

sodium and liquid ammonia reduction of nitroethane¹⁶ and was immediately treated with *p*-hydroxybenzaldehyde in anhydrous ethanol in the presence of sodium bicarbonate.¹⁶

Nitrones.—The phenylnitrones were prepared by mixing centimolar equivalents of the appropriate phenylhydroxylamine and benzaldehyde, dissolved in the minimum quantity of alcohol, and allowing the mixtures to stand at room temperature overnight. The precipitates (yields 80–95%) were recrystallized from alcohol (see Table IV).

Ultraviolet spectra were obtained with lime-dried ethanol solutions, using a Unicam S. P. 500 spectrophotometer.

(16) G. W. Watt and C. M. Knowles, *J. Org. Chem.*, **8**, 540 (1943).

Acknowledgments.—O. H. W. is grateful to the Rockefeller Foundation, New York, for financial assistance. Some preliminary spectroscopic measurements were carried out by Mrs. I. Boston, Spectroscopic Laboratory, Chemistry Department, Imperial College, London. Analyses are by Mr. F. M. Oliver, Analytical Laboratory, of the same college, and by Dr. F. Pascher, Bonn.

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[CONTRIBUTION FROM THE ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

The Action of Lithium Aluminum Hydride and Organometallic Reagents on 4-Hydroxycoumarin¹

BY JEREMIAH P. FREEMAN AND M. FREDERICK HAWTHORNE

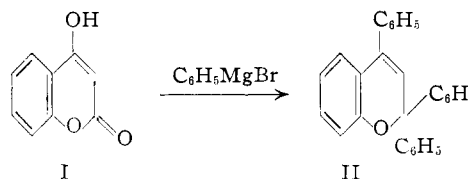
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4-Hydroxycoumarin reacts with phenylmagnesium bromide to produce 2,2,4-triphenylbenzopyran, with phenyllithium to produce *o*-hydroxybenzophenone and acetophenone and with lithium aluminum hydride to yield *o*-hydroxypropiofenone and *o*-hydroxycinnamyl alcohol. The differences between the lithium reagent and the Grignard reagent are discussed in terms of the leaving group properties of the respective oxide ions.

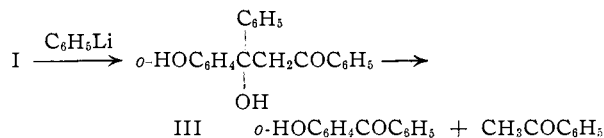
It has been demonstrated in recent years that enolates of β -dicarbonyl compounds, which may be regarded as vinylogs of carboxylate ions,² react additively with Grignard reagents^{2–5} and can be reduced with lithium aluminum hydride.^{6,7} The course of these reactions is dependent upon the nature of the enolate and of the Grignard reagent and upon the concentration of the reagent and the temperature of the reaction. As 4-hydroxycoumarin (I) is the enol of a cyclic β -ketoester, its reactions with organometallic reagents and lithium aluminum hydride are of interest to this general field.

The reaction of 4-hydroxycoumarin with Grignard reagents has been investigated previously. Originally it was reported that the reaction produced chromenols.⁸ The improbability of stable enol formation in this type of compound prompted a reinvestigation of the reaction, and it was recently reported that 4-hydroxycoumarin undergoes only salt formation with the Grignard reagent.⁹ Its enol ether, however, reacted to produce chromanones indicating that the chromenol structure originally proposed for this type of compound was incorrect.

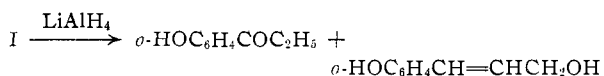
The resistance of the enolate of 4-hydroxycoumarin to further attack by the Grignard reagent seemed contradictory to the observed reactivity of other enols, and a re-examination of this reaction seemed necessary. It has now been found that 4-hydroxycoumarin does react with the phenyl Grignard reagent; the product obtained was 2,2,4-triphenylbenzopyran (II). Most of the 4-hydroxycoumarin was recovered unchanged, but the pyran was isolated in 22% yield.



The reaction of 4-hydroxycoumarin with phenyllithium was next investigated to determine whether any differences existed between these two organometallic reagents with respect to their reaction with enolates. The products isolated from this reaction were acetophenone and *o*-hydroxybenzophenone, but these probably arise through hydrolytic cleavage of the primary reaction product, β -phenyl- β -(*o*-hydroxyphenyl)- β -hydroxypropiofenone (III).



