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PHOTOISOMERIZATION OF *cis*-2-BENZOYLCYCLOPROPANECARBOXYLIC ACID

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Abstract—The *cis* and *trans* isomers of 2-benzoylcyclopropanecarboxylic acid interconvert in refluxing alkaline solution with accompanying exchange of hydrogen in the 2-position and with retention of one asymmetric center. The photochemical conversion produces inactive *trans* acid from optically active *cis* acid and occurs in a hydroxylic solvent with no hydrogen exchange. A diradical mechanism is admissible for the photochemical process.

DURING a study of the base-catalyzed interconversion of the methyl esters of 2-benzoylcyclopropanecarboxylic acid, it became apparent that the materials were photosensitive and moreover that the free acids were susceptible to *cis-trans* isomerization in light as well as by bases. It is now recognized that such photoisomerizations are a common occurrence in cyclopropane chemistry[1–4] and the prevailing view is that these reactions proceed by way of a diradical intermediate. At the time, the nearest precedent was the photochemical interconversion of *cis*- and *trans*-1-benzyl-2-phenyl-3-(*p*-toluyl) ethylenimine observed by Cromwell and Hoeksema[5] who suggested the possibility of a photo-enolization mechanism. In our case a conventional enolization process was demonstrable through the base-catalyzed isomerization with accompanying hydrogen exchange and it was of interest to test the possibility of a photo-enolization in a similar way. On the other hand a diradical mechanism, suggested by the earlier work of Norman and Pitts[6] on quantum yields in the photolysis of cyclopropyl methyl ketone, was subject to a simple stereochemical test. If it occurred by scission of the 1,2-bond, an optically active starting material should isomerize to an optically inactive product. An enolization mechanism, if only one hydrogen is enolizable, would accomplish epimerization with retention of configuration on one of the asymmetric carbons.

When it is recalled that the alpha hydrogen in benzoylcyclopropane is notably inert toward bases,[7] the facility with which the keto-acids isomerize in alkaline solution seems remarkable. An equilibrium state, corresponding to 95% *trans* acid, is attained, for example, in less than one hour in refluxing sodium hydroxide solution. There can be no doubt as to the hydrogen alpha to the benzoyl group being the

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[1] W. von E. Doering and M. Jones, Jr., *Tetrahedron Letters* No. 12, 791 (1963).
[2] G. W. Griffin, E. J. O'Connell and H. A. Hammond, *J. Amer. Chem. Soc.* **85**, 1001 (1963).
[3] R. C. Cookson, M. J. Nye and G. Subrahmanyam, *Proc. Chem. Soc.* 144 (1964).
[4] G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson and G. Klose, *J. Amer. Chem. Soc.* **87**, 1410 (1965).
[5] N. H. Cromwell and H. Hoeksema, *J. Amer. Chem. Soc.* **71**, 708 (1949).
[6] J. N. Pitts, Jr. and I. Norman, *J. Amer. Chem. Soc.* **76**, 4815 (1954).
[7] F. J. Piehl and W. G. Brown, *J. Amer. Chem. Soc.* **75**, 5023 (1953).

labile hydrogen; the isomerization in heavy water is accompanied by the incorporation of one deuterium and the isomerization of a synthetic 1-deutero acid in normal water occurs without loss of deuterium. There is a clear indication here that the carboxylate group strongly assists the ionization of a hydrogen atom in the beta relationship to it possibly by a combination of electronic effects transmitted through the cyclopropane ring[8] and perhaps more importantly through carbanion stabilization by solvation.

That the ring structure remains intact in the base-catalyzed isomerization is demonstrated by the observation that optically active *cis* acid ($[\alpha]_D +112°$) gives rise to an optically active equilibrium mixture of isomers ($[\alpha]_D +176°$). An earlier suggestion[7] that the high protonic activity and ease of interconversion of multiply substituted cyclopropane derivatives might be associated with the formation of an open-chain anion can be discounted since the participation of the proposed anion in an equilibrium process would result in an inactive product.[9]

The photo-isomerization, like the base-catalyzed interconversion, strongly favors the *trans* isomer but it is accompanied to a greater degree by side reactions and a true photo-stationary state is not attained. In the *trans* → *cis* direction, the *cis* isomer is always a minor component, isolable with great difficulty; the significant observations therefore relate to isomerization in the direction, *cis* → *trans*.

Isomerization of an optically active *cis* acid, in ethanol under near ultraviolet (Blacklight) irradiation, was accompanied by a progressive disappearance of optical activity shown not to be due to accidental cancellation by the isolation of pure, inactive *trans* isomer. Moreover, by parallel measurements of optical rotation and of *cis* isomer concentration by IR analysis, which were in good agreement over a considerable range, the loss in activity was identified ratewise with the isomerization process and thus is not an unrelated racemization preceding or following isomerization.

