Ring Opening of Optically Active 1-Methyl-2-phenylcyclopropanol [(−)-XII]. In Acid. In a typical experiment, 2.20 g of optically active XII, $[\alpha]^{25}D$ −41.9° (2% in absolute ethanol), was dissolved in 75 ml of freshly distilled dioxane,[29] and 75 ml of 2 *M* DCl in D_2O[30] was added. The flask was tightly stoppered under an atmosphere of nitrogen and heated at 90° for 67 hr. After cooling and neutralization with concentrated NaOH solution, the contents were extracted six times with

(29) Dioxane was purified according to the procedure of L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 284.

(30) H. C. Brown and C. Groot, *J. Am. Chem. Soc.*, **64**, 2223 (1942).

ether, the extract was dried over anhydrous $MgSO_4$, and the ether and dioxane were distilled through a small packed column. The pot residue, containing only 3- and 4-phenyl-2-butanone, was refluxed with 15 ml of 1.5 *M* NaOD and 5 ml of dioxane for 19 hr, neutralized with 6 *M* HCl solution, and worked up in the manner just described. This time the pot residue was fractionated on a prep scale with a Perkin-Elmer (Model 154C) vapor fractometer using Carbowax 20M 1:5 on 60–80 Chromosorb W (regular). The fraction containing 4-phenyl-2-butanone was examined neat for optical activity using a 10-cm microcell with a precision Rudolph polarimeter. The product ketones were identified by their infrared and nmr spectra and from their 2,4-dinitrophenylhydrazone derivatives which were identical with those reported in the literature.

In Base. The following procedure refers to that of run C in Table III where it is believed we achieved ring opening while best avoiding local high concentrations of protons. To a rapidly stirred solution of 30 ml of 0.2 *M* NaOD in deuterium oxide and 30 ml of freshly distilled dioxane was added 0.90 g of optically active XII, $[\alpha]^{25}D$ −41.6° (2% absolute ethanol), in 51 increments. The flask was securely stoppered over an atmosphere of nitrogen and heated at 90° for 40 hr. After cooling, the contents of the flask were neutralized with concentrated HCl solution, extracted six times with ether, and dried over anhydrous $MgSO_4$. The ether and dioxane were distilled through a small packed column and the residue was purified by prep-scale gas chromatography. The sole product, 4-phenyl-2-butanone, was examined neat for optical activity. See Table III for results. Run B was identical with run C, except that the deuterated base in deuterium oxide was *added to* a solution of the optically active alcohol in dioxane. In run A, the alcohol was added in one portion to the base, deuterium oxide, and the dioxane.

Determination of the Absolute Configuration of (+)-4-Deuterio-4-phenyl-2-butanone (XIII). Preparation of Ethyl D-(−)-Mandelate. In a procedure similar to that described by Eliel and co-workers,[31] 100 g (0.658 mole) of D-(−)-mandelic acid, $[\alpha]^{23}D$ −149.5° (2% H_2O), in 300 ml of absolute ethanol was treated with 100 ml of absolute ethanol containing 8 g of anhydrous HCl. This solution was refluxed for 6 hr, poured into 1 l. of ice water, and neutralized with saturated $NaHCO_3$ solution. The mixture was extracted with ether, and the ether extract was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. The residue remaining after stripping off ether was distilled at 0.28 mm to give 115.5 g of product (94% yield): bp 73°, mp 30.5–31.5°, $n^{23}D$ 1.5116, $[\alpha]^{26}D$ −90.5° (2% acetone).

Ethyl L-(+)-2-Chloro-2-phenylacetate [L-(+)-XVI]. In a procedure similar to that described by Kenyon and co-workers,[20] 77 g (0.660 mole) of thionyl chloride was added with stirring over 6 hr to a solution of 500 ml of anhydrous ether, 52 g (0.660 mole) of pyridine, and 54 g (0.33 mole) of ethyl D-(−)-mandelate kept at 0°. After addition, the reaction mixture was stirred for an additional 6 hr at 0° and then at room temperature for 24 hr. The solution was added to 1 l. of ice water and extracted with ether, and the extract was washed with 10% H_2SO_4 and saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The residue remaining after removal of the ether was distilled at 0.35 mm to give 52 g of product (78% yield): bp 75°, $n^{23}D$ 1.5134, $[\alpha]^{26}D$ +87.3° (2% absolute ethanol).

