## Conformational Analysis. CVII. The Contribution of a $\beta$ -Axial Methyl Group to the Cotton Effect of a Cyclohexanone<sup>1,2</sup>

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trans-3,5-Dimethylcyclohexanone has been prepared in optically active form and with known absolute configuration. For the R,R configuration, the amplitude of the optical rotatory dispersion curve was found to be  $+37^{\circ}$ . The trisubstituted ketone, 3,3,5(R)-trimethylcyclohexanone, was also prepared and found to exhibit a positive optical rotatory dispersion curve. These data are not consistent with the octant rule, and it is concluded that theoretical interpretations of optical rotatory dispersion curves which omit explicit consideration of the  $\sigma$  system connecting the perturbing group and the carbonyl are too crude to be reliable.

The usefulness of Cotton effect curves, obtained either by optical rotatory dispersion or by circular dichroism measurements, for assigning absolute configuration was summarized by Djerassi.<sup>4</sup> It was shown that the carbonyl group possessed properties that made it particularly useful as a probe for carrying out this kind of investigation. The octant rule gave a qualitative theoretical rationalization of the sign of the Cotton effect, as determined by the position of a perturbing substituent in the vicinity of the carbonyl.<sup>5</sup> Cyclohexanones, with their reasonably well-defined geometries, were early candidates for thorough study. It was found that an axial or equatorial group on carbon 2 (the  $\alpha$ carbon) of a cyclohexanone, or an equatorial group on a carbon 3 (the  $\beta$  carbon) of a cyclohexanone, gave a Cotton effect in accord with theoretical predictions.<sup>4</sup>

The theory behind the octant rule was worked out on the level of the one-electron approximation for the case of a perturbing substituent and a carbonyl group interacting in space without regard to the intervening molecular structure.<sup>6</sup> Such a treatment indicated that the  $\beta$ -axial substituent should show a considerably larger Cotton effect than the  $\beta$ -equatorial substituent. At the time the present investigation was undertaken (1965), there were two kinds of  $\beta$ axial methylcyclohexanones known for which absolute configurations and optical rotatory dispersion curves were available.<sup>7</sup> These were the  $5\alpha$ -methyl-3-keto steroids, which showed amplitudes of +18 (predicted about +50), and the corresponding  $5\beta$ -methyl compounds, which showed amplitudes of +7 (predicted -50). Because these examples were somewhat complex, it was considered desirable to prepare simple molecules of known absolute configuration with  $\beta$ -axial methyl groups, so that the experimental data would be on a better footing. After this work was completed, additional similar examples of the failure of the octant rule were described in the literature.<sup>8–10</sup>

The compounds examined in the present investigation were optically active trans-3,5-dimethylcyclohexanone and the further methylated derivative, 3,3,5-trimethylcyclohexanone. The chair conformations in these molecules may be assumed to be close to ideal in geometry. It is at once apparent that carbons 2, 4, and 6, lying as they do in nodal planes, make no contribution to the Cotton effect curve. In addition, the contributions of C-3 and C-5 being equal and opposite, cancel; and the observed Cotton effect is therefore associated with the methyl groups. In trans-3,5-dimethylcyclohexanone, therefore, to the extent that the molecule is in the chair form, the amplitude of the Cotton effect would be the sum of the positive contribution of the axial methyl at C-3 and negative contribution from the equatorial methyl at C-5. In 3,3,5-trimethylcyclohexanone, the amplitude of the Cotton effect would come solely from the C-3 axial methyl group, since the contributions of the equatorial methyl groups at C-3 and C-5, being equal and opposite, would cancel.

In the present work, samples of these compounds were desired which were not only optically active, but of known absolute configuration. There are a number of methods available for the resolution of ketones, but most of them are not very general. Alcohols, on the other hand, can be resolved much more reliably.<sup>11</sup> In the present case, a reduction of the desired ketone to an alcohol would give a resolvable product, but at the expense of the introduction of another asymmetric center. One would then have the problem of establishing the absolute configuration.

An alternative approach to obtaining the required compounds consists of beginning with an available optically active material of known absolute configuration, and transforming it to the desired compounds. The simple terpene (+)-pulegone<sup>12</sup> meets these requirements; it is of known<sup>13</sup> absolute configuration, and acid-catalyzed retroaldolization leads to (+)-3-methylcyclohexanone (see scheme).

Synthesis of *dl-trans-3*,5-Dimethylcyclohexanone. In connection with the synthetic work, large quantities of this compound were required. Since the cis isomer is the thermodynamically stable one, the trans isomer is not obtained in good yield by methods leading to a thermodynamic product. It had been previously obtained in two other ways at the outset of this work, both which were laborious and gave poor yields.<sup>14-18</sup>

Among the methods considered for the synthesis of the desired ketone was the Michael addition of methylmagnesium iodide to 5-methyl-2-cyclohexenone.<sup>19</sup> The 1,4 addition of a Grignard reagent to an  $\alpha,\beta$ -unsaturated ketone appears to be an ordinary Michael-type addition, except that it is irreversible, and the product obtained from the reaction will be governed by kinetic control.<sup>20,21</sup> The Michael reaction has not been very thoroughly studied with respect to the stereochemistry of the product, which may often result from thermodynamic rather than kinetic control.<sup>22–24</sup> The stereochemical result of kinetic control has been explained on the basis of attack by the nucleophile perpendicular to the olefinic bond, and from the least hindered side of the molecule.

