throughout the series, and therefore the relative free energies calculated from the equilibrium constants should compare with the quantities given as ΔH in Table I.

The free energies for the addition of hydrogen cyanide to the cyclanones have been reported,[25] and seem well suited for the comparison at hand. These free energies, relative to cyclohexanone, are shown by the line in Fig. 1. The enthalpies as calculated in the present work for the introduction of the keto group into the cyclanes are indicated by circles on the same figure, and the agreement is fortuitously good.

Many other properties of medium rings which involve conversions of a trigonal ring atom to a tetrahedral atom also vary throughout the series in a manner qualitatively similar to that of the hydrogen cyanide addition,[23,26] but these other properties are all sterically more complicated which might induce other interactions, or else they involve charged species which would render questionable the assumption of the lack of dependence of entropy on ring size.

Prelog has proposed[23] that the "O-inside" conformations of the medium rings are stabilized by transannular hydrogen bonding and this effect increases in importance with increasing nucleophilicity of the atom forming the hydrogen bond. Spectroscopic evidence for transannular hydrogen bonding in cycloöctanone has also been reported.[27] The present work indicates that there is no need to invoke these effects to explain the available energy data, and while it seems likely that these effects are in fact real, they probably lead to only small energy changes.

The ultimate justification for the many severe approximations and assumptions made in the present work comes from the fact that the agreement between the simple calculations and the available experimental data is as good as it is.

DETROIT 2, MICH.

[25] V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).

[26] O. H. Wheeler, THIS JOURNAL, **79**, 4191 (1957).

[27] G. B. B. M. Sutherland, quoted in ref. 23.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Conformational Analysis. IV. The Conformations of the Cycloöctanone Ring[1,2]

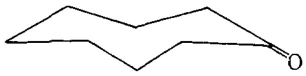
BY NORMAN L. ALLINGER AND SEYMOUR GREENBERG

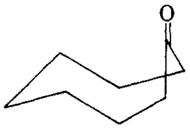
RECEIVED MARCH 26, 1959

5-(4-Chlorophenyl)-cycloöctanone was prepared by an unambiguous method. Its dipole moment in benzene solution was found to be 3.39 D. This value is taken as evidence that the cycloöctanone ring exists in two principal conformations, "O-inside" and "O-outside," and that these are of similar free energy. It is concluded that in general compounds containing simple cycloöctanone rings will exist as mixtures containing comparable amounts of these two conformations.

Introduction

Theoretical considerations have indicated that cycloöctanone may exist in either a crown (I) or in a chair (II) form,[3] and quantitative calculations using a reasonable potential function for rotation about a C–C bond,[1] have suggested that they are of similar energies. No experimental differentiation between these possibilities was made. The principal evidence available earlier which can be interpreted as supporting structure II comes mainly from the infrared spectrum. Cycloöctanone has its carbonyl stretching frequency at 1701 cm.$^{-1}$, considerably less than that of cyclohexanone (1714 cm.$^{-1}$) in carbon tetrachloride.[4] Since in II there exists the possibility of transannular hydrogen bonding, the lowering of the carbonyl frequency here and in the other medium rings has been taken as indicative of the existence of conformation II ("O-inside" conformation).[5]


I


II

An alternative interpretation of the infrared data is possible, however. The carbonyl stretching frequencies of the simple cyclanones can be divided into three groups. One group contains fewer than six-ring members, and the frequencies are quite high. The second group consists of six-membered rings together with rings containing eleven or more carbons. These compounds all absorb at 1709–1714 cm.$^{-1}$ (in carbon tetrachloride) as do typical open-chain compounds. The 7–10-membered rings, on the other hand, absorb uniformly at 1701–1702 cm.$^{-1}$. The work of Halford[6] suggests that, since there is no reason to suspect that the force constants or attached masses of the carbonyls should be grouped together in such a way, the C–C–C bond angle at the carbonyl group is expanded above its normal value in the medium rings. Presumably all of the C–C–C bond angles are so expanded in an effort to relieve both transannular strain and unfavorable dihedral angles. An expansion of each angle by 4° would be sufficient to account for the carbonyl frequency. It would raise the enthalpy of the regular crown by 0.28 kcal. per carbon atom from the bond bending but the more favorable dihedral angles (90° instead of 96°) would lower the en-

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[1] Paper III, N. L. Allinger, THIS JOURNAL, **81**, 5727 (1959).