Finally the reduction of 4 hydroxycoumarin with lithium aluminum hydride was investigated. Two products were obtained upon hydrolysis of the reaction mixture: *o*-hydroxypropiofenone and *o*-hydroxycinnamyl alcohol.



Several reasonable reaction paths may be envisioned which would encompass all the reactions described. For conciseness one which involves a common intermediate for all the reactions is discussed in detail here. A reasonable first step in all

(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) R. C. Fuson and L. R. Melby, *THIS JOURNAL*, **75**, 5402 (1953); R. C. Fuson, W. D. Emmons and G. W. Parshall, *ibid.*, **76**, 5466 (1954).

(3) G. F. Woods, *ibid.*, **69**, 2549 (1947).

(4) G. F. Woods and I. W. Tucker, *ibid.*, **70**, 2174 (1948).

(5) A. S. Dreiding and S. N. Nickel, *ibid.*, **76**, 3965 (1954).

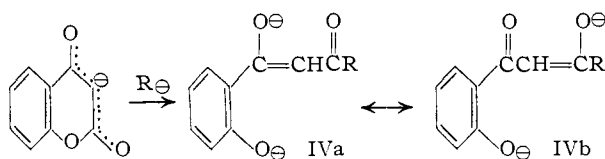
(6) A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 939 (1953).

(7) A. S. Dreiding and J. A. Hartman, *ibid.*, **75**, 3723 (1953).

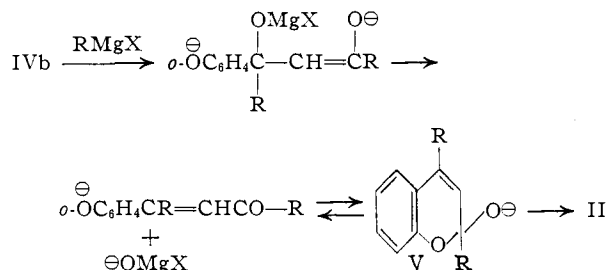
(8) I. M. Heilbron and D. W. Hill, *J. Chem. Soc.*, 2005 (1927).

(9) S. Wawzonek, R. C. Nagler and L. J. Carlson, *THIS JOURNAL*, **76**, 1080 (1954).

the reactions would involve attack at the lactone carbonyl group followed by rupture of the ring.

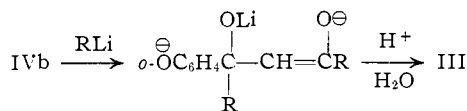


Further reaction with the Grignard reagent may be rationalized in the following manner



It is already known that the salt of 2,4-diphenylchromenol-2 (V) reacts with phenylmagnesium bromide to produce 2,2,4-triphenylbenzopyran.¹⁰ This abnormal reaction path is similar to that proposed by Woods⁴ for the reaction of Grignard reagents with certain cyclic β -diketones.

The reaction with phenyllithium appears to involve structure IVb in the following manner



This reaction path is followed in the reaction of organometallic compounds with enolic β -diketones^{9,11} under the ordinary Grignard conditions. However, the conditions used in this investigation and those employed by Woods and his co-workers^{8,4} must be termed "forcing," and this change in the reaction conditions probably accounts for the different course the reaction follows.¹²

There appears to be a significant difference between the reactivity of the Grignard reagent and the lithium reagent under these forcing conditions, whereas they react in the same way under normal conditions.⁵ Since in these abnormal reactions regeneration of a conjugated system with loss of an oxygen atom must occur during the reaction, it is believed that this difference may be related to the leaving group properties of the two species, $-\text{OMgX}$ and $-\text{OLi}$. Due to a lack of detailed information regarding the structures of lithium and magnesium alkoxides in such non-polar solvents as benzene and diethyl ether, no detailed description of these elim-

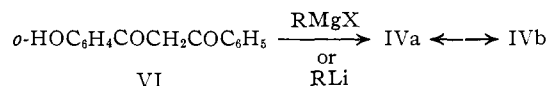
(10) T. A. Geissman and E. Baumgarten, *THIS JOURNAL*, **65**, 2135 (1943).

(11) E. P. Kohler and J. L. F. Erickson, *ibid.*, **53**, 2301 (1931).

