

OPTICAL ROTATORY DISPERSION STUDIES CXI.\*

THE OCTANT RULE AND EQUATORIAL ALKOXYCARBONYL AND CARBOXYL GROUPS.

SYNTHESIS OF OPTICALLY ACTIVE ADAMANTANONES

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The original tenets of the octant rule (1) state that equatorial substituents adjacent to the carbonyl group in an optically active cyclohexanone make no significant contribution to the Cotton effect. For qualitative purposes (2) this assumption has proved to be sufficient, but more accurate studies (3) have indicated that a measurable rotatory contribution is made by an equatorial  $\alpha$ -substituent (e.g. methyl) presumably because the equatorial group lies very near but not exactly in the horizontal symmetry plane of the carbonyl chromophore. The extent of this contribution has as yet not been determined accurately, principally because all optically active model cyclohexanones which have so far been examined were subject to ring conformational mobility (3). The appropriate model should be a strain-free cyclohexanone, incapable of conformational ring distortion, and the adamantane series is ideally suited for this purpose. We should now like to report the synthesis of an optically pure,  $\alpha$ -substituted adamantanone<sup>\*\*\*</sup>, which sheds some light on this question.

Exposure of dimethyl adamantane-2,6-dione-1,5-dicarboxylate (I) (4,5) to one equivalent of ethane dithiol in benzene solution in the presence of boron trifluoride etherate afforded

\* For paper CX see J. Goré, C. Djerassi and J.-M. Conia, Bull. Soc. Chim. France, 950 (1967).

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\*\*\* Dr. G. Snatzke of the University of Bonn has informed us that similar work with  $\beta$ -substituted adamantanones is currently under way in his laboratory (see also G. Snatzke and D. Marquarding, Chem. Ber., 100, 1710 (1967)). This should provide valuable quantitative information on the rotatory contribution of equatorial and axial  $\beta$ -substituents in cyclohexanone.

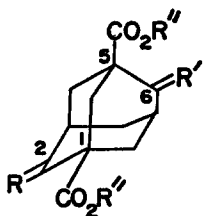
the mono-thioetheral II\* (m.p. 130-131°) accompanied by small amounts of the bis-thioetheral III (m.p. 214-215°) and unchanged starting material. Desulfurization of II in ethanol solution with Raney nickel catalyst (prepared by addition of W. R. Grace and Co., No. 2813 catalyst powder to 10% aqueous potassium hydroxide solution at steam bath temperature) resulted in simultaneous reduction of the carbonyl group to yield dimethyl adamantan-2-one-1,5-dicarboxylate (IV) (m.p. 68-69°), which was oxidized with 8N Jones reagent (6) at 25° to yield the corresponding keto-diester (V) (m.p. 84-85°). Subsequent saponification of V gave the free keto-dicarboxylic acid (VI) (m.p. 223-224°).

Resolution of acid VI was accomplished through the di-dehydroabietylamine salt (7) (m.p. of racemic material 163-167°), which was fractionally crystallized from aqueous methanol and acetone to constant m.p. (176-180°) and maximum CD molecular ellipticity of the resulting acid (as determined in 2% aqueous sodium hydroxide solution). The optically active (-)-antipode of VI obtained by decomposition of the head fraction salt from the above recrystallization had m.p. 211-212° and CD  $[\theta]_{293} + 248 \pm 15$  (c, 0.144 in 2% aqueous sodium hydroxide). Reformation of the salt and additional recrystallization from acetone gave, after cleavage, (-)-keto-diacid VI having CD  $[\theta]_{293} + 260 \pm 26$  (c, 0.0375 in 2% aqueous sodium hydroxide).

The tail fraction from the above recrystallization yielded, upon cleavage, the optically impure (+)-antipode of VI [m.p. 214-215°, CD  $[\theta]_{293} - 128 \pm 12$  (c, 0.101 in 2% aqueous sodium hydroxide)]. This acid was treated with one equivalent of quinine in acetone solution, and the resulting salt recrystallized three times from acetone, then reconverted to the acid [m.p. 208-210°, CD  $[\theta]_{293} - 260 \pm 16$  (c, 0.159 in 2% aqueous sodium hydroxide)]. The molecular ellipticity of this latter acid was not changed upon additional recrystallization of the quinine salt from acetone.

Treatment of portions of the (-)-antipode of acid VI (96-98% optical purity) in methanol solution at 0° with diazomethane and diazobutane led to dimethyl adamantan-2-one-1,5-dicarboxylate (V) (m.p. 108-109°) and di-n-butyl adamantan-2-one-1,5-dicarboxylate (VII) (oil bath distilled at 230-235°/5 mm.), respectively. Both optically active keto-diesteres were purified by vapor phase chromatography prior to instrumental examination.

