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CYCLOPROPANES—XVII

THE ABSOLUTE CONFIGURATIONS OF *TRANS*-1,2-CYCLOPROPANEDICARBOXYLIC ACID AND *TRANS*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID[1]

Y. Inouye, T. Sugita and H. M. Walborsky
Department of Chemistry, Florida State University, Tallahassee, Florida and
The Institute for Chemical Research, Kyoto University, Takatsuki, Japan

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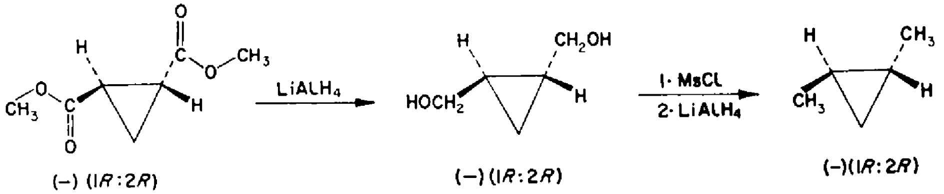
Abstract—The absolute configuration of (−)-*trans*-1,2-cyclopropanedicarboxylic acid was established as 1*R*: 2*R* by a direct chemical correlation with known (−)-(1*R*: 2*R*)-*trans*-1,2-dimethylcyclopropane. Ozonolysis of (+)-*trans*-2-phenylcyclopropanecarboxylic acid yielded (+)-*trans*-1,2-cyclopropanedicarboxylic acid which shows that (+)-*trans*-2-phenylcyclopropanecarboxylic has the 1*S*: 2*S* configuration. The significance of these results to the Wittig reaction involving optically active styrene oxide and phosphonoacetates will be discussed.

As PART of our studies involving the asymmetric synthesis of *trans*-1,2-cyclopropanedicarboxylic acid it became desirable to establish the absolute configuration of this acid by a direct chemical means.[2] The absolute configuration of (−)-*trans*-1,2-dimethylcyclopropane has been established as 1*R*:2*R* by Doering and Kirmse.[3] It was therefore only necessary to convert optically active *trans*-1,2-cyclopropanedicarboxylic acid, by conventional procedures, to the corresponding hydrocarbon and the correlation will have been achieved. This was accomplished as follows:



Dimethyl *trans*-1,2-cyclopropanedicarboxylate, $[\alpha]_D^{22}$ −31°, of 9·3% optical purity was reduced with lithium aluminum hydride in 71% yield to the glycol, $[\alpha]_D$ −3·2°. The glycol was esterified with methanesulfonyl chloride and due to the instability of the dimesylate it was immediately reduced with lithium aluminum hydride to the desired (−)-*trans*-1,2-dimethylcyclopropane, $[\alpha]_D^{22}$ −2·39° (*c*, 13·85, diglyme). On the basis of this chemical conversion the dimethyl (−)-*trans*-1,2-cyclopropanedicarboxylate and the (−)-diacid from which it is derived are assigned the 1*R*:2*R* absolute configuration.

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[1] This work was supported in part by a contract with the division of biology and medicine, U.S. Atomic Energy Division and in part by a grant from the National Science Foundation.

[2] Y. Inouye, S. Inamasu, M. Ohno, T. Sugita and H. M. Walborsky, *J. Amer. Chem. Soc.* **83**, 2962 (1961).

[3] W. von E. Doering and W. Kirmse, *Tetrahedron* **11**, 272 (1960).

Since ozonolysis of *trans*-2-phenylcyclopropanecarboxylic is known[4] to yield *trans*-1,2-cyclopropanedicarboxylic acid this reaction provides the means by which the absolute configuration of optically active *trans*-2-phenylcyclopropanecarboxylic acid[5] can be determined. The absolute configuration of (+)-2-phenylcyclopropanecarboxylic acid is therefore established as 1*S*:2*S* since the ozonolysis of this acid, $[\alpha]_D^{22}$ +300·2° (EtOH) of 96% optical purity[6] produced (+)-(1*S*:2*S*)-*trans*-1,2-cyclopropanecarboxylic acid which after sublimation and recrystallization had m.p. 169·5°–170° and $[\alpha]_D^{22}$ +228° (*c*, 2·34, EtOH). This is the highest rotation reported for this acid. The Buchner value[7] has been used previously[2,5] to calculate optical purity and percentage of asymmetric synthesis and these figures will need to be revised in light of this new result.

