Citraconic Anhydride Photodimer. Structure and Stereochemistry

H. Ziffer and J. R. Williams

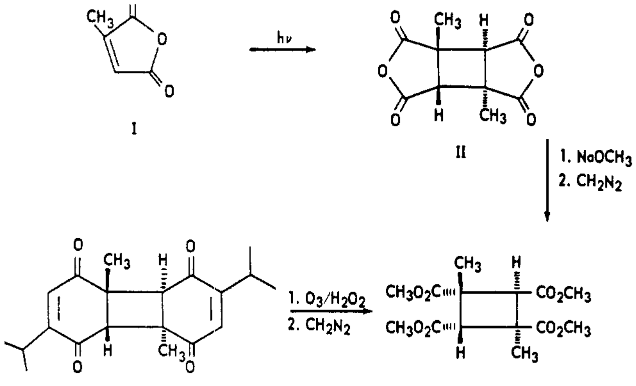
National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received October 2, 1967

As part of an investigation of the stereochemistry of cyclobutane photodimers we have reexamined the sensitized photodimerization of citraconic anhydride (I) first reported by Schenck, *et al.*,[1] and have established the structure of the dimer as II. Four dimers with a *cis*-ring junction are possible[2] and, although Schenck, *et al.*, did not determine whether the dimer of citraconic anhydride was head-to-head (h–h) or head-to-tail (h–t), they did express a preference for an *anti* configuration, reasoning by analogy with the sensitized dimerization of coumarin. It is now possible to distinguish between h–h and h–t dimerization from an examination of the natural abundance C^{13}–H nmr spectrum. This technique was first employed by Anet[3] for the thymine dimer and has been used recently by several investigators in analogous studies.[4]

The photodimer (II) (Scheme I) was prepared as described by Schenck, *et al.;* its nmr spectrum in deuterated dimethyl sulfoxide showed two singlets at δ 3.81 (1 H) and 1.47 (3 H). The dimer was then converted into the tetramethyl ester described by Schenck *et al.;* its nmr spectrum in deuteriobenzene showed four singlets at δ 1.62 (3 H), 3.42 (3 H), 3.50 (3 H), and 3.93 (1 H). The low-field C^{13}–H satellite of the cyclobutane proton at δ 3.93 was observed as a singlet with $J = 142 \pm 2$ cps, lying between the 136 cps value reported by Foote[5] for cyclobutane and the 153 ± 2 cps value reported by Anet[3] for a thymine photodimer. The dimer therefore was formed by h–t dimerization.

Scheme I



The question of the stereochemistry about the cyclobutane ring was resolved by relating II to the photodimer of thymoquinone, whose structure was recently determined by X-ray crystallography as III.[6] Oxidation of III would yield a *cis,anti,cis*-1,3-dimethyl-1,2,3,4-cyclobutanetetracarboxylic acid corresponding to one of the two possible structures for the tetracarboxylic acid derived from II. The *cis,anti,cis*-1,3-dimethyl-1,2,3,4-tetracarbomethoxycyclobutane (IV), obtained by ozonolysis of III and methylation of the acid, was identical with the tetramethyl ester derived from II by hydrolysis and methylation. The complete stereochemistry of the citraconic anhydride photodimer is therefore established as II, a head-to-tail dimer whose stereochemistry about the cyclobutane ring is *anti*.

The hydrolysis of II using sodium methoxide as described by Schenck, *et al.*, and methylation (diazomethane) afforded the solid ester IV described by these investigators as well as a smaller quantity of a second tetramethyl ester. The nmr spectrum of this second ester showed absorption at δ 3.77 (3 H) and 3.66 (6 H) due to the methyl esters, δ 3.42 (2 H) due to the cyclobutane protons, and δ 1.70 (3 H) and 1.59 (3 H) due to methyl groups on the cyclobutane ring.[7] The spectrum is consistent with a *cis,anti,trans*-1,3-dimethyl-1,2,3,4-tetracarbomethoxycyclobutane, in which one of the carboxylic acid groups on a carbon bearing a hydrogen has been epimerized in the hydrolysis with strong base. Treatment of the pure, *cis,anti,cis*-tetramethyl ester with base under the same conditions resulted in the formation of a mixture of the two esters. The isomerization during the hydrolysis was avoided by use of acidic conditions.

Experimental Section

The C^{13}–H satellite spectrum was determined in deuteriobenzene containing tetramethylsilane as an internal standard (δ 0.0 ppm) with a Varian A-60 spectrometer in conjunction with a C-1024 computer of average transients.

