Saponification of Dimethyl *cis*-2,6-Diphenyl-4-oxocyclohexane-1,1-dicarboxylate. A Reinvestigation

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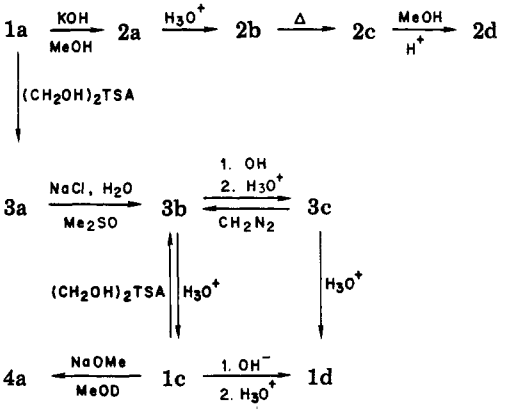
The saponification of dimethyl *cis*-2,6-diphenyl-4-oxocyclohexane-1,1-dicarboxylate was reported over 50 years ago to produce the corresponding diacid. The ease with which the reaction occurred is surprising considering the steric factors involved. We have found that the saponficiation does not proceed as reported but occurs by a retrograde Michael condensation to give an unsaturated acyclic diacid. This diacid was converted to the unsaturated monoacid and its methyl ester which are isomeric with the erroneously reported cyclic monoacid and its ester. The authentic cyclic ester, methyl 2,6-diphenyl-4-oxocyclohexane-1-carboxylate, was synthesized from the cyclic diester by using the decarbalkoxylation procedure of Krapcho. ^{13}C NMR evidence showed that an unexpected inversion of configuration occurred at C-2 during the decarbmethoxylation reaction.

An interest in the configurations and conformations of polysubstituted cyclohexanones led us to a reexamination of work reported by Kohler in 1924. Kohler had shown that cyclohexanones were prepared easily by the Michael condensation of 1,5-disubstituted 1,4-pentadien-3-ones with malonic esters[2] and with methyl cyanoacetate.[3] For example, dimethyl malonate and dibenzalacetone combined in the presence of sodium methylate to give dimethyl *cis*-2,6-diphenyl-4-oxocyclohexane-1,1-dicarboxylate (**1a** Chart I) in excellent yield.[2] Kohler further stated that the oxo diester **1a** was saponified to the dipotassium salt whose diacid (**1b**) was decarboxylated to the oxo monoacid **1d**. Fischer esterification of **1d** gave a methyl ester formulated as **1c**.[2] The structure proof for these compounds was based upon melting points, elemental analyses, and a modicum of qualitative reactions; no yields were given.[2] Recognizing the surprising ease with which the hindered ester groups in **1a** were reported to saponify and the unavailability of spectroscopic methods at the time of Kohler's publication, we duplicated these reactions in order to determine if they in fact do represent a facile means of preparing the highly substituted cyclohexanones in which we were interested.

Discussion

Compound **1a** was prepared in good yield according to the method of Kohler and Dewey.[2] When the oxo diester **1a** was treated with methanolic potassium hydroxide solution,[2] an insoluble salt was obtained whose ^1H NMR spectrum showed doublets characteristic of the coupling of two trans vinyl hydrogens (Scheme I) The spectrum is inconsistent with Kohler's assumption that the material is the salt of 3,5-diphenyl-4-oxocyclohexane-1,1-dicarboxylic acid (**1b**). Acidification of the salt (**2a**) and recrystallization of the product from boiling water[2] produced a diacid dihydrate in minute yield whose melting point was in agreement with that reported[2] for **1b**. The UV spectrum [289.8 nm (ϵ 21 000)] of this compound, however, was no match for constitution **1b** while it was in excellent agreement with the absorption of the model compound benzalacetone [286 nm (ϵ 22 500)].[4] The ^1H NMR spectrum of the diacid showed the characteristic vinyl hydrogen absorptions; the diacid dihydrate obtained by Kohler[2] therefore must be (3-oxo-1,5-diphenyl-4-pentenyl)propanedioic acid (**2b**).

Scheme I



Decarboxylation of **2b** was carried out in the manner described,[2] yielding an oil from which a monoacid could be isolated in low yield. The melting point of this acid checked with the value given by Kohler[2] for **1d**, but UV and ^1H NMR evidence correlate with the isomeric acyclic acid, *trans*-3,7-diphenyl-5-oxo-6-heptenoic acid (**2c**). Finally, Kohler converted the monoacid to a methyl ester, formulated as **1c**, with a melting point of 107 °C.[2,3] Fischer esterification of our monoacid **2c** gave a methyl ester whose UV, IR, and ^1H NMR data fit structure **2d**. Two forms of the ester were obtained (mp 91.5–92 and 82.5–84 °C), but all spectra of the materials were identical. The two forms were obtained randomly when the ester was recrystallized from methanol and therefore are polymorphic structures of **2d**. The model compound benzalacetophenone shows a similar behavior.[5] At no time was a methyl ester with a melting point of 107 °C obtained as reported by Kohler.[2,3] Whether the 107 °C compound is yet another polymorph of **2d** or represents the product of an unpredicted ring closure to **1c** during the esterification procedure conducted by Kohler[2] remains an unanswered question.[6] The melting point of 107 °C in fact checks well, although probably fortuitously, with the value we have found for the authentic cyclic oxo acid **1d** (vide infra).

It is apparent that treatment of the oxo diester **1a** with methanolic potassium hydroxide proceeds through a retrograde Michael condensation and not a simple saponi-

(1) (a) National Science Foundation Undergraduate Research Participant, summer 1980. (b) National Science Foundation Undergraduate Research Participant, summer 1979.