L-(+)-2-Chloro-2-phenylethanol [L-(+)-XVII]. This synthesis was an adaptation of that described by Eliel and co-workers.[21] About 1 l. of dry ether and 129.6 g (0.653 mole) of L-(+)-XVI, $[\alpha]^{26}D$ +87.3° (2% absolute ethanol), were charged to a 2-l. one-neck, round-bottom flask equipped with a pressure-compensated dropping funnel, a Soxhlet extractor, and a condenser. The Soxhlet extractor was charged with a porous thimble containing 13.65 g (0.327 mole) of lithium aluminum hydride. Ether was refluxed through the apparatus for 24 hr, thereby ensuring a slow constant addition of lithium aluminum hydride. The salts formed were then decomposed by addition of 500 ml of water. The reaction mixture was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. After removal of the ether, the residue was vacuum distilled at 0.40 mm to give 66.7 g (68% yield) of product: bp 83°, $n^{23.5}D$ 1.5484, $[\alpha]^{28}D$ +87.0° (2% absolute ethanol).

D-(+)-2-Deuterio-2-phenylethanol [D-(+)-XVIII]. In a manner similar to that described by Eliel and Prosser,[22] 1.1 g (0.055 mole) of deuterium oxide was added to a suspension of 2.70 g (0.064 mole) of lithium aluminum deuteride in 75 ml of dry ether, and this was allowed to stir for 15 min. To this mixture was added 8.74 g (0.055 mole) of L-(+)-XVII, $[\alpha]^{28}D$ +87.0° (2% absolute ethanol), in 50 ml of dry ether. The reaction mixture was refluxed for 24 hr and then decomposed with 100 ml of 10% HCl solution. The aqueous layer was extracted with ether and the combined ether layers were dried over anhydrous $MgSO_4$. The ether was removed and the residue was distilled at 0.05 mm to give 5.9 g of product (90% yield): bp 40°, $[\alpha]^{27.8}D$ +0.664° (10-cm cell). Two prep-scale gas phase chromatographic separations were necessary to obtain a product free of impurities. The pure sample had a specific rotation of $[\alpha]^{25.6}D$ +1.737° and mass spectral analysis showed that the product was 100% monodeuterated on C-2.[32]

D-(−)-2-Phenyl-2-deuterioethyl Tosylate [D-(−)-XIX]. This synthesis was patterned after that of Tipson.[33] To 4.0 g (0.033 mole) of D-(+)-XVII in 40 ml of pyridine cooled to −5° was added 8.1 g (0.039 mole) of *p*-toluenesulfonyl chloride and the flask was swirled until solution was effected. After 24 hr in a refrigerator, crystals formed and the entire contents of the flask was poured into 400 ml of ice water and extracted with ether. The extract was washed with 10% H_2SO_4 solution and a saturated solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. The ether was stripped off without heating and the resulting crystalline residue was recrystallized from ether–pentane to give 8.40 g of product (92% yield): mp 38.5–39.0°, $[\alpha]^{26}D$ −0.221° (10% ether in a 20-cm cell).

D-(−)-3-Deuterio-3-phenylpropionitrile [D-(−)-XX]. To 40 ml of a 1:1 (v/v) mixture of water and acetonitrile containing 6.77 g (1.04 moles) of potassium cyanide and 0.692 g (0.004 mole) of potassium iodide was added 5.75 g (0.02 mole) of D-(−)-XIX, $[\alpha]^{26}D$ −0.221° (10% ether in a 20-cm cell). The reaction mixture was refluxed for 40 hr and extracted with ether, and the extract was washed successively with saturated solutions of $NaHCO_3$ and NaCl and dried over anhydrous $MgSO_4$. The ether was removed and the residue was distilled at 0.035 mm to give 2.22 g of product (81% yield): bp 54°, $[\alpha]^{29.3}D$ −0.364°.

D-(+)-1,1,1,3,3,4-Hexadeuterio-4-phenyl-2-butanone (XIII). Methylmagnesium iodide was prepared by adding 4.03 g (0.028 mole) of methyl iodide in 20 ml of anhydrous ether to a stirred mixture of 0.74 g (0.30 g-atom) of magnesium in 10 ml of anhydrous ether. The mixture was refluxed for 1 hr and 2.5 g (0.019 mole) of D-(+)-XX, $[\alpha]^{29.3}D$ −0.364°, in 25 ml of anhydrous ether was added slowly. The reaction mixture was refluxed for 14 hr and then poured into ice water and acidified with concentrated HCl solution. This mixture was extracted with ether and the ether extract was dried over anhydrous $MgSO_4$. The residue, after removal of the ether, was added to a solution of NaOD in 35 ml of deuterium oxide and 70 ml of dioxane (1.65 g of sodium), and the mixture was heated at reflux for 7 days and then extracted with ether. After removal of ether, the residue was purified by prep-scale gpc to give a yield of 54% of the desired product: bp 59° (0.33 mm), $n^{23}D$ 1.5079, $[\alpha]^{28}D$ +0.372° (neat).