(12) The term "forcing conditions" is, of course, an ambiguous one since it is used widely to describe any variation in the usual Grignard conditions which is made to effect a reaction which does not occur under the ordinary conditions. These variations generally involve higher boiling solvents, longer heating periods or both. It is believed now that for many reactions involving organometallic reagents the ordinary reaction conditions have a leveling effect and that many Grignard reactions which have been reported would follow different courses if more stringent conditions were employed.

ination processes can be advanced. However, it seems quite reasonable to assume that the absence of strongly solvating solvent molecules would force the species in question to exist primarily as ionic aggregates or ion-pairs. Since carbon-oxygen bonds are broken during the elimination process with anionic oxygen leaving groups, the metallic cation which gives the greatest amount of covalent bonding with the leaving oxide ion should be the most effective electrophile. Consideration of the well-known Lewis acid properties of magnesium derivatives¹³ leads to the conclusion that this divalent cation may form bonds which have a moderate proportion of covalent character. Lithium salts, on the other hand, are predominantly ionic and have not been reported to enter into covalent complexes. It is, therefore, concluded that the group $-\text{OMgX}$ is far superior to the group $-\text{OLi}$ as a leaving group due to its greater polarizability and larger heat of formation.¹⁴

Since *o*-hydroxydibenzoylmethane (VI) produces the same enolate ($\text{IVa} \leftrightarrow \text{IVb}$) as that postulated as an intermediate in the 4-hydroxycoumarin reaction, its reactions with phenylmagnesium bromide and phenyllithium were examined. When treated with the phenyl Grignard reagent under conditions identical to those employed in the 4-hydroxycoumarin reaction, *o*-hydroxydibenzoylmethane was converted to 2,2,4-triphenylbenzopyran in 74% yield. The results of the phenyllithium reaction

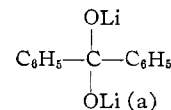


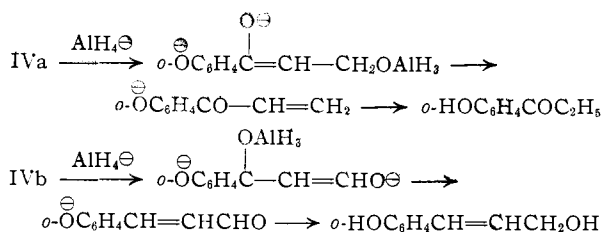
were less clear-cut and also depended upon the isolation procedure. When the reaction mixture was decomposed with ammonium chloride solution, a mixture of keto alcohols was obtained. Acid hydrolysis produced a mixture of ketones from which *o*-hydroxyacetophenone and *o*-hydroxybenzophenone were isolated indicating attack at both carbonyl groups. Significantly a trace amount of the triphenylbenzopyran also was isolated. These results lend considerable support both to the proposed mechanism of the 4-hydroxycoumarin reaction and to the proposal regarding the different reactivities of Grignard reagents and organolithium compounds.

With lithium aluminum hydride both structures IVa and IVb appear to be involved.

(13) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, Chap. IV, VI. Many examples of this type of interaction are cited in this reference.

(14) H. F. Bluhm, H. V. Donn and H. D. Zook, *THIS JOURNAL*, **77**, 4406 (1955), report an example of this phenomenon by the isolation of lithium complexes of the type (a) from the reaction of phenyllithium with lithium benzoate. Similar reactions of carboxylic acids or their salts with Grignard reagents lead predominantly to the production of tertiary alcohols (reference 14, p. 948). The greater tendency of magnesium to form covalent bonds may be rationalized on the basis of the tendency of the unfilled *s* and *p*-orbitals of the magnesium ion to enter into sp^2 -hybridization with electron donors when magnesium possesses a coordination number of four. In a state of coordination number two magnesium may have linear sp -hybridization with some extra stabilization attained by the interaction of non-bonding *p*-electrons of an electron donor with the unfilled *p*- and *d*-orbitals of magnesium.