Ozonolysis of the Thymoquinone Photodimer.—A solution of thymoquinone photodimer (500 mg), mp 201–202° (lit.[8] mp 201–202°), in 90% aqueous acetic acid was ozonized at 25° for 25 hr. Oxidative decomposition was achieved by allowing the reaction mixture to stand 3 days at room temperature in a solution of 35 ml of 30% hydrogen peroxide. The excess peroxide was destroyed with platinum-on-charcoal catalyst. The catalyst was filtered off and the filtrate concentrated to about 5 ml on a rotatory evaporator. Upon standing overnight the solution deposited 200 mg of acid. Methylation of the acid with diazomethane afforded *cis,anti,cis*-1,3-dimethyl-1,2,3,4-tetracarbomethoxycyclobutane (II) as diamond-shaped prisms (120 mg), mp 75.5–77°, from methanol at −10°: $\nu_{max}^{CHCl_3}$ 1734 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.03; H, 6.42.

Reactions of Citraconic Anhydride Photodimer.—Citraconic anhydride photodimer, prepared according to the method of Schenck, *et al.*,[1] was hydrolyzed by refluxing with 6 *M* methanolic sodium methoxide and methylated with diazomethane to yield the corresponding tetramethyl ester, mp 75.5–77° (lit.[1] mp 73–73.5°). This ester was identical (melting point, mixture melting point and ir and nmr spectra) with that obtained by ozonolysis of thymoquinone photodimer.

The mother liquors from recrystallization of the tetramethyl ester were chromatographed on silica gel and elution with ether–hexane (1:1) yielded more IV (1.2 g) followed by ***cis,anti,trans*-1,3-dimethyl-1,2,3,4-tetracarbomethoxycyclobutane** which crystallized as prisms, mp 60–63°, from methanol at −10°: $\nu_{max}^{CHCl_3}$ 1745 cm^{-1}.

---

[1] G. O. Schenck, W. Hartmann, S. P. Mannsfeld, W. Metzner, and C. H. Krauch, *Chem. Ber.*, **95**, 1642 (1962).

[2] Two racemates and two *meso* compounds.

[3] R. Anet, *Tetrahedron Letters*, 3713 (1965).

[4] H. Ziffer, N. E. Sharpless, and R. O. Kan, *Tetrahedron*, **22**, 3011 (1966); G. M. Blackburn and R. J. H. Davies, *J. Chem. Soc.*, 1342 (1966).

[5] C. S. Foote, *Tetrahedron Letters*, 579 (1963).

[6] D. Rabinovich and G. M. J. Schmidt, *J. Chem. Soc., Sect. B*, 144 (1967).

[7] The compound was homogeneous on several tlc systems and on several glpc columns.

[8] E. Zavarin, *J. Org. Chem.*, **23**, 47 (1958).

Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.13; H, 6.58.

Hydrolysis of II (300 mg) using a 1:1 mixture of concentrated hydrochloric acid (10 ml) and water (10 ml) was effected by heating on a steam bath for 6 hr. The water and hydrochloric acid were removed *in vacuo* and the crude acid (solid) was dissolved in diethyl ether–methanol and methylated with excess diazomethane in ether. An nmr spectrum of the crude methyl ester (~250 mg) was identical with the solid IV obtained by alkaline hydrolysis. Also the nmr spectrum of the crude methyl ester showed the absence of *cis,anti,trans*-1,3-dimethyl-1,2,3,4-tetracarbomethoxycyclobutane, 3–5% of which could easily be detected in the nmr spectrum of a mixture of the two esters.

Epimerization of *cis,anti,cis*-1,3-Dimethyl-1,2,3,4-tetracarbomethoxycyclobutane (IV).—IV (100 mg) was hydrolyzed, according to the method of Schenck, and methylated with diazomethane. The nmr spectrum of the mixture of esters with peaks at δ 3.79, 3.75, 3.72, 3.42, 1.73, 1.62, and 1.52 corresponded to a mixture of IV and the unsymmetrical ester. Thin layer chromatography of the mixture on silica gel plates using ether–hexane gave two spots corresponding to the two esters.

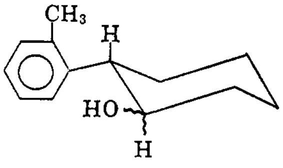
The Use of Nuclear Magnetic Resonance as a Monitor in Optical Resolutions[1a]