(2) E. P. Kohler and C. S. Dewey, *J. Am. Chem. Soc.*, **46**, 1267 (1924).

(3) E. P. Kohler and R. W. Helmkamp, *J. Am. Chem. Soc.*, **46**, 1018 (1924).

(4) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Macmillan, New York, 1964, p 107.

(5) R. Adams, J. R. Johnson, and C. F. Wilcox, Jr., "Laboratory Experiments in Organic Chemistry", 7th ed., Macmillan, New York, 1979, p 356.

(6) Samples of Professor Kohler's compounds are not available for comparison. We thank Mr. Warren Stockwood of Harvard University for this information.

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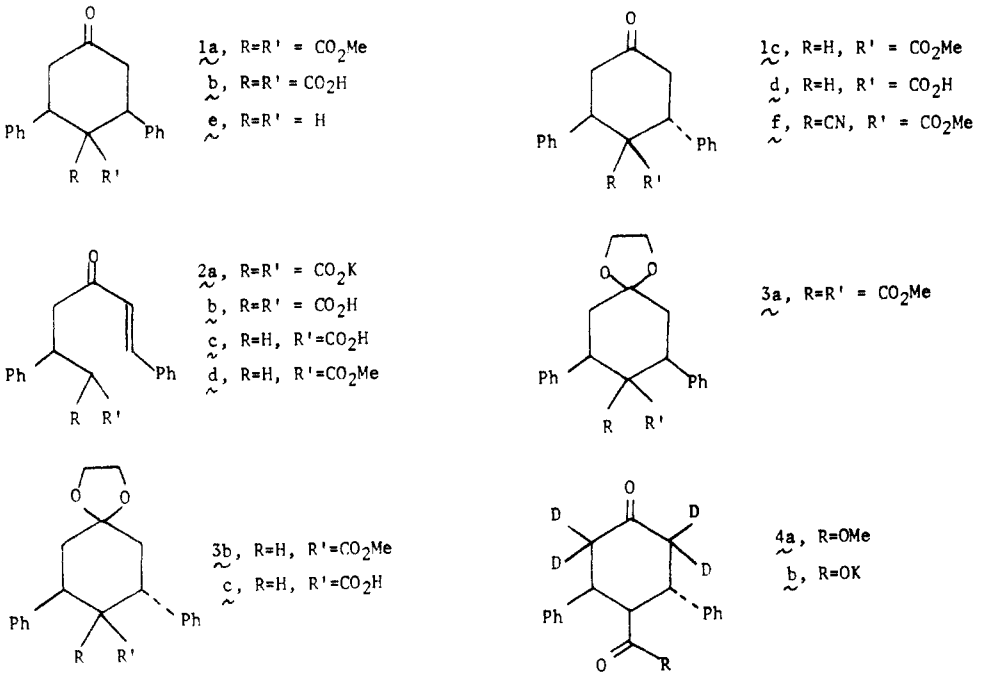
Chart I



fication of the ester groups. While the reaction is a complex one that leads to much intractable material,[2] the ability to isolate the salt **2a** apparently results from its insolubility in methanol, thus removing it from further retrograde Michael and aldol condensations. The earlier claim by Kohler[3] that the ester **1c** was obtained through a similar series of reactions from methyl 1-cyano-*cis*-2,6-diphenyl-4-oxocyclohexane-1-carboxylate is under investigation. The reported[7] saponification of the ethyl ester of the cyano compound also is being examined.

In order to prepare the authentic cyclic oxo acid **1d**, we opted for the procedure of Krapcho,[8] whereby malonic esters and related compounds undergo smooth decarbalkoxylation when heated in wet dimethyl sulfoxide in the presence of salts such as sodium chloride or lithium chloride. When **1a** was employed in an attempt to produce the oxo monoester **1c**, the reaction mixture darkened without the evolution of carbon dioxide. In one run it was possible to separate (column chromatography) a modest yield of dibenzalacetone from the complex mixture of products, indicating a complete retrograde Michael condensation under the conditions of the reaction.

The oxo ester **1a** therefore was converted to the ethylene ketal **3a** in excellent yield by a standard procedure. Ketals are known to survive the decarbalkoxylation conditions,[8a] and when **3a** was heated in dimethyl sulfoxide containing water and sodium chloride, the ketal monoester **3b** was obtained in 93% yield by crystallization of the reaction product. The reaction was uncomplicated by the production of mixtures of diastereomers as often occurs in decarbalkoxylations which may produce isomeric compounds.[8a,9]

Hydrolysis of the ketal monoester **3b** gave the oxo ester **1c** in 87% yield. The UV spectrum of **1c** exhibited a weak $n\rightarrow\pi^*$ absorption (287.7 nm, ϵ 42.9) typical of a cyclohexanone as well as the characteristic B bands of alkyl substituted benzenes.[10] Saponification of **1c** with potassium hydroxide in aqueous ethanol at reflux temperature produced the oxo acid **1d** in 86% yield. Saponification of the ketal ester **3b** gave the ketal acid **3c** (90% yield).

In order to determine that no epimerizations occurred at C-1 during the given saponification and hydrolysis reactions, the ketal acid (**3c**) was reconverted to the ketal ester (**3b**) by treatment with diazomethane in ether solution,[11] the oxo ester (**1c**) was transformed to the ketal ester (**3b**), and the ketal acid (**3c**) was hydrolyzed to the oxo acid (**1d**). Compounds **1c**, **1d**, **3b**, and **3c** therefore have the same configuration at C-1.