Denney *et al.*[8] have recently reported the formation of (−)-*trans*-2-phenylcyclopropanecarboxylic acid, $[\alpha]_D$ −31·3°, from the reaction of (−)-styrene oxide with carbethoxymethylenetriphenylphosphorane. Since the absolute configuration of (−)-*trans*-2-phenylcyclopropanecarboxylic acid was not known at the time, these workers were unable to determine whether the reaction proceeded with retention or inversion of configuration. Denney argued for an inversion mechanism based on the observation that cyclohexene oxide reacted with carbethoxymethylenetriphenylphosphorane to yield a cyclopropanecarboxylate derivative. The inversion mechanism also received support from the work of McEwen, VanderWerf *et al.*[9] Now that the absolute configuration of both styrene oxide[10] and *trans*-2-phenylcyclopropanecarboxylic are known one is now able to say with certainty that the overall reaction proceeds predominantly with inversion of configuration as postulated by Denney.[11] However, the optical yield obtained in this reaction is quite low and this may be due to a number of factors. It is possible that heating the reaction mixture at 200° caused thermal racemization of the reaction product, ethyl *trans*-2-phenylcyclopanecarboxylate. That this may indeed be a factor is indicated by the much higher optical yields obtained by Tömösközi[11] who was able to affect condensation at 70° by using carbethoxymethylenediethoxyphosphonate. However, even under these mild conditions the optical yields were less than 50%.[6] In the Denney mechanism the cyclic intermediate postulated may decompose by the inversion pathway (I–IV) and in a

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[4] H. L. de Waal and G. W. Perold, *Chem. Ber.* **85**, 574 (1952).

[5] After completion of our work a paper by N. Nazaki, K. Kondo, O. Nakanisi and K. Sisido, *Tetrahedron* **19**, 1617 (1963) described the ozonolysis of (−)-*trans*-2-phenylcyclopropanecarboxylic acid, $[\alpha]_D$ −5·7° to (−)-*trans*-1,2-cyclopropanedicarboxylic acid.

[6] H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.* **83**, 2138 (1961) report m.p. 51–52° and $[\alpha]_D^{24}$ −368° (*c*, 0·931, $CHCl_3$) for (−)-*trans*-2-phenylcyclopropanecarboxylic acid. See experimental for data on a sample of higher optical purity, $[\alpha]_D^{14}$ 381° (*c*, 0·960, $CHCl_3$) and $[\alpha]_D^{22}$ 311·7° (*c*, 1·776, EtOH).

