[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY, TALLAHASSEE, FLA.]

# Cyclopropanes. IX. The Relative and Absolute Configurations of 1-Substituted 2,2-Diphenylcyclopropanecarboxylic Acids[1]

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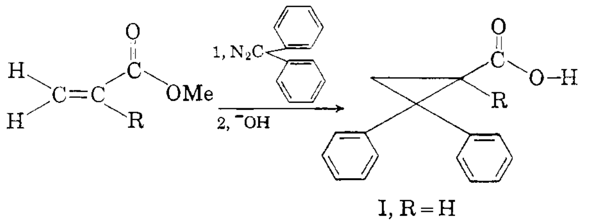
The relative configurations of 2,2-diphenylcyclopropanecarboxylic acid (I), 1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II) and 1-bromo-2,2-diphenylcyclopropanecarboxylic acid (III) have been established by the thermal, X-ray diffraction and infrared examination of the quasi-racemates. These methods demonstrate that (−)-I, (+)-II and (+)-III are related in configuration. The comparison of the infrared spectra of the solid racemates and their enantiomers indicates that the racemates exist as dimers and the enantiomers as polymers in the crystal. The acids I, II and III were converted to their corresponding aldehydes and from the signs of the Cotton effect, obtained from their rotatory dispersion curves, the relationship established above was confirmed. Partial asymmetric syntheses were obtained in the addition of diazodiphenylmethane to (−)-I and (+)-II, respectively. Using the Prelog–Cram model, tentative absolute configurations have been assigned to (−)-I (S), (+)-II (S) and (+)-III (R).

In connection with our studies on the Haller-Bauer cleavage reaction[3] and on the configurational stability of the cyclopropyl carbanion[4] it became necessary to establish the relative configurations of 2,2-diphenylcyclopropanecarboxylic acid (I), 1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II) and 1-bromo-2,2-diphenylcyclopropanecarboxylic acid (III). Since an unambiguous chemical correlation seemed extremely difficult to achieve, purely physical methods were sought. The most promising was the thermal analysis method[5] (the method of quasi-racemates) which is based on the initial observation of Centnerszwer,[6] its significance proposed by Timmermans[7] and its application exploited by Fredga.[8] Quasi-racemate formation can be detected by phase diagrams (m.p. *vs.* % composition),[8] X-ray diffraction[9] and infrared analysis.[10] Each of these techniques has been employed in the present work.

Optical rotatory dispersion has also been used to established the relative configurations.

## Relative Configurations

**Syntheses, Resolution and Properties of I, II and III.**—The addition of diphenyldiazomethane to methyl acrylate,[11] methyl methacrylate[11] and methyl α-bromoacrylate yielded upon saponification the desired acids. The acids were resolved *via* their brucine salts to yield (+)- and (−)-I, m.p. 150–151° (racemic m.p. 170–171°), $[\alpha]^{24}\text{D}$ 230 ± 5° ($CHCl_3$); (+)- and (−)-II, m.p. 190–191° (racemic m.p. 182–183°), $[\alpha]^{24}\text{D}$ 33 ± 1° ($CHCl_3$); (+)- and (−)-III, m.p. 190–109.5° (racemic m.p. 185–186°), $[\alpha]^{24}\text{D}$ 111 ± 2° ($CHCl_3$).



I, R = H
II, R = $CH_3$
III, R = Br

In Fig. 1 are shown the m.p. *vs.* % composition curves of the acids I, II and III which demonstrate that each of these acids forms a racemic compound. The melting point curve for acid I clearly shows that this acid has a great racemic-compound formation tendency. The distance between the eutectics is greater than 80% of the diagram, the racemate-eutectic difference is +28°, and the racemate-enantiomorph difference is +20°. The ratio of the racemate-eutectic difference (28°) to the enantiomorph-eutectic differences (8°) gives a value of 3.5, which according to the Pettersson[5] scale is indicative of a great racemic-compound formation tendency.

In the case of the acid II, the melting point curve indicates a great deal less tendency toward compound formation than that of acid I. The distance between eutectics is somewhat greater than 50% of the diagram, the racemate-eutectic difference is +10°, and the racemate-enantiomorph difference is −7°. The first two criteria indicate a moderate tendency toward compound formation while the latter indicates a low tendency. On the Pettersson scale the value is 0.6 which indicates a weak to moderate tendency.

The melting point curve of acid III is comparable to that of II. The distance between eutectics is *ca.* 50% of the diagram, the racemate-eutectic difference is +8°, and the racemate-enantiomorph difference is −1.5°. The Pettersson scale value is 0.8 indicating a moderate tendency toward racemic compound formation. On the basis of this analysis the tendency toward compound formation is I >> III > II.

**Thermal Analyses.**—Each of these acids (I, II, III) forms a racemic compound and thereby meets one of the criteria for quasi-racemate formation. Another important consideration is whether or not the acids are close enough in their steric relationships. The acids studied differ by having in the 1-position a hydrogen (I), methyl (II) and bromine

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[1] This study was supported by the Office of Ordnance Research, United States Army and by the National Science Foundation.

[2] Ethyl Corporation Fellow, 1958–1959.

[3] H. M. Walborsky and F. J. Impastato, *Chemistry & Industry*, 1690 (1958).

[4] H. M. Walborsky and F. J. Impastato, *J. Am. Chem. Soc.*, **81**, 5835 (1959).

[5] For an excellent discussion of the use and limitations of this method see K. Pettersson, *Arkiv. Kemi*, **10**, 297 (1956).

[6] M. Centnerszwer, *Z. physik. Chem.*, **29**, 715 (1899).

[7] J. Timmermans, *Rec. trav. chim.*, **48**, 890 (1929).

[8] A. Fredga, "Thé Svedberg Anniversary Volume," Almqvist and Wiksells, Uppsala, 1945.

[9] K. Pettersson, *Arkiv. Kemi*, **7**, 347 (1954).

[10] A. Rosenberg and L. Schotte, *ibid.*, **8**, 143 (1955).

[11] H. M. Walborsky and F. M. Hornyak, *J. Am. Chem. Soc.*, **77**, 6126 (1955).

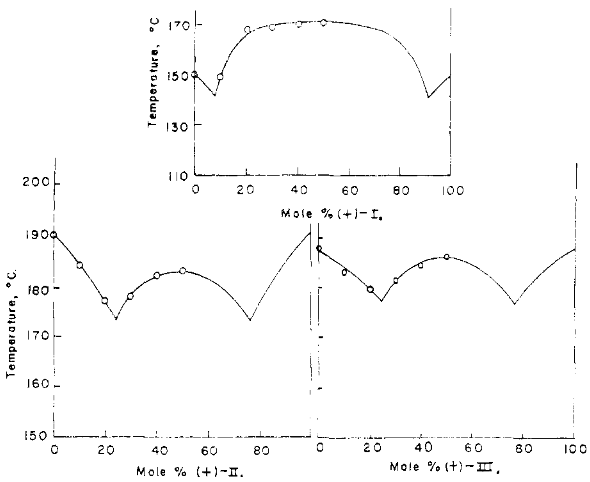

Fig. 1.—Phase diagrams of (+)- and (−)-2,2-diphenylcyclopropanecarboxylic acid (I), (+)- and (−)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II), and (+)- and (−)-1-bromo-2,2-diphenylcyclopropanecarboxylic acid (III).

