

Nuclear Magnetic Resonance Studies of cis- and trans-2,3-Dimethylcycloalkanones

P. E. PFEFFER* AND S. F. OSMAN

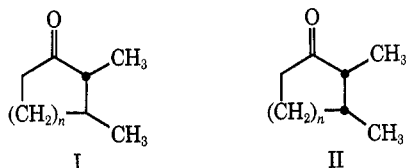
Eastern Regional Research Laboratory,¹ Philadelphia, Pennsylvania 19118

Received January 24, 1972

The nmr methyl shifts of six cis- and trans-2,3-dimethylcycloalkanones were identified by deuteration and pseudocontact shift techniques. The chemical shift assignments in 2,3-dimethyl-substituted C₅, C₆, and C₇ ketones indicate a preferential axial orientation of the 3-methyl protons in the respective cis isomers, while the 2-methyl protons maintain a predominant equatorial position. Conformational considerations are proposed to support this hypothesis.

Nmr investigations concerned with the configuration and conformation of 1,2-dimethylcycloalkanes have been reported.² The purpose of these studies was to assign the ring proton resonances of both equatorial and axial protons and to correlate these chemical shift positions with the environments of the ring.

Surprisingly, the nmr spectra of cycloalkanones of structures I and II have received little attention. In



fact, no rigorous assignment for the 2- or 3-methyl groups in either of these isomers has been made.³

In the present study we describe some of the nmr studies we have made to elucidate the chemical shifts of the methyl groups in 2,3-dimethylcycloalkanones (I and II, $n = 1, 2, 3$) and the conformational preferences inherent in these assignments.

Results

Nmr Assignments.—By use of Eu(fod)₃ shift reagent,⁴ chemical shift assignments were made for the 2- and 3-CH₃ group protons in all of the trans-2,3-dimethylcycloalkanones (I). Upon complexation, the high-field methyl doublet underwent a preferential downfield displacement. This displacement was found to be twice the magnitude of the one exhibited by the low-field doublet. On the basis of this evidence, the upfield doublet was assigned to the 2-CH₃ protons and the lowfield doublet to the 3-CH₃ protons.⁵ Incorporation of three deuterium atoms α to the carbonyl group through equilibration with NaOCH₃ in CH₃OD also supports this conclusion. The nmr spectra of the uncomplexed deuterated isomers (III) exhibited singlets in place of the high-field doublets observed in the corresponding proteo compounds (I).

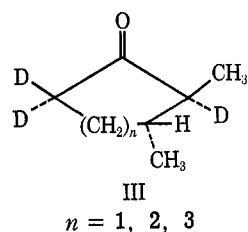
(1) Eastern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) (a) N. Muller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962); (b) J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960).

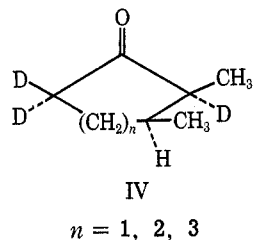
(3) One report of trans-2,3-dimethylcyclobutanone has made assignments for the methyl resonances. (a) J. L. Ripoll and J. M. Conia, *Bull. Soc. Chim. Fr.*, 2755 (1965). Another study has reported the nmr spectra both of cis- and trans-2,3-dimethylcyclobutanone without reference to the methyl proton assignments. (b) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2036 (1970).

(4) R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1522 (1971).

(5) This assignment is not unexpected since one might expect the α -carbonyl to exert a shielding effect on the 2 position. See L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1959, p 122. Note also that in 2- and 3-methylcyclohexanones and pentanones the 2-methyl groups resonate at higher fields due to the shielding effects of the carbonyl group.



Methyl group chemical shift assignments of the cis isomers II, unlike those of the trans isomers I, could not be readily made using the Eu(fod)₃ complexation technique because of the indistinguishability of the 2- and 3-CH₃ group resonances (both doublets have the same coupling constants). However, the methyl proton chemical shift assignments for the cis isomers II were made, using the corresponding deuterated compounds IV. The nmr spectra of the uncomplexed IV,



unlike those of III, showed collapse of the low-field doublets to singlets. Thus, in the cis isomers II, the 2-CH₃ protons were assigned to the low-field resonance while the 3-CH₃ protons were assigned the high-field resonance position.