[2] This work was supported by a research grant from the National Science Foundation.

[3] See ref. 1 for a summary and references.

[4] N. J. Leonard and F. H. Owens, THIS JOURNAL, **80**, 6039 (1958). We wish to thank Dr. Leonard for sending us a copy of this manuscript prior to publication.

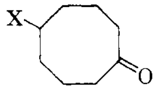
[5] V. Prelog, *J. Chem. Soc.*, 420 (1950).

[6] J. O. Halford, *J. Chem. Phys.*, **24**, 830 (1956).

thalpy by 0.43 kcal. per carbon. The ten-membered ring could similarly obtain more favorable dihedral angles (110° instead of 115°). With the twelve-membered ring the dihedral angles are 126°, and expanding the bond angles would bring the dihedral angles nearer 120°, making them worse. There is no simple way to find the dihedral angles in the odd-membered rings,[7] but the experimental carbonyl frequencies for the even-membered rings are just as predicted and those of the odd-membered rings fall in between in a reasonable way.

Discussion

It appeared that the method by which the preferred conformation for cycloöctanone (I or II) might be most readily determined would be by measurement of the dipole moment of a suitable 5-substituted cycloöctanone (III) in which X was a polar substituent.

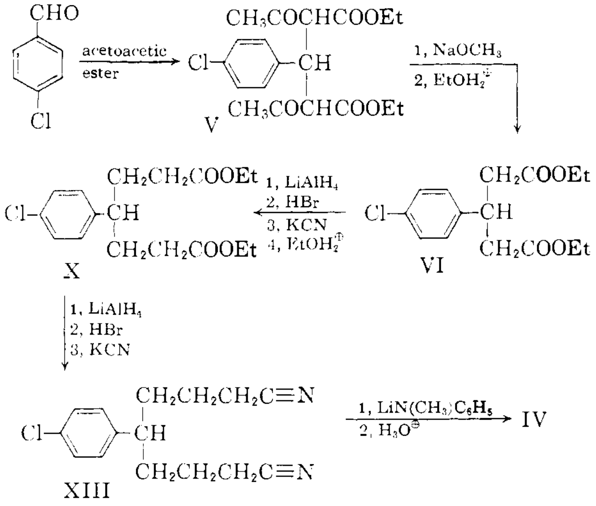


III; IV, X = *p* chlorophenyl

It was necessary for the group X to have certain properties to make the method convenient and unambiguous. The group had to be bulky enough to make plausible the assumption that it would stay in the equatorial position. The polarity of the group had to be large enough to be measured conveniently, but not so large that the dipole interaction with the carbonyl would deform III into a conformation different from that of cyclooctanone itself. Furthermore, the group had to have an exactly definable moment, and it had to survive the synthetic operations used to prepare III. The *p*-chlorophenyl group seemed to fulfill these requirements. It is effectively large since it has been shown[8] that the group is not in the axial position in a six-membered ring to any extent. The axial[1] positions of cycloöctanone in either conformation II or III point somewhat inward toward the center of the ring, and it seems safe to assume that the group will remain equatorial[1] here also. The moment of the group is large, and its magnitude and direction are well known. The bulk of the charge separation is, however, well removed from the vicinity of the keto group.

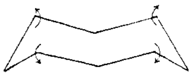
The synthesis of compound IV is outlined on the flow sheet. The condensation[9] of two moles of acetoacetic ester with *p*-chlorobenzaldehyde yielded V, which was cleaved by a reverse Claisen reaction to give VI. This ester was reduced[10] to the diol with lithium aluminum hydride, which was in turn converted *via* the bromide[11] and nitrile[12] to the homologous ester.[13] Repetition of these steps gave the homologous nitrile XIII. Cyclization of this compound using a modified Ziegler reaction[14] gave a small yield of the desired ketone, IV.

The structure of the ketone was supported by the presence of a carbonyl band at 1702 cm.$^{-1}$ in the infrared spectrum, by the formation of a dinitrophenylhydrazone, and by the oxidation of the compound to *p*-chlorobenzoic acid.



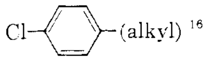
Results

The O-inside and O-outside conformations of the cycloöctanone ring are not rigid but show a considerable freedom with respect to various vibrational motions of the kind indicated by XIV. The mean position of the atoms in either conformation can be rather easily established from examination and direct measurement employing scale models. Although this procedure is not of high accuracy, it is quite adequate for present purposes.