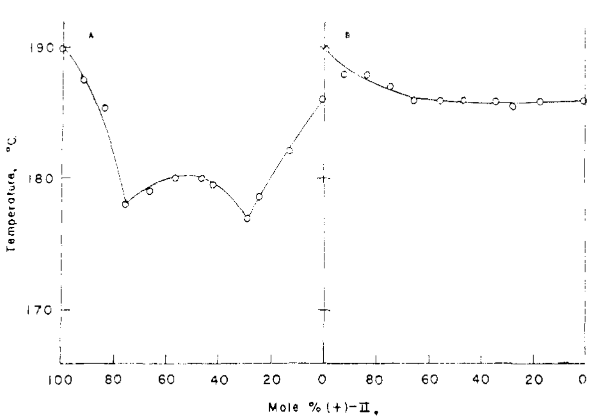

Fig. 2.—Phase diagrams of (+)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II) *vs.* (−)- and (+)-1-bromo-2,2-diphenylcyclopropanecarboxylic acid (III) (curves A (left) and B (right), respectively).

(III). The van der Waals radii[12] for these substituents are 1.2, 2.0 and 1.95 Å., respectively. The steric relationship of acids II and III is quite favorable since methyl and bromine are comparable in size; however, such is not the case between I and II (hydrogen *vs.* methyl).

The diagrams in Fig. 2 show that (+)-II and (−)-III form a quasi-racemic compound whereas (+)-II and (+)-III yield a solid solution. These results clearly demonstrate that *(+)-II and (+)-III are configurationally related.*

The steric relationship between acids I and II is not so favorable since the hydrogen and methyl group differ in their van der Waals radii by 0.8 Å. As can be seen in Fig. 3, the melting point curves are inconclusive since neither shows compound formation. That the thermal analysis method failed in this instance is not surprising in view of the unfavorable steric relationship.[8]

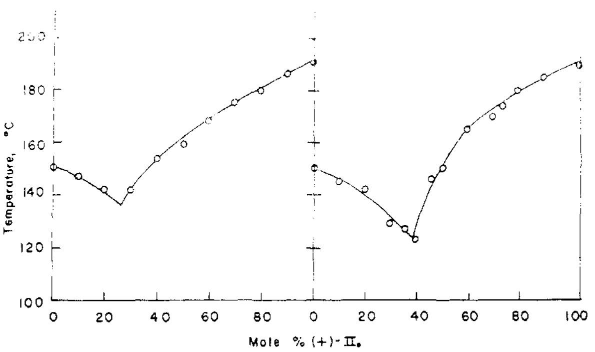

Fig. 3.—Phase diagrams of (+)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II) *vs.* (−)- and (+)-2,2-diphenylcyclopropanecarboxylic acid (I) (curves A (left) and B (right), respectively).

**X-Ray Diffraction.**—Since the thermal analysis was inconclusive in establishing the relative configurations of acids I and II, another method of analysis was sought. X-Ray powder diagrams have previously been used in establishing compound formation in quasi-racemates.[9,13] In the present study, X-ray diffraction patterns[14] show that *(−)-I is related to (+)-II and (+)-II to (+)-III.* The interpretation[14] of the X-ray diffraction patterns is as follows.

The (−)-I crystals and the (±)-I crystals give different patterns; therefore the racemate forms a single (±)-crystal, rather than separate (+)-crystals and (−)-crystals.[15] This is consistent with the large compound formation tendency of I.

The (+)-II crystals and the (±)-II crystals give different patterns; therefore the racemate forms a single (±)-crystal, rather than separate (+)-crystals and (−)-crystals. This is of interest in view of the low compound formation tendency of II.

The (+)-III crystal and the (±)-III crystals give different patterns but with some similarities. Therefore the racemate consists mainly of (±)-crystals with some (+)- and (−)-crystals as impurities. This is consistent with the moderate tendency of III to form a racemic compound. (However, see above.)

The cocrystallized ((−)-I (+)-II) give a pattern with the same line intensity sequence as the (+)-II crystals. The measured interplanar spacings, however, are significantly smaller for corresponding planes, which can only be interpreted as a solid solution of (−)-I in the (+)-II crystal structure. The comparative measurements are listed in Table II (see Experimental) and clearly show the shrinkage in the racemate unit cell dimensions.

The quasi-racemate crystals composed of (+)-I and (+)-II give a pattern different from all the others. Due to the non-isomorphism of the components of this mixture, the best explanation here is compound formation.

The cocrystallized ((+)-II (+)-III) gives a diffraction pattern similar to that of (+)-II. This

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(12) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 30.

(13) S. Gronowitz, *Arkiv. Kemi*, **11**, 361 (1957).

(14) We wish to express our appreciation to Dr. R. F. Pfeiffer for recording the X-ray powder photograms, and for his expert advice with regard to their interpretation. The photographs are on file in Dr. Pfeiffer's laboratory at Eli Lilly and Co., Indianapolis, Ind.

(15) This assumes uniform solvation and crystallizing conditions throughout.

Table I

The Infrared Absorption Bands (Cm.$^{-1}$) Associated with Carboxyl Group[a]

| Compound | Bonded OH | COOH dimer submaxima | Carbonyl stretching | Broad in-plane C—O—H | Broad out-of-plane carboxyl H |
|---|---|---|---|---|---|
| (−)-I | 3200 | ...., ...., .... | 1733, 1696 | 1163 | ..., 820 |
| (±)-I | .... | 2685, 2615, 2550 | ...., 1696 | .... | 939, ... |
| (+)-II | 3230 | ...., ...., .... | 1725, 1692 | 1145 | ..., 830 |
| (±)-II | .... | 2800–2550 | ...., 1690 | .... | 935, ... |
| (+)-III | 3490, 3210 | ...., ...., .... | 1728, 1711 | 1243, 1219 | ..., 875 |
| (±)-III | .... | 2750–2500 | 1688 | | 932, ... |
| (+)-I (+)-II | .... | 2800–2550 | 1698 | .... | 938, ... |
| (−)-I (+)-II | 3230 | ...., ...., .... | 1726, 1692 | 1150 | ..., 830 |
| (+)-II (−)-III | .... | 2800–2500 | 1694, 1680 | | 950, ... |
| (+)-II (+)-III | 3280 | ...., ...., .... | 1727, 1694 | 1200, 1146 | ..., 863, 830 |

[a] Values above 2500 cm.$^{-1}$ are correct to ±5 cm.$^{-1}$ and those below 1800 cm.$^{-1}$ are correct to ±2 cm.$^{-1}$.

confirms the identity of configuration of (+)-II and (+)-III and also indicates the greater stability of the enantiomer of II over the enantiomer of III.

The quasi-racemate (+)-II (−)-III has a diffraction pattern similar to (±)-III. This shows compound formation and therefore (+)-II and (−)-III have opposite configuration. It also indicates the greater stability of (±)-III over (±)-II. This latter point is further confirmed by the observation that the (±)-III shows little (+)-III or (−)-III present in the cocrystallized sample as opposed to that found in (±)-II[16] (*vide supra*).

In summary, the X-ray analyses demonstrate that *(−)-I, (+)-II and (+)-III are related in configuration.*

**Infrared Analyses.**—In the gaseous state or in solution the infrared spectra of enantiomers and any mixture thereof are identical. In the solid state significant differences between racemate and enantiomer should be observed if the racemate forms a racemic compound rather than a racemic mixture or solid solution. In 1937, Wright[17] examined the infrared spectra of a series of amino acids in mulls and found that the spectra of the enantiomers and the racemates of certain of the amino acids differed markedly. He ascribed these differences as being due to compound formation in the racemate. Lecomte[18] found significant differences in the Raman as well as infrared spectra between salts of active and racemic tartaric acid. More recently, Eliel and Kofron[19] have shown that the spectrum of the racemic compound *p*-ethylphenylcarbinyl phthalate differed significantly from the spectrum of the active enantiomer. Rosenberg and Schotte[10] and also Pettersson[5] applied these findings to detect quasi-racemic compound formation.

