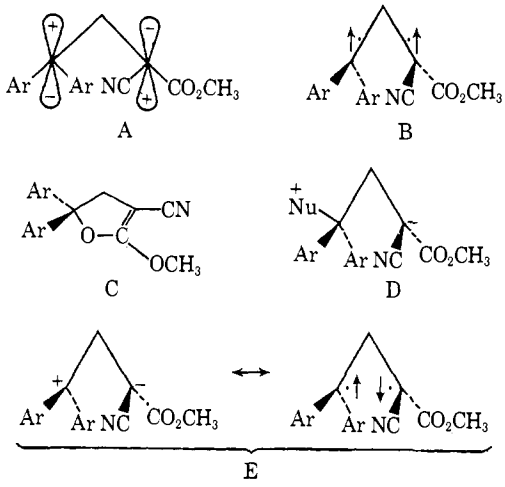
mized in both media much faster than IV–VII were produced, by a factor of at least 10^2 in methanol at 150°, and a factor of at least 23 in dimethylformamide–0.1 *M* lithium bromide at 126°. These factors were measured by product isolation experiments and first-order rate constant estimates.

Preliminary rates of loss of optical activity of (+)-III at 0.05 *M* concentration in various solvents were measured polarimetrically at 125°. About a half-life was followed by ampoule technique (1–3 points per run), and less than 3% (glc on 20% SE30 on Firebrick) of any compound other than III could be detected at the end of the run. The first-order rate constant for benzene as solvent was 0.46×10^{-5} sec^{-1}, and the ratios of rate constants in other solvents to that in benzene were: CH_3OH, 18; $(CH_3)_2SO$, 9.4; $(CH_3)_2NCHO$, 3.7; CH_3CN, 2.3; $(CH_3)_3COH$, 2.0; C_6H_6, 1.0. Careful kinetic studies (Table I) indicated racemization followed strictly first-order kinetics through at least 1.5 half-lives. The solutions used for the last two points in every run contained less than 1% of any other product (glc). In runs 1, 2, 5, and 6, the last two points yielded 94–98% of sublimed III, pure to glc.

The rate factor increase of 15 (runs 4 and 7) was demonstrated due to bromide and not lithium ion with four parallel runs in dimethylformamide at 125° from which one-point rate constants were calculated and compared: run 9, no added salt, relative rate = 1; run 10, 0.1 *M* LiBr, relative rate = 14; run 11, 0.1 *M* $LiClO_4$, relative rate = 1; run 12, 0.1 *M* $(C_2H_5)_4NBr$, relative rate = 13. Four simultaneous one-point rate constant runs were made in dimethylformamide at 125°: run 13, 0.05 *M* LiBr, 1.4×10^{-4} sec^{-1}; run 14, 0.10 *M* LiBr, 2.3×10^{-4} sec^{-1}; run 15, 0.20 *M* LiBr, 3.8×10^{-4} sec^{-1}; run 16, 0.40 *M* LiBr, 7.0×10^{-4} sec^{-1}. A plot of these rate constants against bromide ion concentration is linear. Extrapolation of the plot to zero bromide ion concentration provides a rate constant four times that calculated from runs 3 and 4 made without bromide. Thus bromide salts at low concentration produce a sizable "special salt effect"[9] superimposed on which is a second-order process.



General mechanisms for racemization of (+)-III can be envisioned in terms of intermediate structures, A–E. The π-cyclopropane intermediate[10] A is sterically improbable and is inconsistent with medium effects on rate. The triplet diradical intermediate B is inconsistent with the substantial response of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to solvent changes. Thus $\Delta H^{\ddagger}$ is ~5 kcal/mol higher in benzene than in methanol, and $\Delta S^{\ddagger}$ is about −8 in benzene and −14 eu in methanol. Homolytic cleavage reactions show much smaller changes in $\Delta H^{\ddagger}$ with changes in medium, have $\Delta S^{\ddagger}$ values around zero,[3,4,11] and show no special salt effects. *Concerted* formation and decomposition of ketene acetal C is a mechanism also inconsistent with the large $\Delta H^{\ddagger}$ changes with medium and the special salt effect. The solvent-assisted zwitterionic mechanism leading to intermediate D is impossible in benzene, and if it occurred in methanol, racemization in methanol would not be $>10^2$ faster than methanolysis.