When the Michael addition of methylmagnesium iodide to 5-methyl-2-cyclohexenone was carried out with the aid of cuprous chloride,<sup>25</sup> trans-3,5-dimethylcyclohexanone was obtained in a yield of 55–68%. The purity of the product was 94–96%, with 4–6% of the cis isomer. This useful way for obtaining the trans-3,5-dimethylcyclohexanone has been previously described.<sup>20</sup>

The necessary dl-5-methyl-2-cyclohexenone is a known compound, its synthesis and physical properties having been described in the literature by Blanchard and Goering.<sup>19</sup> The present synthesis followed their method, and



began with 5-methyl-1,3-cyclohexanedione.<sup>26</sup> The preparation of such cyclic enol ethers has been studied by others, and an improved procedure was reported by Frank and Hall.<sup>27</sup> Reduction of the cyclic enol ether by means of lithium aluminum hydride, followed by hydrolysis, gave the desired 5-methyl-2-cyclohexenone in 94% yield.

It is possible to resolve 3-methylcyclohexanone, and then to convert this to trans-3(S),5(S)-dimethylcyclohexanone through the corresponding  $\alpha,\beta$ -unsaturated ketone. While this was a successful approach, a more convenient synthesis (which gave the other enantiomer) is to begin with pulegone. This was converted by retroaldolization into (+)-3(R)-methylcyclohexanone.<sup>28</sup> This compound was converted to 2-bromo-5-methylcyclohexanone by modification of published procedures.<sup>28-30</sup>

Dehydrobromination<sup>31</sup> of trans-2-bromo-5-methylcyclohexanone was accomplished in either of two ways: (a) via ethylene ketal formation followed by dehydrobromination with alkali and hydrolysis to the  $\alpha,\beta$ -unsaturated ketone; or (b) direct dehydrobromination with semicarbazide, followed by hydrolysis to the ketone. Of the two procedures, a gave a higher overall yield (65%) but was time consuming, whereas b gave a reduced overall yield (55%) but was faster and involved fewer steps. The addition of methyl Grignard to the  $\alpha,\beta$ -unsaturated ketone gave trans-3(R),5(R)-dimethylcyclohexanone, which was purified via this semicarbazone followed by vapor phase chromatography.

Synthesis and Resolution of 3,3,5-Trimethylcyclohexanone. The desired product was synthesized in two ways. Beginning with *trans*-3(R),5(R)-dimethylcyclohexanone obtained as previously described, bromination in ethylene glycol gave in 87% yield a mixture of the ethylene ketals of the diastereomeric 2-bromo derivatives. Dehydrobromination with alcoholic alkali gave 3,5-dimethyl-2-cyclohexenone. To this was added methylmagnesium iodide in the presence of cuprous chloride, which gave the desired 3,3,5(R)-trimethylcyclohexanone.

The enantiomer of the latter was also obtained beginning with isophorone. The latter was reduced to the corresponding dihydro ketone with hydrogen and platinum oxide. When this ketone was reduced with aluminum isopropoxide, according to the modified method of Wicker,<sup>32</sup> there was obtained a 68% yield of the stable cis alcohol. This was converted to the acid phthalate, which was resolved with brucine. The salt was hydrolyzed with acid to give back the phthalate, which upon saponification gave the optically active alcohol, which was oxidized with Jones reagent<sup>33</sup> to the 3,3,5(S)-trimethylcyclohexanone.



Determination of Optical Purity and Absolute Configuration. Stringent precautions were taken during the course of all reactions and purifications to eliminate contamination. There was no possibility of racemization throughout the reaction scheme. In the step where the Grignard reagent was added to 5-methyl-2-cyclohexenone, any addition from the wrong side of the ring leads not to the enantiomer, but to the diastereomeric meso compound. The latter is separable by vapor phase chromatography, and therefore the trans-3(R),5(R)-dimethylcyclohexanone obtained from pulegone was considered to be optically pure.

The 3,3,5-trimethylcyclohexanone obtained from pulegone must similarly be optically pure, and of the R configuration. The sample obtained by resolution of dl-cis-3,3,5trimethylcyclohexanyl acid phthalate had a rotation only 75% that of the sample obtained from pulegone, and of the opposite sign. It was accordingly assigned the S configuration and an optical purity of 75%. The optical rotatory dispersion (ORD) and circular dichroism data (CD) are summarized in Table I.

### **Results and Discussion**

The amplitude of the ORD curve for trans-3(R),5(R)cyclohexanone is +37°, and the contribution of the equatorial methyl should be +26°, so this leaves a contribution of +11° for the axial methyl. The trimethyl ketone also has a positive contribution from the axial methyl. Since the second extremum could not be located, its magnitude cannot be ascertained.