Further confirmation of the methyl group assignments in all six deuterated ketones have been made using Eu(fod)₃. In all cases the singlet methyl group resonances underwent proportionally larger downfield displacements than did the methyl group doublets [at a ratio of Eu(fod)₃/ketone of 0.5]. These findings further substantiate our assignments and establish unambiguously that the 2-CH₃ group resonances undergo greater displacements than the 3-CH₃.

In Table I chemical shift data are tabulated for the cis- and trans-2,3-dimethylcycloalkanones (I and II). Two representative examples of deuterated and non-deuterated cis- and trans-2,3-dimethylcycloalkanones examined are shown in Figure 1.

Structural Assignments.—In both the cyclopentanone and cyclohexanone series, isomeric structure assignments were readily made through equilibration to the known thermodynamic mixtures respectively. In each case the trans isomer was predominant (see Experimental Section). For the cycloheptanone series, equilibration techniques were of no value, since equilibration yielded an equimolar mixture of cis and trans

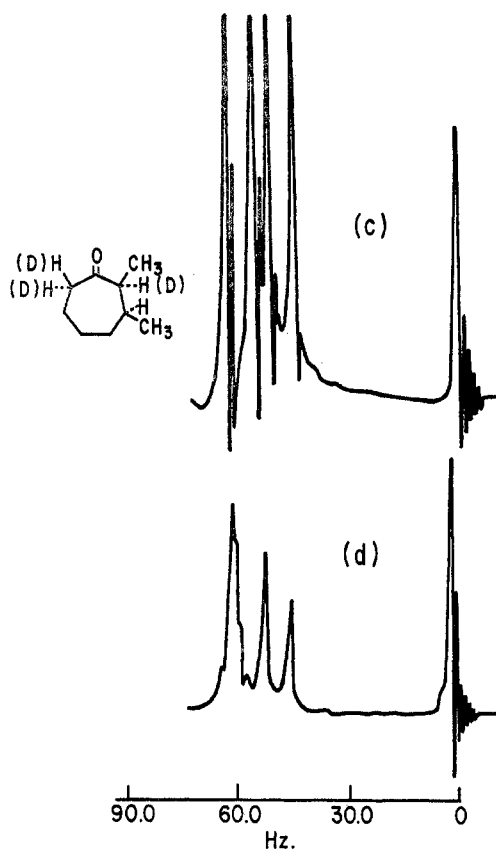
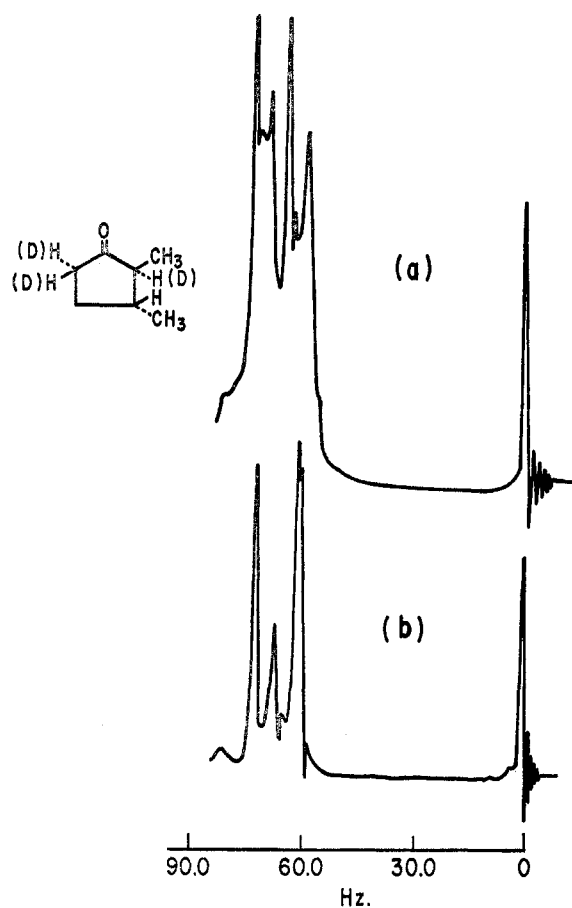