A mechanism in which E is formed as a first intermediate is consistent with all the facts. This intermediate is visualized as a resonance hybrid, since the orbitals on the 1,3-carbon atoms are close enough together to provide some overlap. Intermediate E can have high zwitterionic character and substantial response to medium. The special salt effect could reflect capture of E and in effect prevention of its direct collapse to optically active III. Although E might form C or D in a second stage, it seems unlikely that D would give III in methanol or C would give III in any solvent. The second-order bromide ion catalysis of racemization is probably an SN2 reaction in its first stage, followed by rotational equilibration of the carbanion and ring closure by expulsion of bromide by C$^-$.

(8) See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 615, for references.
(9) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2780 (1956).
(10) R. Hoffmann, *ibid.*, **90**, 1475 (1968).
(11) (a) H. M. Frey, *Advan. Phys. Org. Chem.*, **4**, 147 (1966); (b) E. S. Huyser and R. M. Van Scoy, *J. Org. Chem.*, **33**, 3524 (1968).

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Stereochemistry of the Methanolysis of a System with Carbon as Leaving Group[1]

Sir:

We have examined the stereochemical course of the methanolysis with ring opening of the substituted cyclopropane derivative, (+)-methyl 1-(*S*)-cyano-2-(*R*)-phenylcyclopropanecarboxylate [(+)-(*S*),(*R*)-I], and demonstrated that the reaction occurs with 99 ± 2% stereospecificity and inversion at the center (C-2) that underwent nucleophilic substitution. The preparation of all four stereomers of I of maximum rotation was accomplished, and their absolute configurations were assigned. The methanolysis product, methyl 2-cyano-4-methoxy-4-phenylbutanoate (II), was converted to (−)-(*S*)-methyl 4-methoxy-4-phenylbutanoate, whose absolute configuration and maximum rotation were also determined.

Treatment of (*E*)-ethyl 2-cyanocinnamate[2] with di-

(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) J. Zabicky, *J. Chem. Soc.*, 683 (1961). (b) For 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).

methyloxosulfonium methylide[3] in dimethyl sulfoxide gave (55%) ethyl 1-cyano-2-phenylcyclopropanecarboxylate[4,5] (bp 131–132°, 65 μ), hydrolysis of which in potassium hydroxide–ethanol gave (55%) 1-cyano-2-phenylcyclopropanecarboxylic acid[4] (III), mp 137–138° (the *E* isomer,[2b] see below). This acid was resolved by five crystallizations of its brucine salt from methanol and conversion back to (−)-(*E*)-III[4a] (29%): mp 135–138° (from chloroform); $[\alpha]^{25}_{546}$ −239° (*c* 0.5, ethyl acetate). Four recrystallizations of the brucine salt residues from acetone gave a second salt, which was converted to (+)-(*E*)-III[4a] (40%): mp 139–140° (from benzene); $[\alpha]^{25}_{546}$ +235° (*c* 0.805, ethyl acetate). Treatment of (−)-(*E*)-III with diazomethane in ether gave (−)-(*E*)-I,[4a] which after one recrystallization from pentane gave (8%) a maximum rotation: mp 53–54°; $[\alpha]^{25}_{546}$ −251° (*c* 0.62, ethyl acetate). Similar treatment of (+)-(*E*)-III gave (14%) (+)-(*E*)-I;[4a] mp 53–54°; $[\alpha]^{25}_{546}$ +251° (*c* 0.54, ethyl acetate). From racemic (*E*)-III, (*E*)-I[4a] was similarly prepared (97%): bp 115–120° (0.15 mm); nmr (in $CDCl_3$ at 60 MHz with internal TMS) δ 2.09 (2, 2, J = 9 Hz; higher field signal split to another doublet, J = 1.5 Hz), 3.15 (t, 1, J = 9 Hz), 3.82 (s, 3), 7.32 (s, 5); ir (cm^{-1}) 3000 (m), 2250 (m), 1740 (s), 1260–1320 (s).