The circular dichroism curve for 3,5-dimethylcyclohexanone is in reasonable agreement with the ORD curve, and when the curves were determined as functions of temperature, no qualitative change was observed. For the 3,3,5-trimethylcyclohexanone, the circular dichroism curve is very weakly positive at room temperature, and becomes more positive as the temperature is lowered. The ORD curve is qualitatively positive.

The octant rule indicates that a negative contribution is to be expected from the axial methyl in question, and the one-electron theory<sup>6</sup> gives the magnitude on the order of  $-50^{\circ}$  for this group. Since the experimental values and absolute configurations seem secure, the result was quite surprising at the time, and required rationalization. There seemed to be three possible explanations: (1) anomalous

ORD Cotton Effect Curve (MeOH), at 25°							
	Extrema						
Compd	[~]	λ, nm	[0]	λ, nm	[A]		
trans-3(R),5(R)-Dimethyl- cyclohexanone	+1191	308	-1708	268	+37		
3,3,5(R)-Trimethylcyclo- hexanone	-17	330ª	-10	$310^{a}$			
3,3,5(S)-Trimethylcyclo- hexanone (75% resolved)	+24	<b>33</b> 0ª	+18	310 <sup>a</sup>			

# Table I Optical Rotatory Dispersion and Circular Dichroism Data ORD Cotton Effect Curve (MeOH) at 25°

CD Cotton Effect Curves	
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Α.	trans-3(R	),5	(R	)-Dimethylcyclohexanone	(EPA)	)
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 Temp, <sup>°</sup> K	[0] <sub>max</sub>	λ, nm	[A]	
 298	+1904	298	+23	
199	+1925	298	+24	
81	+2745	298	+33	
	B. $3,3,5(R)$ -Trimethyld	cyclohexanone (EPA)		
 Temp, <sup>°</sup> K	[0] <sub>max</sub>	λ, nm	[A]	
298	+96	296	+1	
244	+140	295	+2	
199	+277	295	+3	
81	+867	293	+11	

<sup>a</sup> The extrema at 330 nm are not those directly pertaining to the Cotton effect, but are a result of the Cotton effect being superimposed on a plain curve of opposite sign. The first extrema of the Cotton effect curves are those at 310 nm. The second extrema were not detected down to 270 nm.

solvent effects are present; (2) boat forms contribute appreciably to the Cotton effect; (3) the octant rule is invalid. These possibilities will be examined.

(1) The possibility of an equilibrium involving differently solvated species may be considered. Such equilibria are known to occur, but generally involve  $\alpha$ -substituted cyclohexanones or their analogs.<sup>34</sup> Although in the present case the possibility of solvational equilibria cannot be ruled out, it seems an unlikely interpretation of the facts.

(2) In principle, the possibility always exists that a small concentration of a conformation with a very large Cotton effect will override the modest Cotton effect of the major conformation present. In this case, the question is whether or not sufficient nonchair form could be present to account for the observed results. In each of the molecules studied there is present one axial methyl group at C-3 in the chair form. Because of the 3-alkyl ketone effect, the conformational enthalpy of a 3-axial methyl group is approximately 1.4 kcal/mol.<sup>35</sup> This repulsion could be relieved if the molecule were to adopt a suitable boat or twist conformation. The most thorough studies reported on the energies of nonchair forms of cyclohexanone give values for the twist boat  $(C_2)$  of 2.72 kcal/mol,<sup>36</sup> for the  $C_1$  boat 3.77 kcal/mol, and for the  $C_s$  boat, 5.33 kcal/mol. If the unfavorable steric effects of the axial methyl could be completely relieved in the twist-boat conformation, the latter would still have an energy of 1.3 kcal/mol, relative to the chair form. Thus if the anomalous positive Cotton effect were a result of the minor concentration of boat forms, the Cotton effect would have to shift in the negative direction upon the reduction of the temperature. This is not what is observed, and it rules out the possibility that the anomaly is due to boat forms.

(3) The only remaining alternative is the failure of the octant rule in the case at hand. The octant rule in its origi-

nal form was concerned only with perturbing groups placed in the environment of the carbonyl. To the extent that that simple picture is correct, the quantitative theory developed should probably also be correct, although it was a one-electron theory, and not free from the various shortcomings associated with such a theory. Thus while the quantitative value predicted by the theory might be questioned, it seems clear that the qualitative result predicted by the octant rule is simply not borne out by experiment.

When this work was completed in 1966, we were unable to proceed beyond this point. However, subsequent publications now make it clear what the situation actually is. First, there is the important paper by Pao and Santry,<sup>10</sup> which takes into account the entire valence shell of the molecule, and predicts anti-octant behavior of modest magnitude for the effect of the  $\beta$ -axial methyl. They did not speculate in any detail as to why anti-octant behavior was calculated for the methyl, but say it is a result of the *n* orbital being mixed into the  $\sigma$  part of the carbon framework.

Note that the theoretical work to date has not allowed for deformations of the cyclohexanones from ideal geometry, but for the cases at hand, such deformation will probably lead to only small numerical differences, not to qualitative differences. Finally, additional experimental examples have been found<sup>8,9</sup> where a  $\beta$ -axial methyl leads to a small or anti-octant behavior in other systems which are rigid, so deformation into boat structures is impossible.