The deuteration experiments relating to the possibility of photoenolization[10] fell short of completion for lack of a successful synthesis of *cis*-2-benzoylcyclopropanecarboxylic acid-2-d_1. The isomeric acid, deuterated in the 1 position, was converted to the corresponding *trans* form in ethanol without loss of deuterium. An indication that hydrogen in the 2 position is likewise not involved in the isomerization was provided by the absence of deuterium uptake on isomerization of the (normal) *cis* isomer in carboxyl-deuterated acetic acid. However, the significance of this observation is lessened by the possibility of a large isotope effect.

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[8] Other evidence bearing on the transmission of electrical effects by the cyclopropane ring has been reviewed by R. Fuchs, S. A. Kaplan, J. J. Bloomfield and L. F. Hitch, *J. Org. Chem.* **27**, 733 (1962). Additional examples of cooperative substituent effects in cyclopropane derivatives, evidenced by deuterium exchange reactions, have been noted in this laboratory [J. F. Neumer, Ph.D. Dissertation, The University of Chicago, December, 1957].

[9] A referee, making the point that other possibilities for a mechanism invoking an open-chain anion are not excluded, has proposed a mechanism involving two consecutive displacements with net retention of configuration on one asymmetric carbon. The first is a nucleophilic displacement on ring carbon 1 by the base, hydroxyl ion, to generate an intermediate represented as the enolate derivable from α-hydroxy-γ-benzoylbutyric acid. The second step is the re-cyclization with extrusion of hydroxyl ion. The comment may be made that this and other mechanisms not involving proton abstraction would demand serious consideration if it should prove that the isomerization is too fast to be accounted for in the simple proton abstraction mechanisms.

[10] An example of photo-enolization, detected by deuterium exchange, has been reported by N. C. Yang and C. Rivas, *J. Amer. Chem. Soc.* **83**, 2213 (1961).

What emerges from this study is, first, that the base-catalyzed and the photochemical isomerizations have no common element in mechanism, and secondly, that the latter occurs with racemization on two carbon atoms consistent with, and perhaps most easily explained by, a diradical dissociative mechanism.

EXPERIMENTAL

Diethyl 2-benzoyl-1,1-*cyclopropanedicarboxylate.* The diethyl ester was prepared by the method applied by Allen and Cressman[11] for the preparation of the dimethyl ester. Purification by treatment of the crude yellow product with $KMnO_4$ in aqueous acetone solution, followed by distillation and chromatographic fractionation on a silicic acid-Celite column, furnished an almost colorless liquid, b.p. 135·5–137° (0·4 mm), n_D^{20} 1·5162. (Found: C, 66·00; H, 6·50. $C_{16}H_{18}O_5$ requires: C, 66·21; H, 6·25%.)

2-*Benzoyl*-1,1-*cyclopropanedicarboxylic acid.* Hydrolysis of the diester was performed in 74% yield by refluxing with $Ba(OH)_2aq$ for 4 hr with vigorous stirring. The method of hydrolysis suggested by Allen and Cressman[11] was less satisfactory and gave red oils from which the product could be obtained only with difficulty. The acid, recrystallized from ether–ligroin, melted at 181–181·5° as compared with the reported 170–172°.

2-*Benzoylcyclopropanecarboxylic acid,* cis *and* trans. Thermal decarboxylation of the dibasic acid was carried out under high vacuum and at a bath temp of 171–186°. The product distilled rapidly as formed. Fractional crystallization of the distillate from acetone provided the *cis* acid, m.p. 146·5–147·5° (lit.[11] 145°) in 45% yield and a small amount (2·5%) of the *trans* acid, m.p. 122–123° (lit.[11] 118–120°) after several recrystallizations from water.

Methyl 2-*benzoylcyclopropanecarboxylate,* cis *and* trans. Esterification of the separate acids by diazomethane produced the *cis* ester, purified by sublimation, m.p. 21–32°, and the *trans* ester as a colorless liquid, b.p. 303° (755 mm) and 110° (0·5 mm), n_D^{20} 1·5417. Verification of the structural assignments was accomplished by reaction of either the *cis* acid or the *cis* ester with hydrazine hydrate in EtOH to form a pyridazinone, m.p. 166–167° (lit.[12] 165°).

Base-catalyzed isomerization. The conversion of either *cis* or *trans* acid to an equilibrium mixture in refluxing 0·09N NaOH was followed by m.p. observations on material recovered at intervals. The m.p. of the *cis* isomer was at first strongly depressed, e.g. 102° at 15 min; it then increased to 121–122° with no further change after 45 min. The composition of the equilibrium mixture was estimated from measurements on the *cis* peak at 733 cm^{-1} in KBr pellets, standardized on known mixtures, to be 5–6% *cis* isomer.

Treatment of the *cis* acid with 2N $Ba(OD)_2$ in D_2O, 45 min at reflux temp, with recovery by way of the Aq salt to normalize carboxyl hydrogen, furnished a *trans* acid, m.p. 121·5–123°, containing 0·99 ± 0·01 atoms D per molecule.[13] The material exhibited strong peaks at 736, 874, 995, 1185 and 1360 cm^{-1} not present in the normal *trans* acid. An identical material was obtained from the normal *trans* acid on deuteration by a similar procedure.