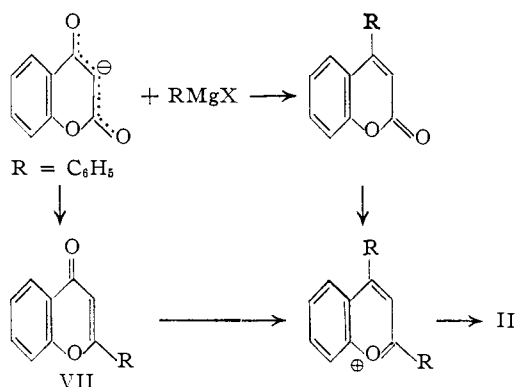




The interesting feature of this reaction is the production of *o*-hydroxypropiophenone, which is difficult to explain other than by the 1,4-addition outlined.¹⁵ Another possibility is that 1,2-addition occurred to produce the unsaturated alcohol expected which then isomerized during the isolation procedure to the ketone. Rearrangements of this type are quite rare and similar unsaturated carbinols have been isolated under identical work-up conditions. However, the reduction of 2-hydroxy-methylene-1-keto-1,2,3,4-tetrahydrophenanthrene is known to produce 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene among other products. It was suggested that this ketone may have been produced from the unsaturated alcohol during the isolation procedure.⁵

The intermediate aluminum adduct has been formulated in accordance with previous suggestions.¹⁶ The electron deficiency of aluminum salts indicates that the elimination of the aluminum oxide fragment should be even more facile than the corresponding magnesium species due to the greater covalent character of the aluminum-oxygen bond. Thus it has been observed that lithium aluminum hydride will add twice to enolates under the same conditions in which only a single addition of a Grignard reagent occurs.^{5,6}

While all of these reactions can be accommodated by the mechanistic proposals previously made,³⁻⁷ an alternative formulation of the Grignard reaction is worthy of consideration. The distinctive feature of this reaction path is that ring rupture need not occur.



This route is analogous to that proposed to explain the production of disubstituted cyclohexadienes from dihydroresorcinol,⁴ except that in this instance the "diene" (the flavylium salt) may be generated in the reaction mixture and is capable of

(15) E. P. Kohler, *Am. Chem. J.*, **42**, 375 (1909) has reported that Grignard reagents react exclusively with acrylophenone to give 1,4-addition products exclusively.

(16) W. G. Brown in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 472.

adding an additional molecule of Grignard reagent. Flavylium salts are known to be intermediates in the reactions of certain coumarins with Grignard reagents. For example, 4-phenyl- and 4-methylcoumarin react with phenylmagnesium bromide to produce 2,2-diphenylbenzopyrans *via* the corresponding flavylium salts.¹⁷ In order to determine whether flavone VII could be converted to the benzopyran, it was treated with phenylmagnesium bromide under the forcing conditions of the 4-hydroxycoumarin reaction. 2,2,4-Triphenylbenzopyran II was isolated in 50% yield. Previously the reactions of flavones with Grignard reagents have been examined only under the ordinary mild conditions and chromenols were produced.¹⁸ Recently it has been demonstrated that xanthone is converted to 2,2-diphenylxanthone by phenylmagnesium bromide.¹⁹ This reaction appears to proceed through the intermediate formation of a xanthylum salt. Such a path may be followed in those cases where rupture of the coumarin ring is known not to occur.²⁰

Experimental²¹

Reaction of 4-Hydroxycoumarin with Phenylmagnesium Bromide.—To a solution of 38 ml. of 3 *M* ethereal phenylmagnesium bromide²² in 250 ml. of dry benzene was added slowly a slurry of 5.0 g. (0.031 mole) of 4-hydroxycoumarin in 200 ml. of dry benzene. The mixture took on a yellow-green color and a solid precipitated. The mixture was heated under reflux for 5 hr. during which period the solid gradually dissolved and the solution became bright yellow. It was then cooled and poured into ice and hydrochloric acid. A solid identified as unchanged 4-hydroxycoumarin separated out and was collected, yield 2.8 g. (56%). The organic extracts were concentrated and distilled to remove bromobenzene and biphenyl. Upon crystallization of the gummy residue from ethanol, a light yellow solid, m.p. 125–130°, was obtained, yield 2.5 g. (22%). Several recrystallizations from ethanol produced small white plates, m.p. 131–132°.

Anal. Calcd. for $\text{C}_{27}\text{H}_{20}\text{O}$: C, 90.00; H, 5.56. Found: C, 89.75; H, 5.51.

2,2,4-Triphenylbenzopyran is reported to melt at 130° by several investigators.^{10,12,23} The infrared spectrum of this compound had bands at 1622 and 1598 cm^{-1} , attributable to a conjugated olefinic double bond and to an aromatic ring, respectively.