The octant rule as originally proposed was a simple model, based on an isolated carbonyl group and a perturbing group. Whether the octant rule for predicting the sign of an ORD curve would work depended on the accuracy to which this model represented the real situation. As the work of Pao and Santry shows, the octant rule is simply

wrong in the case of a  $\beta$ -axial methyl group. The model predicts an effect opposite from that which is given by more complete calculations, and the latter are borne out by experiment. The important point to be made is that if the model used to develop the octant rule fails, then it fails, and the fact that it works in a great many cases is of limited consolation. It means that the rule will be successful and will work in cases which are essentially identical with those where it is already known to work, but when one faces structural situations which are novel, one cannot count on the octant rule. On the other hand, presumably the method of Pao and Santry, perhaps with further refinement if necessary, should be extendable to the general case. There has been some recent discussion about the "front octants", and their location, and the effect of putting substituents into those octants.<sup>37</sup> The important point made here is that because of extra nodal surfaces appearing in the orbital which is nominally considered to be the n orbital on oxygen, the original octant rule is quite invalid. The observed effects may well result from something quite different than the presence of a "front octant". Quantitative calculations on the experimentally studied systems are needed to settle the point.

### **Experimental Section**

dl-5-Methyl-2-cyclohexenone. 5-Methyl-1,3-cyclohexanedione was prepared from the ethoxide-promoted reaction of ethyl crotonate with acetoacetic ester.<sup>26</sup> The dione was converted to the enol ether (3-ethoxy-5-methyl-2-cyclohexenone) with p-toluenesulfonic acid in ethanol.<sup>27</sup> The enol ether was reduced with lithium aluminum hydride to give, after fractional distillation through a 1-ft Podbielniak column, a 94% yield of a colorless oil: bp 54° (5 mm);  $n^{25}$ D 1.4740 [reported<sup>19</sup> bp 60° (8 mm),  $n^{25}$ D 1.4739];  $\nu_{C=0}$ 1691 cm<sup>-1</sup> (neat). A sample of the ketone was purified through the semicarbazone. Recrystallization gave plates, mp 178-179° (reported<sup>19</sup> mp 177.5-179°).

The 2,4-dinitrophenylhydrazone, from ethyl acetate-ethanol, was obtained as orange-red needles, mp 152-152.3° (reported<sup>19</sup> mp  $152 - 152.5^{\circ}$ )

dl-trans-3,5-Dimethylcyclohexanone. The dimethyl ketone was prepared according to the method used by Kharasch and Taw $ney^{25}$  for the preparation of 3,3,5,5-tetramethylcyclohexanone. Magnesium turnings (2.7 g) were covered with 110 ml of dry ether under nitrogen, and 15.6 g of methyl iodide in 50 ml of ether was added with stirring at a rate so as to keep the ether refluxing. More ether (110 ml) was added at the end of 15 min and 1 hr (50 ml). As the magnesium was dissolved and the refluxing ceased, 100 mg of dry curpous chloride was added and the mixture was cooled to 5°. A solution of 11 g of ketone in 50 ml of ether was added in the course of 1 hr. The mixture was stirred and maintained at about 10° during the addition of the ketone, heated for an hour, and then allowed to stand overnight. Ice and glacial acetic acid were added to decompose the reaction complex, with cooling. The ether layer was separated and dried over sodium carbonate and the ether was evaporated. The residue was distilled through a 1-ft Podbielniak column, bp 36-37° (1.5 mm). The yield of colorless oil was 55-68%. The 2,4-dinitrophenylhydrazone was obtained as orange needles, mp 109.6-110.5° (reported<sup>16</sup> mp 109.6-110.3°). The mixture melting point with the cis isomer (mp 167-168°) was depressed but that with the authentic trans compound<sup>16</sup> was not. A sample of the ketone was purified further by means of vapor phase chromatography using a column of tricyanoethoxypropane (20%) of 60-80 mesh firebrick, and comparison with authentic samples<sup>16</sup> showed that the ketone contained 94-96% of the trans isomer and 4-6% of the cis isomer.

Synthesis of trans-(-)-3(R),5(R)-Dimethylcyclohexanone. (+)-3(R)-Methylcyclohexanone. Commercially available (+)pulegone (Aldrich Chemical Co., 300 g) was converted to (+)-3methylcyclohexanone, bp 47° (10 ml) (146 g, 66%), according to usual methods.<sup>28</sup> An equimolar amount of semicarbazide hydrochloride (147 g) was dissolved in 500 ml of water and 160 ml of pyridine and the ketone in 500 ml of methanol was added. The mixture was then warmed gently on the steam bath until the solution was clear and it was then seeded and cooled. The crude solid was recrystallized from 70% ethanol. Three crystallizations were necessary to obtain a constant melting point and specific rotation, and furnished 189.5 g of product in 86% yield, mp 180–181°,  $[\alpha]^{25}$ D -20.7° (c 1.45, absolute ethanol).

Anal. Calcd for C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O: C, 56.78; H, 8.93. Found: C, 56.53; H, 8.71

Hydrolysis of the semicarbazone with aqueous hydrochloric acid solution followed by distillation furnished 124 g of the pure ketone, bp 167-167.5° (745 mm),  $d^{25}$  0.9109,  $[\alpha]^{25}$ D +12.56° (neat) [reported<sup>28</sup>  $[\alpha]^{25}$ D +12.01° (neat), bp 166.5–168° (735 mm)].