In the present work, infrared spectra were taken of the enantiomers and racemates of I, II and III and enantiomer mixtures of I and II and of II and III. The samples were examined both in potassium bromide disks and in mulls with identical results. The spectra obtained fell into a definite pattern which permitted facile and conclusive interpretation. The results clearly show that *(−)-I is related to (+)-II and (+)-II is related to (+)-III*, which is in complete agreement with the results of the X-ray and thermal analysis findings.

The above interpretation is based on the observations summarized in Table I as taken from the spectra shown in Fig. 4. Table I shows that the racemic compounds (±)-I (±)-II and (±)-III are characterized by having the distinctive carboxyl dimer absorption bands (2500–2900 cm.$^{-1}$), one main carbonyl absorption band (1698–1700 cm.$^{-1}$), and the broad out-of-plane carboxyl hydrogen deformation absorption in the 940 cm.$^{-1}$ region.

In contradistinction to this the enantiomers of I, II and III show a strong absorption in the 3200–3300 cm.$^{-1}$ region, no or very slight absorption in the carboxyl dimer region; the carbonyl is split into two bands with the higher frequency band more intense, a strong broad absorption in the 1145–1243 cm.$^{-1}$ region and the broad out-of-plane carboxyl hydrogen deformation (940 cm.$^{-1}$) is shifted to lower frequencies to *ca.* 835 cm.$^{-1}$.

Inspection of the quasi-racemates ((+)-I (+)-II) and ((+)-II (−)-III) in Table I shows them to possess the characteristic absorption bands of the racemic compounds (±)-I, (±)-II and (±)-III whereas the solid solutions ((−)-I (+)-II) and ((+)-II (+)-III) have spectra similar to those observed for the enantiomers of I, II and III. One can conclude that ((+)-I (+)-II) forms a compound and ((−)-I (+)-II) does not, and therefore (−)-I and (+)-II are related in configuration. From the comparison of ((+)-II (−)-III) and ((+)-II (+)-III) one deduces that (+)-II and (+)-III are related in configuration. These findings are in perfect accord with the previous conclusions based on the thermal and X-ray analyses.

**Discussion of Infrared.**[20]—The dramatic differences in the infrared spectra between the racemates and enantiomers is worthy of further comment. The absorption bands cited above are all associated with the carboxyl grouping. The 3200 cm.$^{-1}$ band is due to O–H stretching, the 1680–1730 cm.$^{-1}$ absorption to carbonyl stretching, the 1150 cm.$^{-1}$ band to a combined C–O stretch, C–O–H

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[16] The analogous conclusions cannot be reached in a comparison of the diffraction patterns of (±)-I and (±)-II with the quasi-racemate (+)-I (+)-II, since the quasi-racemate is an independently stable structure.

[17] N. Wright, *J. Biol. Chem.*, **120**, 641 (1937); **127**, 137 (1939).

[18] J. Lecomte in "Contribution à l'Étude de la Structure Moleculaire," Maison Desoer, Liège, 1947.

[19] E. L. Eliel and J. T. Kofron, *J. Am. Chem. Soc.*, **75**, 4585 (1953).

[20] It is a pleasure to acknowledge the many stimulating discussions with Dr. Harold Boaz and the many helpful suggestions that he has given.

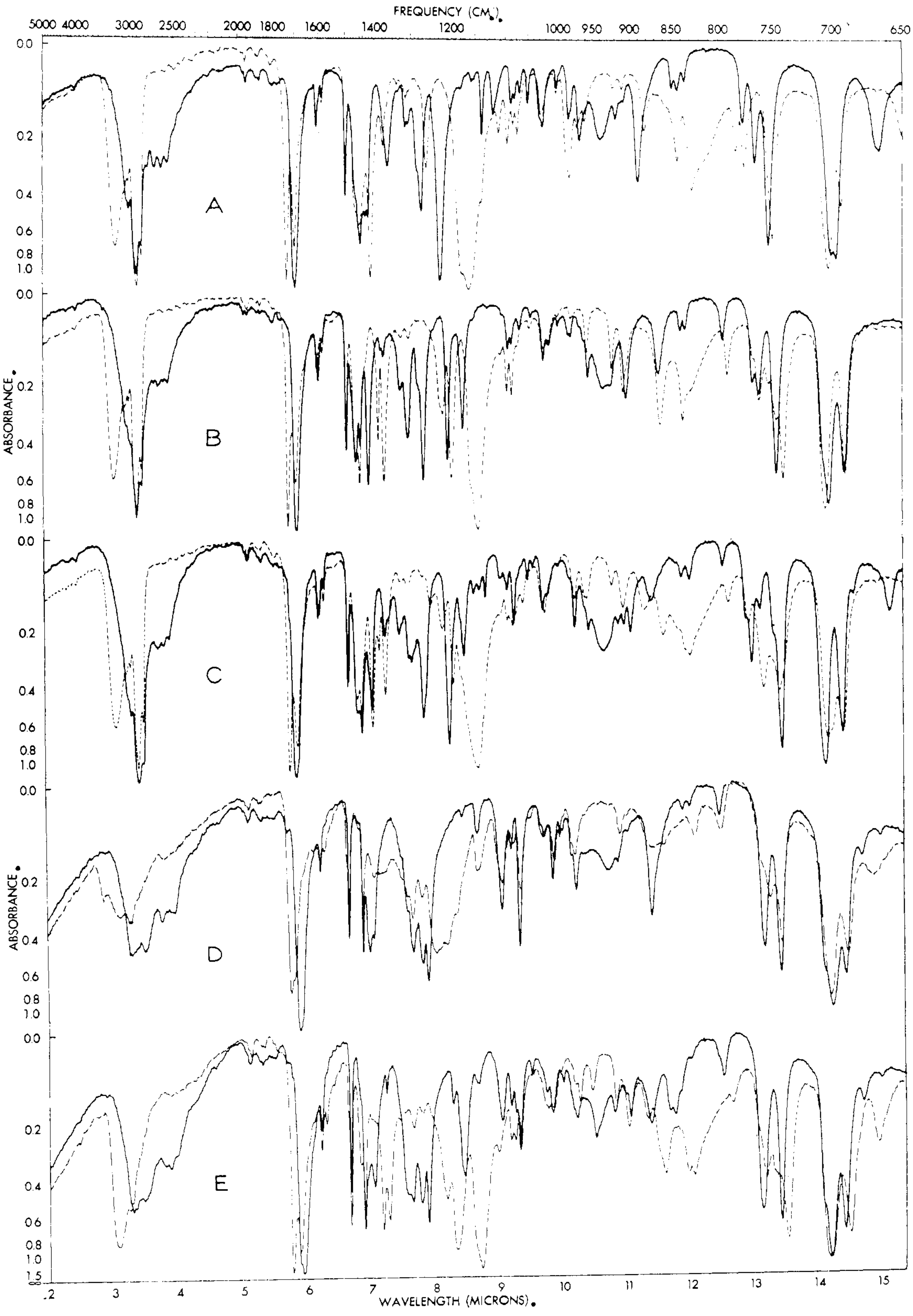
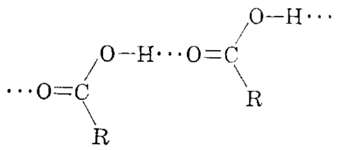


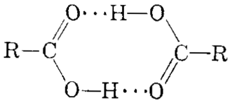
Fig. 4.—Infrared spectra: A, (±)- and (−)-2,2-diphenylcyclopropanecarboxylic acid (I) (solid line (±), dotted line (−)); B, (±)- and (−)-1-methyl-2,2-diphenylcyclopropanecarboxylic acid (II) (solid line (±), dotted line (+)); C, quasi-racemate (+)-I (+)-II (solid line) and solid solution (−)-I (+)-II (dotted line); D, (±)- and (+)-1-bromo-2,2-diphenylcyclopropanecarboxylic acid (III) (solid line (±), dotted line (+)); E, quasi-racemate (+)-II (−)-III (solid line) and solid solution (+)-II (+)-III (dotted line). A, B, and C are from mineral oil mulls over entire wave length range. D and E are Fluorolube mulls above 1334 cm.$^{-1}$ and mineral oil mulls below 1334 cm.$^{-1}$.

deformation, and the 830 and 935 cm.$^{-1}$ bands to the out-of-plane carboxyl hydrogen deformation.