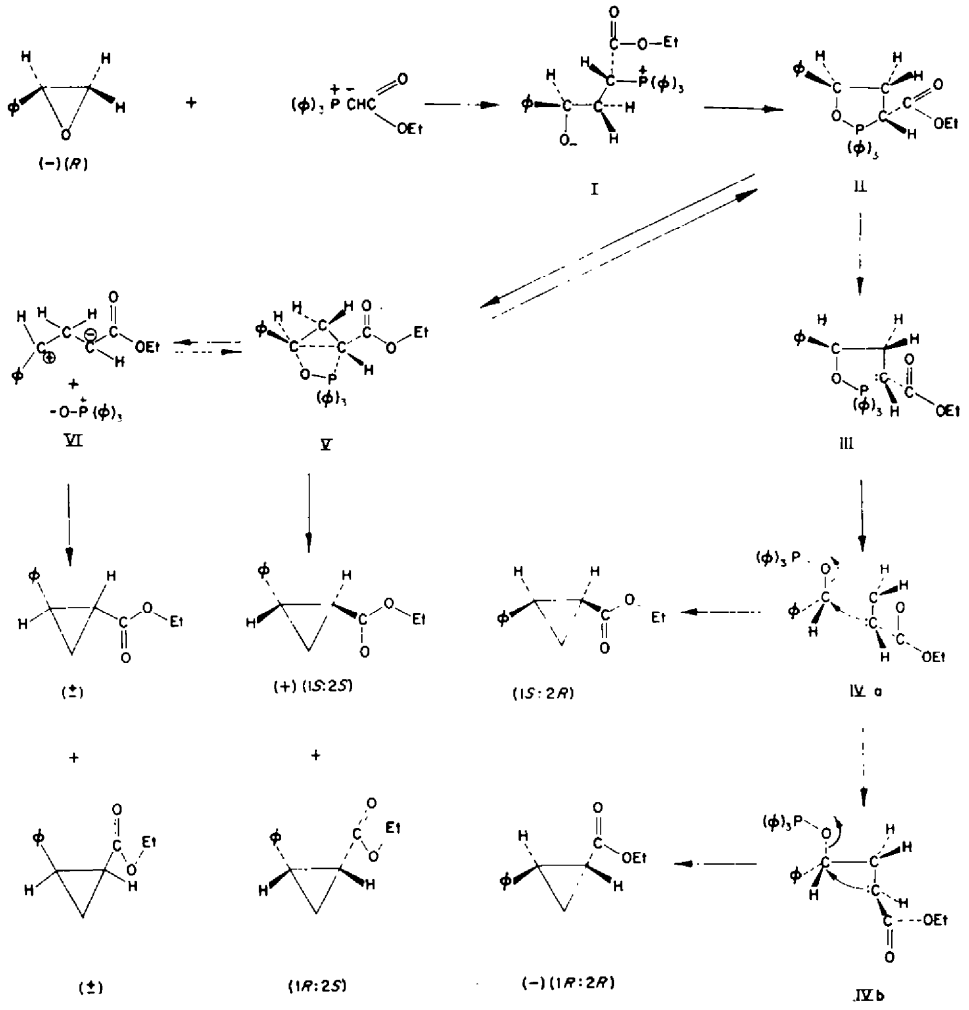
[7] E. Buchner and R. V. D. Heide, *Ber. Dtsch. Chem. Ges.* **38**, 3112 (1905) reported $[\alpha]_D$ −84·5°.

[8] D. B. Denney, J. J. Vill and M. J. Boskin, *J. Amer. Chem. Soc.* **84**, 3944 (1962).

[9] W. E. McEwen and A. P. Wolf, *J. Amer. Chem. Soc.* **84**, 676 (1962); W. E. McEwen and A. Blade-Font and C. A. VanderWerf, *Ibid.* **84**, 677 (1962).

[10] E. L. Eliel and D. W. Delmonte, *J. Org. Chem.* **21**, 596 (1956).

[11] I. Tömösközi, *Tetrahedron* **19**, 1969 (1963) has also determined the absolute configuration *trans*-2-phenylcyclopropanecarboxylic acid by using the method of asymmetric synthesis. This method, although it has had some success, is not unambiguous (see, H. M. Walborsky and C. G. Pitt, *J. Amer. Chem. Soc.* **84**, 4831 (1962)). In this case, fortunately, the results from asymmetric synthesis and direct chemical correlation are in agreement. However, see also reference 5.



formal sense this is analogous to the "diazo-exchange" that has been suggested[12] for the addition of diphenyldiazomethane to acrylate esters. The 1,3-dipolar addition[13] adduct postulated for the latter reaction resembles the intermediate V that is postulated here. The direct collapse of intermediate V would lead to the formation of *trans*-2-phenylcyclopropanecarboxylate with retained configuration and if this is indeed the case it would account for the low optical yields. On the other hand V can collapse to the zwitterion VI[14] which, if its lifetime is sufficiently long to permit rotation about its bonds, would lead to racemic product. At this time a decision between these alternatives cannot be made and it is possible that both intermediates V and VI are involved. It should be noted that no mention is made of the isolation of the *cis* acid from the condensation of styrene oxide with the phophorane[8] or phosphonate[11]

[12] H. M. Walborsky and C. G. Pitt, *J. Amer. Chem. Soc.* **84**, 4831 (1961).

[13] R. Huisgen, *Agnew. Chem. internat. Edit.* **2**, 565 (1963).