XIV

The group moments used for the calculations were 2.93 D. for C=O (the value for cycloöctanone in benzene[15]), and 1.84 D. for the whole group



[16]

The angles between the dipole of the C=O group and that of the C—Cl group, assuming the substituent is in the equatorial position, in conformations I and II, respectively, are 148° and 64° (from direct measurement on scale models). The corresponding moments calculated are 1.68 and 4.09 D.

The experimental moment is 3.39 D., and therefore the compound is best interpreted as being a mixture of the two conformational isomers. From the equation $\mu^2 = \mu^2_A N_A + \mu^2_B N_B$, where μ is the observed moment, μ_A and N_A are, respectively, the moment and mole fractions of con-

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[7] L. Pauling, *Proc. Natl. Acad. Sci.*, **35**, 495 (1949).

[8] A. C. Huitric and W. D. Kumler, THIS JOURNAL, **78**, 614 (1956).

[9] W. T. Smith, Jr., and P. G. Kort, *ibid.*, **72**, 1877 (1950).

[10] R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197, 2548 (1947).

[11] W. L. McEwen, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 227.

[12] J. R. Ruhoff, *ibid.*, Coll. Vol. II, p. 292.

[13] R. Adams and C. S. Marvel, THIS JOURNAL, **42**, 310 (1920).

[14] K. Ziegler, H. Eberle and H. Ohlinger, *Ann.*, **504**, 94 (1933).

[15] H. H. Gunthard and T. Gaümann, *Helv. Chim. Acta*, **34**, 39 (1951).

[16] Kumler[8] has used the value 1.56 D. for the latter, which is the value for an aromatic carbon–halogen bond moment. The aryl–alkyl bond moment (0.3–0.4 D.) should be added to this value. The two values for the moment of *p*-chlorotoluene (in benzene) reported in the literature are 1.94 D. (L. Tiganik, *Z. Physik*, **B13**, 425 (1931)) and 1.74 (P. Walden and O. Werner, *ibid.*, **B2**, 10 (1929)). We have taken the value 1.84 D. as being most consistent with these data.

formational isomer A and μ_B and N_B have the corresponding meaning with respect to B, the conformational composition of the mixture can be calculated. It is found that 62% of the compound is in the boat form (II), the remainder being as the crown (I).

Several approximations have been made in interpreting the observed moment, and they limit the accuracy of the results. It seems clear, however, that the boat form is of slightly greater stability. Of more general interest is the conclusion that the forms differ in free energy by only some 0.4 kcal. and any simple cycloöctanone may therefore be expected to be a mixture containing comparable amounts of the two forms.

Acknowledgment.—We are very grateful to Dr. M. T. Rogers, Michigan State University, for kindly allowing us to use his apparatus for the dipole moment measurement reported herein.

Experimental[17]

β-(*p*-Chlorophenyl)-glutaric Acid.—A mixture of 170 g. of hexamethylenetetramine, 160 g. (1.0 mole) of *p*-chlorobenzyl chloride, one liter of 95% ethyl alcohol and 500 ml. of water was heated under reflux for two hours. An additional 85 g. of hexamethylenetetramine was added and refluxing was continued overnight. Concentrated hydrochloric acid, 750 ml., was added and the mixture was refluxed an additional two hours. After addition of one liter of water and cooling of the reaction mixture, the organic layer was separated and the water layer was extracted with ether. The extracts were washed with water and dried over anhydrous magnesium sulfate and the solvent was evaporated.

The crude *p*-chlorobenzaldehyde was mixed with 260 g. of ethyl acetoacetate and 20 ml. of piperidine, and the mixture was allowed to stand overnight. The resultant solid mass was heated under reflux for 18 hours with a mixture of 1.5 liters of 95% ethyl alcohol and 270 g. of sodium methoxide. The alcohol was distilled *in vacuo* until the residual mixture was a thick paste. The residue was washed twice by suspending it in one liter of ether, stirring the suspension, and then filtering the solution. The resultant solid was taken up in 2 l. of water, and the solution was filtered. The filtrate was acidified with concentrated hydrochloric acid, the mixture was cooled and filtered, and the solid was collected. A small sample, recrystallized from ethyl acetate–benzene, had m.p. 164–165°.