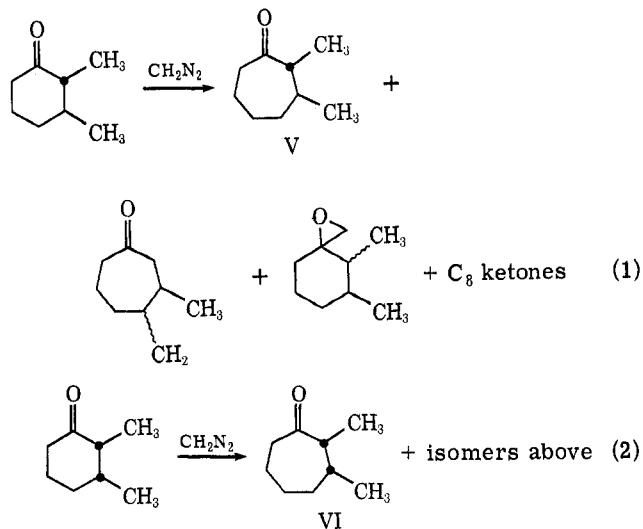
Figure 1.—Nmr spectra of the methyl protons in α -deuterated and nondeuterated *cis*- and *trans*-2,3-dimethylcycloalkanes: (a) *trans*-2,3-dimethylcyclopentanone; (b) *trans*-2,3-dimethylcyclopentanone-2,5,5- d_3 ; (c) *cis*-2,3-dimethylcycloheptanone-2,5,5- d_3 ; (d) *cis*-2,3-dimethylcycloheptanone-2,7,7- d_3 .

TABLE I
CHEMICAL SHIFTS^a AND METHINE COUPLING CONSTANTS^b
FOR 2- AND 3-METHYL GROUP PROTONS IN
2,3-DIMETHYLCYCLOALKANONES

| Registry no. | Ketone | $\delta_{2\text{CH}_3}$ (J, Hz) | $\delta_{3\text{CH}_3}$ (J, Hz) | $\Delta\delta$ (upfield) CH ₃ shift in <i>cis</i> isomer relative to <i>trans</i> isomer | |
|--------------|--------|---------------------------------|---------------------------------|---|-------------------|
| | | | | 2-CH ₃ | 3-CH ₃ |
| 2867-24-5 | | 60.0 (6.2) | 69.0 (5.2) | 4.1 | 14.9 |
| 2865-86-3 | | 55.9 (7.1) | 54.1 (6.9) | | |
| 1551-89-9 | | 58.2 (6.5) | 63.0 (5.6) | 2.4 | 13.2 |
| 766-42-7 | | 55.8 (6.9) | 49.8 (7.0) | | |
| 34759-52-9 | | 59.2 (5.9) | 63.0 (6.9) | 0 | 15.3 |
| 34759-53-0 | | 59.1 (6.9) | 47.7 (6.9) | | |

^a In hertz at 60 MHz downfield from TMS as an internal standard. ^b In hertz.

isomers. However, assignments for the latter compounds could be made through an unequivocal synthesis from its next lower homolog. The isomeric cycloheptanones were each prepared by a homologization reaction of diazomethane with the corresponding cyclohexanone derivative.⁶ A mixture of products was obtained.



The basic structural assignment of the 2,3-dimethylcycloheptanones V and VI was confirmed by mass spectral fragmentation of the deuterated compounds. The 2,3-dimethylcycloheptanones-2,7,7- d_3 (143) were readily distinguishable from the 3,4-dimethylcyclo-

(6) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).

heptanones-2,7,7- d_3 (144) as well as the 2,3-dimethylcyclooctanones-2,8,8- d_3 (157) and the 3,4-dimethylcyclooctanones-2,8,8- d_3 (158) by the m/e values of the respective molecular ions. Acyclic olefinic isomers were also eliminated as possible structures for the designated products since acyclic olefinic isomers incorporate two or four deuteriums. The stereochemistry of the 2,3 isomers V and VI (eq 1 and 2) was unequivocally the same as that of the respective starting materials, since formation of V and VI through the insertion of methylene into the unsubstituted side of the carbonyl group does not disturb the original methyl-methyl relationship.

Mass spectral data substantiate the configurational assignments made for all of the 2,3-dimethylcycloalkanones. Under mass spectrometer source conditions, a preionization process occurs, giving rise to the loss of two hydrogens.⁷ Since this process occurs more readily with the cis isomer, structural assignments of the cis and trans isomers were readily confirmed. The greater relative intensity of the $[M - 2]^+$ ion for each cis isomer is clearly demonstrated in Table II.