Photolytic isomerization of (*E*)-I with a Hanovia medium pressure 450-W lamp with a Vycor filter (λ > 210 nm) in acetone gave a 2.2:1 mixture of (*E*)-I:(*Z*)-I, separated by silica gel chromatography with 10–15% ether in pentane to give (20%) (*Z*)-I,[4a] mp 62–63°. The substance was assigned the (*Z*)[2b] structure from its nmr spectrum ($CDCl_3$, at 60 MHz with internal TMS): δ 1.8–2.4 (m, 2), 3.25 (t, 1, J = 9 Hz), 3.49 (s, 3), 7.27 (s, 5). The higher field shift of the methyl of (*Z*)-I (compared to (*E*)-I) with the phenyl and carbomethoxy groups cis to one another has considerable precedent.[6] The assignment of configuration was confirmed by the observed higher thermodynamic stability[7a] of isomer (*E*)-I. Ester (*Z*)-I was hydrolyzed to acid (*Z*)-III[4b] (97%), mp 151° dec, a sample of which was converted back to (*Z*)-I (mp and mmp 61–62°). Three recrystallizations of the quinine salt of (*Z*)-III from methanol and conversion to acid gave (+)-(*Z*)-III (36%), $[\alpha]^{25}_{546}$ +199° (*c* 0.16, ethyl acetate). The quinine salt's mother liquors gave a second salt, which was converted to (−)-(*Z*)-III (64%) ($[\alpha]^{25}_{546}$ −143° (*c* 0.28, ethyl acetate)), which with diazomethane gave (−)-(*Z*)-I. This ester after seven recrystallizations from ethanol provided (7%) material[4a] of maximum rotation: $[\alpha]^{25}_{546}$ −175° (*c* 0.145, ethyl acetate); mp 91–91.5°. Similarly (+)-(*Z*)-III gave (44%) (+)-(*Z*)-I[4a] (one recrystallization from ethanol): $[\alpha]^{25}_{546}$ +175° (*c* 0.15, ethyl acetate), mp 90.5–91.5°.

Treatment of (+)-(*Z*)-I (37% maximum rotation) with potassium hydroxide in ethylene glycol at 70° for 1 hr gave a solution that was heated to 200° (1 hr), diluted with water, and refluxed at 185° (5 hr). The resulting carboxylic acid without purification was treated with diazomethane to give (30%) (+)-methyl *trans*-2-phenylcyclopropanecarboxylate[4a] [(+)-IV] (bp 75–80° (0.12 mm); $[\alpha]^{25}D$ +111° (*c* 0.29, ethyl acetate)), whose configuration has been established as being 2-(*S*),1-(*S*).[8] Thus (+)-(*Z*)-I possesses the 1-(*R*),2-(*R*) configuration. Unless the hydrolysis of (+)-(*Z*)-I was carried out at the low temperature, the cyclopropane ring underwent solvolytic ring opening (see methanolysis results below) to give ethers of ethylene glycol. Once the carboxylate anion formed, the cyclopropane ring stabilized and decarboxylation was favored. It is a good assumption that solvolysis in ethylene glycol should eliminate epimerization at benzyl carbon[7b] just as does methanol (see below). The relative configurations of (+)-(*E*)-I and (−)-(*Z*)-I at the benzyl center (and therefore the absolute configuration of (+)-(*E*)-I) were determined by the conversion of their respective derived acids to 1,1-dicyano-2-phenylcyclopropane (V). Thionyl chloride–dimethylformamide in chloroform[9] converted (+)-(*E*)-III ($[\alpha]^{25}_{546}$ +234° (*c* 0.55, ethyl acetate)) to its acid chloride, treatment of which with aqueous ammonia gave (37%) (+)-(*E*)-1-cyano-2-phenylcyclopropanecarboxamide:[4a] mp 121–123°; $[\alpha]^{25}_{546}$ +235° (*c* 0.63, acetone). Dehydration of this amide with phosphorus pentoxide gave (18%) (+)-1,1-dicyano-2-phenylcyclopropane [(+)-V]:[4a] bp 85–95° (0.1 mm); $[\alpha]^{25}_{546}$ +227° (*c* 0.14, acetone). Similar reactions converted (−)-(*Z*)-III ($[\alpha]^{25}_{546}$ −17.2° (*c* 0.615, ether)) to (−)-(*Z*)-amide[4a] (75%) (mp 115–120°, $[\alpha]^{25}_{546}$ −17.5° (*c* 0.63, ether)), dehydration of which gave (−)-V[4a] (bp 90–100° (0.15 mm), $[\alpha]^{25}_{546}$ −10.1° (*c* 3.4, acetone)). The nmr and ir spectra of the two samples of V were identical with that reported for V.[10] Thus (+)-(*E*)-I and (−)-(*Z*)-I have opposite configurations at the benzyl position, and (+)-(*E*)-I possesses the 1-(*S*),2-(*R*) configuration.