An attractive explanation for the observed changes in spectra between the enantiomer and racemate is that *the enantiomer exists as polymeric chains (IV) in the crystal lattice whereas the racemate exists as dimers (V).*[21]



IV



V

The basis for the above hypothesis is the observation that the racemate spectra show the typical broad stretching absorption with the sub-maxima between 2500–2800 cm.$^{-1}$ and the broad out-of-plane carboxyl hydrogen deformation absorption at *ca.* 935 cm.$^{-1}$ which are characteristic of the carboxyl dimer IV.[22,23] In comparison, the enantiomers exhibit a bonded O–H stretching absorption at *ca.* 3200 cm.$^{-1}$ and the broad out-of-plane hydrogen deformation band is shifted to lower frequencies (820–860 cm.$^{-1}$) which is in accord with the weaker hydrogen bonding that is expected in the polymer IV. The virtual absence, in the enantiomer spectra, of the sub-maxima (2500–2800 cm.$^{-1}$) which are associated with the dimer, is striking.

Davies and Sutherland[24] have suggested that associated with the out-of-plane hydrogen deformation at 930 cm.$^{-1}$ is an in-plane hydrogen deformation at 1250 cm.$^{-1}$. It will be noted in Fig. 4 that bands which appear in the 1250–1300 cm.$^{-1}$ region in the racemate disappear, or are markedly reduced in intensity in the enantiomer spectra and a new strong broad band appears in the 1150 cm.$^{-1}$ region in the spectra of the enantiomers. This shift to lower frequencies and broadening is suggestive that this band corresponds to the in-plane hydrogen deformation which is associated with the out-of-plane hydrogen deformation found at 830 cm.$^{-1}$ in the enantiomer spectra. Again this shift to lower frequencies is consistent with the idea of producing weaker hydrogen bonds in going from the dimer structure to a polymeric structure.

Attention should now be called to the carbonyl region where the racemates show a single absorption band at *ca.* 1700 cm.$^{-1}$ whereas the enantiomers exhibit two carbonyl absorption bands in this region with the higher frequency absorption band having the greater intensity. The proposal of Davies and Sutherland[24] provides a reasonable rationalization for this phenomenon. The dimer V possesses a center of symmetry and only the asymmetrical carbonyl stretching vibration in the dimer would be infrared active, thereby giving rise to a single absorption band. In the polymer structure IV interaction of adjacent carbonyls gives rise to two stretching frequencies, the in-phase motion associated with a change in dipole moment approximately parallel to the polymer chain, and the out-of-phase motion to a net change in dipole moment perpendicular to the chain.[25]

In connection with the above observations the work of Corish and Davison[26] is pertinent. In a comparison of the spectra of crystalline and molten adipic acid it was found that on melting, the main OH stretching absorption shifted from 2700 to 3200 cm.$^{-1}$. At the same time the band at 930 cm.$^{-1}$, which has been assigned to the out-of-plane hydrogen deformation of a dimeric associated carboxyl group,[23] practically disappears. Also the carbonyl absorption shifts from 1700 cm.$^{-1}$ to about 1730 cm.$^{-1}$ on melting. Corish and Davison interpret their results as a break-up of the tightly associated dimer in the crystalline state to a more loosely associated polymer in the molten state. The above changes correspond to the differences observed in the spectra of racemic I and its enantiomer. The enantiomer (+)-III is of further interest because it not only has an absorption band at 3210 cm.$^{-1}$ but another absorption band at 3490 cm.$^{-1}$. This may signify that the crystal contains linear dimers or trimers[27] as well as polymers since the absorption band at 3490 cm.$^{-1}$ is in the region ascribed to the free O–H stretching in carboxylic acids.[28]

Although the spectra clearly indicate that in this series of acids the racemates form dimers and the enantiomers polymers, the reason for this is not apparent. Indeed, this need not always be the case and the reverse could just as readily occur, *i.e.* the enantiomer exist as dimer and the racemate as polymer in the crystal. It is also possible that both the enantiomer and racemate can exist as either polymer or dimer[29] as well. The infrared spectra merely reflect the state of the molecules in the crystal lattice.

**Rotatory Dispersion.**—The use of optical rotatory dispersion as a means of relating configurations has been magnificently exploited by Djerassi.[30] Our initial attempts to use this method were not satisfactory since the acids I, II and III gave plain dispersion curves as did the phenyl ketones that were derived from I. The aldehydes that corre-

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[21] This suggestion was first advanced by Eliel and Kofron to account for the differences in spectra of active and racemic *p*-ethylphenylmethylcarbinyl phthalate.

[22] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 164; R. N. Jones and C. Sandorfy in Weisberger's "Technique of Organic Chemistry," Vol. IX, Interscience Publishers, Inc., New York, N. Y., 1956, p. 426.

[23] D. Hadži and N. Sheppard, *Proc. Roy. Soc.* (*London*), **A216**, 247 (1953).

[24] M. M. Davies and G. B. B. M. Sutherland, *J. Chem. Phys.*, **6**, 755 (1938).

[25] In this connection, Dr. Pfeiffer has informed us that single crystal work on (+)-I and (+)-II shows that (+)-I belongs to the space group $P2_1$ with two molecules per unit cell and (+)-II belongs to the space group $P2_12_12_1$ with four molecules per unit cell. These results can accommodate the polymer structure but not the dimer. These data will be published elsewhere.

[26] P. J. Corish and W. H. T. Davison, *J. Chem. Soc.*, 2431 (1955).

[27] This is a linear dimer as opposed to the cyclic dimer V.

[28] O. D. Schreve, M. R. Heether, H. B. Knight and D. Swern, *Anal. Chem.*, **22**, 1499 (1950), have ascribed the absorption band at *ca.* 3500 cm.$^{-1}$ to free O–H stretching in carboxylic acids.

[29] Although acids I, II and III each form a racemic compound it should be pointed out that this is not a necessary condition to observe the differences in the infrared reported here. Eliel and Kofron[19] reported that although α-phenylethyl phthalate exists as a racemic compound the infrared spectra of the racemate and enantiomer are the same.