DONALD R. GALPIN[1b] AND ALAIN C. HUITRIC

College of Pharmacy, University of Washington, Seattle, Washington 98105

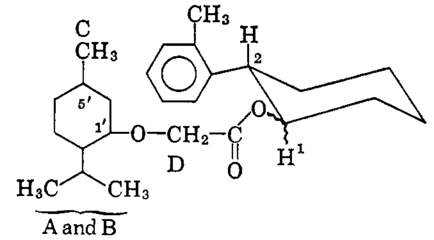
Received August 21, 1967

There are a number of examples in the literature of the magnetic nonequivalence of geminal hydrogens and geminal methyl groups in the vicinity of an asymmetric center[2-5] and also of magnetic nonequivalence of corresponding hydrogens in diastereomers.[6,7] Observed chemical shift differences are most notable when there is a group in the molecule which possesses a large inherent magnetic anisotropy, such as phenyl,[3,4,6,7] carboxyl,[2,4,5,7] or nitrile[5] groups. Recently, Raban and Mislow[7] have demonstrated the applicability of nmr spectroscopy to the analysis of mixtures of diastereoisomers as a method of determining optical purity. We have successfully utilized this method to follow the resolution of *trans*-2-*o*-tolylcyclohexanol (1) and *cis*-2-*o*-tolylcyclohexanol (2) through their (−)-menthoxyacetate esters by taking advantage of the nonequivalence of the methylene hydrogens of the acetate portion (hydrogens D) and the isopropyl methyl groups (A and B) of the menthol moiety and of the fact that these nonequivalences are different for members of a pair of diastereoisomeric esters. The signals of the methylene hydrogens were the most useful in following the progress of separation of the diastereomers. Basic hydrolysis of the diastereomers, reported elsewhere,[8] yielded the optically active alcohols. The assignment of the absolute configurations of these optically active alcohols is reported in another communication.[8]



1, OH equatorial; H axial
2, OH axial; H equatorial

Compound 1 was prepared from cyclohexene oxide and the lithium derivative of *o*-bromotoluene following the method of McKusick.[9] The *cis* alcohol 2 was obtained by a stereospecific reduction of 2-*o*-tolylcyclohexanone (3) with triisobutylaluminum[10] yielding predominantly the axial isomer. The (−)-menthoxyacetate esters of 1 (6 and 7) and 2 (8 and 9) were synthesized following the procedures outlined by Ingersoll.[11] The esters 6 and 7 were solids, whereas 8 and 9 were thick viscous liquids. The details of their separation are described in the Experimental Section.



6 and **7** H-1, axial
8 and **9** H-1, equatorial

The important chemical shifts of the four esters are given in Table I. The pertinent portions of the spectra of the optically pure esters of the *trans* alcohol, compounds 6 and 7, are shown in Figure 1. The nonequivalence of the two methylene hydrogens D in a given ester is clearly demonstrated. The signals of these methylene hydrogens for each diastereomer ap-

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR THE (−)-MENTHOXYACETATE ESTERS OF *trans*- AND *cis*-2-*o*-TOLYLCYCLOHEXANOL[a]

	CH_2 (D)		CH_3 (C)[b]	Isopropyl CH_3
Compd	τ, ppm	J_{gem}, Hz	τ, ppm	(A and B)[c] τ, ppm
6	6.16	16.0	9.15	9.15
	6.34			9.30
7	6.16	16.0	9.15	9.15
	6.36			9.28
8	6.08[d]		9.13	9.11
				9.21
9	5.98	16.0	9.10	9.14
	6.18			9.30

[a] The spectra were obtained in chloroform or chloroform-*d* at 60 MHz and 37°. The chemical shifts of the D hydrogens represent the calculated centers of gravity of the signals of the AB systems. The centers of gravity are approximated for the doublets of the methyl hydrogens because the uncertainty of the chemical shifts of the coupled methine hydrogens precludes accurate calculations. [b] The two components of the doublets were not always discernible because of overlapping of signals. [c] Doublets with separation of 7.0 Hz due to coupling with the isopropyl methine hydrogen. [d] Identical chemical shifts, single peak.

---

(1) (a) This investigation was supported in part by Research Grant MH 11942-01 from the National Institute of Mental Health, U. S. Public Health Service. (b) To whom all correspondence should be addressed at the College of Pharmacy, Washington State University, Pullman, Wash. 99163.

(2) E. I. Snyder, *J. Am. Chem. Soc.*, **85**, 2624 (1963).

(3) G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964).

(4) N. S. Bowman, D. E. Rice, and B. R. Switzer, *ibid.*, **87**, 4477 (1965).

(5) H. J. Jakobsen, P. Madsen, and S. O. Lawesson, *Tetrahedron*, **22**, 1851 (1965).

(6) J. L. Mateos and D. J. Cram, *J. Am. Chem. Soc.*, **81**, 2756 (1959).

(7) M. Raban and K. Mislow, *Tetrahedron Letters*, 4249 (1965).

(8) D. R. Galpin and A. C. Huitric, *J. Pharm. Sci.*, in press.

(9) B. C. McKusick, *J. Am. Chem. Soc.*, **70**, 1976 (1948).

(10) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

(11) A. W. Ingersoll in "Organic Reactions," Vol. II, R. Adams, W. E. Bachman, L. F. Fieser, J. R. Johnson, and H. R. Snyder, Ed., John Wiley and Sons, Inc., New York, N. Y., 1944, Chapter 9, p 376.