Reaction of Phenyllithium with 4-Hydroxycoumarin.—An ethereal solution of phenyllithium was prepared from 2.8 g. (0.4 g. atom) of lithium foil, 31.4 g. (0.2 mole) of bromobenzene and 200 ml. of dry ether. To this solution was added a slurry of 5.0 g. (0.031 mole) of 4-hydroxycoumarin in 200 ml. of dry benzene. The mixture was stirred under reflux for 4 hr. and then decomposed with ice and hydrochloric acid. Unchanged 4-hydroxycoumarin (3.2 g., 64%) separated and was collected by filtration. The organic layer was separated, concentrated and steam distilled. Only a small amount of tarry residue remained which proved to be intractable. The steam distillate was ex-

(17) I. M. Heilbron, D. W. Hill and H. N. Walls, *J. Chem. Soc.*, 1701 (1931).

(18) (a) K. Ziegler, F. A. Fries and F. Salzer, *Ann.*, **448**, 249 (1926); (b) S. Wawzonek in R. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 255.

(19) A. Schönberg and W. Askir, *J. Chem. Soc.*, 609 (1946).

(20) R. L. Shriner and A. G. Sharp, *J. Org. Chem.*, **4**, 575 (1939).

(21) We are indebted to Dr. K. S. McCallum for infrared interpretations.

(22) Arapahoe Chemical Co., Boulder, Colorado.

(23) A. Lowenbein and B. Rosenbaum, *Ann.*, **448**, 223 (1926). The proof of this material's structure appears to rest upon an unpublished observation of Lowenbein mentioned in this article that 2,4-diphenylbenzopyrylium salts are converted to this pyran when treated with the phenyl Grignard reagent. As no examples of 1,4-addition to pyrylium salts appear to have been found, the structure of this pyran seems certain.

tracted with ether and these extracts were dried and concentrated to yield an oily liquid which was chromatographed on an alumina column. The liquid was put on the column with benzene and eluted with benzene. Bromobenzene and biphenyl were removed and finally 1.2 g. (32%) of acetophenone, m.p. of 2,4-dinitrophenylhydrazone, 243–245° (lit.²⁴ m.p. 250°), was eluted.

Anal. Calcd. for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.00; N, 18.67. Found: C, 55.94; H, 3.68; N, 18.33.

Further elution with benzene and then methylene chloride removed nothing from the column. Elution with ethyl acetate produced 1.7 g. (28%) of *o*-hydroxybenzophenone, m.p. of 2,4-dinitrophenylhydrazone, 250–252° (lit.²⁶ m.p. 253°).

Anal. Calcd. for $C_{13}H_{14}N_4O_6$: C, 60.32; H, 3.70; N, 14.81. Found: C, 60.59; H, 3.84; N, 14.60.

Reduction of 4-Hydroxycoumarin with Lithium Aluminum Hydride.—To a slurry of 19.0 g. (0.5 mole) of lithium aluminum hydride in 200 ml. of dry ether was added a slurry of 16.2 g. (0.1 mole) of 4-hydroxycoumarin in 200 ml. of dry benzene. The resulting mixture was heated under reflux for 6 hr., then allowed to stand at room temperature overnight. The excess hydride was destroyed with ethanol and the mixture was poured onto ice and hydrochloric acid. (In one work-up Rochelle salts were used to decompose the mixture and the same product mixture was obtained.) The organic layer was separated, dried and concentrated to yield a viscous brown oil which was distilled. The distillate proved to be *o*-hydroxypropiofenone, m.p. of 2,4-dinitrophenylhydrazone, 189–190° (lit.²⁶ m.p. 189°), yield 5.7 g. (38%).

(24) R. L. Shriner and R. C. Fuson, "The Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 263.

(25) G. D. Johnson, *THIS JOURNAL*, **73**, 5888 (1951).

(26) C. Torres and J. Amargos, *Anales soc. espana fis. quim.*, **21**, 37 (1933); *C. A.*, **27**, 1624 (1933).

Anal. Calcd. for $C_{16}H_{14}N_4O_6$: C, 54.54; H, 4.24; N, 16.97. Found: C, 54.65; H, 4.16; N, 16.86.

The residue from the distillation was chromatographically purified on alumina to yield a pale yellow solid, m.p. 106–109°, yield 6.9 g. (35%). This solid was converted to a dibenzoate, m.p. 91–93°. *o*-Hydroxycinnamyl alcohol is reported²⁷ to melt at 110° and to form a dibenzoate, m.p. 92.5–93.5°.