No isomerization of the ketal monoester **3b** occurred after treatment with sodium methylate in methanol under reflux for 24 hours and no exchange at C-1 took place when **3b** was heated for two hours in methanol-d_1 containing sodium methylate. Compounds **1c**, **1d**, **3b**, and **3c** therefore are the thermodynamically stable isomers with respect to the configuration at C-1.

Configuration Determinations

The preparation of **1a** was the subject of a recent study by Otto,[12] who correctly determined **1a** to be the cis (meso) isomer by examination of its ^1H NMR spectrum in $CDCl_3$ solution. We have found that the ABX pattern displayed by protons at C-2(6) and C-3(5) in **1a**, however, is not interpretable from the 60-MHz spectrum as reported,[12] even at high amplitude. While the X portion yielded a four-line signal, only three lines were readily apparent for the AB portion of our spectrum. When the spectrum of **1a** was obtained at 300 MHz, the characteristic eight-line AB pattern was observed along with the four-line X portion. The 300-MHz spectrum was analyzed according to the methods of Garbisch[13] and of Bible;[14] the results are

(7) C. S. Marvel and A. C. Moore, *J. Am. Chem. Soc.*, **71**, 28 (1949).
(8) (a) A. P. Krapcho and J. F. Weimaster, *J. Org. Chem.*, **45**, 4105 (1980). (b) A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, and W. P. Stephens, *ibid.*, **43**, 138 (1978), and references cited therein.
(9) H. D. Banks, *J. Org. Chem.*, **46**, 1743 (1981).
(10) R. M. Silverstein, G. C. Bassler, and T. C. Morrilll, "Spectrometric Identification of Organic Compounds", 3rd ed., Wiley: New York, 1974, pp 242, 248.
(11) The oxo ester **1d** was unchanged after 48 h when heated under reflux in methanol containing a catalytic amount of H_2SO_4. The hindrance to esterification in these 2,6-diphenyl-1-carboxylic acids is illustrated further by the conversion of **3c** to **3b** by diazomethane in only 28% yield. See the Experimental Section.
(12) H. H. Otto, *Monatsh. Chem.*, **104**, 526 (1973).

Table I. ^{1}H NMR Data for Compound 1a[a]

	δ[b]			J, Hz			
	H-2(6)a	H-3(5)a	H-3(5)e	gem	aa	ae	$J_{aa} + J_{ea}$, Hz
300 MHz	4.36	3.07	2.97	−16.4	11.1	4.4	15.74
60 MHz[c]	4.41	3.1	2.9	−13.5	9	7	15.8

[a] Cyclohexanone ring hydrogen only. At 300 MHz, δ(Me) 3.37; at 60 MHz, δ(Me) 3.32.[12] [b] Shifts in parts per million downfield from Me$_4$Si in CDCl$_3$ solutions. [c] Values from ref 12.

Table II. ^{13}C NMR Signals of Cyclohexanones and Derivatives

	shift[a]						
compd	C-1	C-2	C-3	C-4	C-5	C-6	others
1a	63.99	44.07	42.48	210.5	42.48	44.07	Me, 51.89; Ar, 139.78 (ipso), 128.56, 128.16, 127.53; ester C=O, 171.05
1d	52.20	44.38	41.20	213.47	40.77	43.21	Ar, 142.49 and 140.08 (ipso), 128.92, 128.54, 127.70, 127.34, 127.20; acid C=O, 182.23 and 177.78[b]
1e[c]	40.68	43.63	48.23	208.82	48.23	43.63	
1f	55.70	48.21	42.92	206.1	41.67	42.45	Me, 53.09; Ar, 137.42 and 136.77 (ipso), 128.78, 128.47, 127.94; ester C=O, 166.66; CN, 118.27
3b	50.88	39.49	40.17	109.50	40.05	36.13	Me, 52.73; Ar, 144.12 and 141.79 (ipso), 128.51, 128.31, 128.07, 127.28, 126.62, 126.50; ester C=O, 173.48; ketal, 64.30, 64.06
3c	51.93	39.08	40.01	109.29	39.92	36.14	Ar, 143.86 and 141.42 (ipso), 128.50, 128.29, 128.12, 127.29, 126.67, 126.52; acid C=O, 178.37; ketal, 64.23, 64.04

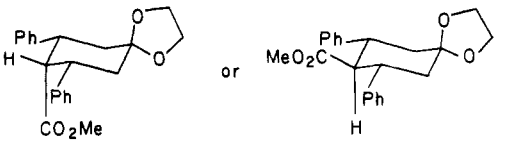
[a] Shifts in parts per million downfield from Me$_4$Si in CDCl$_3$ solutions. [b] Two signals presumably due to free and hydrogen bonded species. [c] Values for 1e from ref 15. Carbons renumbered to make C-4 the C=O for consistency with other compounds.

listed in Table I along with the values obtained by Otto at 60 MHz.[12] When the spectrum of **1a** was determined in CD$_3$CN at 300 MHz, the cyclohexanone ring hydrogens exhibited a clean A$_2$X pattern. First-order analysis gave $J_{ae} = J_{aa} = 7.7$ Hz. (See Experimental Section for all signals of **1a** in CD$_3$CN). In CDCl$_3$ and CD$_3$CN solutions at 60 *and* 300 MHz the diastereotopic methyl groups in **1a** absorb fortuitously at the same field position. Although a single average signal for these methyls would be anticipated for rapidly equilibrating conformations of constitution **1a** in which the phenyl groups are trans, the ^{1}H NMR spectrum of the ethylene ketal (**3a**) of **1a** exhibits cyclohexyl ring hydrogens whose *J* values are in accord with a *cis*-phenyl arrangement.