TABLE II
INTENSITY OF $[M - 2]^+$ ION RELATIVE TO
 $[M]^+$ IN CIS AND TRANS CYCLOALKANONES

| Cycloalkanone | — $[M - 2]^+ / [M]^+$ — | |
|----------------------------|-------------------------|-------|
| | cis | trans |
| 2,3-Dimethylcyclopentanone | 0.25 | 0.1 |
| 2,3-Dimethylcyclohexanone | 0.3 | <0.01 |
| 2,3-Dimethylcycloheptanone | 1 | 0.2 |

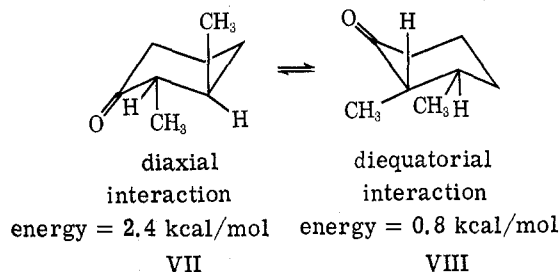
Discussion

All of the trans compounds exhibit higher field shifts associated with the 2- CH_3 protons, relative to the 3- CH_3 , while the corresponding cis compounds show higher field shift positions for the 3- CH_3 protons (relative to the 2- CH_3). In both the trans and cis compounds of each respective ring size, the resonance positions of the 2- CH_3 protons remain constant within 4 Hz, whereas the 3- CH_3 proton resonances of the cis compounds appear at 13–15 Hz higher fields than the corresponding trans compounds. These results may be adequately explained in terms of conformational preferences.

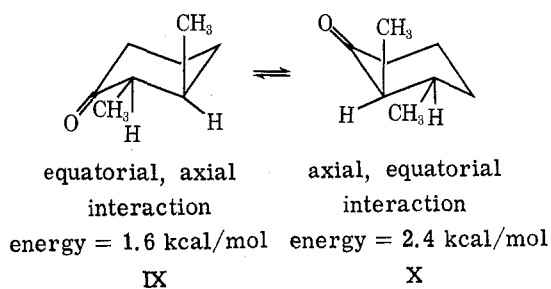
Cyclohexanone differs very little in its geometry (chair conformation) from cyclohexane, if we disregard small deformations of the valence angles.⁸ The energy differences between an axial and equatorial methyl group in 2-methyl-4-*tert*-butylcyclohexanone is 1.6 kcal/mol. The same energy is observed for the corresponding cyclohexanes. Thus, the value for the 1,3-diaxial $\text{CH}_3\text{--H}$ interactions is given as 0.8 kcal/mol.⁹ Furthermore, the 2,3-axial, equatorial, and diequatorial $\text{CH}_3\text{--CH}_3$ interactions of 2,3-dimethylcyclohexanones have an energy value of 0.8 kcal/mol each.⁹ This

value corresponds to the energy of interaction found for the $\text{CH}_3\text{--CH}_3$ interactions in 1,2-dimethylcyclohexane.

Examination of the interaction energies associated with the conformations of *trans*-2,3-dimethylcyclohexanone reveals that the diequatorial conformer VIII



predominates by about 1.6 kcal/mol. Introduction of a carbonyl group into an α position of the 1,2-dimethylcyclohexane ring has the effect of lowering the total energy of the system by removal of one 1,3-axial $\text{CH}_3\text{--H}$ interaction.¹⁰ Examination of *trans*-2,3-dimethylcyclohexanone reveals that one 1,3-axial $\text{CH}_3\text{--H}$ interaction is absent in conformer VII relative to the respective cyclohexane conformer while conformer VIII has essentially the same energy content as its cyclohexane counterpart. In effect, the carbonyl group lowers the energy of the diaxial conformer VII by 0.8 kcal/mol. This is not a sufficient energy drop to change the conformer population significantly, since the diequatorial conformer VIII still predominates by 1.6 kcal/mol, a value that indicates that 93% of the molecules are in conformation VIII at room temperature. Comparison of the conformations of the *cis*-2,3-dimethylcyclohexanones shows that the carbonyl does assume a structurally important role in causing a conformational preference. This role is evident when we consider the energies associated with the corresponding *cis*-1,2-dimethylcyclohexane conformers. Since both cyclohexane conformers (equatorial, axial or axial, equatorial) have equal energy contents before introduction of the carbonyl group, preferential removal of any nonbonded interactions in one conformer should cause a shift in the equilibrium. With the introduction of the carbonyl group, the derived cyclohexanone conformer IX loses one axial $\text{CH}_3\text{--H}$ interaction



while conformer X remains essentially constant in energy content relative to the corresponding cyclohexane. Removal of the 1,3-axial $\text{CH}_3\text{--H}$ interaction in conformer IX lowers its energy by 0.8 kcal/mol, making it more stable than X by 0.8 kcal/mol. This energy difference represents approximately a 3:1 preference for conformer IX at room temperature.