Anal. Calcd. for $C_{11}H_{11}O_4Cl$: C, 54.44; H, 4.57. Found: C, 54.51; H, 4.36.

Ethyl β-(*p*-Chlorophenyl)-glutarate (VI).—The dried crude acid was esterified by heating with a 10-mole excess of absolute ethanol containing 10 wt. % sulfuric acid for two hours. The cooled reaction mixture was diluted with water and extracted with ether. The extracts were washed and dried, the ether was evaporated and the residue was distilled through a two-foot Vigreux column, b.p. 151–161° (1–1.7 mm.), n^{25}D 1.5015, yield 41% (based on *p*-chlorobenzyl chloride).

Anal. Calcd. for $C_{15}H_{19}O_4Cl$: C, 60.30; H, 6.41. Found: C, 60.30; H, 6.52.

3-(4-Chlorophenyl)-1,5-dihydroxypentane (VII).—To two liters of anhydrous ether was added 19 g. of lithium aluminum hydride. A solution of 120 g. of ethyl β-(*p*-chlorophenyl)-glutarate in one liter of anhydrous ether was added dropwise rapidly. When the addition was complete, stirring was continued for a short time and then the reaction mixture was decomposed with 10% hydrochloric acid. The reaction mixture was extracted with ether, the extracts were washed and dried, and the ether was evaporated. A small sample was distilled, b.p. 166° (0.8 mm.), n^{25}D 1.5516.

Anal. Calcd. for $C_{11}H_{15}O_2Cl$: C, 61.53; H, 7.04. Found: C, 61.65; H, 6.75.

3-(4-Chlorophenyl)-1,5-dibromopentane (VIII).—The crude lithium aluminum hydride reduction product was treated with anhydrous hydrogen bromide at 120–130° for several hours. The resultant oil was mixed with ether and water and the water layer was separated and discarded. The organic layer was washed thoroughly with sodium bicarbonate solution and then with water. The ether solution was dried and the ether was evaporated. The residue was distilled through a two-foot Vigreux column, b.p. 192–194° (7 mm.), n^{25}D 1.5759, yield 68.5% (based on VI).

Anal. Calcd. for $C_{11}H_{13}Br_2Cl$: C, 38.80; H, 3.85. Found: C, 38.91; H, 4.05.

3-(4-Chlorophenyl)-1,5-dicyanopentane (IX).—Bromide VIII, 85 g., was stirred under reflux with 300 ml. of 95% ethyl alcohol and 40 g. (0.58 mole) of potassium cyanide for 20 hours. An additional 40 g. of potassium cyanide was added and refluxing and stirring was continued for an additional 20 hours.

Part of the ethanol was distilled, and the mixture was cooled. Ether was added, and the precipitated salt was filtered. The ether layer was washed with water and dried, the solvent was evaporated and the nitrile was distilled through a two-foot Vigreux column, b.p. 187–192° (0.7 mm.), n^{25}D 1.5338, yield 48.6 g. (82%).

Anal. Calcd. for $C_{13}H_{13}N_2Cl$: C, 67.09; H, 5.63. Found: C, 67.11; H, 5.50.

Ethyl γ-(*p*-Chlorophenyl)-pimelate (X).—Compound IX, 48.6 g. was heated under reflux with a mixture of 100 ml. of 95% ethyl alcohol and 50 ml. of concentrated sulfuric acid for 65 hours. The mixture was then cooled and diluted with water. Ether was added and the organic layer was separated. The water layer was extracted with ether, and the combined organic layers were washed well with sodium bicarbonate solution and water. The ether solution was dried, and the ether was removed. The residue was distilled through a two-foot Vigreux column, b.p. 159–161° (0.5 mm.), n^{25}D 1.4980, yield was 59.5 g. (87%).

Anal. Calcd. for $C_{17}H_{23}O_4Cl$: C, 62.48; H, 7.09. Found: C, 62.50; H, 6.88.

4-(4-Chlorophenyl)-1,7-dihydroxyheptane (XI).—Ester X, 59.5 g., was reduced with 8.4 g. of lithium aluminum hydride as described for the preparation of VII. A small sample of the crude reaction product was recrystallized from ether–pentane, m.p. 69–70°.

Anal. Calcd. for $C_{13}H_{19}O_2Cl$: C, 64.32; H, 7.89. Found: C, 64.19; H, 7.67.