The results of the ^{13}C NMR spectrum of **1a** in CDCl$_3$ solution are given in Table II as well as the carbon shifts for the reference compound *cis*-3,5-diphenylcyclohexanone (**1e**).[15] The equivalency of C-2 and C-6 and of C-3 and C-5 in **1a** in addition to the coupling constants obtained from the ^{1}H NMR spectrum at 300 MHz suggest that **1a** exists (in CHCl$_3$ solution) as a slightly flattened chair in agrement with Otto's conclusion.[12] The 300 MHz data of **1a** in CD$_3$CN suggest a more severe flattening of the cyclohexanone ring with an extra π contribution of ~4 Hz.[16]

The decarbalkoxylation[8b] of **3a** gave an excellent yield of the ketal monoester **3b**, as noted earlier. The ^{1}H NMR spectrum of **3b** in CDCl$_3$ was complex and attempts to simplify its interpretation by the use of a shift reagent [Eu(fod)] failed due to the concomitant shifting of the C-1 and C-2(6) hydrogens. Similar attempts to interpret the ^{1}H NMR spectra of the oxo ester **1c** and its 3,3,5,5-tetradeuterio derivative **4a** with the aid of Eu(fod) were unsuccessful for the same reason. The configuration at C-1 in these compounds therefore could not be determined by ^{1}H NMR spectroscopy.

The ^{13}C NMR spectrum of the ketal monoester **3b** was enlightening. Each of the cyclohexyl ring carbons gave a unique signal. This observation is not consistent with the cis orientation of phenyl groups expected on the basis of the stereochemistry in **3a** since a symmetrical chair or

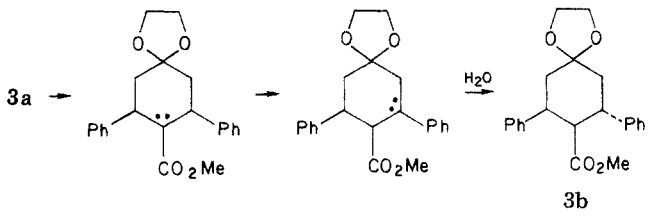


3a

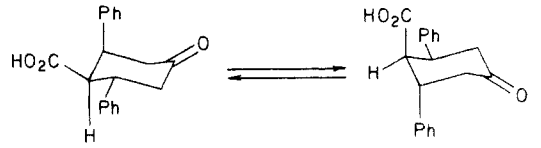
rapidly equilibrating twist conformations of either of the two possible meso esters should give rise to just four cyclohexyl ring carbon signals (cf. **1a**, Table II). *An inversion of configuration at C-2 therefore must have occurred during the decarbalkoxylation reaction.* The ^{13}C NMR spectra of the ketal acid **3c** and the oxo acid **1d** also showed six signals for the ring carbons. In addition, the phenyl groups in **3b,c** and **1d** exhibited the multiple signals expected from magnetically dissimilar substituents. For comparison, the ^{13}C NMR spectrum of methyl 1-cyano-*trans*-2,6-diphenyl-4-oxocyclohexane-1-carboxylate (**1f**)[3,17] was obtained; each of the cyclohexanone ring carbons gave rise to a separate signal, as expected for a rapidly equilibrating mixture of nonsuperimposable conformations. (Complete data from all ^{13}C NMR spectra are given in Table II.)

(13) E. W. Garbisch, Jr., *J. Chem. Educ.*, **45**, 402 (1968).
(14) R. H. Bible, Jr., "Interpretation of NMR Spectra", Plenum Press, New York, 1965, p 89.
(15) K. Ramalingam, K. D. Berlin, N. Satyamurthy, and R. Sivakumar, *J. Org. Chem.*, **44**, 471 (1979).
(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, p 59.
(17) H. H. Otto, *Arch. Pharm. (Weinheim, Ger.)*, **305**, 913 (1972).
(18) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).

Scheme II



Compounds **1c,d** and **3b,c** therefore must be *dl* pairs for which each enantiomer may be represented as a mixture of two chair (or twist) confromations (A and B). The



complexity of the ^1H NMR spectra is understandable since each of these compounds contains seven magnetically dissimilar cyclohexyl ring hydrogens with similar chemical shifts. In order to gain further information about the contribution of the confromations, the tetradeuterio oxo ester **4a** was prepared by treatment of **1c** with methanol-*d* containing methylate ion. The 60-MHz ^1H NMR spectrum in $CDCl_3$ indicated complete exchange of the C-3 and C-5 hydrogens, but the C-1, C-2, and C-6 hydrogens overlapped the methyl signal. In CD_3CN, however, two distinct but closely space signals in a 1/2 ratio were observed. The signal corresponding to two hydrogens was a doublet with a splitting of ~3.5 Hz while the other appeared to be a doublet of doublets with a splitting of ~3 Hz. While these absorptions may result from an ABC or AB_2 pattern not amenable to first-order treatment, they suggest an important contribution of conformation B to the equilibrium mixture. A similar result with less defined splittings was obtained by examination of the ^1H NMR spectrum of the salt **4b** formed by treatment of the oxo acid **1d** with D_2O containing KOD.