(7) (a) S. F. Osman, C. J. Dooley, and T. A. Foglia, 19th Annual Conference on Mass Spectrometry, Atlanta, Ga., May 7–14, 1971; (b) S. Osman, C. J. Dooley, T. A. Foglia, and L. M. Gregory, *Org. Mass Spectrom.*, **4**, 139 (1970).

(8) The inner angle of the carbonyl is 116° and the C–C bond of the trigonal carbon atom of the carbonyl is 1.5 Å compared to the normal C–C bonds of 1.54 Å. (a) C. C. Costain and B. P. Stoieheff, *J. Chem. Phys.*, **30**, 777 (1959). (b) R. D. Stolow, *J. Amer. Chem. Soc.*, **84**, 686 (1962).

(9) (a) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961). (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p. 109.

(10) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962).

Since the 3-CH₃ protons of conformer IX are in the axial position, one might anticipate that the weighted average nmr chemical shift of the 3-CH₃ protons would be at higher fields.¹¹ This indeed is observed. Furthermore, since the 2-CH₃ protons still remain predominately in an equatorial environment, the chemical shift position of these protons remains relatively unchanged with respect to the trans isomer.¹²

The cycloheptanones exhibit the same chemical shift behavior as the cyclohexanones. This is not surprising, since the skewed butane 1,3-CH₃-H interactions and 1,2-CH₃-CH₃ interaction energies of cycloheptanones are the same order of magnitude as in the cyclohexanone series.¹³ Again the nmr spectrum of the cis isomer shows a large upfield shift (15 Hz) for the 3-CH₃ protons, while the 2-CH₃ resonances remain relatively constant in position in both cis and trans isomers (see Table I). Although the shielding of the ring bonds on axial substituents in C₇ ring systems has not been reported, such an effect should not be considered unusual in light of the fact that the ring conformations for cycloheptanes are not very different from those of cyclohexanes.

The cyclopentanones, like the corresponding C₆ and C₇ homologs, show the same trend in the nmr shift data. However, the large number of ring conformations of the cyclopentanones (low energy barriers to interconversion) make it a difficult system to evaluate from a conformational point of view.¹⁴ For this reason it is hard to interpret on conformational grounds why the same chemical shift phenomena are observed.

3,4-Dimethylcyclopentanone is a good model compound for demonstrating the shielding effects associated with the 3-axial CH₃ substituent. The chemical shift of the CH₃ groups in the trans isomer (equatorial, equatorial is 66.1 Hz. The CH₃ groups (equatorial, axial) in the cis isomer have an average chemical shift of 58.0 Hz. Since the cis isomer is a 50:50 mixture of equatorial and axial methyl groups, we can calculate that the chemical shift of the 3-axial CH₃ should be two times (66.1-58.0 Hz) or 16.2 Hz higher than the equatorial. Clearly, when the 3-CH₃ group occupies the axial position a large upfield shift is evident. This effect could be closely related to the interaction of the methyl and carbonyl group as well as the effects of the ring bonds. Again, the unusually high field resonance position exhibited by the 3-CH₃ of cis-2,3-dimethylcyclopentanone would lead us to believe that these protons are in an axial environment relative to the equatorial

environment of the trans isomer. However, it is difficult to understand at this time why this is so, since the conformational preferences for this system are not well defined.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Jeolco C-60H¹⁵ high-resolution nmr spectrometer. All data were verified on a Varian HA-100 high-resolution nmr spectrometer. Mass spectra were obtained on a Dupont 492 or CEC 103 mass spectrometer and samples were introduced *via* the batch inlet system at ambient temperature. Analytical and preparative glpc analysis were performed on a Hewlett-Packard 800 gas chromatograph using 9 ft × 0.125 in. and 20 ft × 0.5 in. columns, respectively, packed with Carbowax 20M (10%) on Chromosorb W (40/60 mesh).