[30] C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

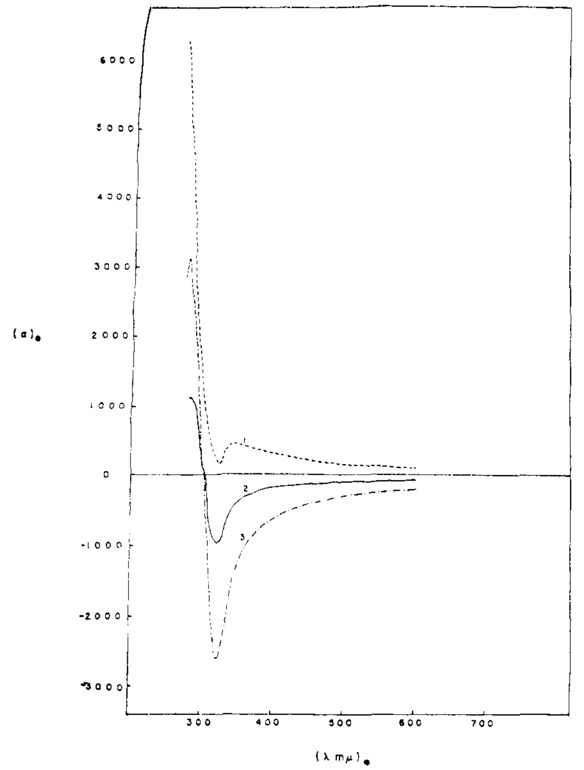


Fig. 5.—The optical rotatory dispersion curves (dioxane) of: 1, (+)-2,2-diphenylcyclopropanecarboxaldehyde; 2, (−)-1-methyl-2,2-diphenylcyclopropanecarboxaldehyde; 3, (−)-1-bromo-2,2-diphenylcyclopropanecarboxaldehyde.

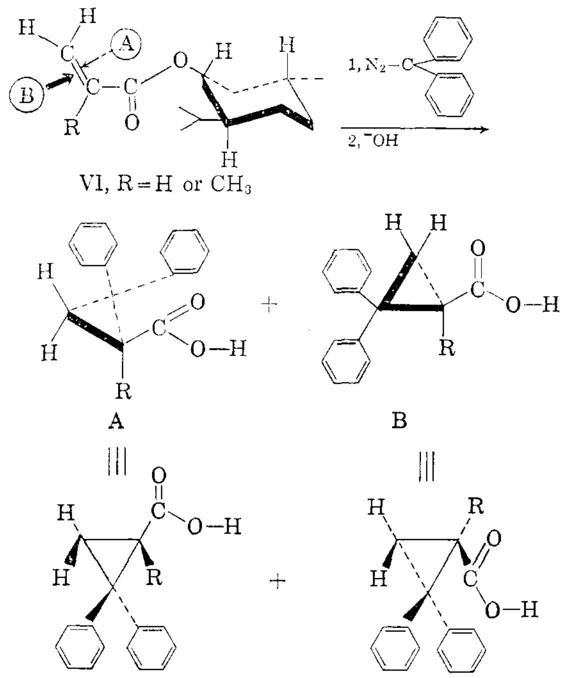
spond to I, II and III, however, showed the desired Cotton effects.

The aldehydes were prepared by the reduction of the acids to their corresponding alcohols which were in turn oxidized to the aldehydes by chromic anhydride.[31]

Figure 5 shows the rotatory dispersion curves of the aldehydes corresponding to (+)-I, (−)-II and (−)-III. It can be seen that each exhibits a negative Cotton effect and that each has a positive background curve superimposed upon it.

These data combined with the data obtained from the thermal, X-ray and infrared examination of the quasi-racemates leave little doubt that *(−)-I, (+)-II and (+)-III are related in configuration.*

**Absolute Configurations.**—Cram and Elhafez[32] and Prelog and co-workers[33] have studied the course of asymmetric syntheses in a number of systems and have found that it was dependent on the conformation of the asymmetric center. Furthermore, if the absolute configuration of the asymmetric center is known, then the absolute configuration of the newly created asymmetric center could be obtained. The concepts derived from this work have been applied, with success, to the correlation of configuration and to the determination of absolute configuration.[33,34] These studies involved addition reactions to a carbonyl function which was located adjacent to or near an asymmetric center. Asymmetric syntheses by the addition to an olefinic moiety in both catalytic[35] and non-catalytic[36] reactions have also been observed.



(−)—Ia (R = H) Ib
(+)—IIa (R = CH₃) IIb

It was reasoned that since diazo derivatives add readily to acrylate esters[11] that perhaps if one used an optically active ester a partial asymmetric synthesis would be achieved. The (−)-menthyl esters were chosen because they are known substances[37] and also because the absolute configuration of (−)-menthol has been established.[38] Using the Prelog–Cram model[39] one would predict that

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[31] This reaction sequence does not involve the asymmetric center.

[32] D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

[33] V. Prelog, *et al.*, *Helv. Chim. Acta*, **36**, 308 (1953). For a review of this work see J. A. Mills and W. Klyne, Ch. 5 in "Progress in Stereochemistry," Vol. I, Academic Press, Inc., New York, N. Y., pp. 198–201.

[34] For an excellent recent example, see J. A. Berson and M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445 (1958).

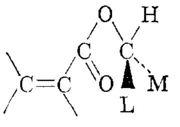
[35] M. G. Vavon and B. Jakubowicz, *Bull. soc. chim.*, **53**, 1111 (1933); D. Lipkin and T. D. Stewart, *J. Am. Chem. Soc.*, **61**, 3295 (1939); S. Akabori, *et al.*, *J. Chem. Soc. Japan*, **61**, 1054 (1940); *Biochimia*, **22**, 154 (1957); C. L. Arcus and D. G. Smyth, *J. Chem. Soc.*, 35 (1955); C. L. Arcus, *et al.*, *ibid.*, 1195 (1960); G. Maeda, *J. Chem. Soc. Japan*, **77**, 1011 (1956); A. Pedrazzoli, *Helv. Chim. Acta*, **40**, 80 (1957); V. Prelog, *et al.*, *ibid.*, **42**, 2227 (1959).

[36] M. P. Balfe, J. Kenyon and D. Y. Wadden, *J. Chem. Soc.*, 1367 (1954).

[37] C. S. Marvel and R. L. Frank, *J. Am. Chem. Soc.*, **64**, 1675 (1942); C. E. Rehberg, M. B. Dixon and C. H. Fisher, *ibid.*, **67**, 210 (1945).

[38] A. J. Birch, *Ann. Reports*, **47**, 192 (1950); J. Read and W. J. Grubb, *J. Chem. Soc.*, 1779 (1934).

[39] Using a transoidal coplanar conformation for the system and a staggered orientation of the asymmetric center such that two



substituents (L and M) (or H and M) flank the carbonyl and the third is in the plane of the coplanarity, the incoming reagent will enter from the side in which the least bulky group flanks the carbonyl.

the incoming reagent would enter predominantly from below the plane to produce A in excess rather than from above the plane to yield B. Justification for the use of this model in this type of reaction has recently been provided.[40]

Since it has been shown that I and II of opposite sign are related in configuration, the acids produced in the addition of diphenyldiazomethane to (−)-menthylacrylate and methacrylate should also have opposite signs of rotation. As will be seen (*vide infra*) asymmetric syntheses were achieved[41] and VI (R = H) produced (−)-I, and VI (R = $CH_3$) yielded (+)-II. Based on the known absolute configuration of (−)-menthol, *(S)-(−)-IA and (S)-(+)-IIA represent the absolute configuration of these acids.* Since (+)-II is configurationally related to (+)-III, (*R*)-(+)-IIIa (R = Br) represents its absolute configuration.

The addition of diazodiphenylmethane to (−)-menthyl acrylate occurred readily and was accompanied by immediate decolorization and evolution of nitrogen. In order to avoid any possibility of the resolution of the diastereomers that are formed, isolation of products at this point was avoided. The reaction mixture was saponified to completeness as evidenced by the absence of carbonyl absorption at 1720 cm.$^{-1}$ in the neutral fraction.[42] The acid was isolated in 60% yield and its infrared spectrum in solution ($CCl_4$) was identical in all respects with an authentic sample. The rotation of the acid, $[\alpha]^{24}\text{D}$ −4.7° ($CHCl_3$), corresponds to 2.2% asymmetric synthesis.[43]

The above procedure was repeated using (−)-menthyl methacrylate (IV, R = $CH_3$) which after complete saponification gave in 74% yield the acid II, the infrared spectrum of which was identical with that of an authentic sample and the rotation of which, $[\alpha]^{24}\text{D}$ + −3.7° ($CHCl_3$), corresponds to 10% asymmetric synthesis.