(-)-trans-2-Bromo-5-methylcyclohexanone. The bromination of (+)-3(R)-methylcyclohexanone was carried out by a modification of the procedure of Djerassi,<sup>29</sup> as follows. To the 35.75 g of ketone in 100 ml of water was added 50.94 g of bromine dropwise with vigorous stirring. The reaction flask was cooled to 15-20° and the rate of addition was adjusted so as to maintain a faint coloration of bromine at all times (ca. 8 hr). Sodium chloride was added to saturate the water layer, and the product was extracted with ether. The combined ether solutions were washed with water, sodium carbonate solution and water, the solution was dried over magnesium sulfate, and the solvent was evaporated, leaving 64 g of a pale yellow oil. The oil was twice distilled, and the fraction boiling at 72-77° (3 mm) was collected (54 g). The colorless oil was dissolved in a minimum amount of pentane and placed in a Dry Iceacetone bath. After the collection of crystalline product, the mother liquor was condensed and the crystallization was repeated. After recrystallization of the crude product from ether-pentane, there was obtained a 32% yield of the pure bromo ketone, bp 58° (0.5 mm), mp 82.5-83°,  $[\alpha]^{25}$ D -64.8° (c 1.16, toluene) [reported<sup>29</sup> mp 83.5–84°,  $[\alpha]D$  –64.4° (c 1.06, toluene)]. This procedure gives a much better yield than that previously reported<sup>28-30</sup> (21%). The infrared spectrum was identical with that reported.

(-)-5-Methyl-2-cyclohexenone. A. From the Ethylene Ketal of (-)-trans-2-Bromo-5-methylcyclohexanone. (-)trans-2-Bromo-5-cyclohexenone (12.5 g) was heated in 200 ml of benzene containing some ethylene glycol and 100 mg of p-toluenesulfonic acid for 6 hr, with continuous removal of the water formed. The mixture was washed with sodium carbonate solution and extracted with pentane, and the extracts were dried. Anhydrous sodium carbonate (20 g) was added to the pentane solution to take up excess glycol. Filtration of the solution, evaporation of the solvent, and distillation of the residue yielded 92% of the ketal, bp 77° (1 mm),  $d^{25}$  1.3806,  $[\alpha]^{25}$ D –173.0° (neat). Anal. Calcd for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub>Br: C, 45.98; H, 6.43. Found: C, 46.17; H,

6.36

The dehydrobromination of 10 g of the bromo ketal was carried out by refluxing in 50 ml of methanol containing 12.5 g of sodium hydroxide for 72 hr. The solution was diluted with water, and the product was extracted with ether. The extracts were washed, and dried, and the solvent was evaporated. Distillation gave the unsaturated ketal (71%), bp 71° (10 mm),  $[\alpha]^{25}D - 127.66°$  (c 1, chloroform).

The hydrolysis of the unsaturated ketal in dilute hydrochloric acid gave 96.3% of (-)-5-methyl-2-cyclohexenone,  $[\alpha]^{25}D$  -90.17° (c 0.767, chloroform), and the infrared spectrum was identical with those of the dl and (+) isomers. A sample of the ketone was converted to its semicarbazone derivative, mp 176.5-178°,  $[\alpha]^{25}D$ -206.01° (c 0.505, absolute ethanol) (reported<sup>19</sup> mp 177.5-179°).

B. By Direct Formation of the Semicarbazone of (-)-5-Methyl-2-cyclohexenone. (-)-2-Bromo-5-methylcyclohexenone (1.91 g) in 10 ml of glacial acetic acid in a flask under a nitrogen atmosphere was heated with stirring, 1.125 g of freshly prepared semicarbazide was added, and the solution was maintained at boiling for 5 min. After dilution of the solution with water, the product was collected and recrystallized from ethyl acetate-ethanol. A 65% yield of the semicarbazone was obtained,  $[\alpha]^{25}D = 205.88$  (c 0.601, EtOH), mp 175-177.5° (reported<sup>19</sup> mp 177.5-179°). There was no depression of the mixture melting point with the sample obtained from A described above. Hydrolysis of the semicarbazone gave the ketone (-)-5-methyl-2-cyclohexenone, identical with that prepared from procedure A. The 2,4-dinitrophenylhydrazone had  $[\alpha]^{25}$ D -221.9° (c 0.261, chloroform) [reported<sup>29</sup> mp 143-145°,  $\left[\alpha\right]$ D –219° (c 0.06, chloroform)].

trans-3(R),5(R)-Dimethylcyclohexanone. From 9 g of (-)-5-methyl-2-cyclohexenone, 7.2 g (69.8%) of trans-3(R), 5(R)-dimethylcyclohexanone was obtained occording to the method described above for the preparation of the dl compound. The ketone was purified via the semicarbazone derivative, mp 180–181°,  $[\alpha]^{25}$ D -54.89° (c 1, absolute ethanol).