cis- and trans-2,3-Dimethylcyclopentanone.—*cis-* and *trans-*2,3-dimethylcyclopentanones were obtained as a commercial mixture. Equilibration of the two isomers was effected in 12 hr with a 100 molar excess of CH₃OH or CH₃OD and a catalytic amount of NaOCH₃. This procedure gave a mixture that was 93% trans and 7% cis.¹⁶ The isomers were separated by preparative glpc. The mass spectrum of CH₃OD-exchanged samples showed that trideuteration was greater than 95%. Identification of each isomer was determined by mass spectral analysis (see results), and comparison with reported glpc retention data and equilibration values.¹⁶

cis- and trans-2,3-Dimethylcyclohexanone.—*cis-* and *trans-*2,3-dimethylcyclohexanones were prepared by chromic acid oxidation of commercially available isomeric 2,3-dimethylcyclohexanols. The stereochemical assignments were made on the basis of mass spectral data (see Results), and semicarbazone derivatization. The semicarbazone of the cis isomer had mp 176-177° (lit.¹⁷ mp 179°). The semicarbazone of the trans isomer had mp 202° (lit.¹⁷ mp 205°).

Equilibration as described above using CH₃OH or CH₃OD was performed on a mixture of *cis-* and *trans-*2,3-dimethylcyclohexanones (60:40, respectively). This mixture gave after equilibration 82% *trans-* and 18% *cis-*2,3-dimethylcyclohexanone. The isomers were separated by preparative glpc, and the deuterated isomers showed greater than 95% trideuteration by mass spectrometry.

cis- and trans-2,3-Dimethylcycloheptanones.—Each pure isomer (*cis* or *trans*) of 2,3-dimethylcyclohexanone was ring expanded to the corresponding cycloheptanone according to the method described by Marshall.⁶ 2,3-Dimethylcyclohexanone (2 g, 0.016 mol) was added to an ether-methanol (1:1) solution (125 ml) of diazomethane (1.5 g, 0.035 mol). After 48 hr the solution was concentrated. The product mixture was determined by glpc-mass spectral analysis. It showed the presence of starting material, 2,3-dimethylcycloheptanone, 3,4-dimethylcycloheptanone, isomeric dimethylcyclooctanones, and cyclohexane epoxides. The structures of the 2,3-dimethylcycloheptanones were verified by mass spectrometry (see Results). The total product yield was ca. 50%, of which 50% was the desired 2,3-dimethylcycloheptanone.

Each isomer of *cis-* and *trans-*2,3-dimethylcycloheptanones was equilibrated as described above, to an equilibrium mixture of 53% trans and 47% cis. The isomers were separated by preparative glpc. Trideuteration in each isomer was greater than 95% as determined by mass spectrometry.

Acknowledgment.—The authors thank Dr. David Weisleder for the 100-MHz nmr spectra of our compounds.

(15) Reference to a particular manufactured product does not constitute a recommendation by the U. S. Department of Agriculture over similar products not mentioned.

(16) D. Varch, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1662 (1965).

(17) W. Cocker, T. B. H. McMurray, and E. R. Simons, *J. Chem. Soc.*, 3022 (1965).

(11) In cyclohexane the axial proton resonances are found at 29 Hz higher field than for the equatorial protons. (a) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *J. Amer. Chem. Soc.*, **82**, 1256 (1960); **84**, 386 (1962). In acetone diperoxide the axial methyl proton resonances are at 26.5 Hz higher field than the equatorial. (b) R. W. Murray, P. R. Story, and M. L. Kaplan, *ibid.*, **88**, 526 (1966). In 1,2-dimethylcyclohexane there is only an 8-Hz difference between the axial and equatorial methyl chemical shifts (see ref 2a).

(12) This small upfield shift in position could be due to the small contribution of conformer X, whose 2-CH₃ protons maintain an axial position.

(13) Energy differences between the diequatorial *cis*-3,5-dimethylcycloheptanone and the equatorial, axial *trans*-3,5-dimethylcycloheptanone is 0.8-0.9 kcal/mol, about the same as between *cis-* and *trans*-3,5-dimethylcyclohexanone. N. L. Allinger, *J. Amer. Chem. Soc.*, **81**, 232 (1959).

(14) C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3611 (1965).