It should be emphasized that the above assignments of absolute configurations must be viewed as tentative until further work establishes the general validity of the method.[44]

Recently, Brewster[45] has proposed a set of empirical rules which in conjunction with conformational analysis allows one to predict not only the sign but the magnitude of rotation of a large number of cyclic and acyclic compounds. Application of this method to acids I, II and III produced some conflicting results. Based on our assignment of relative and absolute configurations the sign and $[M]\text{D}$ of acids I, II and III are −547°, +85° and +351°, respectively. Using the Brewster method the signs and magnitudes of rotation are +210°, +70° and −210°. It can be seen that the Brewster method fails to predict two out of three signs in this series of compounds. It should also be noted that these discrepancies are independent of the absolute configurational assignments.

**Acknowledgment.**—We are indebted to Dr. R. Pfeiffer and Dr. H. Boaz of Eli Lilly and Co. for the X-ray and infrared measurements and for the many stimulating discussions pertaining to their interpretation, and to Dr. M. O'Dwyer for the R.D. measurements.

## Experimental[46]

**Melting Point Diagrams.**—The procedure followed was essentially that of Gronowitz and Larsson.[47] The melting points were determined by the capillary method with a Hershberg melting point apparatus and in the case of the quasi-racemate II III a Kofler apparatus. The heating rate was 1–2°/min. and the final melting temperatures were recorded.

**X-Ray Powder Photographs.**—The photographs were obtained with a Norelco camera of 114.6 mm. diameter with radiation from a chromium or copper target; exposure time was 1.5 hours at 35 kv. and 10 milliamperes. The preparations were the same ones used for the melting point diagrams, (see Table II).

**Infrared Spectra.**—The Nujol mulls and potassium bromide disks were prepared by standard procedures,[10] and the spectra were obtained with a Perkin-Elmer model 21 spectrophotometer.

**Optical Rotatory Dispersion.**—The optical rotatory dispersion curves were obtained on a recording Rudolf spectropolarimeter using a xenon high-pressure arc lamp as a light source.

**2,2-Diphenylcyclopropylcarbinol.**—An ethereal solution of 4.8 g. (0.002 mole) of 2,2-diphenylcyclopropanecarboxylic acid (I) was added dropwise to a stirred solution of 0.05 mole of lithium aluminum hydride in anhydrous ether. The mixture was stirred for 2 hours after the addition. Hydrolysis was effected by cautious, dropwise addition of saturated aqueous ammonium chloride solution. The precipitated salts were collected on a filter and washed thoroughly with ether. The solvent was evaporated from the combined filtrates, and the residue distilled under vacuum, yielding 3.6 g. (80%) of the desired carbinol as a clear, very viscous liquid, boiling at 138–140° (0.5 mm.); spectra: infrared, 3555 (free OH), 3420 cm.$^{-1}$ (bonded OH); near infrared, 1.64 μ.

*Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.46; H, 7.18.

In an identical experiment, 3 g. (0.013 mole) of optically active acid with $[\alpha]^{24}\text{D}$ +230 ± 5° (*c* 0.280, $CHCl_3$) and m.p. 148.5–150° gave 1.5 g. of optically active carbinol boiling at 147° (0.5 mm.) (bath, 195°) and having $[\alpha]^{24}\text{D}$ + 167 ± 3° (*c* 0.303, $CHCl_3$). The infrared spectra ($CHCl_3$) of the active and racemic carbinols were identical.

*Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.36; H, 7.27.

**(+)-2,2-Diphenylcyclopropanecarboxaldehyde.**—To a solution of 2.5 g. of chromic acid in pyridine[48] was added a pyridine solution of 4.0 g. (0.0178 mole, $[\alpha]^{24}\text{D}$ +148°, 89% optical purity) of carbinol and allowed to stand at room temperature for 15 hours. The reaction mixture was diluted with water and extracted with ether. The ether was washed successively with cold dilute hydrochloric acid, saturated sodium bicarbonate, water, and then dried over anhydrous sodium sulfate. The residual oil, upon removal of the solvent, was chromatographed on an alumina column to give a alcohol-free fraction which was distilled to yield 0.53 g. (13%) of aldehyde, b.p. 143–144° at 0.7 mm. and $[\alpha]^{23}\text{D}$ + 99.1° (*c* 1.875, $CHCl_3$), infrared 1710 cm.$^{-1}$ (C=O), $\lambda_{max}$ 292 mμ (ε 44.2, dioxane); R.D. in dioxane (*c* 1.075),

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[40] H. M. Walborsky, T. Sugita, M. Ohno and Y. Inouye, *J. Am. Chem. Soc.*, **82**; 5225 (1960).

[41] F. J. Impastato, L. Barash and H. M. Walborsky, *ibid.*, **1514** (1959).

[42] Incomplete saponification would be equivalent to partial resolution.[32]

[43] The possibility exists that asymmetric synthesis did, in fact, not occur during the addition reaction but during the saponification. This would involve removal of the α-hydrogen from the (−)-menthyl ester of I to produce the carbanion[11] and asymmetric synthesis occurring in the protonation step. One would also have to assume that the rate of this reaction is faster than the rate of saponification.

To check this possibility the (−)-menthyl ester of (±)-I was prepared and, without isolation, saponified. The acid isolated in 81% yield was completely racemic (see Experimental).

[44] Work is now in progress to affect a direct chemical correlation.

[45] J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959); **81**, 5483 (1959); **81**, 5493 (1959).

[46] Elemental analyses were performed by E. Thommen, Basel, Switz.

[47] S. Gronowitz and S. Larsson, *Arkiv. Kemi*, **8**, 567 (1956).