In run 1, methanolysis of (+)-(*E*)-I of maximum rotation at 126° for 5 days gave (88%) II[6] as a mixture of diastereomers: bp 105–110° (50 μ); $[\alpha]^{25}_{546}$ −75.9° (*c* 0.63, ethyl acetate); nmr ($CDCl_3$ at 60 MHz with internal TMS), δ 2.0–2.7 (m, 2), 3.17 and 3.20 (two s, 3), 3.77 and 3.80 (two s, 3), 2.5–4.1 (m, 1), 4.2–4.5 (m, 1), and 7.34 (s, 5); ir (cm^{-1}) 3000 (m), 2250 (w), 1740 (s), 1420 (m), 1200–1310 (s), 1120 (m), and 1060–1110 (s). Methanolysis of racemic (*Z*)-I at 126° was incomplete after 2 hr (run 2) and after 11 hr (run 3). The composition was determined by glc (20% SE 30 on Firebrick). In run 2, 81% of (*Z*)-I and 19% of II, and in run 3, 23% of (*Z*)-I and 77% of II were observed and no (*E*)-I was detected (1% sensitivity). The configurational homogeneity and absolute configuration at the benzyl carbon of II produced in run 1 were established as follows. The ester was hydrolyzed in potassium hydroxide–ethylene glycol at 100° for 2 hr and the solution held at 200° for 20 hr, diluted with water, and refluxed at 180° for 6 hr. The resulting acid was esterified with diazomethane to give (75%) (−)-methyl 4-methoxy-4-phenylbutanoate [(−)-VI]: bp 75–85° (75–80 μ); $[\alpha]^{25}_{546}$ −93.8° (*c* 0.78, ethyl acetate). Optically active (+)-(*R*)-3-me-

(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(4) (a) Purified samples gave elemental analysis within 0.3% of theory. (b) These samples gave parent ions (in their mass spectra) compatible with their structural assignment.

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

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

(7) (a) E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 6328 (1970); (b) E. W. Yankee and D. J. Cram, *ibid.*, **92**, 6331 (1970).

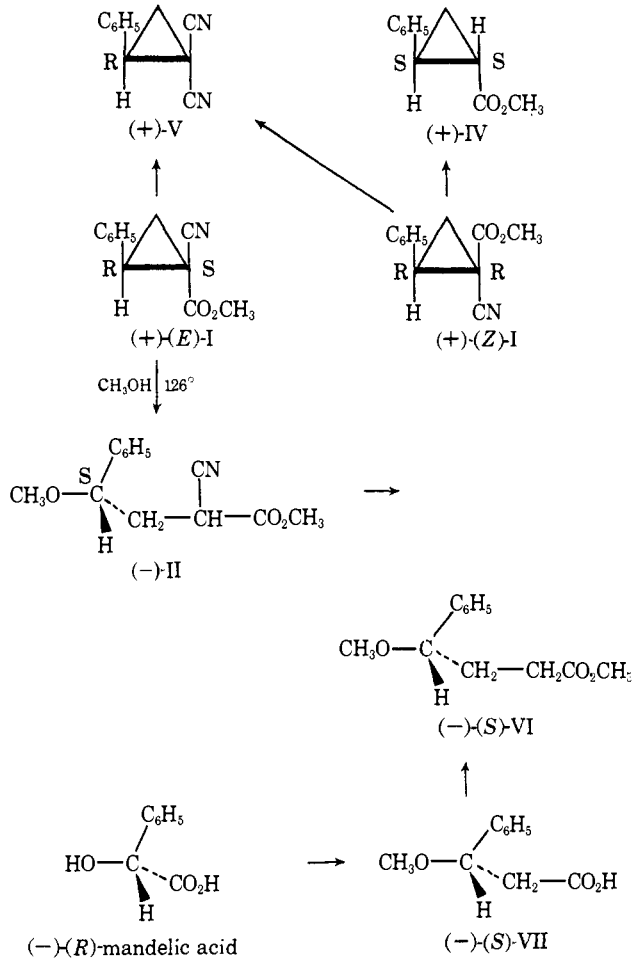
(8) (a) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964); (b) T. Sugita and Y. Inouye, *Bull. Chem. Soc. Jap.*, **39**, 1075 (1966).

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 286.

(10) E. Ciganek, *J. Amer. Chem. Soc.*, **88**, 1979 (1966).