4-(4-Chlorophenyl)-1,7-dibromoheptane (XII).—The crude glycol XI was treated with anhydrous hydrogen bromide and the product was isolated as described for the preparation of bromide VIII. The compound was distilled, b.p. 155–162° (0.3–0.8 mm.), n^{25}D 1.5646.

Anal. Calcd. for $C_{13}H_{17}Br_2Cl$: C, 42.36; H, 4.65. Found: C, 42.14; H, 4.45.

4-(4-Chlorophenyl)-1,7-dicyanoheptane (XIII).—The crude dibromide XII was treated with potassium cyanide in 95% ethyl alcohol as described for the preparation of IX. The product was distilled through a two-foot Vigreux column, b.p. 200–205° (0.7 mm.), n^{25}D 1.5263. A sample was recrystallized from ethanol–water, m.p. 55–56°.

Anal. Calcd. for $C_{15}H_{17}N_2Cl$: C, 69.09; H, 6.57. Found: C, 68.83; H, 6.84.

5-(4-Chlorophenyl)-cycloöctanone (IV).—A solution of phenyllithium in anhydrous ether was prepared by the addition of a solution of 9.70 g. of bromobenzene in 100 ml. of anhydrous ether to a stirred, refluxing suspension of 0.88 g. of lithium metal in about one liter of anhydrous ether, the system being kept under an atmosphere of nitrogen. The addition required about two hours. N-Methylaniline, 7.48 g., then was added rapidly and stirring and refluxing were continued for an additional hour. The addition of a solution of 4-(4-chlorophenyl)-1,7-dicyanoheptane (4.09 g., 0.0157 mole) and 150 ml. of anhydrous tetrahydrofuran (distilled from lithium aluminum hydride) was then begun under high dilution[18] and regulated so that addition was complete in 8–12 hours. The reaction mixture was then decomposed with water which usually resulted in the production of two clear liquid phases with no appreciable quantity of insoluble gums. The water layer was separated and extracted with ether and the ether solutions were combined and washed with water. The ether solution was concentrated to a viscous oil which

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[17] Microanalyses by Miss M. A. DaRooge.

[18] N. L. Allinger, M. Nakazaki and V. Zalkow, THIS JOURNAL, **81**, 4074 (1959).

was refluxed for six hours with 300 ml. of 33% (by volume) sulfuric acid. After the reflux period, a liquid–liquid extractor (for use with solvents heavier than water) was attached to the reaction flask and refluxing was continued for an additional 18 hours. The volatile material was slowly steam distilled and collected in the extractor. When the reaction was complete, the material which had steam distilled (approximately 250 mg.) was extracted with ether. The ether solution was dried with anhydrous magnesium sulfate and the filtered solution was concentrated. The steam-volatile material from five experiments employing a total of 20.45 g. of nitrile was chromatographed on 30 g. of ordinary alumina. It was put on the column with petroleum ether (boiling point 35–45°) and elution was begun with the same solvent, 15- to 20-ml. fractions being collected. Approximately 450 mg. of material, ranging from oily solid to crystals, was collected in fractions 1–6. This material is believed to be biphenyl because of its odor, mixed melting point with authentic biphenyl, and absence of a carbonyl band in the infrared spectrum. Fractions 7–16 gave nothing with petroleum ether and the solvent was changed first to 10% and then to 20% ether–petroleum ether. In fractions 20–30 a total of 805 mg. of odorless crystals was obtained which was recrystallized slowly once from petroleum ether to give 743 mg. (4% of theory based on the open chain dinitrile) of hard, well-formed, transparent crystals, m.p. 66–66.7°. The compound showed an asymmetric but unresolvable carbonyl stretching band at 1702 cm.$^{-1}$ (carbon tetrachloride), which was similar in form to that shown by cycloöctanone itself at the same frequency.

Anal. Calcd. for $C_{14}H_{17}OCl$: C, 71.03; H, 7.24; mol. wt., 236.9. Found: C, 70.93; H, 7.43; mol. wt., 222 (Rast).

The use of lithium diphenylamide as the base in the manner described above led to no isolable yield of the desired compound.

The 2,4-dinitrophenylhydrazone was prepared in the usual way.[19] A benzene solution of the crude derivative was filtered through a small column of alumina. The benzene was evaporated, and the product was twice crystallized from ethanol, m.p. 146.8–147.3°.