Anal. Calcd for C<sub>9</sub>H<sub>17</sub>N<sub>3</sub>O: C, 58.98; H, 9.35. Found: C, 59.03; H, 9.43

After hydrolysis of the semicarbazone, the ketone was further purified by vapor phase chromatography,  $[\alpha]^{25}D - 15.05^{\circ}$  (neat),  $[\alpha]^{25}D - 12.28^{\circ}$  (c 1.118, chloroform). The infrared and NMR spectra were identical with those of the dl compound.

Synthesis of 3,3,5(R)-Trimethylcyclohexanone. A. By Resolution of dl-3,3,5-Trimethylcyclohexanone. dl-cis- and trans-3,3,5-Trimethylcyclohexanol. Purified isophorone<sup>37</sup> was reduced with 1 mol of hydrogen and platinum oxide. Distillation gave 93% of 3,3,5-trimethylcyclohexanone, bp 67-69° (10 mm). This ketone was then reduced with aluminum isopropoxide according to Hardly and Wicker<sup>32</sup> as follows: 140.5 g of the ketone was mixed with aluminum isopropoxide solution (900 ml of 10% solution in isopropyl alcohol) and the resulting solution was refluxed for 24 hr and then very slowly distilled until acetone was no longer detectable in the distillate by dinitrophenylhydrazone formation (6 hr). Most of the isopropyl alcohol was then removed, the residue was poured into 2 l. of water, and hydrochloric acid was added until the solid had dissolved. The mixture was extracted with ether using a continuous extractor. The ether solution was washed with water and dilute carbonate solution, and the solvent was evaporated. The residue was distilled to give a 68% yield of cis-3,3,5-trimethylcyclohexanol, after fractional recrystallization from hexane as described above.

The cis alcohol (128 g) was dissolved in 400 ml of dry pyridine, the solution was cooled to 0°, and 185.6 g of purified *p*-nitrobenzoyl chloride was added in small portions. The solution was allowed to stand overnight with stirring. The mixture was poured into water, and the crude product was collected by filtration, dried, and extracted with petroleum ether through a Soxhlet tube to remove insoluble *p*-nitrobenzoic acid. The product was allowed to crystallize, and recrystallization from petroleum ether and methanol gave the ester (86%), mp 80.5–81°.

Anal. Calcd for  $C_{16}H_{21}NO_4$ : C, 65.96; H, 7.27. Found: C, 65.79; H, 7.42.

The benzoate (65 g) was added to 400 ml of hot, stirred 2.5 N sodium hydroxide solution. The alcohol was removed as formed by azeotropic distillation with water. The distillate was extracted with ether, the combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated. The residue was distilled through a 1-ft Podbielniak column at reduced pressure, yield 87%, mp 36–36.4° (reported<sup>38</sup> mp 37°).

*dl-cis-3,3,5-Trimethylcyclohexanyl Acid Phthalate.* A solution of *dl-cis-3,3,5-trimethylcyclohexanol* (72 g) with 74 g of phthalic anhydride in 300 ml of benzene was refluxed for 16 hr. After cooling, the reaction mixture was filtered and the solvent was distilled. The residue was dissolved in anhydrous ether and cooled in the refrigerator. After three recrystallizations there was obtained 132.9 g (91%) of pure acid phthalate, mp 129–129.5° (reported<sup>39</sup> mp 129°).

Cinchonine Salt of *dl-cis*-3,3,5-Trimethylcyclohexanyl Acid Phthalate. The *dl-cis*-3,3,5-trimethylcyclohexanyl acid phthalate (58 g) in 500 ml of dry acetone-chloroform (1:1) with 58 g of cinchonine was refluxed until the solution was clear. The solvent was removed, and the residual oil was dissolved in a minimum amount of warm chloroform. The solution was then cooled to room temperature and allowed to stand. After about seven crystallizations, the rotation remained constant,  $[\alpha]^{24.5}D + 93.83^{\circ}$  (*c* 5, chloroform), mp 99-101°.

Anal. Calcd for  $C_{36}H_{44}N_2O_5$ : C, 73.93; H, 7.53. Found: C, 73.87; H, 7.44.

(-)-cis-3,3,5-Trimethylcyclohexanyl Acid Phthalate. The cinchonine salt (15 g) was added to hot 10% hydrochloric acid, and the solution was stirred for 30 min. The suspension was cooled and filtered. The solid collected was ground in a mortar with a small amount of water, refiltered, and washed with dilute hydrochloric acid and distilled water. After air drying, the solid was recrystallized from ether to constant rotation, yield 5.5 g, mp 129–129.5°,  $[\alpha]^{24.5}D-3.19^{\circ}$  (c 5, chloroform).

(-)-cis-3,3,5-Trimethylcyclohexanol. The acid phthalate (18 g) was dissolved in 100 ml of 0.5 N sodium hydroxide solution and the solution was refluxed for 1 hr, then cooled and extracted with ether. The extracts were dried over magnesium sulfate, and the solvent was evaporated. The residual oil was distilled through a 1-ft Podbielniak column and gave an almost quantitative yield of the alcohol, which boiled at 85° (10 mm). The alcohol was further purified by sublimation, mp 34-34.5°. The specific rotation of the alcohol was not changed by the sublimation,  $[\alpha]^{24.5}D$  -2.99° (c 1, chloroform).