For comparison, a sample of *trans*-1-deutero acid was prepared, together with the *cis* isomer, by decarboxylation of carboxyl-deuterated 2-benzoyl-1,1-cyclopropanedicarboxylic acid. This *trans* acid had characteristic peaks at 850, 975 and 1185 cm^{-1}. The synthetic *cis*-1-deutero acid by deuterium analysis, and also the *trans*-1-deuteroacid by inference, contained only 0·50 atoms D, evidently through some inadvertent failure to maintain complete deuteration during the synthesis[14] of the dicarboxylic acid. A mixture of the synthetic *cis*- and *trans*-1-deutero acids, the former predominating (m.p. 105–136°), was converted to an equilibrium mixture on refluxing 45 min in 0·09N NaOH; the recovered *trans* acid, m.p. 121–122·5°, was spectroscopically identical with the pure synthetic deuterated acid. These observations show that H in the 1-position does not exchange under the conditions of isomerization and that the *trans* acid formed on isomerization of *cis* acid in D_2O is deuterated in the 2-position.

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[11] C. F. H. Allen and H. W. J. Cressman, *J. Amer. Chem. Soc.* **55,** 2953 (1933).

[12] G. Maier, *Angew. Chem.* **75,** 920 (1963).

[13] Deuterium analyses were performed by the method of J. Graff and D. Rittenberg, *Analyt. Chem.* **24,** 878 (1952).

[14] D. J. G. Ives and M. R. Nettleton, *J. Chem. Soc.* 1085 (1948).

Optically active cis-2-*benzoylcyclopropanecarboxylic acid.* An optically active specimen of the *cis* acid was obtained through the brucine salt, m.p. 205–206°, $[\alpha]_D^{24\cdot5}$ +15·4° (c 1·066, water), that had been purified by thorough extraction with hot acetone followed by 3 recrystallizations from MeOH–acetone. A basic solution of the salt, after extraction with $CHCl_3$, was acidified and the resulting acid was sublimed at 145° (0·5 mm), m.p. 132·5–133·5°, $[\alpha]_D^{23\cdot8}$ +112° (c 0·759, EtOH). A sample of this material was isomerized in refluxing 0·10N NaOH for 45 min; the recovered acid, purified by vacuum sublimation, exhibited increased optical rotatory power, $[\alpha]_D^{27\cdot2}$ +176° (c 0·319, EtOH).

Photochemical isomerization. The isomerization of the *cis* acid in acetic acid, MeOH or ether solution with light from a Sylvania F8T5/BLB source was invariably accompanied by the formation of material other than the *trans* isomer. This greatly complicated product isolation and made impractical the observation of a photo-stationary state. Nevertheless the *trans* isomer was identified, by mixture m.p. and IR spectrum, as the major component of the sublimable portion of the phototransformed material. The irradiation of 300 mg *cis*-2-benzoylcyclopropanecarboxylic acid-1-*d* (containing 0·50 atoms D) in 25 ml 95% EtOH for 20 hr produced a mixture form which 15 mg pure *trans* acid, with unchanged D content, was isolated. An exposure of a solution of 58 mg (normal) *cis* acid in 10 ml carboxyl-deuterated acetic acid for 16 hr resulted in recovery of 13 mg purified *trans* acid, m.p. 121·5–122·5°, containing no deuterium detectable by IR spectrum.

Isomerization of the optically active *cis* acid, 270 mg in 25 ml 95% EtOH, irradiated with agitation over a 24 hr period, occurred with progressive decrease in the observed optical rotation from −0·83° to −0·02° (1-dm tube). There was recovered 28 mg pure *trans* acid, m.p. 122–123°, which was optically inactive. In a more detailed study, 300 mg *cis* acid, $[\alpha]_D$ −76°, in 25 ml 95% EtOH was irradiated and aliquots were removed at scheduled intervals for observations on optical rotation and IR spectrum. The IR analysis relied mainly on peaks at 643 and 729 cm^{-1} as characteristic for the *trans* and *cis* acids, respectively. The concentration of *trans* acid first increased, as the radiation progressed, to a maximum concentration at 18–25 hr, corresponding to 45% of the original concentration of the *cis* isomer, and then decreased. At an earlier stage, 9–12 hr, the *trans* acid amounted to 53% of the *cis* acid consumed. The optical activity diminished by 70% over the first 12 hr and had virtually disappeared at 24 hr. The specific rate constants, over the first 12 hr, were $2\cdot7 \pm 0\cdot1 \times 10^{-5}$ sec^{-1}, based on loss of activity, and $2\cdot5 \pm 0\cdot2 \times 10^{-5}$ sec^{-1}, based on the disappearance of *cis* isomer by IR analysis.