[14] This is the type of intermediate that may also be involved in the thermal isomerization of *trans*-2-phenylcyclopropanecarboxylate.

reagents. One might have expected some *cis* since both II and its epimer (H and COOEt inverted) would be expected to be formed. If the epimeric *cis* and *trans*-2-phenylcyclopropanecarboxylic acids have opposite signs of rotation, then this too might cause a loss in optical yield. However, it is more likely that the *cis* ester was either epimerized to the *trans* during saponification or that the *cis* acid was lost during the workup since it is more soluble in water than the *trans*.[6]

The Brewster method[15] of conformational asymmetry correctly predicts the absolute configurations of (−)-(1*S*:2*S*)-2-phenylcyclopropanecarboxylic acid, $[M]_D$ +210° (calc.);[15] $[M]_D$ +617° (found; $CHCl_3$), $[M]_D$ −505 (found; EtOH) and of (−)-(1*R*:2*R*)-*trans*-1,2-cyclopropanecarboxylic acid, $[M]_D$ −135° (calc.); $[M]_D$ −308° (found; EtOH), $[M]_D$ −321 (found; H_2O). It should, be noted that the agreement between the observed and calculated magnitudes of rotation is not very good. Considering the empirical nature of the method and since solvent interaction is not taken into consideration the results are not surprising. However, for the intermediate (−)-(1*R*:2*R*)-*trans*-1,2-bis(hydroxymethyl)cyclopropane $[M]_D$ −60° (calc.); $[M]_D$ −63° (found; EtOH)[16] and for (−)-(1*R*:2*R*)-*trans*-1,2-dimethylcyclopropane, $[M]_D$ −60° (calc.); $[M]_D$ −32° (found; diglyme)[17] the agreement between the calculated and the observed rotations is somewhat better.

Now that the absolute configurations of *trans*-1,2-cyclopropanecarboxylic acid and *trans*-2-phenylcyclopropanecarboxylic acid have been established we hope to report shortly on the asymmetric syntheses that lead to the formation of these acids.

EXPERIMENTAL

(+)-trans-2-*Phenylcyclopropanecarboxylic acid* was obtained by resolution of its quinine salt. The optically pure acid had b.p. 128°/0·18 mm, m.p. 25–26°, n_D^{22} 1·5530, $[\alpha]_D^{22}$ −311·7° (*c*, 1·776, 1 dm, EtOH); $[\alpha]_D^{14}$ 381·0° (*c*, 0·960, 1 dm, chloroform).

Ozonolysis of (+)-trans-2-*phenylcyclopropanecarboxylic acid.* A stream of crude ozone (ca. 3%) was passed through a solution of (+)-*trans*-2-phenylcyclopropanecarboxylic acid (1·7 g; b.p. 130·5°/0·12 mm, $n_D^{22\cdot5}$ 1·5523, $[\alpha]_D^{22}$ +300·2° in ethanol; 96·3% optical purity) in acetic acid at 40–50°. The reaction product was allowed to stand at room temp overnight with 20 ml 10% H_2O_2 and then evaporated to dryness on a water bath. Another 10 ml 10% H_2O_2 were added and evaporated to dryness again and this procedure was repeated 3 times. The crystalline product obtained was taken up in ether, filtered and pet. ether was added to the clear filtrate to cause precipitation of the product. The crystalline precipitate was sublimed (at 125–140°; 0·10 mm), to give 1·0 g (73%) of (+)-*trans*-1,2-cyclopropanedicarboxylic acid, (m.p. 160–163°, $[\alpha]_D^{22}$ 208·2° ethanol), which after one recrystallization from water melted at 169·5–170°. The IR-spectrum (KBr disc) was identical in every respect with that of an authentic sample. (Found C, 45·96; H, 4·73. Calc. for $C_5H_6O_4$: C, 46·16; H, 4·65%). $[\alpha]_D^{22}$ 227·9° (*c*, 2·342, 1 dm, ethanol); $[\alpha]_D^{14}$ +238·0° (*c*, 1·035, 2 dm, water).