The mechanism (or mechanisms) involved in decarbalkoxylation reactions have been probed.[8a,9] To our knowledge no previous case has been reported of a change in configuration at a β-position in the geminal diester as occurs in the conversion of **3a** to **3b**. It is possible that proton migration from C-2 to C-1 in the intermediate carbanion[8a] generates a new ion at C-2 which is protonated selectively by water to give **3b** (Scheme II). On the other hand, the decarbalkoxylation may produce the *cis*-phenyl isomer of **3b** which subsequently undergoes an isomerization to **3b**. We are continuing the study of this and related reactions to determine the effect of β substituents upon the stereochemistry of the reaction products.

Experimental Section

Melting points were taken in a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc. UV spectra were obtained with a Perkin-Elmer Model 552 UV–vis spectrometer in 95% ethanol solutions, except where noted. IR spectra were measured with a Perkin-Elmer Model 735 spectrometer in 10% chloroform solutions; only major frequencies are listed below. ^1H NMR spectra of all compounds except **1a** were obtained with a Varian T-60 spectrometer in the indicated solvents with Me_4Si as an internal standard. The spectra of **1a** were measured at 300 MHz on a Varian SC300 spectrometer. The coupling constants are given in hertz. ^{13}C NMR spectra were obtained in $CDCl_3$ solutions with a Varian CFT-20 spectrometer with a deuterium lock, a pulse width of 6 μs, a spectral width of 4000 Hz, 8 K data points, and Me_4Si as an internal standard.

Dimethyl *cis*-2,6-diphenyl-4-oxocyclohexane-1,1-dicarboxylate (1a) was prepared in 89% yield by the condensation of dibenzalacetone with dimethyl malonate in the presence of sodium methylate according to the method of Kohler and Dewey.[2] Pure product crystallized directly from the reaction solution: mp 135–136 °C (lit.[2] mp 135 °C); IR 1720 (sh at 1755) cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 2.92 (d, J = 7.7, 4 H), 3.37 (s, 6 H), 4.28 (t, J = 7.7, 2 H), 7.16 (narrow m, 4 H), 7.28 (narrow m, 6 H).

Reaction of 1a with Methanolic Potassium Hydroxide.[2] A solution of 112 g (85%, 1.70 mol) of KOH in 350 mL of MeOH was added to a hot solution of 46.6 g (0.127 mol) of **1a** in 500 mL of MeOH. The mixture was allowed to stand at room temperature for 40.5 h, by which time the deep red colored solution had deposited an orange precipitate. After the mixture was cooled in an ice bath for 30 min, the solid was collected and washed well with MeOH and then ether to give 20.6 g of impure salt **2a**: UV (H_2O) 296.3 nm (ϵ 16 100); ^1H NMR (D_2O, MeOH as internal standard) δ 3.17 (br d, J = 8, 2 H), 3.77 (br m, 2 H), 6.40 (d, J = 15, 1 H), 7.12 (d, J = 15, 1 H), 7.22 ("s", 5 H), ~7.42 (m, 5 H).

A solution of 12.413 g (29.95 mmol) of **2a** in 85 mL of water was filtered to remove traces of insoluble material and acidified with 13 mL of 6 M HCl. The voluminous precipitate was collected, washed with water, and suspended in 400 mL of boiling water. The hot mixture was filtered to remove much insoluble orange oil. The cooled filtrate deposited 904 mg (8%) of (3-oxo-1,5-diphenyl-4-pentenyl)propanedioic acid (**2b**) as the dihydrate which melted with loss of water at ~90 °C, resolidified, and then decomposed at 144–155 °C with evolution of CO_2 (lit.[2] for **1b**: mp 100 °C, resolidified after loss of water, melted with "effervescence at about 150 °C"): UV 289.8 nm (ϵ 21 000); ^1H NMR (CD_3CN) δ 3.27 (br d, $J \approx 7$, 2 H), 3.87 (m, 2 H), 4.88 (br s, 6 H including $2H_2O$, signal disappeared upon D_2O treatment), 6.75 (d, J = 16, 1 H), 7.34 ("s", 5 H), ~7.53 (m, 5 H), 7.62 (d, J = 16, 1 H).

Anal. Calcd for $C_{20}H_{18}O_5 \cdot 2\,H_2O$ (mol wt 374.38): C, 64.16; H, 5.92. Found: C, 64.37; H, 5.60.

***trans*-3,7-Diphenyl-5-oxo-6-heptenoic Acid (2c).** The unsaturated diacid dihydrate **2b** (1.855 g, 4.955 mmol) was heated at 170–175 °C under aspirator vacuum for 30 min. The resulting yellow oil was covered with 60 mL of ether, the suspension was heated to boiling, and the ether was decanted. The remaining oil was treated similarly with a fresh 40-mL portion of ether. The combined decantates were reduced to a volume of ca. 80 mL and cooled, resulting in the separation of a mixture of large yellow crystals (mp 158.5–161.5 °C) and a fine white powder (mp 163–170 °C, softens at 130 °C). The yellow crystals (456 mg) were recrystallized by dissolving them in CH_3CN, reducing the volume to ca. 1 mL, and adding EtOH, giving 306 mg (21%) of **2c** as a white powder: mp 159–161 °C (lit.[2] mp (for **1d**) 162 °C); UV 290.8 nm (ϵ 22 200); ^1H NMR (CD_3CN) δ 2.72 (br d, J = 7, 2 H), 3.07 (d, J = 7, 2 H), 3.67 (br m, J = 7, 1 H), 6.77 (d, J = 16, 1 H), 7.33 ("s", 5 H), 7.50 (m, 5 H), 7.58 (d, J = 16, 1 H), CO_2H buried under aromatic proton absorptions.