Reaction of *o*-Hydroxydibenzoylmethane with Phenylmagnesium Bromide.—To 40 ml. of a 3 *M* ethereal solution of phenylmagnesium bromide in 200 ml. of dry benzene was added 4.8 g. (0.02 mole) of *o*-hydroxydibenzoylmethane²⁸ in 150 ml. of dry benzene. During the addition the mixture took on a green color which darkened rapidly after heating was begun. The mixture was heated under reflux for 3 hr. and then decomposed with ammonium chloride solution. The organic extracts were concentrated and steam distilled to yield an orange residue which crystallized from warm ethanol, yield 5.3 g. (74%). Recrystallization from ethanolic yielded white plates, m.p. 131–132°. This material did not depress the melting point of the 2,2,4-triphenylbenzopyran obtained from the 4-hydroxycoumarin reaction.

Reaction of Flavone with Phenylmagnesium Bromide.—To 80 ml. of a 3 *M* solution of phenylmagnesium bromide²² in 200 ml. of dry benzene was added a solution of 11.1 g. of flavone²⁸ in 150 ml. of benzene. The resultant mixture was heated under reflux for 3 hr. and then decomposed with ammonium chloride. The organic extracts were steam distilled and the orange residue was crystallized from ethanol, yield 9.0 g. (50%). Recrystallization from ethanol produced white plates of 2,2,4-triphenylbenzopyran, m.p. 130–132°.

(27) F. A. Hochstein, *THIS JOURNAL*, **71**, 395 (1949); P. Karrer and P. Banerjee, *Helv. Chim. Acta*, **32**, 1692 (1949).

(28) T. S. Wheeler, *Org. Syntheses*, **32**, 72 (1952).

HUNTSVILLE, ALABAMA

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA AND THE UNIVERSITY OF SAN FRANCISCO]

Dipole Moments, Spectra and Structure of α -Halocyclohexanones, α -Halocyclopentanones and Related Compounds

BY W. D. KUMLER AND ALAIN C. HUITRIC

RECEIVED NOVEMBER 9, 1955

The dipole moments of α -bromo- and α -chlorocyclohexanones are not consistent with the halogens occupying axial positions in these compounds as has been concluded by others from infrared data. Contributions from forms with a separation of charge are not able to account for the observations. Some contribution from flexible forms appears to be a way of adequately explaining the observed facts. The α -halocyclohexanones show a larger variation in dipole moment in different solvents than do the α -halocyclopentanones. The $n \rightarrow \pi^*$ blue shift shows a greater variation with different cyclohexanones than with different cyclopentanones. The 5.6 kcal. usually assigned as the difference between the boat and chair form of cyclohexane is more nearly the difference in energy between the stretched conformation of the flexible form and the chair form. Cyclohexane derivatives likely to have appreciable contributions from flexible forms are (1) those with an atom in the ring with other than sp^3 binding and a strong dipole on an adjacent atom, (2) those with two or more atoms in the ring with other than sp^3 binding such as heteroatoms or carbonyl carbons. *N,N'*-Dinitropiperazine probably exists to an appreciable extent in the flexible form. The ultraviolet spectrum of cyclopentanone in heptane has much fine structure while that of cyclohexanone has virtually none.

Corey¹ has reported that β -bromocyclohexanone and α -chlorocyclohexanone have the halogen atoms in the axial position. This conclusion was based on the observation that the introduction of an α -bromine atom caused a small shift in the frequency of the carbonyl band coupled with the hypothesis of Jones, *et al.*,² "that large positive shifts of the C=O stretching frequency on α -bromination in the cyclohexanone ring system in the chair configuration occur only when the bromine atom occupies an equatorial position." The

(1) E. J. Corey, *THIS JOURNAL*, **75**, 2301 (1953).

(2) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *ibid.*, **74**, 2828 (1952).

latter hypothesis was derived from measurements on steroids where the attachment of other rings would cause the cyclohexane ring to be held in a rigid conformation. One cannot be certain, however, that the same hypothesis would apply to an unattached cyclohexane ring such as is present in the compounds under consideration.

The dipole moments of these compounds should, on the other hand, give a direct, unequivocal answer as to whether the halogens are axial since the theoretical dipole moments are 2.30 *D* axial and 4.22 *D* equatorial.

The recent papers by Hassel³ and by Kwestroo,

(3) O. Hassel, *Quart. Rev.*, **7**, 22 (1953).