Since this acid was derived from (+)-*trans*-2-phenylcyclopropanecarboxylic acid of 96·3% optical purity, the maximum rotation of (+)-*trans*-1,2-cyclopropanedicarboxylic acid should be $[\alpha]_D$ +247° in water.[7]

(−)-trans-1,2-*Bis(hydroxymethyl)cyclopropane.* Dimethyl-(−)-*trans*-1,2-cyclopropanedicarboxylate[18] (b.p. 98–99°/18 m, $[\alpha]_D^{22}$ −31·0 in ethanol; 35 g, 0·224 mole) in dry ether (500 ml) was added dropwise over 2·2 hr into a slurry of $LiAlH_4$ (30 g, 0·72 mole) in dry ether (500 ml) under effective stirring and cooling. After the addition of the ester was completed, the mixture was refluxed for an additional 5 hr. Water was added cautiously to the chilled mixture to decompose the excess $LiAlH_4$

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[15] J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5493 (1959).

[16] Based on the maximum $[\alpha]_D$ −61·5 calculated from $[\alpha]_D$ −3·2 of 5·2% optical purity.

[17] Based on $[\alpha]_D$ −46° (diglyme).[3]

[18] This dimethyl ester was prepared by the standard method with diazomethane from (−)-*trans*-1,2-cyclopropanedicarboxylic acid of $[\alpha]_D^{22}$ −23·0° (water); optical purity being 9·3% based on $[\alpha]_D$ −247°.

and the resulting hydroxides were dissolved in conc. HCl (ca. 280 ml). The acidified solution was continuously extracted with ether for 4 days. Ether was removed and the crude glycol was dried by azeotropic distillation with benzene. Distillation of the glycol gave 16·6 g (70·6%) pure product, b.p. 112–113°/3 mm, $[\alpha]_D^{22}$ −3·2° (*c*, 8·0, 2 dm, EtOH) n_D^{25} 1·4694. The IR-spectrum was identical in every respect with that of an authentic specimen.[19]

(−)-trans-1,2-*Bis(mesyloxymethyl)cyclopropane*. To a solution of the (−)-glycol (8·5 g, 0·083 mole) in 75 g dry lutidine (freshly distilled over BaO) were added dropwise 21 g mesyl chloride (0·18 mole, 10% excess) under effective stirring and cooling (0–7°). The mixture was stirred for 3 additional hr at 7° and then poured into ice-water containing 53 ml conc. HCl. After the solution was thoroughly stirred, white crystals were collected on a filter paper and washed with cold water. The crystalline product was dried over Drierite in a refrigerator since it decomposes at room temp. The yield of the crude glycol, which after a quick recrystallization from acetone–water (2: 7), m.p. 60–62 (dec), was 19 g (88·4%).

(−)-trans-1,2-*Dimethylcyclopropane*. The (−)-glycol mesylate (19 g, 0·073 mole) was added to a slurry of $LiAlH_4$ (30 g, 0·8 mole) in dry diglyme (300 ml) at room temp and the mixture was slowly warmed to 50°. The low-boiling product was collected in a receiver cooled in a dry ice–acetone bath which on distillation gave (−)-*trans*-1,2-dimethylcyclopropane; b.p. 28–29°, n_D^{16} 1·3699, yield 2·6 g (50·9%). The IR-spectrum (liquid phase) was identical with that of an authentic spectrum kindly provided by Dr. Derfer,[20] and also with a gas phase spectrum provided by Dr. Skell. Vapor phase chromatography of our sample by Dr. Skell[21] indicated the following contaminants (less than 0·1%); 2-, and 3-methylbutene, 1-pentene and *cis*-1,2-dimethylcyclopropane. The sample gave $[\alpha]_D^{5}$ −2·88° (neat); $[\alpha]_D^{22}$ −2·39° (*c*, 13·85, 1 dm, diglyme), optical purity 5·2% based on $[\alpha]_D^{20}$ −46·0° (diglyme);[8] $[\alpha]_{5461}^{20}$ −3·02° (*c*, 3·18, 0·4 dm, diglyme) on a Bendix Ericsson Automatic Polarimeter.

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[19] A. T. Blomquist and D. T. Longone, *J. Amer. Chem. Soc.* **81**, 2012 (1959).

[20] R. G. Kelso, K. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Amer. Chem. Soc.* **77**, 1751 (1955).

[21] We are indebted to Professor P. S. Skell for these determinations.