3,3,5(R)-Trimethylcyclohexanone. To the alcohol (4.3 g), in 20 ml of acetone was added Jones reagent (8 N),<sup>33</sup> over a period of

10 min with stirring. The addition was stopped as the solution turned to a slightly brown color. The stirring was continued for an additional 10 min, and the solution was poured into 200 ml of water. The resulting solution was extracted with ether, the extracts were dried over sodium sulfate, and the solvent was evaporated. The residual oil was distilled through a 1-ft Podbielniak column, yield 93%, bp 67° (ca. 10 mm). The rotation,  $[\alpha]^{24.5}D - 6.52^{\circ}$  (c 5, chloroform), indicated that the ketone was only partially resolved.

**B.** From trans-3(R)-5(R)-Dimethylcyclohexanone. (-)-3,5-Dimethyl-2-cyclohexenone. To trans-3(R),5(R)-dimethylcyclohexanone (4.5 g) in 45 ml of ethylene glycol was added 5.73 g of bromine during 6 hr. The reaction mixture was worked up according to the procedure described for the preparation of the ethylene ketal of 2-bromo-5-methylcyclohexanone and gave 7.66 g (87.6%) of the bromo ketal, bp 73° (0.3 mm),  $[\alpha]^{25}D - 16.72^{\circ}$  (c 1, chloroform). The bromo ketone was dehydrobrominated in 29% yield, applying the same procedure as was described for the preparation of the ketal of 5-methyl-2-cyclohexenone. Hydrolysis of the ketal with 10% hydrochloric acid gave 470 mg of (-)-3,5-dimethyl-2-cyclohexenone, which was purified further by vapor phase chromatography, bp 73° (ca. 10 mm),  $n^{25}D$  1.4820,  $[\alpha]^{25}D$  -138.39° (c 0.8, chloroform) [reported<sup>40</sup> bp 84-85° (11 mm),  $n^{20}D$  1.4843].

**3,3,5(***R***)-Trimethylcyclohexanone.** The (-)-3,5-dimethyl-2cyclohexenone purified by vapor phase chromatography (470 mg) in 5 ml of anhydrous ether was allowed to react with the Grignard reagent prepared from 96.6 mg of magnesium, 564 mg of methyl iodide, and 5 mg of cuprous chloride following the procedure described for the synthesis of *trans*-3,5-dimethylcyclohexanone. There was obtained, after further purification by vapor phase chromatography, 414 mg (78%) of the trimethyl ketone,  $[\alpha]^{25}D$ -27.04° (c 0.9, chloroform). The infrared spectrum was identical with that of the *dl* isomer.

Synthesis of 3,3,5(S)-Trimethylcyclohexanone. Brucine Salt of *dl-cis*-3,3,5-Trimethylcyclohexyl Acid Phthalate. A solution of 58 g of *dl-cis*-3,3,5-trimethylcyclohexyl acid phthalate in 500 ml of reagent acetone with 79 g of powdered anhydrous brucine was warmed until the solution was clear. It was then placed in a refrigerator overnight and gave an almost quantitative yield of the salt. This mass was crushed to a powder and subjected to fractional extraction through a Soxhlet tube with dry acetone. The less soluble isomer which remained in the thimble after the extraction with about 2 l. of acetone was removed and recrystallized twice from acetone, three times from methanol, and five times from ethyl acetate until the specific rotation was constant, mp 130–  $132^{\circ}$ ,  $[\alpha]^{24.5}D - 15.2^{\circ}$  (c 5, chloroform).

Anal. Calcd for  $C_{40}H_{48}N_2O_8$ : C, 69.53; H, 8.46; N, 3.47. Found: C, 69.61; H, 8.34; N, 3.59.

(+)-cis-3,3,5-Trimethylcyclohexanyl Acid Phthalate. The hydrolysis of the brucine salt was carried out by the same procedure as described for that of the cinchonine salt. The half-ester had mp 129.5°,  $[\alpha]^{24.5}D$  +8.16° (c 5, chloroform).

(+)-cis-3,3,5-Trimethylcyclohexanol. The (+) acid phthalate (22 g) was saponified by the procedure used for the preparation of (-)-cis alcohol. A 94.6% yield of (+)-cis alcohol having  $[\alpha]^{24.5}$ D +9.43° (c 1, chloroform), mp 37.5°, was obtained.

**3,3,5(S)-Trimethylcyclohexanone.** The Jones oxidation was carried out as described for the *R* isomer. The yield was 4.67 g (92%), bp 67° (ca. 10 mm),  $[\alpha]^{24.5}$ D +20.29° (*c* 1, chloroform). The ultraviolet absorption spectrum showed a peak at 292 m $\mu$  ( $\epsilon$  19.7, 0.03914 g/100 ml of ethanol solution). A sample of the ketone was purified via the semicarbazone. Recrystallization gave plates, mp 194–195°,  $[\alpha]^{25}$ D +201.2° (*c* 1, chloroform).

Anal. Calcd for  $\rm C_{10}H_{19}N_{3}O:$  C, 60.88; H, 9.71. Found: C, 60.93; H, 9.88.