Anal. Calcd for $C_{19}H_{18}O_3$ (mol wt 294.33): C, 77.53; H, 6.16. Found: C, 77.20; H, 6.13.

Methyl *trans*-3,7-Diphenyl-5-oxo-6-heptenoate (2d). Method A. The unsaturated diacid dihydrate **2b** (904 mg, 2.41 mmol) was heated at 145–165 °C under water aspirator vacuum for 60 min, after which time CO_2 evolution had ceased. The resulting oil (**2c**) was covered with 30 mL of MeOH, treated with 3 drops of concentrated H_2SO_4, and allowed to stand at room temperature for 17 h. The clear solution was diluted with water and the white precipitate which formed was collected, washed with water, and recrystallized from acetone–MeOH to yield 551 mg (74%) of **2d**, mp 91.5–92.5 °C (opaque melt at 81 °C).

The product was chromatographed on 23 g of silica gel. Elution with petroleum ether yielded 406 mg of product in one fraction which, when recrystallized from MeOH, gave 299 mg of white needles, mp 91.5–92.5 °C. Elution with acetone yielded a fraction containing 59 mg of material which crystallized from MeOH to yield 43 mg of needles, mp 82.5–83.5 °C. The two materials had the same TLC mobilities and identical NMR, IR, and UV spectra and are polymorphic forms of the unsaturated mono ester **2d**.

Chromatography (silica gel) of the combined crops, totaling 923 mg of **2d** produced in similar esterifications, gave 782 mg of a solid upon elution with petroleum ether. Recrystallization from MeOH yielded 623 mg of **2d** as white needles: mp 82.5–84 °C;

IR 1730, 1690, 1660, 1610 cm^{-1}; UV 291.2 nm (ϵ 22 000); ^{1}H NMR ($CDCl_3$) δ 2.73 (br d, $J \approx 7$, 2 H), 3.07 (d, $J = 7$, 2 H), 3.60 (s, 3 H), 3.83 ("quintet", $J \approx 7$, 1 H), 6.67 (d, $J = 16$, 1 H), 7.30 ("s", 5 H), ~7.42 (narrow m, 5 H), 7.52 (d, $J = 16$, 1 H). When the spectrum of **2d** was obtained in CD_3OD containing 2 drops of 40% KOD/D_2O solution, the signal at δ 3.07 disappeared, indicating exchange of the hydrogens α to the ketone group.

Anal. Calcd for $C_{20}H_{20}O_3$ (mol wt 308.36): C, 77.90; H, 6.54. Found: C, 77.68, H, 6.42.

Method B. A suspension of 215 mg (0.731 mmol) of the unsaturated monoacid **2c** in 12 mL of MeOH was treated with 3 drops of concentrated H_2SO_4 for 23 h. A workup as in method A and recrystallization from MeOH gave 122 mg (54%) of the ester **2d**, mp 91.5–92°C (softens at 81 °C).

Dimethyl *cis*-2,6-Diphenyl-4,4-ethylenedioxycyclohexane-1,1-dicarboxylate (3a). A mixture of 101.4 g (0.2767 mol) of the oxo diester **1a**, 100 mL (111 g, 1.79 mol) of ethylene glycol, and 4.9 g of *p*-toluenesulfonic acid monohydrate in 2 L of benzene was heated under reflux for 5.7 h as the water produced was removed in a Dean–Stark apparatus. The warm solution was treated with 100 mL of 0.5 M NaOH and 300 mL of water. After cooling, the mixture was diluted with 300 mL of water and shaken, and the layers were separated. The aqueous phase was extracted with 200 mL of benzene, and the combined organic layers were washed once with 500 mL of water and dried over anhydrous K_2CO_3. The solution was concentrated by distillation to a volume of ca. 200 mL and then diluted with 100 mL of CH_2Cl_2 and 400 mL of ether. Upon concentration of this solution to ca. 600 mL, precipitation of product commenced; an additional 200 mL of ether was added, and precipitation was allowed to proceed at 0 °C. Filtration yielded 90.7 g of **3a**, mp 152–153 °C. An additional crop (15.5 g, mp 152–153.5 °C) was obtained by concentration of the mother liquor: total yield 93%; IR 1730 (sh), 1712, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (dd, $J = 14.5$, 3, 2 H), 2.58 (br t, $J = 14.5$ and 12.5, 2 H), 3.15 (s, 6 H), 3.92 (narrow m, 4 H), 4.30 (dd, $J = 12.5$, 3, 2 H), 7.23 ("s", 10 H).

Anal. Calcd for $C_{24}H_{26}O_6$ (mol wt 410.4): C, 70.23; H, 6.39. Found: C, 70.02; H, 6.37.

Methyl *trans*-2,6-Diphenyl-4,4-ethylenedioxycyclohexane-1-carboxylate (3b). Method A. A mixture of 50.0 g (0.122 mol) of the ketal diester **3a**, 12.0 g (0.205 mol) of NaCl, and 13 mL (0.72 mol) of water in 500 mL of Me_2SO^{18} was heated with magnetic stirring at 184 ± 2 °C for 8 h. The mixture was cooled for several minutes and then poured onto 1.2 L of crushed ice. The sticky tan precipitate was collected, washed with 4 L of water, and recrystallized from acetone to give 39.2 g of **3b** as white needles, mp 130–131 °C. Concentration of the mother liquor gave a solid which was recrystallized from acetone–MeOH to yield an additional 832 mg of **3b**: mp 129–130 °C; total yield 93%; IR 1725, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75–2.81 (m, 4 H), 3.10 (s, 3 H), 3.16–3.78 (m, 3 H), 3.86 (narrow m, 4 H), 7.26 ("s", 10 H).