[48] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

TABLE II

X-RAY DIFFRACTION DATA

| (+)-II[a] |  | (−)-I (+)-II[a] |  | (±)-II[b] |  | (+)-II (+)-III[b] |  | (±)-III[b] |  | (+)-II (−)-III[b] |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *d* | *I/I*$_1$ | *d* | *I/I*$_1$ | *d* | *I/I*$_1$ | *d* | *I/I*$_1$ | *d* | *I/I*$_1$ | *d* | *I/I*$_1$ |
| 9.88 | 0.37 | 9.88 | 0.30 | 11.1 | 0.05 | 10.1 | 0.50 | 12.9 | 1.00 | 12.9 | 0.26 |
| 9.26 | .15 | 9.07 | .12 | 9.96 | .30 | 9.16 | .50 | 8.41 | 0.40 | 11.4 | .24 |
| 7.23 | .03 | 7.08 | .04 | 8.71 | .20 | 7.24 | .02 | 6.96 | .03 | 9.45 | .32 |
| 5.99 | 1.00 | 5.92 | 1.00 | 7.23 | .20 | 6.02 | 1.00 | 6.58 | .53 | 8.37 | .80 |
| 5.59 | 0.10 | 5.52 | 0.60 | 6.72 | .20 | 5.69 | 0.02 | 5.98 | .40 | 7.72 | .32 |
| 5.35 | .25 | 5.26 | .60 | 6.05 | .40 | 5.35 | 1.00 | 5.69 | .53 | 6.55 | .60 |
| 4.74 | .03 | 4.73 | .04 | 5.64 | .30 | 5.03 | 0.02 | 5.26 | .27 | 5.90 | .05 |
| 4.57 | .20 | 4.54 | .60 | 5.48 | 1.00 | 4.84 | .06 | 5.05 | .20 | 5.67 | 1.00 |
| 4.33 | .03 | 4.20 | .20 | 5.33 | 0.05 | 4.60 | .08 | 4.91 | .27 | 5.50 | 0.03 |
| 4.24 | .10 | 4.07 | .02 | 5.02 | .10 | 4.39 | .15 | 4.71 | .53 | 5.24 | .40 |
| 3.89 | .50 | 3.83 | .80 | 4.58 | .30 | 4.02 | .15 | 4.56 | .20 | 5.00 | .32 |
| 3.61 | .20 | 3.59 | .30 | 4.36 | .40 | 3.90 | 1.00 | 4.26 | .05 | 4.89 | .40 |
| 3.53 | .15 | 3.50 | .30 | 4.24 | .10 | 3.85 | 1.00 | 4.17 | 1.00 | 4.70 | .32 |
| 3.30 | .15 | 3.28 | .16 | 4.11 | .10 | 3.61 | 0.50 | 3.91 | 0.01 | 4.51 | .40 |
| 3.13 | .10 | 3.11 | .12 | 4.00 | .40 | 3.55 | .10 | 3.76 | .53 | 4.33 | .05 |
| 2.05 | .10 | 3.02 | .12 | 3.88 | .30 | 3.37 | .02 | 3.65 | .27 | 4.17 | 1.00 |
| 2.95 | .10 | 2.93 | .08 | 3.73 | .40 | 3.29 | .15 | 3.58 | .27 | 3.84 | 0.05 |
| 2.65 | .03 | 2.85 | .02 | 3.58 | .20 | 3.15 | .15 | 3.39 | .27 | 3.74 | 0.80 |
| 2.53 | .03 | 2.70 | .02 | 3.34 | .20 | 3.04 | .15 | 3.29 | .53 |  |  |
| 2.47 | .03 | 2.63 | .02 | 3.28 | .10 | 2.91 | .20 |  |  |  |  |
| 2.21 | .03 | 2.50 | .02 |  |  |  |  |  |  |  |  |

[a] Filtered chromium radiation. [b] Filtered copper radiation.

23°: $(\alpha)_{600}$ + 92.1, $(\alpha)_{559}$ + 96.3, $(\alpha)_{349}$ + 437, $(\alpha)_{326}$ + 183.8, $(\alpha)_{273}$ + 6330.

*Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.25; H, 6.38.

**Optically Active 1-Methyl-2,2-diphenylcyclopropanecarboxylic Acid (II).**—The racemic acid[11] (0.2 mole) was resolved by the use of brucine (0.1 mole) to yield the optically active acid in 71% yield, m.p. 190–191°, and $[\alpha]^{23}\text{D}$ +34 ± 1° (*c* 1.025, $CHCl_3$).

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.16; H, 6.23.

**1-Methyl-2,2-diphenylcyclopropylcarbinol.**—Racemic 1-methyl-2,2-diphenylcyclopropanecarboxylic acid (26 g., 0.103 mole) was dissolved in 750 ml. of dry ether and added to a slurry of 16 g. of lithium aluminum hydride in 500 ml. of dry ether. The solution was allowed to stir for 12 hours. The complex was decomposed by the addition of aqueous ammonium chloride. The ether was separated, dried, and removed to yield a solid residue, m.p. 101–102° in quantitative yield; infrared 3800, 3640 cm.$^{-1}$ (–OH), near infrared 1.64 μ.

*Anal.* Calcd. for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.50; H, 7.71.

The optically active carbinol, prepared in an analogous manner from optically pure (−)-II, had m.p. 117–117.5°, $[\alpha]^{22}\text{D}$ −32° (*c* 0.984, $CHCl_3$). The infrared spectra of the racemic and optically active carbinols were identical.

*Anal.* Calcd. for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.76; H, 7.56.

**1-Methyl-2,2-diphenylcyclopropanecarboxaldehyde.**—A mixture of 1.0 g. of chromic anhydride in 10 ml. of pyridine was added to a solution of 2.0 g. (0.0083 mole) of 1-methyl-2,2-diphenylcyclopropylcarbinol ($(\alpha)\text{D}$ −32°) in 10 ml. of pyridine, and allowed to stand for 36 hours. The black mixture was poured onto ice. Chloroform was added, and the insoluble materials were filtered off. The chloroform layer was washed with cold dilute hydrochloric acid, saturated sodium bicarbonate, water, and the solvent was removed. The residue was chromatographed on an alumina column using petroleum ether (30–60°) as the eluting solvent. A total of 0.9 g. (0.0038 mole) of the desired aldehyde was obtained, m.p. 118–120°. The eluting solvent was changed to benzene and 0.5 g. of unreacted carbinol was recovered. The yield was 59%, based on recovered starting material. The analytical sample was recrystallized from petroleum ether (30–60°); m.p. 119–120°, $[\alpha]^{22}\text{D}$ + 80° (*c* 0.803, $CHCl_3$), infrared 1705 cm.$^{-1}$ (C=O), near infrared 1.64 μ, $\lambda_{max}$ 287 mμ (ε 54.3, dioxane); R.D. in dioxane (*c* 1.020), 23°: $(\alpha)_{600}$ −58.7, $(\alpha)_{589}$ −80.3, $(\alpha)_{322}$ −980, $(\alpha)_{282}$ +1125, $(\alpha)_{281}$ +1121.

*Anal.* Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.17; H, 6.73.

The racemic aldehyde, prepared in an analogous manner, had m.p. 88–91°.

Lithium aluminum hydride reduction of the racemic aldehyde gave a compound that did not depress the m.p. of an authentic sample of 1-methyl-2,2-diphenylcyclopropylcarbinol.

**(±)-Methyl 1-Bromo-2,2-diphenylcyclopropanecarboxylate.**—To a refluxing solution of 289 g. (1.74 moles) of methyl α-bromoacrylate[49] dissolved in 500 ml. of petroleum ether (30–60°) was added 800 ml. of a petroleum ether (30–60°) solution of 186 g. (1 mole) of diphenyldiazomethane. Heating was continued until the solution decolorized. Removal of the solvent yielded 260 g. (78.5%) of product, m.p. 103–105°, which on one recrystallization from methanol gave m.p. 105–107°, and near infrared absorption at 1.64 μ.

*Anal.* Calcd. for $C_{17}H_{15}BrO_2$: C, 61.64; H, 4.57. Found: C, 61.81; H, 4.81.

**(±)-1-Bromo-2,2-diphenylcyclopropanecarboxylic Acid (III).**—Saponification of the ester by aqueous methanolic potassium hydroxide produced III in 97% yield, m.p. 185–188°.

*Anal.* Calcd. for $C_{16}H_{13}BrO_2$: C, 60.58; H, 4.13. Found: C, 60.71; H, 4.29.

**(+)- and (−)-1-Bromo-2,2-diphenylcyclopropanecarboxylic Acid (III).**—Resolution by brucine gave (+)-III, m.p. 184–185.5°, $(\alpha)^{23}\text{D}$ +112.2 ± 2.5° (*c* 1.061, $CHCl_3$).

*Anal.* Calcd. for $C_{16}H_{13}BrO_2$: C, 60.58; H, 4.13. Found: C, 60.57; H, 4.16.

The partially resolved (−)-III from the mother liquors was resolved by quinine to give m.p. 185–186°, $[\alpha]^{22}\text{D}$ −109 ± 2.5° (*c* 1.104, $CHCl_3$).

*Anal.* Calcd. for $C_{16}H_{13}BrO_2$: C, 60.58; H, 4.13. Found: C, 60.73; H, 4.29.