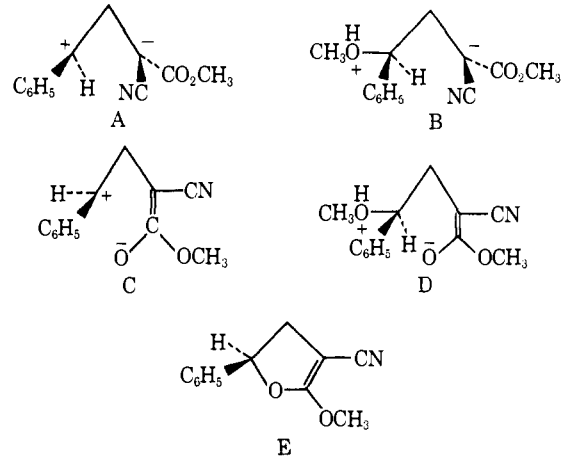
thoxy-3-phenylpropanoic acid, (+)-(*R*)-VII (prepared[11] from (+)-(*S*)-mandelic acid), was brought to optical purity by fractional crystallization of its brucine salt from acetone to give (+)-(*R*)-VII:[4a] mp 65–66°; $[\alpha]^{25}_{546}$ +72.3°; and $[\alpha]^{25}D$ +58.3° (*c* 0.23, ethyl acetate). Arndt–Eistert homologation[12] of 95.2% optically pure (+)-(*R*)-VII gave (22%) (+)-(*R*)-VI[6a] (bp 85–95° (0.12 mm); $[\alpha]^{25}_{546}$ +90.5° (*c* 0.74, ethyl acetate)), whose nmr and ir spectra were identical with (−)-VI prepared above. These data demonstrate that (−)-(*S*)-VI of 99% optical purity was produced from the sample of II, which in turn was the methanolysis product of (+)-(*E*)-I. *Clearly the nucleophilic substitution reaction at the benzyl carbon of (+)-(E)-I (run 1) proceeded with essentially complete inversion of configuration.* In some cases to save space, the structural formulas have configurations opposite to those used.

The rate of methanolysis of (*Z*)-I in runs 2 and 3 exceeded the rates of isomerization of (*Z*)-I to (*E*)-I by a factor of $>10^2$. The factor by which the rate of inversion at benzyl carbon exceeded that of retention in the methanolysis of (+)-(*E*)-I is also $>10^2$. No retention or isomerization components were detectable in this system, unlike (+)-methyl 1-cyano-2,2-diphenylcyclopropanecarboxylate which isomerized $>10^2$ faster



than it methanolyzed.[7b] Another comparison involves methanolysis of optically active α-phenylethyl chloride[13] at 70°, which was reported to have occurred with 32% net inversion. This figure is minimal since racemization of starting material might have been a competing reaction.

Several possible mechanisms explain the high inversion in the methanolysis of (+)-(*E*)-I to give (−)-II, the possible intermediates being A–E. Sequences I → B → II and I → A → B → II are the simplest, but I → A → C → D → II, and I → A → C → E → D → II also are possible. Probably once formed, B and D would undergo proton transfers faster than other covalent bonds are made or broken. Mechanisms



$$I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E \xrightarrow{k_2} C \text{ or } D \rightarrow II$$

definitely are compatible with rate-determining ionization and nonaccumulation of E only if $k_{-1} \gg k_1 > k_2$. The fact that no epimerization accompanied methanolysis of (*Z*)-I (racemization of the benzhydryl analog occurred 10^2 times as fast as methanolysis)[7b] eliminates this possibility. Strong evidence that the rate-determining stage involves ionization is found in the adjacent paper.[7a]

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

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

(13) (a) E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1201 (1937); (b) H. M. R. Hoffman and E. D. Hughes, *ibid.*, 1244 (1964).

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The Question of Zwitterionic *vs.* Singlet Diradical Intermediates in Epimerization Reactions of Substituted Cyclopropanes[1]

Sir:

In the preceding communication,[2a] the absolute configurations of (+)-(*E*)-I and (+)-(*Z*)-I were established. In cleavage of a cyclopropane ring, the answer to the question of whether the bond breaks homolytically to give a singlet diradical or heterolytically to give a zwitterion is elusive, since the sites of charge and spin

(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) E. W. Yankee and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 6328 (1970); (b) E. W. Yankee and D. J. Cram, *ibid.*, **92**, 6329 (1970).