Anal. Calcd for $C_{22}H_{24}O_4$ (mol wt 352.4): C, 74.98; H, 6.86. Found: C, 74.93; H, 6.90.

Method B. A solution of 309 mg (1.00 mmol) of the oxo monoester **1c**, 0.80 mL (0.88 g, 14 mmol) of ethylene glycol, and 33 mg of *p*-toluenesulfonic acid in 10 mL of benzene was heated under reflux for 100 min with constant water separation. Workup was conducted as in the conversion of **1a** to **3a**. Recrystallization from ether gave 194 mg of **3b**, mp 129.5–131 °C. The solid obtained from the mother liquor was recrystallized from acetone–MeOH, giving a further 107 mg of **3b**: mp 129–130 °C; total yield 86%.

Method C. A solution of 79 mg (0.23 mmol) of the ketal monoacid **3c** in 4 mL of absolute ether was treated for 100 min with CH_2N_2 generated from 140 mg of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in a commercial CH_2N_2 apparatus.[19] The colorless solution was filtered to remove a small amount of solid, concentrated to 1 mL and diluted with petroleum ether. The resulting precipitate (73 mg, mp 117–145 °C) was dissolved in ether; the solution was extracted twice with 10% NaOH and once with water and dried over Na_2SO_4. The solution was evaporated, and the residual solid was recrystallized from ether–petroleum ether to give 23 mg (28%) of **3b**, mp 129–130 °C. This material was identical with **3b** prepared from **3a** by mixture melting point and IR comparisons.

Methyl *trans*-2,6-Diphenyl-4-oxocyclohexane-1-carboxylate (1c). A solution of 1.025 g (2.909 mmol) of the ketal monoester **3b**, 3.0 mL of water, and 20 drops of concentrated HCl in 25 mL of acetone was heated under reflux for 1.7 h. The solution was added to ice–water, and the mixture was extracted twice with ether. The combined extracts were washed once with water, dried, and evaporated to give an oil which crystallized from MeOH, yielding 654 mg of **1c**, mp 106–107 °C. An additional 124 mg of **1c** (mp 105–106.5 °C) was obtained by concentration of the mother liquor: total yield 87%; IR 1710 (br) cm^{-1}; UV 287.7 nm (ϵ 42.9), 263.6 (300), 257.8 (366), 252.5 (317); ^{1}H NMR ($CDCl_3$) δ 2.27–3.77 (m, 7 H), 3.40 (s, 3 H), 7.33 ("s", with m sh at higher field, 10 H).

Anal. Calcd for $C_{20}H_{20}O_3$ (mol wt 308.4): C, 77.90; H, 6.54. Found: C, 78.48; H, 6.61.

***trans*-2,6-Diphenyl-4-oxocyclohexane-1-carboxylic Acid (1d). Method A.** A solution of 444 mg (1.44 mmol) of the oxo ester **1c** in 10 mL of 95% EtOH and 506 mg (85%, 7.67 mmol) of KOH in 2 mL of water was heated under reflux for 22.5 h. The pale yellow solution was diluted with 25 mL of water, filtered from a small amount of precipitate, and diluted with 12 mL of water. The solution was extracted once with ether and acidified with 2 mL of 6 M HCl. The acidified mixture was extracted twice with ether, and the combined extracts were washed with water and dried with anhydrous Na_2SO_4. The solution was concentrated to ca. 1 mL and treated dropwise with petroleum ether. The product gradually crystallized after each addition, giving 364 mg (86%) of acid **1d**: mp 160–161.5 °C; IR 3550–2400 (br), 1710 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.48–3.88 (m, 7 H), 7.33 ("s", with m sh at higher field, 10 H), 10.73 (br s, 1 H); ^{1}H NMR (D_2O, KOD) δ 3.43 (unresolved d, 2 H), 3.67 (m, 1 H), 7.27 ("s", with slight m at higher field, 10 H).

Anal. Calcd for $C_{19}H_{18}O_3$ (mol wt 294.3): C, 77.53; H, 6.16. Found: C, 77.68; H, 6.11.

Method B. A solution of 603 mg (1.78 mmol) of the ketal acid **3c**, 2 mL of water, and 12 drops of concentrated HCl in 17 mL of acetone was heated under reflux for 70 min. The solution was concentrated to half volume, diluted with water, and extracted twice with ether. The combined extracts were washed once with water, dried over anhydrous Na_2SO_4, and evaporated. The resulting oil was crystallized from a small amount of ether by the careful addition of petroleum ether to yield 474 mg (90%) of the keto acid **1d**, mp 160–161.5 °C.

***trans*-2,6-Diphenyl-4,4-ethylenedioxycyclohexane-1-carboxylic Acid (3c).** A mixture of 1.376 g (3.905 mmol) of the ketal monoester **3b** in 25 mL of 95% EtOH and 1.356 g (85%, 20.6 mmol) of KOH in 5 mL of water was heated under reflux for 26.5 h. The warm solution was diluted with 70 mL of water and a small quantity of precipitate was removed by vacuum filtration. The solution was then treated with 40 mL of water and extracted once with ether. The aqueous phase was acidified with 5 mL of 6 M HCl and extracted twice with ether. The combined extracts were washed once with water, dried, concentrated to ca. 2 mL, and diluted with 3 mL of petroleum ether. After the mixture was cooled in the refrigerator, 1.193 g (90%) of **3c** separated as small white crystals: mp 165.5–166.5 °C; IR 3530–2400 (br), 1710, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78–2.73 (m, 4 H), 2.97–3.67 (m, 3 H), 3.87 (narrow m, 4 H), 7.22 and 7.30 ("s", 10 H).