\* All substances in this communication gave correct elementary analyses and/or mass spectrometrically determined molecular weight values and were homogeneous by thin layer and/or vapor phase chromatography.



	R	R'	R''
I	0	0	CH <sub>3</sub>
II	0	$\begin{matrix} \text{S} \\ \text{S} \end{matrix}$	CH <sub>3</sub>
III	$\begin{matrix} \text{S} \\ \text{S} \end{matrix}$	$\begin{matrix} \text{S} \\ \text{S} \end{matrix}$	CH <sub>3</sub>
IV	$\begin{matrix} \text{H} \\ \text{OH} \end{matrix}$	H <sub>2</sub>	CH <sub>3</sub>
V	0	H <sub>2</sub>	CH <sub>3</sub>
VI	0	H <sub>2</sub>	H
VII	0	H <sub>2</sub>	n-C <sub>4</sub> H <sub>9</sub>

Optical rotatory dispersion and circular dichroism measurements were performed with a JASCO Model ORD/UV 5 spectropolarimeter fitted with circular dichroism attachment and demonstrated the occurrence of very weak Cotton effects and associated CD maxima. Thus the keto dimethyl ester V exhibited Cotton effect extrema (in methanol solution) of  $[\phi]_{310} - 115^\circ$  and  $[\phi]_{275} + 213^\circ$  corresponding to the extremely low molecular amplitude value\* of  $\underline{a} = -3.28$ . Measurements were performed in three solvents of differing polarity (methanol, dioxane and acetonitrile), and the results for the dimethyl and dibutyl esters (V and VII) as well as for the dicarboxylic acid VI are summarized in Table 1. As the rotatory dispersion curves of optically active keto-diacid VI and keto-diesters V and VII are apparently affected by moderately strong plain background curves, more meaningful information regarding quantitative substituent contributions may be derived from consideration of the molecular ellipticity maxima of the related circular dichroism curves where such effects are absent. Hence, the results cited in Table 1 are reported in terms of this parameter. Of particular interest is the observation that the negative Cotton effect (and associated CD maximum) of the keto dicarboxylic acid VI in the three organic solvents is inverted in sign in sodium hydroxide solution. Presumably, this is due to restricted rotation of the carboxylate group around C-1 caused by electrostatic repulsion, which favors a rotamer with a positive rotatory contribution.

\* The molecular amplitude ( $\underline{a}$ ) is defined in ref. (2) as the difference between the molecular rotation at the extremum of longer wavelength  $[\phi]_1$  minus the molecular rotation at the extremum of shorter wavelength  $[\phi]_2$  divided by 100 for convenience:  $\underline{a} = ([\phi]_1 - [\phi]_2)/100$ .

TABLE I  
Circular Dichroism Molecular Ellipticities  $[\theta]$  and Rotational  
Strengths  $^8 (R_0^{+25})$  of 1,5-Disubstituted Adamantan-2-ones<sup>a</sup>

Solvent	Dimethyl Ester (V)		Di-n-butyl Ester (VII)		Dicarboxylic Acid (VI)				
	$\lambda_{\max}$ (m $\mu$ )	$[\theta]_{\max}$ (cgs)	$\lambda_{\max}$ (m $\mu$ )	$[\theta]_{\max}$ (cgs)	$\lambda_{\max}$ (m $\mu$ )	$[\theta]_{\max}$ (cgs)			
Methanol	295	-116 $\pm$ 9	-0.073 $\pm$ 0.005	295	-124 $\pm$ 12	-0.077 $\pm$ 0.007	295	-110 $\pm$ 8	-0.090 $\pm$ 0.006
Dioxane	297	-68 $\pm$ 8	-0.031 $\pm$ 0.003	-	-	-	273	+36 $\pm$ 5	
Acetonitrile	297	-150 $\pm$ 14	-0.094 $\pm$ 0.008	-	-	-	295	-124 $\pm$ 15	-0.082 $\pm$ 0.010
2% Sodium Hydroxide	-	-	-	-	-	-	293	+260 $\pm$ 16	+0.205 $\pm$ 0.012

<sup>a</sup> All values have been corrected to correspond to those of 100% optically pure material, although certain curves were run on material of 96-98% optical purity.

<sup>b</sup> This rotational strength value reflects the development of the two positive maxima in this solvent.

In summary, it may be stated that the present study demonstrates that the adamantanone system is ideally suited for establishing quantitatively the octant contributions of various substituents in the undisturbed chair form of cyclohexanone and that an equatorial alkoxy-carbonyl or carboxyl group makes only a very small rotatory contribution in accordance with the earlier qualitative assumptions of the octant rule (1).

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8. See W. S. Briggs and C. Djerassi, Tetrahedron, **21**, 3455 (1965).