1-Deuterio-1-phenylethane (XXI). D-(−)-XIX, $[\alpha]^{26}D$ −0.221° (10% ether, 20-cm cell), was treated with lithium aluminum hydride according to the procedure of Eliel and Prosser[22] to give D-(−)-1-deuterio-1-phenylethane, $[\alpha]^{24}D$ −0.236° (neat).

2-Pyranyl Ether of L-(+)-2-Chloro-2-phenylethanol [L-(+)-XXII]. According to the procedure of Woods and Kramer,[34] a mixture of 6.45 g (0.041 mole) of L-(+)-XVII, $[\alpha]^{28}D$ +87.0° (2% absolute ethanol), and 5.20 g of (0.062 mole) dihydropyran was treated with a trace of *p*-toluenesulfonic acid and swirled occasionally for 6 hr. The mixture was diluted with 300 ml of ether, washed with a saturated solution of $NaHCO_3$, and dried over anhydrous $MgSO_4$. After removal of the ether, the residue was retreated with dihydropyran and *p*-toluenesulfonic acid after an infrared spectrum showed that 20% of the residue was unreacted alcohol. Work-up in the usual manner and distillation at 0.28 mm gave 8.99 g of product (91% yield): bp 110°, $n^{21.5}D$ 1.5232, $[\alpha]^{21.5}D$ +61.3° (2% acetone).

D-(−)-α-Methyl-β-phenyl-γ-butyrolactone. A solution of sodium diethylmalonate was prepared by adding 5.18 g (0.032 mole) of diethyl malonate to a solution of 2.04 g (0.088 g-atom) of

(31) E. L. Eliel, M. T. Fisk, and T. Prosser, *Org. Syn.*, **36**, 3 (1956).

(32) The authors are indebted to Dr. Peter Butler of Esso Research and Engineering Co. for the mass spectral analysis.

(33) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(34) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, **69**, 2246 (1947).

sodium in 120 ml of absolute ethanol. To this solution was added 7.0 g (0.029 mole) of the 2-pyranyl ether derivative of L-(+)-XVII, $[\alpha]^{21.5}D$ 61.3° (2% acetone), and the mixture was refluxed for 24 hr. After cooling, 6.27 g (0.044 mole) of methyl iodide was added and the mixture was refluxed for 30 hr. The ethanol was distilled and 100 ml of 10% H_2SO_4 solution was added. The mixture was extracted with ether and dried over anhydrous $MgSO_4$. The residue, after removal of the ether, was added to 100 ml of 10% NaOH solution; this was refluxed for 12 hr and cooled, and 100 ml of concentrated HCl solution was added. The mixture was extracted with ether and dried over anhydrous $MgSO_4$, and after removal of the ether, the residue was distilled at 0.33 mm to give 2.68 g of product (52% yield): bp 106°, $[\alpha]^{28}D$ −5.55° (neat).

Methyl D-(−)-2-Methyl-3-phenyl-4-hydroxybutyrate. To 50 ml of 10% NaOH solution was added 5.0 g (0.029 mole) of D-(−)-α-methyl-β-phenyl-γ-butyrolactone, $[\alpha]^{28}D$ −5.55° (neat), and the mixture was heated to reflux for 4 hr. The solution was carefully neutralized with 6 *N* HCl solution and *immediately* extracted with ether. The ether solution was added directly to an excess of diazomethane in ether. After 1 hr, 2 ml of formic acid was added and the solution was washed once with saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. The ether was removed and the residue was used directly in the following preparation.

Methyl D-(−)-2-Methyl-3-phenyl-4-tosylbutyrate [D-(−)-XXIV]. The procedure used was the same as that previously described for the preparation of XIX. A batch of crystals formed while concentrating the ether solution of the desired tosylate. These crystals were shown by nmr and carbon, hydrogen, and sulfur analyses to be methyl D-(−)-3-phenyl-4-tosylbutyrate resulting from incomplete methylation in the step involving the preparation of D-(−)-II. After recrystallization, the melting point was 91–92° and $[\alpha]^{28}D$ −1.31° (2% chloroform).

Anal. (derivative). Calcd for $C_{18}H_{20}O_5S$: C, 62.06; H, 5.79; S, 9.19. Found: C, 61.66; H, 6.02; S, 9.22.