Anal. Calcd. for $C_{20}H_{21}N_4O_4Cl$: C, 57.62; H, 5.08. Found: C, 57.78; H, 5.39.

A small sample of ketone IV was oxidized in a basic solution of potassium permanganate,[20] and yielded a white solid, soluble in alkali, m. p. 232–233° (sealed tube). The mixture melting point with authentic *p*-chlorobenzoic acid showed no depression, and the two samples had identical infrared spectra (in chloroform).

TABLE I

DIPOLE MOMENT DATA FOR 5-(4-CHLOROPHENYL)-CYCLOÖCTANONE IN BENZENE AT 25°

N_2	D.	ϵ
0.0046382	0.875419	2.3482
.0023639	.873978	2.3105
.0017956	.873623	2.3001
.0012689	.873254	2.2942
.0008233	.873023	2.2855
.0004573	.872768	2.2798
.0000000	.872482	2.2723

$\alpha = 16.3056$, $\beta = 0.633352$, $P_{2\infty} = 301.374$ cc., $\epsilon_1 = 2.2723$, $d_1 = 0.872480$, $\mu = 3.39$ D.

Dipole Moments.—The apparatus used for the dielectric constant measurements has been described.[21] The benzene solvent was purified by refluxing thiophene-free benzene with sodium followed by distillation from sodium. The density of the solution and its dielectric constant were measured at 25° at various mole fractions as indicated in Table I. The calculations were made following the general procedure of Halverstadt and Kumler[22] as described earlier.[23] The molar refractivity was calculated from standard values[24] of atomic refractivities and had the value 65.929 cc. Atomic polarization was neglected. Experimental error is about 0.02 D.

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[19] R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," fourth edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

[20] Reference 19, p. 250.

[21] M. T. Rogers, THIS JOURNAL, **77**, 3681 (1955).

[22] I. F. Halverstadt and W. D. Kumler, *ibid.*, **64**, 2988 (1942).

[23] N. L. Allinger, *ibid.*, **79**, 3443 (1957).

[24] J. A. Leermakers and A. Weissberger, in H. Gilman "Organic Chemistry," Vol. II, second edition, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 1751.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Conformational Analysis. V. 2-Bromocycloöctanone[1,2]

BY JANET ALLINGER AND NORMAN L. ALLINGER

RECEIVED MARCH 26, 1959

Theoretical considerations indicate that 2-bromocycloöctanone is a mixture of several conformational isomers. The dipole moment of 2-bromocycloöctanone in benzene solution has been found to have the value 3.36 D. The carbonyl stretching band in the infrared spectrum in various solvents is broad and poorly resolved. These data offer qualitative support for the correctness of the theoretical predictions.

Introduction

Earlier studies have shown that it is possible to determine the axial or equatorial nature of a halogen adjacent to a carbonyl in a cyclohexanone by means of various physical methods such as dipole moments,[3] infrared spectra,[4] ultraviolet spectra[5] and rotatory dispersion.[6] The infrared and ultraviolet spectra have also been examined and interpreted for α-bromocyclanones having rings larger than six membered.[7] It is clear from earlier work[2] that a simple cycloöctanone derivative will exist as an equilibrium mixture containing comparable amounts of crown (I) and boat (II) forms. In the special case of 2-bromocyclo-

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[1] Sponsored by the Office of Ordnance Research, U. S. Army. Some of the results of this work were recorded earlier; A.C.S. Meeting Abstracts, San Francisco, Calif., April, 1958, p. 29N.

[2] Paper IV, THIS JOURNAL, **81**, 5733 (1959).

[3] W. D. Kumler and A. C. Huitric, *ibid.*, **78**, 3369 (1956).

[4] (a) R. N. Jones D. A. Ramsay, F. Herling and K. Dobriner, *ibid.*, **74**, 2828 (1952); (b) E. J. Corey, *ibid.*, **75**, 2301, 3297 (1953); **76**, 175 (1954); E. J. Corey, T. H. Topie and W. A. Wozniak, *ibid.*, **77**, 5415 (1955).

[5] R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

[6] (a) C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958); (b) C. Djerassi and W. Klyne, THIS JOURNAL, **79**, 1506 (1957).

[7] N. J. Leonard and F. H. Owens, THIS JOURNAL, **80**, 6039 (1958). The authors wish to thank Dr. Leonard for making this manuscript available to them in advance of its publication.