After hydrolysis of the semicarbazone, the ketone obtained was further purified by vapor phase chromatography; however, there was no change in the optical rotation, indicating that the material was only  $75.0 \pm 0.2\%$  optically pure.

**Registry No.**—5-Methyl-1,3-cyclohexanedione, 4341-24-6; dl-5-methyl-2-cyclohexenone, 54352-35-1; dl-5-methyl-2-cyclohexenone semicarbazone, 54307-70-9; dl-5-methyl-2-cyclohexenone 2,4-dinitrophenylhydrazone, 54307-71-0; dl-trans-3,5-dimethylcyclohexanone, 54362-36-2; (+)-3(R)-methylcyclohexanone, 13368-65-5; (+)-3(R)-methylcyclohexanone semicarbazone, 54307-73-2; (-)trans-2-bromo-5-methylcyclohexanone, 18951-83-2; (-)-5-methyl-2-cyclohexenone, 54307-74-3; (-)-trans-2-bromo-5-methylcyclohexanone ethylene ketal, 54307-75-4; ethylene glycol, 107-21-1; (-)-5-methyl-2-cyclohexenone ethylene ketal, 54307-76-5; (-)-5-

semicarbazone, methyl-2-cyclohexenone 54352-37-3: (-).5methyl-2-cyclohexenone 2,4-DNP, 54307-77-6; trans-3(R),5(R)dimethylcyclohexanone semicarbazone, 54307-78-7; 3,3,5(R)-trimethylcyclohexanone, 33496-82-1; dl-cis-3,3,5-trimethylcyclohexanol, 54307-79-8; p-nitrobenzoic acid, 62-23-7; dl-cis-3,3,5-trimethylcyclohexanyl p-nitrobenzoate, 54307-80-1; dl-cis-3,3,5-trimethylcyclohexanyl acid phthalate, 54307-81-2; phthalic anhydride, 85-44-9; dl-cis-3,3,5-trimethylcyclohexanyl acid phthalate cinchonine salt, 54307-82-3; cinchonine, 24831-03-6; (-)-*cis*-3,3,5-trimethylcyclohexanyl acid phthalate, 54352-38-4; (-)-*cis*-3,3,5trimethylcyclohexanol, 54352-39-5; (-)-3,5-dimethyl-2-cyclohexenone, 54307-83-4; 3,3,5(S)-trimethylcyclohexanone, 33496-83-2; brucine, 357-57-3; dl-cis-3,3,5-trimethylcyclohexanyl acid phthalate brucine salt, 54307-84-5; (+)-cis-3,3,5-trimethylcyclohexanyl acid phthalate, 54352-40-8; (+)-cis-3,3,5-trimethylcyclohexanol, 54352-41-9; 3,3,5(S)-trimethylcyclohexanone semicarbazone. 54307-85-6.

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### Effect of Changes in Surfactant Structure on Micellarly Catalyzed Spontaneous Decarboxylations and Phosphate Ester Hydrolysis<sup>1</sup>

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Micelles of the zwitterionic surfactant, N,N-dimethyl-N-dodecylglycine, catalyze the spontaneous decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion 170-fold and that of cyanophenyl acetate ion 690-fold, and they, and micelles of the corresponding alanine surfactant, are better catalysts than dodecyltrimethylammonium bromide by factors of almost 3-fold. The catalytic efficiency of cationic micelles of N,N-dimethyl-N-hydroxylethyl-2hexadecylammonium bromide is also increased 2-fold by conversion of this surfactant into a zwitterion at high pH. Lecithin and lysolecithin are very poor catalysts, showing that the arrangement of charge in the zwitterionic head group is of key importance. Catalysis by micelles of N,N-dimethyl-N-dodecylglycine is subject to large salt effects which depend upon the anion, but differ from those typical of micellar catalysis. Salts having hydrophilic anions tend to increase catalysis and those having hydrophobic anions decrease it. Chemically inert solutes such as phenols and aliphatic amines change the catalytic effectiveness of micelles of cetyltrimethylammonium bromide, but these micelles in aqueous ethylene glycol, or the reverse micelles in hexanol-water, are poor catalysts both for decarboxylation and for the spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion.

The spontaneous decarboxylations of 6-nitrobenzisoxazole-3-carboxylate ion  $(I)^3$  and 2-phenylcyanoacetate ion  $(II)^4$  are catalyzed strongly by cationic micelles<sup>5,6</sup> and by cyclodextrins.<sup>7</sup> The micellar catalysis is enhanced by some electrolytes, which is an unusual feature because micellar catalysis is generally decreased by added electrolytes.<sup>8</sup>

These decarboxylations are much faster in organic or aqueous organic solvents than in water,<sup>3,4</sup> and these observations together with the unusual electrolyte effect on micellar catalysis suggest that these reactions may provide a useful probe of the nature of the micellar surface.<sup>5,6</sup> The enhancement of the rate of decarboxylation of I in cationic micelles of cetyltrimethylammonium bromide (CTABr)



containing less than 1 equiv of sodium tosylate was explained in part in terms of an initial state electrostatic re-