Further concentration of the ether solution gave the desired product, D-(−)-XXIV, mp 71–73°, $[\alpha]^{28}D$ −1.96° (2% ether).

Anal. (derivative). Calcd for $C_{19}H_{22}O_5S$: C, 62.97; H, 6.12; S, 8.83. Found: C, 63.16; H, 6.19; S, 8.86.

D-(−)-1-Methyl-2-phenylcyclopropanecarboxylic Acid [D-(−)VI]. Two grams of potassium was dissolved in 50 ml of dry *t*-butyl alcohol and to this refluxing solution was added dropwise 0.73 g (0.002 mole) of D-(−)-XXIV dissolved in 50 ml of dry *t*-butyl alcohol. After complete addition the reaction mixture was refluxed for 20 hr, cooled, and acidified with 10% HCl solution. The reaction mixture was diluted with 100 ml of water and extracted with ether. The extract was dried over anhydrous $MgSO_4$ and after removal of the ether, 0.22 g of solid product was obtained (yield 68%), $[\alpha]^{26}D$ −12.9° (2% ether).

D-(−)-2-Phenylcyclopropanecarboxylic Acid [D-(−)-XXV]. This synthesis was carried out in the manner described in the previous synthesis except that methyl D-(−)-3-phenyl-4-tosylbutyrate was used as the substrate. The acid obtained was treated directly with diazomethane in ether to give the methyl ester, $[\alpha]^{26}D$ −28.6° (2% absolute ethanol).

Homoenolization and Related Phenomena. VI.[1] Stereospecificity in Alkaline and Acid Media[2,3]

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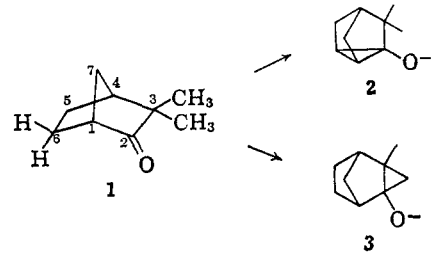
Abstract: 1-Acetoxynortricyclene has been used as a substrate to generate the related homoenolate ion and homoenol under mild conditions. In deuterated alkaline or acidic media these species homoketonized to 6-deuterionorbornan-2-one, which incorporated additional deuterium by enolization at C-3. The label was washed out from C-3 and the configuration of the C-6 deuterium was determined by Wolff–Kishner reduction of the ketone followed by infrared spectroscopic analysis of the derived deuterionorbornane. In various alkaline media the homoketonization produced an *exo* C–D bond with high stereospecificity (94.5–98%), whereas in acid medium *endo* attack was favored to at least 90–95%. The results indicate that homoenolization at C-6 in a bicyclo[2.2.1]heptan-2-one system would involve preferential abstraction of the *exo* hydrogen in base and the *endo* hydrogen in acid.

Keto–enol tautomerism in carbonyl compounds is associated with the known ability of a carbonyl group to activate α hydrogens. Recent work with camphenilone (**1**) has revealed that some activation is also extended to more distant hydrogens and that under vigorous enough conditions (*e.g.*, potassium *t*-butoxide in *t*-butyl alcohol at 185°) such hydrogens can exchange with protons in the medium by way of homoconjugated carbanions, termed homoenolate anions.[4] As many as nine deuteriums have been introduced into camphenilone and by a combination of techniques including the use of optically active ketone, nuclear magnetic resonance and infrared spectroscopy, and specifically labeled substrates it was shown that exchange occurred at C-6, at C-1, and on the methyl carbons, thereby implicating the homoenolate ions **2** and **3**. No exchange at C-7, C-5, or C-4 was detected and so these sites are not homoenolizable, or at least sufficiently less so to have escaped detection by the methods used.



(1) For Part V see A. Nickon, J. L. Lambert, and J. E. Oliver, *J. Am. Chem. Soc.*, **88**, 2787 (1966).

(2) A preliminary account of this work has been published: A. Nickon, J. H. Hammons, J. L. Lambert, and R. O. Williams, *ibid.*, **85**, 3713 (1963).

(3) This work was supported by the Petroleum Research Fund, administered by the American Chemical Society. We are grateful to the donors of this fund. The mass spectrometer was obtained with instrument grants from the Atomic Energy Commission and the National Science Foundation.

(4) (a) A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, **84**, 4604 (1965); (b) A. Nickon and J. L. Lambert, *ibid.*, **88**, 1905 (1966).