Anal. Calcd for $C_{21}H_{22}O_4$ (mol wt 338.4): C, 74.53; H, 6.55. Found: C, 74.72; H, 6.37.

Methyl 2,6-Diphenyl-3,3,5,5-Tetradeuterio-4-oxocyclohexane-1-carboxylate (4a). To a warm solution of 851 mg (2.76 mmol) of the oxo monoester **1c** in 25 mL of CH_3OD was added 47 mg of NaOMe. The solution was magnetically stirred for 1.5 h, during which time precipitation occurred. Half of the solvent was removed by boiling; the cooled solution deposited 697 mg (81%) of **4a**: mp 106.5–108 °C; ^{1}H NMR ($CDCl_3$) δ 3.28–3.77 (m, 3 H), 3.47 (s, 3 H), 7.40 ("s", with m sh at higher field, 10 H); ^{1}H NMR (CD_3CN) δ 3.33 (s, 3 H), 3.53 ("d", splitting of 3.5, 2 H), 3.78 ("dd", splitting of 3, 1 H), 7.30 ("s", with m sh at higher field, 10 H).

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(19) "Aldrich Catalog 20", Aldrich Chemical Co., Milwaukee, WI, 1981, p 1128.

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Registry No. *meso*-**1a**, 54105-33-8; (±)-**1c**, 79803-35-3; (±)-**1d**, 79815-46-6; (±)-**2a**, 79803-36-4; (±)-**2b**, 79803-37-5; (±)-**2c**, 79803-38-6; (±)-**2d**, 79803-39-7; *meso*-**3a**, 79803-40-0; (±)-**3b**, 79803-41-1; (±)-**3c**, 79803-42-2; (±)-**4a**, 79803-43-3.

Octant Rule. 9.[1] Circular Dichroism of Axial and Equatorial 4-(Trideuteriomethyl)adamantan-2-ones and a Comparison with 4-Methyladamantan-2-ones

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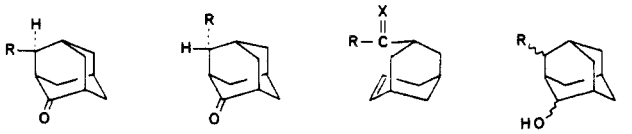
The title compounds were prepared optically active, and their variable-temperature circular dichroism (CD) spectra were measured. The β-axial ketones (1*S*,3*R*,4*S*)-4(a)-(trideuteriomethyl)adamantan-2-one (**1**) and (1*S*,3*R*,4*S*)-4(a)-methyladamantan-2-one (**2**) underwent considerable changes in their CD spectra: at −175 °C moderately intense ($\Delta\epsilon \sim 0.5$) negative n → π* Cotton effects (CEs) were observed in both polar (EPA) and nonpolar (methylcyclohexane–isopentane) solvents. Those findings contrast with the room temperature n → π* CE signs and magnitudes of **1** and **2**: $\Delta\epsilon \sim -0.04$ in ethyl ether–isopentane–ethanol and $\Delta\epsilon \sim +0.02$ in methylcyclohexane–isopentane. The β-equatorial ketones (1*S*,3*R*,4*R*)-4(e)-(trideuteriomethyl)adamantan-2-one (**3**) and (1*S*,3*R*,4*R*)-4(e)-methyladmantan-2-one (**4**) gave the expected (+) CEs ($\Delta\epsilon \sim 1$) which are relatively insensitive to temperature and solvent. Comparison of CD_3 and CH_3 rotatory strengths indicates that the heavier isotope makes the inherently more dissignate octant contribution.

Introduction

During recent years there has been an increasing interest in understanding how deuterium influences the conformational[2-4] and chiroptical[4-7] properties of ketones with special reference to the octant rule.[8,9] Most of this work has focused on cyclic compounds in which optical activity was due to substitution of a ring hydrogen by deuterium. There are, however, relatively few examples which contrast the behavior of the rotatory contributions of CD_3 and CH_3 to the carbonyl n → π* Cotton effect (CE). In the first of those examples, Meyer and Lobo[10] found that (+)-camphor-*9,9,9-d*$_3$ had an ORD molecualr amplitude (+60.92°) 3% smaller than that of the protio analogue.[7] Subsequently, Pak and Djerassi[11] found that 3(*S*)-methyl-5(*R*)-(trideuteriomethyl)cyclohexanone exhibited a negative CE, $[R]^{20} = -0.082$, and concluded that *the heavier isotope is the weaker* perturber—as has proved true in other examples involving deuterium[2-13] and even carbon-13.[11,12,14] That conclusion was supported by more recent work with α-(trideuteriomethyl)-4-*tert*-butylcyclohexanones and other α-(trideuteriomethyl)-4-alkylcyclohexanones and prompted Djerassi et al.[12] to suggest that the emerging generalization, if upheld, could "lead to a useful application for obtaining estimates of methyl octant contributions in more complicated situations where the observed Cotton effect amplitude results from a larger

Chart I



1: R = CD_3 **2**: R = CH_3 **3**: R = CD_3 **4**: R = CH_3 **5**: R = OH, X = O **6**: R = CD_3, X = O **7**: R = CD_3, X = **8**: R = CH_3, X = O **9**: R = CH_3, X = **10**: R = CD_3 **11**: R = CH_3

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