**(+)-1-Bromo-2,2-diphenylcyclopropanecarbinol.**—Lithium aluminum hydride reduction of (+)-III gave the desired carbinol (70%), m.p. 132–133°, $[\alpha]^{24}\text{D}$ +108.7 ± 2.5° (*c* 1.017, $CHCl_3$).

*Anal.* Calcd. for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99. Found: C, 63.64; H, 5.07.

**(+)-1-Bromo-2,2-diphenylcyclopropanecarboxaldehyde.**—The same procedure was followed as for the previously de-

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[49] C. S. Marvel, *et al.*, *J. Am. Chem. Soc.*, **61**, 2158 (1939).

scribed oxidations. The above carbinol (2 g.) was oxidized to yield 450 mg. (22%) of the desired aldehyde, m.p. 102–103,° $[\alpha]^{23}\text{D}$ +183.1 ± 2.3° (*c* 1.016, $CHCl_3$), infrared 1725 cm.$^{-1}$ (C═O), $\lambda_{max}$ 297 mμ (ε 96.5, dioxane); R.D. in dioxane (*c* 1.115), 23°: $(\alpha)_{600}$ −210°, $(\alpha)_{589}$ −219°, $(\alpha)_{321}$ −2614°, $(\alpha)_{277}$ +3100°, $(\alpha)_{273}$ +2820°.

Due to its instability an elemental analysis was not obtained. The aldehyde was reduced by lithium aluminum hydride to the corresponding alcohol, the m.p., mixed m.p. and infrared spectrum of which were identical with those of an authentic sample.

**Addition of Diphenyldiazomethane to (−)-Menthyl Acrylate.**—Diphenyldiazomethane (1.48 g., 0.0076 mole) dissolved in petroleum ether (30–60°) was added slowly to 1.61 g. (0.0076 mole) of (−)-menthyl acrylate at 110°. Immediate decoloration and nitrogen evolution occurred. The residual oil was dissolved in benzene, washed with hydrochloric acid, 5% sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was removed and in order to avoid any possibility of resolution of the diastereomers isolation at this point was avoided.

This viscous oil was saponified by refluxing with a solution of 0.85 g. of potassium hydroxide in 60 ml. of ethylene glycol for 52 hours. The reaction mixture was cooled, diluted with water, and extracted with ether. The neutral ether extract was dried and the ether evaporated. The residue was examined in the infrared and showed less than 0.1% of carbonyl absorption at 1720 cm.$^{-1}$.

The aqueous layer was acidified to yield 1.1 g. (60%) of 2,2-diphenylcyclopropanecarboxylic acid, m.p. 163–164.5°, $[\alpha]^{24}\text{D}$ −4.7° ($CHCl_3$), the infrared spectrum of which ($CCl_4$) was identical in all respects with that of an authentic sample.

**Addition of Diphenyldiazomethane to (−)-Menthyl Methacrylate.**—(−)-Menthyl methacrylate (2.1 g., 0.009 mole) was treated with an excess of diphenyldiazomethane as described above. The viscous residual oil was refluxed with a solution of 10.0 g. of potassium hydroxide in 40 ml. of ethylene glycol for 60 hours. The reaction mixture was cooled to room temperature, diluted with water, extracted with ether and dried over anhydrous sodium sulfate. The residue from the ether extract showed no carbonyl absorption at 1720 cm.$^{-1}$ in the infrared.

The aqueous layer was acidified and the crude acid collected by filtration and dried to yield 1.82 g. (77.5%) of II. The crude acid was dissolved in ether and extracted with aqueous sodium bicarbonate. The aqueous solution was treated with charcoal, filtered and reacidified to yield 1.71 g. (74%) of the acid, m.p. 96–98°, $[\alpha]^{24}\text{D}$ +3.7° ($CHCl_3$), the infrared spectrum of which ($CCl_4$) was identical in all respects with that of an authentic sample.

**Saponification of (−)-Menthyl (±)-2,2-Diphenylcyclopropane-carboxylate.**—To 0.5 g. (0.021 mole) of the acid (±)-I was added 6.0 g. (0.05 mole) of thionyl chloride and the reaction mixture was allowed to stand at room temperature for 8 hours. The excess thionyl chloride was removed *in vacuo* and the residue added to a solution of 4.0 g. (0.03 mole) of (−)-menthol in dry benzene. One equivalent of pyridine (6.0 ml.) was added; the reaction mixture was stirred for 1.5 hours, poured onto ice, and extracted with ether. The ether extract was washed with aqueous sodium hydroxide, water until neutral, and dried. Removal of the ether yielded 6.5 g. (82%) of product.

The ester (4.2 g.), without purification, was added to 6.2 g. of potassium hydroxide in 50 ml. of ethylene glycol and the solution heated to reflux for 48 hours. The reaction mixture was cooled, diluted with water and extracted with ether. The aqueous layer was acidified, yielding 2.1 g. (82%) of I, m.p. 170–171° and $[\alpha]^{24}\text{D}$ 0°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

# Carbonyl Reactions. XII. The Kinetics and Mechanism of the *cis* to *trans* Isomerization of Substituted Chalcones[1,2]

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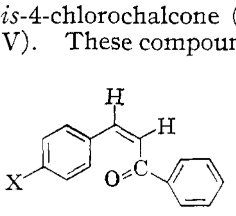
The rate and mechanism for the acid-catalyzed isomerization of substituted benzalacetophenones (chalcones) have been studied. The behavior of *cis*-4-methoxychalcone (II) differs from that of *cis*-chalcone (I), *cis*-4-chlorochalcone and *cis*-4-nitrochalcone. It is proposed that a new mechanism intervenes for the isomerization of II, involving direct rotation about the $C_\alpha$–$C_\beta$ bond in the salt of II. Arguments supporting this mechanism are presented, and deuterium isotope studies are reported which are consistent with this mechanism.

## Introduction

In recent reports[4,5] we have shown that the acid-catalyzed isomerization of *cis*-benzalacetophenone (I) proceeds *via* a rate-determining addition of water to the oxonium salt of I, leading to the formation of the enol of the β-hydroxyketone. It was also demonstrated that the rate of ketonization of the enol is slower than the loss of the elements of water to give *trans*-chalcone. The related studies[6] of the mechanism of the dehydration of β-aryl-β-hydroxyketones provided evidence that the normal mechanism involved at the rate-determining process was the enolization step. However, in the case of 4-(*p*-methoxyphenyl)-4-hydroxy-2-butanone, the normally operating mechanism is supplanted by a new mechanism. This new mechanism involves the benzylic carbonium ion in the rate-determining sequence, rather than the enol.

It thus seemed of value to study the acid-catalyzed isomerization of a group of substituted chalcones, in order to determine whether there was also a change in mechanism within this group of compounds and with this type of reaction as well. With this purpose in mind, we have examined the kinetics of the isomerization of *cis*-4-methoxychalcone (II), *cis*-4-chlorochalcone (III) and *cis*-4-nitrochalcone (IV). These compounds were chosen



I, X = -H; III, X = -Cl
II, X = $-OCH_3$; IV, X = $-NO_2$

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[2] Presented in part at the 8th Conference on Reaction Mechanisms, Princeton, N. J., September 6–10, 1960.

[3] National Institutes of Health Postdoctoral Fellow, 1959–1961.

[4] D. S. Noyce, W. A. Pryor and P. A. King, *J. Am. Chem. Soc.*, **81**, 5423 (1959).

[5] D. S. Noyce, G. L. Woo and M. J. Jorgenson, *ibid.*, **83**, 1160 (1961).

[6] D. S. Noyce and W. L. Reed, *ibid.*, **80**, 5539 (1958).